1 CELL BIOLOGY

Introduction

There is an unbroken chain of life from the first cells on Earth to all cells found in organisms alive today. Eukaryotes have a much more complex cell structure than prokaryotes. The evolution of multicellular organisms allowed cell specialization and cell replacement. Cell division is essential but is carried out differently in prokaryotes and eukaryotes. While evolution has resulted in a biological world of enormous diversity, the study of cells shows us that there are also universal features. For example, the fluid and dynamic structure of biological membranes allows them to control the composition of cells.

1.1 Introduction to cells

Understanding

- According to the cell theory, living organisms are composed of cells.
- Organisms consisting of only one cell carry out all functions of life in that cell.
- Surface area to volume ratio is important in the limitation of cell size.
- Multicellular organisms have properties that emerge from the interaction of their cellular components.
- Specialized tissues can develop by cell differentiation in multicellular organisms.
- Differentiation involves the expression of some genes and not others in a cell's genome.
- The capacity of stem cells to divide and differentiate along different pathways is necessary in embryonic development. It also makes stem cells suitable for therapeutic uses.

Applications

- Questioning the cell theory using atypical examples, including striated muscle, giant algae and aseptate fungal hyphae.
- Investigation of functions of life in *Paramecium* and one named photosynthetic unicellular organism.
- Use of stem cells to treat Stargardt's disease and one other named condition.
- Ethics of the therapeutic use of stem cells from specially created embryos, from the umbilical cord blood of a new-born baby and from an adult's own tissues.

Nature of science

- Looking for trends and discrepancies: although most organisms conform to cell theory, there are exceptions.
- Ethical implications of research: research involving stem cells is growing in importance and raises ethical issues.

Skills

- Use of a light microscope to investigate the structure of cells and tissues.
- Drawing cell structures as seen with the light microscope.
- Calculation of the magnification of drawings and the actual size of structures shown in drawings or micrographs.

The cell theory

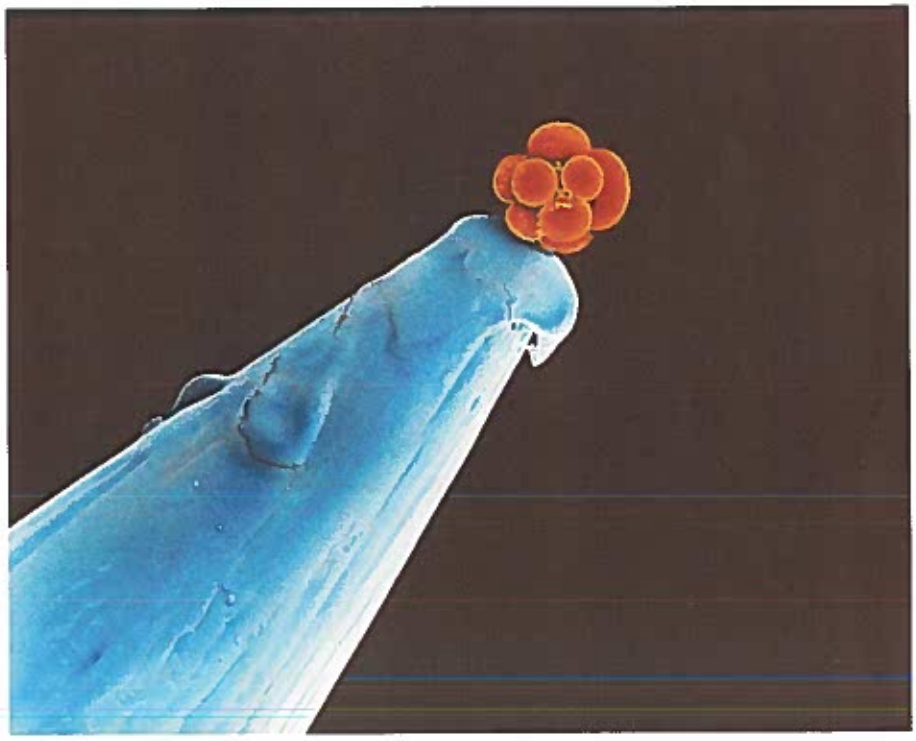
Living organisms are composed of cells.

The internal structure of living organisms is very intricate and is built up from very small individual parts. Organs such as the kidney and the eye are easily visible. If they are dissected we can see that large organs are made of a number of different tissues, but until microscopes were invented little or nothing was discovered about the structure of tissues. From the 17th century onwards biologists examined tissues from both plants and animals using microscopes. Although there was much variation, certain features were seen again and again. A theory was developed to explain the basic features of structure – the cell theory. This states that cells are the fundamental building blocks of all living organisms. The smallest organisms are unicellular – they consist of just one cell. Larger organisms are multicellular – they are composed of many cells.

Cells vary considerably in size and shape but they share certain common features:

- Every living cell is surrounded by a membrane, which separates the cell contents from everything else outside.
- Cells contain genetic material which stores all of the instructions needed for the cell's activities.
- Many of these activities are chemical reactions, catalysed by enzymes produced inside the cell.
- Cells have their own energy release system that powers all of the cell's activities.

So, cells can be thought of as the smallest living structures – nothing smaller can survive.



▲ Figure 1 Coloured scanning electron micrograph (SEM) of a human embryo on the tip of a pin

Exceptions to the cell theory

Looking for trends and discrepancies: although most organisms conform to cell theory, there are exceptions.

An early stage in scientific investigation is to look for trends – things that appear to be found generally rather than just in specific cases. These trends can lead to the development of a theory. A scientific theory is a way of interpreting the natural world. Theories allow us to make predictions. Sometimes exceptions to a general trend are found. These are called discrepancies. Scientists have to judge whether the discrepancies are common or serious enough to make predictions too unreliable to be useful. The theory is then discarded.

The cell theory is an example of where scientists have looked for trends and discrepancies. Robert Hooke was the first to use the word cell for structures in living organisms. He did this in 1665 after examining cork and other parts of plants. After describing cells in cork he wrote this:

> *Nor is this kind of texture peculiar to cork only, for upon examination with my microscope I have found that the pith of the Elder or almost any other tree, the inner pith of the Cany hollow stems of several other vegetables: as of Fennel, Carrets, Daucus, Bur-docks, Teasels, Fearn, some kind of Reeds etc. have much such a kind of Schematisme, as I have lately shown that of cork.*

So Hooke wasn't content with looking at just one type of plant tissue – he looked at many and discovered a general trend. Since Hooke's day biologists have looked at tissues from a huge variety of living organisms. Many of these tissues have been found to consist of cells, so the cell theory has not been discarded. However, some discrepancies have been discovered – organisms or parts of organisms that do not consist of typical cells. More discrepancies may be discovered, but it is extremely unlikely that the cell theory will ever be discarded, because so many tissues do consist of cells.

▲ Figure 2 Robert Hooke's drawing of cork cells

Activity

▲ Figure 3 What is the unit of life: the boy or his cells?

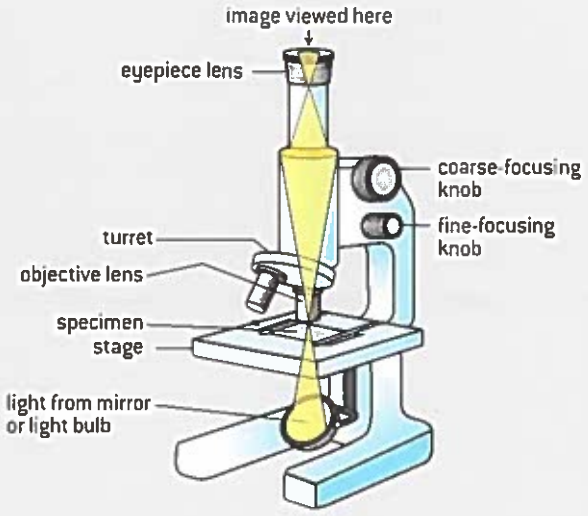
These two answers represent the holistic and the reductionist approach in biology.

Using light microscopes

Use of a light microscope to investigate the structure of cells and tissues.

Try to improve your skill at using microscopes as much as you can.

- Learn the names of parts of the microscope.
- Understand how to focus the microscope to get the best possible image.
- Look after your microscope so it stays in perfect working order.
- Know how to troubleshoot problems.



▲ Figure 4 Compound light microscope

Focusing

- Put the slide on the stage, with the most promising region exactly in the middle of the hole in the stage that the light comes through.
- Always focus at low power first even if eventually you need high power magnification.
- Focus with the larger coarse-focusing knobs first, then when you have nearly got the image in focus make it really sharp using the smaller fine-focusing knobs.
- If you want to increase the magnification, move the slide so the most promising region is exactly in the middle of the field of view and then change to a higher magnification lens.

Looking after your microscope

- Always focus by moving the lens and the specimen further apart, never closer to each other.
- Make sure that the slide is clean and dry before putting it on the stage.
- Never touch the surfaces of the lenses with your fingers or anything else.
- Carry the microscope carefully with a hand under it to support its weight securely.

Troubleshooting

Problem: Nothing is visible when I try to focus.

Solution: Make sure the specimen is actually under the lens, by carefully positioning the slide. It is easier to find the specimen if you focus at low power first.

Problem: A circle with a thick black rim is visible.

Solution: There is an air bubble on the slide. Ignore it and try to improve your technique for making slides so that there are no air bubbles.

Problem: There are blurred parts of the image even when I focus it as well as I can.

Solution: Either the lenses or the slide have dirt on them. Ask your teacher to clean it.

Problem: The image is very dark.

Solution: Increase the amount of light passing through the specimen by adjusting the diaphragm.

Problem: The image looks rather bleached.

Solution: Decrease the amount of light passing through the specimen by adjusting the diaphragm.

Types of slide

The slides that we examine with a microscope can be permanent or temporary.

Making permanent slides is very skilled and takes a long time, so these slides are normally made by experts. Permanent slides of tissues are made using very thin slices of tissue.

Making temporary slides is quicker and easier so we can do this for ourselves.

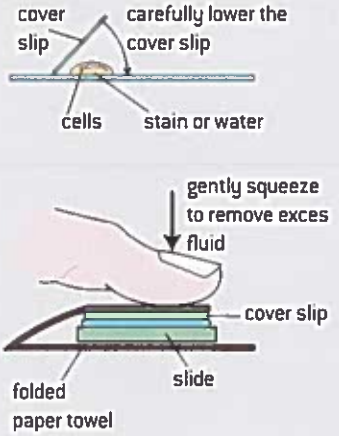
Examining and drawing plant and animal cells

Almost all cells are too small to be seen with the naked eye, so a microscope is needed to study them.

It is usually easy to see whether a cell is from a plant or an animal, even though there are many different cell types in both the plant and animal kingdoms.

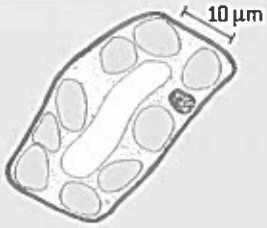
- Place the cells on the slide in a layer not more than one cell thick.
- Add a drop of water or stain.
- Carefully lower a cover slip onto the drop. Try to avoid trapping any air bubbles.
- Remove excess fluid or stain by putting the slide inside a folded piece of paper towel and pressing lightly on the cover slip.

It is best to examine the slide first using low power. Move the slide to get the most promising areas in the middle of the field of view and then move up to high power. Draw a few cells, so you remember their structure.



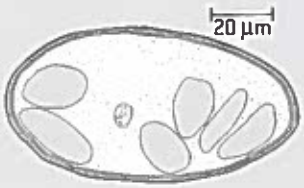
▲ Figure 5 Making a temporary mount

1 Moss leaf



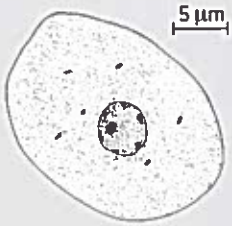
Use a moss plant with very thin leaves. Mount a single leaf in a drop of water or methylene blue stain.

2 Banana fruit cell



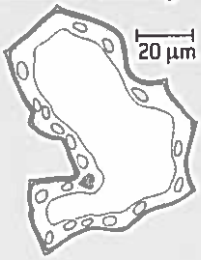
Scrape a small amount of the soft tissue from a banana and place on a slide. Mount in a drop of iodine solution.

3 Mammalian liver cell



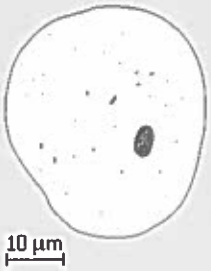
Scrape cells from a freshly cut surface of liver (not previously frozen). Smear onto a slide and add methylene blue to stain.

4 Leaf lower epidermis



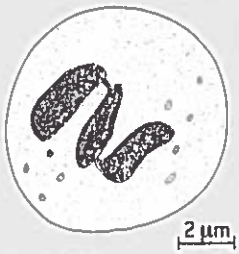
Peel the lower epidermis off a leaf. The cell drawn here was from *Valeriana*. Mount in water or in methylene blue.

5 Human cheek cell



Scrape cells from the inside of your cheek with a cotton bud. Smear them on a slide and add methylene blue to stain.

6 White blood cell



A thin layer of mammalian blood can be smeared over a slide and stained with Leishman's stain.

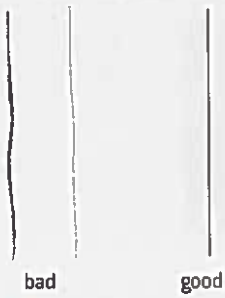
▲ Figure 6 Plant and animal cell drawings

Drawing cells

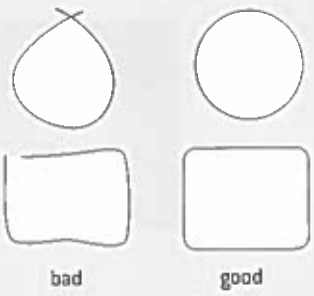
Drawing cell structures as seen with the light microscope.

Careful drawings are a useful way of recording the structure of cells or other biological structures. Usually the lines on the drawing represent the edges of structures. Do not show unnecessary detail and only use faint shading. Drawings of structures seen using a microscope will be larger than the structures actually are – the drawing shows them magnified. On page 6 the method for calculating the magnification of a drawing is explained. Everything on a drawing should be shown to the same magnification.

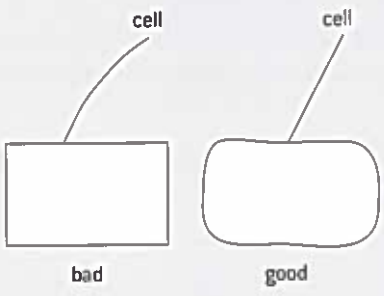
a) Use a sharp pencil with a hard lead to draw single sharp lines.



b) Join up lines carefully to form continuous structures such as cells



c) Draw lines freehand, but use a ruler for labelling lines.



▲ Figure 7 Examples of drawing styles

Calculation of magnification and actual size

Calculation of the magnification of drawings and the actual size of structures shown in drawings or micrographs.

When we look down a microscope the structures that we see appear larger than they actually are. The microscope is magnifying them. Most microscopes allow us to magnify specimens by two or three different factors. This is done by rotating the turret to switch from one objective lens to another. A typical school microscope has three levels of magnification:

- × 40 (low power)
- × 100 (medium power)
- × 400 (high power)

If we take a photo down a microscope, we can magnify the image even more. A photo taken down a microscope is called a micrograph. There are many micrographs in this book, including electron micrographs taken using an electron microscope.

When we draw a specimen, we can make the drawing larger or smaller, so the magnification of the drawing isn't necessarily the same as the magnification of the microscope.

To find the magnification of a micrograph or a drawing we need to know two things: the size of the image (in the drawing or the micrograph) and the actual size of the specimen. This formula is used for the calculation:

$$\text{magnification} = \frac{\text{size of image}}{\text{actual size of specimen}}$$

If we know the size of the image and the magnification, we can calculate the actual size of a specimen.

It is very important when using this formula to make sure that the units for the size of the image and actual size of the specimen are the same. They could both be millimetres (mm) or micrometres (μm) but they must not be different or the calculation will be wrong. Millimetres can be converted to micrometres by multiplying by one thousand. Micrometres can be converted to millimetres by dividing by one thousand.

Scale bars are sometimes put on micrographs or drawings, or just alongside them. These are straight lines, with the actual size that the scale bar represents. For example, if there was a 10 mm long scale bar on a micrograph with a magnification of ×10,000 the scale bar would have a label of 1 μm.

EXAMPLE:

The length of an image is 30 mm. It represents a structure that has an actual size of 3 μm. Determine the magnification of the image.

Either:

$30\,\text{mm} = 30 \times 10^{-3}\,\text{m}$

$3\,\mu\text{m} = 3 \times 10^{-6}\,\text{m}$

$$\text{Magnification} = \frac{30 \times 10^{-3}}{3 \times 10^{-6}}$$

$= 10{,}000\times$

Or:

$30\,\text{mm} = 30{,}000\,\mu\text{m}$

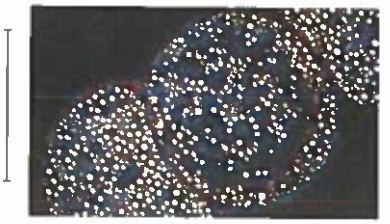
$$\text{Magnification} = \frac{30{,}000}{3}$$

$= 10{,}000\times$

Data-based questions

1 a) Determine the magnification of the string of *Thiomargarita* cells in figure 8, if the scale bar represents 0.2 mm [3]

b) Determine the width of the string of cells. [2]



▲ Figure 8 *Thiomargarita*

2 In figure 9 the actual length of the mitochondrion is 8 μm.

a) Determine the magnification of this electron micrograph. [2]

b) Calculate how long a 5 μm scale bar would be on this electron micrograph. [2]

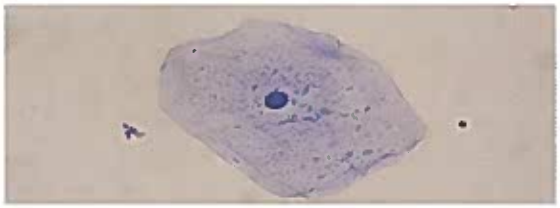
c) Determine the width of the mitochondrion. [1]

▲ Figure 9 Mitochondrion

3 The magnification of the human cheek cell from a compound microscope (figure 10) is 2,000 ×.

a) Calculate how long a 20 μm scale bar would be on the image. [2]

b) Determine the length of the cheek cell. [2]



▲ Figure 10 Human cheek cell

4 a) Using the width of the hen's egg as a guide, estimate the actual length of the ostrich egg (figure 11). [2]

b) Estimate the magnification of the image. [2]

▲ Figure 11 Ostrich egg

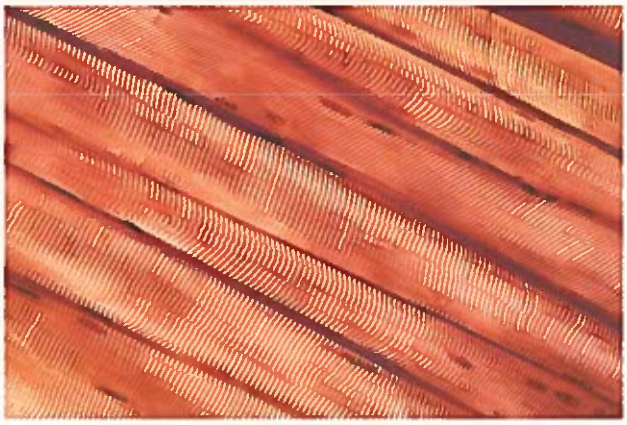
Testing the cell theory

Questioning the cell theory using atypical examples, including striated muscle, giant algae and aseptate fungal hyphae.

To test the cell theory you should look at the structure of as many living organisms as you can, using a microscope. Instructions for microscope use are given on page 4. In each case you should ask the question, "Does the organism or tissue fit the trend stated in the cell theory by consisting of one or more cells?"

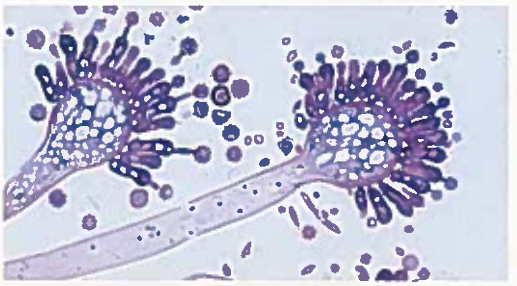
Three atypical examples are worth considering:

- Striated muscle is the type of tissue that we use to change the position of our body. The building blocks of this tissue are muscle fibres, which are similar in some ways to cells. They are surrounded by a membrane and are formed by division of pre-existing cells. They have their own genetic material and their own energy release system. However muscle fibres are far from typical. They are much larger than most animal cells. In humans they have an average length of about 30 mm, whereas other human cells are mostly less than 0.03 mm in length. Instead of having one nucleus they have many, sometimes as many as several hundred.



▲ Figure 12 Striated muscle fibres

- Fungi consist of narrow thread-like structures called hyphae. These hyphae are usually white in colour and have a fluffy appearance. They have a cell membrane and, outside it, a cell wall. In some types of fungi the hyphae are divided up into small cell-like sections by cross walls called septa. However, in aseptate fungi there are no septa. Each hypha is an uninterrupted tube-like structure with many nuclei spread along it.
- Algae are organisms that feed themselves by photosynthesis and store their genes inside nuclei, but they are simpler in their structure and organization than plants. Many algae consist of one microscopic cell. There are vast numbers of these unicellular algae in the oceans and they form the basis of most marine food chains. Less common are some algae that grow to a much larger size, yet they still seem to be single cells. They are known as giant algae. *Acetabularia* is one example. It can grow to a length of as much as 100 mm, despite only having one nucleus. If a new organism with a length of 100 mm was discovered, we would certainly expect it to consist of many cells, not just one.



▲ Figure 13 Aseptate hypha

▲ Figure 14 Giant alga

Unicellular organisms

Organisms consisting of only one cell carry out all functions of life in that cell.

The functions of life are things that all organisms must do to stay alive. Some organisms consist of only one cell. This cell therefore has to carry out all the functions of life. Because of this the structure of unicellular organisms is more complex than most cells in multicellular organisms.

Unicellular organisms carry out at least seven functions of life:

- Nutrition – obtaining food, to provide energy and the materials needed for growth.
- Metabolism – chemical reactions inside the cell, including cell respiration to release energy.
- Growth – an irreversible increase in size.
- Response – the ability to react to changes in the environment.
- Excretion – getting rid of the waste products of metabolism.
- Homeostasis – keeping conditions inside the organism within tolerable limits.
- Reproduction – producing offspring either sexually or asexually.

Many unicellular organisms also have a method of movement, but some remain in a fixed position or merely drift in water or air currents.

Limitations on cell size

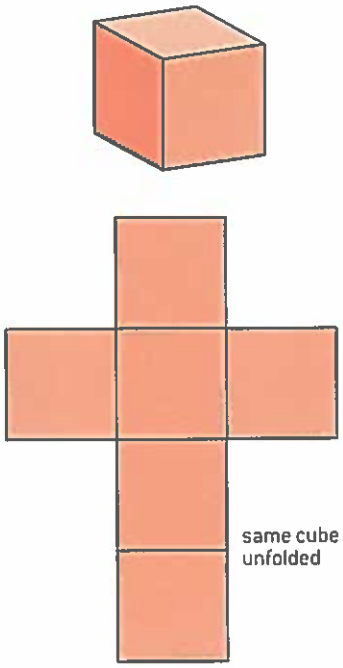
Surface area to volume ratio is important in the limitation of cell size.

In the cytoplasm of cells, large numbers of chemical reactions take place. These reactions are known collectively as the metabolism of the cell. The rate of these reactions (the metabolic rate of the cell) is proportional to the volume of the cell.

For metabolism to continue, substances used in the reactions must be absorbed by the cell and waste products must be removed. Substances move into and out of cells through the plasma membrane at the surface of the cell. The rate at which substances cross this membrane depends on its surface area.

The surface area to volume ratio of a cell is therefore very important. If the ratio is too small then substances will not enter the cell as quickly as they are required and waste products will accumulate because they are produced more rapidly than they can be excreted.

Surface area to volume ratio is also important in relation to heat production and loss. If the ratio is too small then cells may overheat because the metabolism produces heat faster than it is lost over the cell's surface.



▲ Figure 15 Volume and surface area of a cube

Functions of life in unicellular organisms

Investigation of functions of life in *Paramecium* and one named photosynthetic unicellular organism.

Paramecium is a unicellular organism that can be cultured quite easily in the laboratory. Alternatively collect some pond water and use a centrifuge to concentrate the organisms in it to see if *Paramecium* is present.

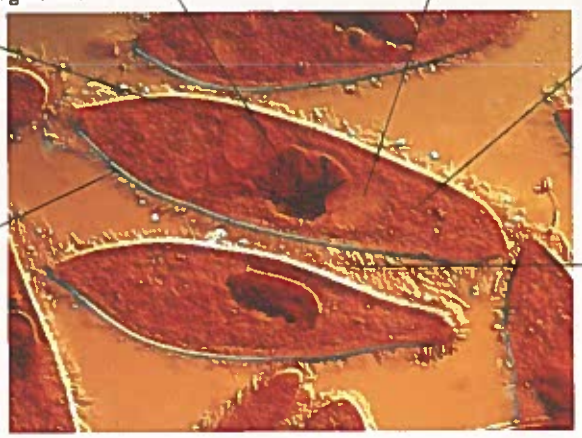
Place a drop of culture solution containing *Paramecium* on a microscope slide.

Add a cover slip and examine the slide with a microscope.

The nucleus of the cell can divide to produce the extra nuclei that are needed when the cell reproduces. Often the reproduction is asexual with the parent cell dividing to form two daughter cells.

The contractile vacuoles at each end of the cell fill up with water and then expel it through the plasma membrane of the cell, to keep the cell's water content within tolerable limits.

Food vacuoles contain smaller organisms that the *Paramecium* has consumed. These are gradually digested and the nutrients are absorbed into the cytoplasm where they provide energy and materials needed for growth.



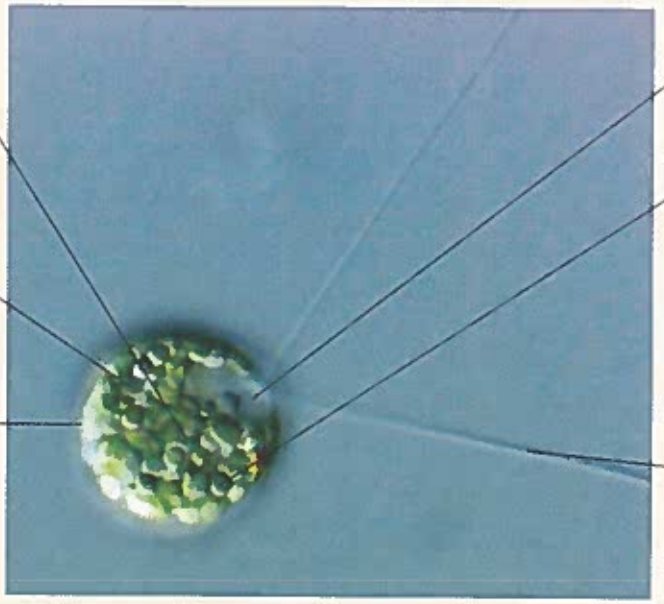
Metabolic reactions take place in the cytoplasm, including the reactions that release energy by respiration. Enzymes in the cytoplasm are the catalysts that cause these reactions to happen.

The cell membrane controls what chemicals enter and leave. It allows the entry of oxygen for respiration. Excretion happens simply by waste products diffusing out through the membrane.

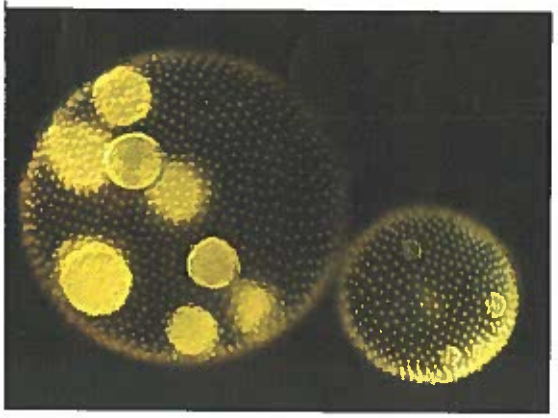
Beating of the cilia moves the *Paramecium* through the water and this can be controlled by the cell so that it moves in a particular direction in response to changes in the environment.

▲ Figure 16 *Paramecium*

Chlamydomonas is a unicellular alga that lives in soil and freshwater habitats. It has been used widely for research into cell and molecular biology. Although it is green in colour and carries out photosynthesis it is not a true plant and its cell wall is not made of cellulose.



▲ Figure 17 *Chlamydomonas*



▲ Figure 18 *Volvox* colonies

Multicellular organisms

Multicellular organisms have properties that emerge from the interaction of their cellular components.

Some unicellular organisms live together in colonies, for example a type of alga called *Volvox aureus*. Each colony consists of a ball made of a protein gel, with 500 or more identical cells attached to its surface. Figure 18 shows two colonies, with daughter colonies forming inside them. Although the cells are cooperating, they are not fused to form a single cell mass and so are not a single organism.

Organisms consisting of a single mass of cells, fused together, are multicellular. One of the most intensively researched multicellular organisms is a worm called *Caenorhabditis elegans*. The adult body is about one millimetre long and it is made up of exactly 959 cells. This might seem like a large number, but most multicellular organisms have far more cells. There are about ten million million cells in an adult human body and even more in organisms such as oak trees or whales.

Although very well known to biologists, *Caenorhabditis elegans* has no common name and lives unseen in decomposing organic matter. It feeds on the bacteria that cause decomposition. *C. elegans* has a mouth, pharynx, intestine and anus. It is hermaphrodite so has both male and female reproductive organs. Almost a third of the cells are neurons, or

nerve cells. Most of these neurons are located at the front end of the worm in a structure that can be regarded as the animal's brain.

Although the brain in *C. elegans* coordinates responses to the worm's environment, it does not control how individual cells develop. The cells in this and other multicellular organisms can be regarded as cooperative groups, without any cells in the group acting as a leader or supervisor. It is remarkable how individual cells in a group can organize themselves and interact with each other to form a living organism with distinctive overall properties. The characteristics of the whole organism, including the fact that it is alive, are known as *emergent properties*.

Emergent properties arise from the interaction of the component parts of a complex structure. We sometimes sum this up with the phrase: the whole is greater than the sum of its parts. A simple example of an emergent property was described in a Chinese philosophical text written more than 2,500 years ago: *"Pots are fashioned from clay. But it's the hollow that makes the pot work."* So, in biology we can carry out research by studying component parts, but we must remember that some bigger things result from interactions between these components.

Cell differentiation in multicellular organisms

Specialized tissues can develop by cell differentiation in multicellular organisms.

In multicellular organisms different cells perform different functions. This is sometimes called division of labour. In simple terms, a function is a job or a role. For example the function of a red blood cell is to carry oxygen, and the function of a rod cell in the retina of the eye is to absorb light and then transmit impulses to the brain. Often a group of cells specialize in the same way to perform the same function. They are called a tissue.

By becoming specialized, the cells in a tissue can carry out their role more efficiently than if they had many different roles. They can develop the ideal structure, with the enzymes needed to carry out all of the chemical reactions associated with the function. The development of cells in different ways to carry out specific functions is called differentiation. In humans, 220 distinctively different highly specialized cell types have been recognized, all of which develop by differentiation.

Gene expression and cell differentiation

Differentiation involves the expression of some genes and not others in a cell's genome.

There are many different cell types in a multicellular organism but they all have the same set of genes. The 220 cell types in the human body have the same set of genes, despite large differences in their structure and activities. To take an example, rod cells in the retina of the eye produce a pigment that absorbs light. Without it, the rod cell would not be able to do its job of sensing light. A lens cell in the eye produces no pigments and is transparent. If it did contain pigments, less light would

TOK

How can we decide when one model is better than another?

An emergent property of a system is not a property of any one component of the system, but it is a property of the system as a whole. Emergence refers to how complex systems and patterns arise from many small and relatively simple interactions. We cannot therefore necessarily predict emergent properties by studying each part of a system separately (an approach known as reductionism). Molecular biology is an example of the success that a reductionist approach can have. Many processes occurring in living organisms have been explained at a molecular level. However, many argue that reductionism is less useful in the study of emergent properties including intelligence, consciousness and other aspects of psychology. The interconnectivity of the components in cases like these is at least as important as the functioning of each individual component.

One approach that has been used to study interconnectivity and emergent properties is computer modelling. In both animal behaviour and ecology, a programme known as the "Game of Life" has been used. It was devised by John Conway and is available on the Internet. Test the "Game of Life" by creating initial configurations of cells and seeing how they evolve. Research ways in which the model has been applied.

pass through the lens and our vision would be worse. While they are developing, both cell types contain the genes for making the pigment, but these genes are only used in the rod cell.

This is the usual situation – cells do not just have genes with the instructions that they need, they have genes needed to specialize in every possible way. There are approximately 25,000 genes in the human genome, and these genes are all present in a body cell. However, in most cell types less than half of the genes will ever be needed or used.

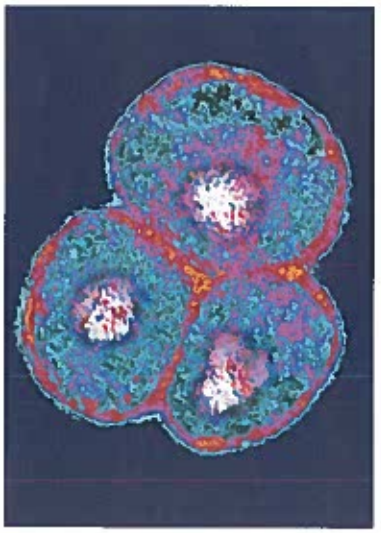
When a gene is being used in a cell, we say that the gene is being expressed. In simple terms, the gene is switched on and the information in it is used to make a protein or other gene product. The development of a cell involves switching on particular genes and expressing them, but not others. Cell differentiation happens because a different sequence of genes is expressed in different cell types. The control of gene expression is therefore the key to development.

An extreme example of differentiation involves a large family of genes in humans that carry the information for making receptors for odorants – smells. These genes are only expressed in cells in the skin inside the nose, called olfactory receptor cells. Each of these cells expresses just one of the genes and so makes one type of receptor to detect one type of odorant. This is how we can distinguish between so many different smells. Richard Axel and Linda Buck were given the Nobel Prize in 2004 for their work on this system.

Stem cells

The capacity of stem cells to divide and differentiate along different pathways is necessary in embryonic development. It also makes stem cells suitable for therapeutic uses.

A new animal life starts when a sperm fertilizes an egg cell to produce a zygote. An embryo is formed when the zygote divides to give two cells. This two-cell embryo divides again to produce a four-cell embryo, then eight, sixteen and so on. At these early stages in embryonic development the cells are capable of dividing many times to produce large amounts of tissue. They are also extremely versatile and can differentiate along different pathways into any of the cell types found in that particular animal. In the 19th century, the name stem cell was given to the zygote and the cells of the early embryo, meaning that all the tissues of the adult stem from them.



▲ Figure 19 Embryonic stem cells

Stem cells have two key properties that have made them one of the most active areas of research in biology and medicine today.

- Stem cells can divide again and again to produce copious quantities of new cells. They are therefore useful for the growth of tissues or the replacement of cells that have been lost or damaged.
- Stem cells are not fully differentiated. They can differentiate in different ways, to produce different cell types.

Embryonic stem cells are therefore potentially very useful. They could be used to produce regenerated tissue, such as skin for people who have suffered burns. They could provide a means of healing diseases such as type 1 diabetes where a particular cell type has been lost or is malfunctioning. They might even be used in the future to grow whole replacement organs – hearts or kidneys, for example. These types of use are called therapeutic, because they provide therapies for diseases or other health problems.

There are also non-therapeutic uses for embryonic stem cells. One possibility is to use them to produce large quantities of striated muscle fibres, or meat, for human consumption. The beef burgers of the future may therefore be produced from stem cells, without the need to rear and slaughter cattle.

It is the early stage embryonic stem cells that are the most versatile. Gradually during embryo development the cells commit themselves to a pattern of differentiation. This involves a series of points at which a cell decides whether to develop along one pathway or another. Eventually each cell becomes committed to develop into one specific cell type. Once committed, a cell may still be able to divide, but all of these cells will differentiate in the same way and they are no longer stem cells.

Small numbers of cells remain as stem cells, however, and they are still present in the adult body. They are present in many human tissues, including bone marrow, skin and liver. They give some human tissues considerable powers of regeneration and repair. The stem cells in other tissues only allow limited repair – brain, kidney and heart for example.

Therapeutic uses of stem cells

Use of stem cells to treat Stargardt's disease and one other named condition.

There are a few current uses of stem cells to treat diseases, and a huge range of possible future uses, many of which are being actively researched. Two examples are given here: one involving embryonic stem cells and one using adult stem cells.

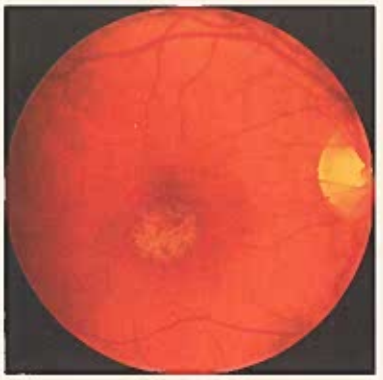
Stargardt's disease

The full name of this disease is Stargardt's macular dystrophy. It is a genetic disease that develops in children between the ages of six and twelve. Most cases are due to a recessive mutation of a gene called ABCA4. This causes a membrane protein used for active transport in retina cells to malfunction. As a consequence, photoreceptive cells in the retina degenerate. These are the cells that detect light, so vision becomes progressively worse. The loss of vision can be severe enough for the person to be registered as blind.

Researchers have developed methods for making embryonic stem cells develop into retina cells. This was done initially with mouse cells, which were then injected into the eyes of mice that had a condition similar to Stargardt's disease. The injected cells were not rejected, did not develop into tumours or cause any other problems. The cells moved to the retina where they attached themselves and remained. Very encouragingly, they caused an improvement in the vision of the mice.

In November 2010, researchers in the United States got approval for trials in humans. A woman in her 50s with Stargardt's disease was treated by having 50,000 retina cells derived from embryonic stem cells injected into her eyes. Again the cells attached to the retina and remained there during the four-month trial. There was an improvement in her vision, and no harmful side effects.

Further trials with larger numbers of patients are needed, but after these initial trials at least, we can be optimistic about the development of treatments for Stargardt's disease using embryonic stem cells.



▲ Figure 20 Stargardt's disease

Leukemia

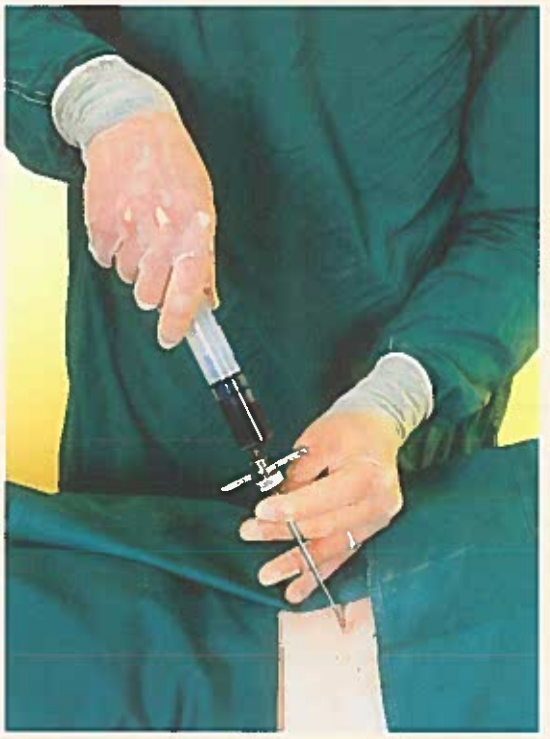
This disease is a type of cancer. All cancers start when mutations occur in genes that control cell division. For a cancer to develop, several specific mutations must occur in these genes in one cell. This is very unlikely to happen, but as there are huge numbers of cells in the body, the overall chance becomes much larger. More than a quarter of a million cases of leukemia are diagnosed each year globally and there are over 200,000 deaths from the disease.

Once the cancer-inducing mutations have occurred in a cell, it grows and divides repeatedly, producing more and more cells. Leukemia involves the production of abnormally large numbers of white blood cells. In most cancers, the cancer cells form a lump or tumour but this does not happen with leukemia. White blood cells are produced in the bone marrow, a soft tissue in the hollow centre of large bones such as the femur. They are then released into the blood, both in normal conditions and when excessive numbers are produced with leukemia. A normal adult white blood cell count is between 4,000 and 11,000 per mm^3 of blood. In a person with leukemia this number rises higher and higher. Counts above 30,000 per mm^3 suggest that a person may have leukemia. If there are more than 100,000 per mm^3 it is likely that the person has acute leukemia.

To cure leukemia, the cancer cells in the bone marrow that are producing excessive numbers of white blood cells must be destroyed. This can be done by treating the patient with chemicals that kill dividing cells. The procedure is known as chemotherapy. However, to remain healthy in the long term the patient must be able to produce the white blood cells needed to fight disease. Stem cells that can produce blood cells must be present, but they are killed by chemotherapy. The following procedure is therefore used:

- A large needle is inserted into a large bone, usually the pelvis, and fluid is removed from the bone marrow.
- Stem cells are extracted from this fluid and are stored by freezing them. They are adult stem cells and only have the potential for producing blood cells.
- A high dose of chemotherapy drugs is given to the patient, to kill all the cancer cells in the bone marrow. The bone marrow loses its ability to produce blood cells.
- The stem cells are then returned to the patient's body. They re-establish themselves in the bone marrow, multiply and start to produce red and white blood cells.

In many cases this procedure cures the leukemia completely.



▲ Figure 21 Removal of stem cells from bone marrow

The ethics of stem cell research

Ethical implications of research: research involving stem cells is growing in importance and raises ethical issues.

Stem cell research has been very controversial. Many ethical objections have been raised. Scientists should always consider the ethical implications of their research before doing it. Some of the research that was carried out in the past would not be considered ethically acceptable today, such as medical research carried out on patients without their informed consent.

Decisions about whether research is ethically acceptable must be based on a clear understanding of the science involved. Some people dismiss all stem cell research as unethical, but this shows a misunderstanding of the different possible sources of the stem cells being used. In the next section, three possible sources of stem cells and the ethics of research involving them are discussed.

Sources of stem cells and the ethics of using them

Ethics of the therapeutic use of stem cells from specially created embryos, from the umbilical cord blood of a new-born baby and from an adult's own tissues.

Stem cells can be obtained from a variety of sources.

- Embryos can be deliberately created by fertilizing egg cells with sperm and allowing the resulting zygote to develop for a few days until it has between four and sixteen cells. All of the cells are embryonic stem cells.
- Blood can be extracted from the umbilical cord of a new-born baby and stem cells obtained from it. The cells can be frozen and stored for possible use later in the baby's life.
- Stem cells can be obtained from some adult tissues such as bone marrow.

These types of stem cell vary in their properties and therefore in their potential for therapeutic use. The table below gives some properties of the three types, to give the scientific basis for an ethical assessment.

Embryonic stem cells	Cord blood stem cells	Adult stem cells
• Almost unlimited growth potential. • Can differentiate into any type in the body. • More risk of becoming tumour cells than with adult stem cells, including teratomas that contain different tissue types. • Less chance of genetic damage due to the accumulation of mutations than with adult stem cells. • Likely to be genetically different from an adult patient receiving the tissue. • Removal of cells from the embryo kills it, unless only one or two cells are taken.	• Easily obtained and stored. • Commercial collection and storage services already available. • Fully compatible with the tissues of the adult that grows from the baby, so no rejection problems occur. • Limited capacity to differentiate into different cell types – only naturally develop into blood cells, but research may lead to production of other types. • Limited quantities of stem cells from one baby's cord. • The umbilical cord is discarded whether or not stem cells are taken from it.	• Difficult to obtain as there are very few of them and they are buried deep in tissues. • Less growth potential than embryonic stem cells. • Less chance of malignant tumours developing than from embryonic stem cells. • Limited capacity to differentiate into different cell types. • Fully compatible with the adult's tissues, so rejection problems do not occur. • Removal of stem cells does not kill the adult from which the cells are taken.

Stem cell research has been very controversial. Many ethical objections have been raised. There are most objections to the use of embryonic stem cells, because current techniques usually involve the death of the embryo when the stem cells are taken. The main question is whether an early stage embryo is as much a human individual as a new-born baby, in which case killing the embryo is undoubtedly unethical.

When does a human life begin? There are different views on this. Some consider that when the sperm fertilizes the egg, a human life has begun. Others say that early stage embryos have not yet developed human characteristics and cannot suffer pain, so they should be thought of simply as groups of stem cells. Some suggest that a human life truly begins when there is a heartbeat, or bone tissue or brain activity. These stages take place after a few weeks of development. Another view is that it is only when the embryo has developed into a fetus that is capable of surviving outside the uterus.

Some scientists argue that if embryos are specially created by **in vitro fertilization (IVF)** in order to obtain stem cells, no human that would otherwise have lived has been denied its chance of living. However, a counterargument is that it is unethical to create human lives solely for the purpose of obtaining stem cells. Also, IVF involves hormone treatment of women, with some associated risk, as well as an invasive surgical procedure for removal of eggs from the ovary. If women are paid for supplying eggs for IVF this could lead to the exploitation of vulnerable groups such as college students.

We must not forget ethical arguments in favour of the use of embryonic stem cells. They have the potential to allow methods of treatment for diseases and disabilities that are currently incurable, so they could greatly reduce the suffering of some individuals.

▲ Figure 22 Harvesting umbilical cord blood

1.2 Ultrastructure of cells

Understanding

- Prokaryotes have a simple cell structure without compartments.
- Eukaryotes have a compartmentalized cell structure.
- Prokaryotes divide by binary fission.
- Electron microscopes have a much higher resolution than light microscopes.

Applications

- The structure and function of organelles within exocrine gland cells of the pancreas.
- The structure and function of organelles within palisade mesophyll cells of the leaf.

Nature of science

- Developments in scientific research follow improvements in apparatus: the invention of electron microscopes led to greater understanding of cell structure.

Skills

- Drawing the ultrastructure of prokaryotic cells based on electron micrographs.
- Drawing the ultrastructure of eukaryotic cells based on electron micrographs.
- Interpretation of electron micrographs to identify organelles and deduce the function of specialized cells.

The invention of the electron microscope

Developments in scientific research follow improvements in apparatus: the invention of electron microscopes led to greater understanding of cell structure.

Much of the progress in biology over the last 150 years has followed improvements in the design of microscopes. In the second half of the 19th century improved light microscopes allowed the discovery of bacteria and other unicellular organisms. Chromosomes were seen for the first time and the processes of mitosis, meiosis and gamete formation were discovered. The basis of sexual reproduction, which had previously eluded William Harvey and many other biologists, was seen to be the fusion of gametes and subsequent development of embryos. The complexity of organs such as the kidney was revealed and mitochondria, chloroplasts and other structures were discovered within cells.

There was a limit to the discoveries that could be made though. For technical reasons that are explained later in this sub-topic, light microscopes cannot produce clear images of structures smaller than 0.2 micrometres (μm). (A micrometre is a thousandth of a millimetre.) Many biological structures are smaller than this. For example, membranes in cells are about 0.01 μm thick. Progress was hampered until a different type of microscope was invented – the electron microscope.

Electron microscopes were developed in Germany during the 1930s and came into use in research laboratories in the 1940s and 50s. They allowed images to be produced of things as small as 0.001 μm – 200 times smaller than with light microscopes. The structure of eukaryotic cells was found to be far more intricate than most biologists had expected and many previous ideas were shown to be wrong. For example, in the 1890s the light microscope had revealed darker green areas in the chloroplast. They were called grana and interpreted as droplets of chlorophyll. The electron microscope showed that grana are in fact stacks of flattened membrane sacs, with the chlorophyll located in the membranes. Whereas mitochondria appear as tiny structureless rods or spheres under the light microscope, the electron microscope revealed them to have an intricate internal membrane structure.

The electron microscopes revealed what is now called the ultrastructure of cells, including previously unknown features. Ribosomes, lysosomes and the endoplasmic reticulum were all discovered and named in the 1950s, for example. It is unlikely that there are structures as significant as these still to be discovered, but improvements in the design of electron microscopes continue and each improvement allows new discoveries to be made. A recent example, described in sub-topic 8.2, is electron tomography – a method of producing 3-D images by electron microscopy.

The resolution of electron microscopes

Electron microscopes have a much higher resolution than light microscopes.

If we look at a tree with unaided eyes we can see its individual leaves, but we cannot see the cells within its leaves. The unaided eye can see things with a size of 0.1 mm as separate objects, but no smaller. To see the cells within the leaf we need to use a light microscope. This allows us to see things with a size of down to about 0.2 μm as separate objects, so cells can become individually visible – they can be distinguished.

Making the separate parts of an object distinguishable by eye is called **resolution**.

The maximum resolution of a light microscope is 0.2 μm, which is 200 nanometres (nm). However powerful the lenses of a light microscope are, the resolution cannot be higher than this because it is limited by the wavelength of light (400–700 nm). If we try to resolve smaller objects by

▲ Figure 1 An electron microscope in use

making lenses with greater magnification, we find that it is impossible to focus them properly and get a blurred image. This is why the maximum magnification with light microscopes is usually × 400.

Beams of electrons have a much shorter wavelength, so electron microscopes have a much higher resolution. The resolution of modern electron microscopes is 0.001 μm or 1 nm. Electron microscopes therefore have a resolution that is 200 times greater than light microscopes. This is why light microscopes reveal the structure of cells, but electron microscopes reveal the ultrastructure. It explains why light microscopes were needed to see bacteria with a size of 1 micrometre, but viruses with a diameter of 0.1 micrometres could not be seen until electron microscopes had been invented.

	Resolution		
	Millimetres (mm)	Micrometres (μm)	Nanometres (nm)
Unaided eyes	0.1	100	100,000
Light microscopes	0.0002	0.2	200
Electron microscopes	0.000001	0.001	1

Activity

Commerce and science

While still a young student in Berlin in the late 1920s Ernst Ruska developed magnetic coils that could focus beams of electrons. He worked on the idea of using these lenses to obtain an image as in a light microscope, but with electron beams instead of light. During the 1930s he developed and refined this technology. By 1939 Ruska had designed the first commercial electron microscope. In 1986 he was awarded the Nobel Prize in Physics for this pioneering work. Ruska worked with the German firm Siemens. Other companies in Britain, Canada and the United States also developed and manufactured electron microscopes.

- Scientists in different countries usually cooperate with each other but commercial companies do not. What are the reasons for this difference?

Prokaryotic cell structure

Prokaryotes have a simple cell structure without compartments.

All organisms can be divided into two groups according to their cell structure. Eukaryotes have a compartment within the cell that contains the chromosomes. It is called the nucleus and is bounded by a nuclear envelope consisting of a double layer of membrane. Prokaryotes do not have a nucleus.

Prokaryotes were the first organisms to evolve on Earth and they still have the simplest cell structure. They are mostly small in size and are found almost everywhere – in soil, in water, on our skin, in our intestines and even in pools of hot water in volcanic areas.

All cells have a cell membrane, but some cells, including prokaryotes, also have a cell wall outside the cell membrane. This is a much thicker and stronger structure than the membrane. It protects the cell, maintains its shape and prevents it from bursting. In prokaryotes the cell wall contains peptidoglycan. It is often referred to as being extracellular.

As no nucleus is present in a prokaryotic cell its interior is entirely filled with cytoplasm. The cytoplasm is not divided into compartments by membranes – it is one uninterrupted chamber. The structure is therefore simpler than in eukaryotic cells, though we must remember that it is still very complex in terms of the biochemicals that are present, including many enzymes.

Organelles are present in the cytoplasm of eukaryotic cells that are analogous to the organs of multi-cellular organisms in that they are distinct structures with specialized functions. Prokaryotes do not have cytoplasmic organelles apart from ribosomes. Their size, measured in Svedberg units (S) is 70S, which is smaller than those of eukaryotes.

Part of the cytoplasm appears lighter than the rest in many electron micrographs. This region contains the DNA of the cell, usually in the form of one circular DNA molecule. The DNA is not associated with proteins, which explains the lighter appearance compared with other parts of the cytoplasm that contain enzymes and ribosomes. This lighter area of the cell is called the nucleoid – meaning nucleus-like as it contains DNA but is not a true nucleus.

Cell division in prokaryotes

Prokaryotes divide by binary fission.

All living organisms need to produce new cells. They can only do this by division of pre-existing cells. Cell division in prokaryotic cells is called binary fission and it is used for asexual reproduction. The single circular chromosome is replicated and the two copies of the chromosome move to opposite ends of the cell. Division of the cytoplasm of the cell quickly follows. Each of the daughter cells contains one copy of the chromosome so they are genetically identical.

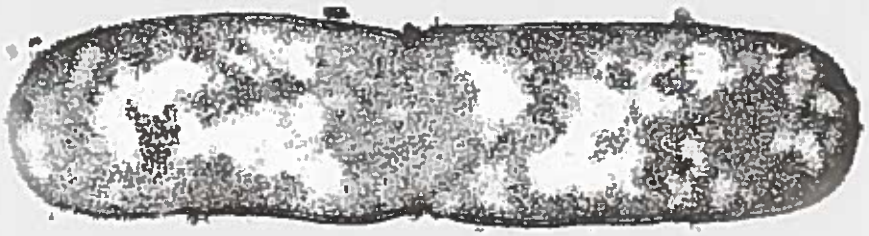
Drawing prokaryotic cells

Draw the ultrastructure of prokaryotic cells based on electron micrographs.

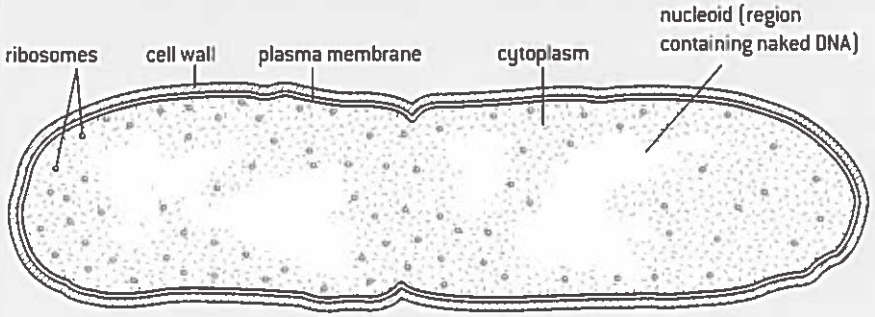
Because prokaryotes are mostly very small, their internal structure cannot be seen using a light microscope. It is only with much higher magnification in electron micrographs that we can see the details of the structure, called the ultrastructure. Drawings of the ultrastructure of prokaryotes are therefore based on electron micrographs.

Shown below and on the next page are two electron micrographs of *E. coli*, a bacterium found in our intestines. One of them is a thin section and shows the internal structure. The other has been prepared by a different technique and shows the external structure. A drawing of each is also shown. By comparing the drawings with the electron micrographs you can learn how to identify structures within prokaryotic cells.

Electron micrograph of *Escherichia coli* (1–2μm in length)



Drawing to help interpret the electron micrograph



Activity

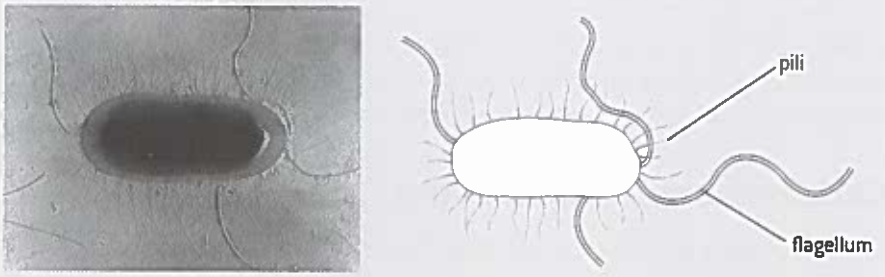
Other names for prokaryotes

Biologists sometimes use the term "bacteria" instead of "prokaryote". This may not always be appropriate because the term prokaryote encompasses a larger group of organisms than true bacteria (Eubacteria). It also includes organisms in another group called the Archaea.

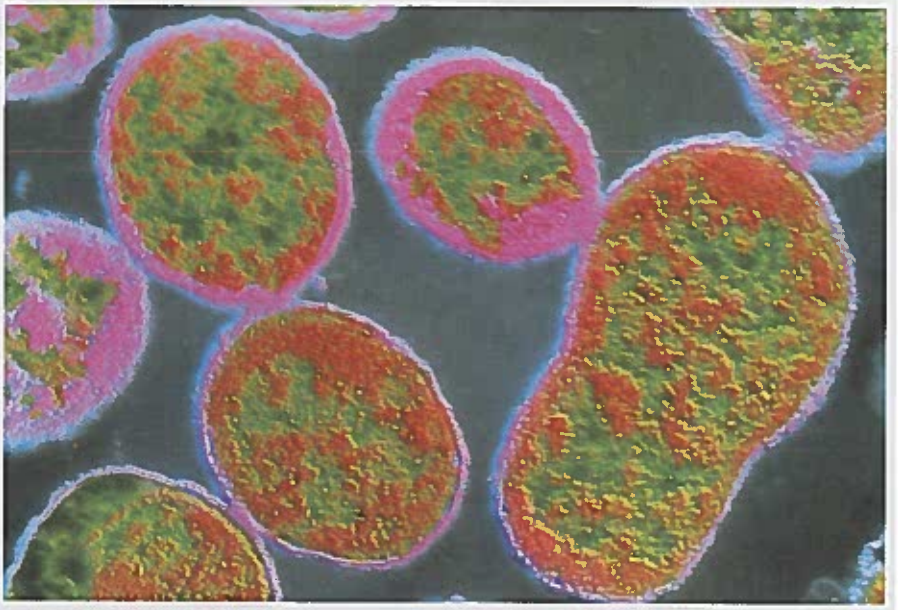
There is a group of photosynthetic organisms that used to be called blue-green algae, but their cell structure is prokaryotic and algae are eukaryotic. This problem has been solved by renaming them as Cyanobacteria.

- What problems are caused by scientists using different words for things than non-scientists?

Electron micrograph of *Escherichia coli* showing surface features



Shown below is another micrograph of a prokaryote. You can use it to practice your skill at drawing the ultrastructure of prokaryotic cells. You can also find other electron micrographs of prokaryotic cells on the internet and try drawing these. There is no need to spend a long time drawing many copies of a particular structure, such as the ribosomes. You can indicate their appearance in one small representative part of the cytoplasm and annotate your drawing to say that they are found elsewhere.



▲ Figure 2 *Brucella abortus* (Bang's bacillus), 2 μm in length

Activity

Garlic cells and compartmentalization

Garlic cells store a harmless sulphur-containing compound called alliin in their vacuoles. They store an enzyme called alliinase in other parts of the cell. Alliinase converts alliin into a compound called allicin, which has a very strong smell and flavour and is toxic to some herbivores. This reaction occurs when herbivores bite into garlic and damage cells, mixing the enzyme and its substrate. Perhaps surprisingly, many humans like the flavour, but to get it garlic must be crushed or cut, not used whole.

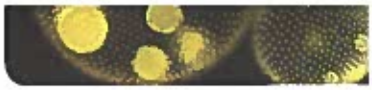
- You can test this by smelling a whole garlic bulb, then cutting or crushing it and smelling it again.

Eukaryotic cell structure

Eukaryotes have a compartmentalized cell structure.

Eukaryotic cells have a much more complicated internal structure than prokaryotic cells. Whereas the cytoplasm of a prokaryotic cell is one undivided space, eukaryotic cells are compartmentalized. This means that they are divided up by partitions into compartments. The partitions are single or double membranes.

The most important of these compartments is the nucleus. It contains the cell's chromosomes. The compartments in the cytoplasm are known as organelles. Just as each organ in an animal's body is specialized



to perform a particular role, each organelle in a eukaryotic cell has a distinctive structure and function.

There are several advantages in being compartmentalized:

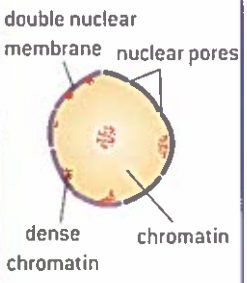
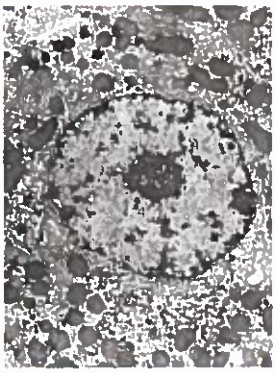
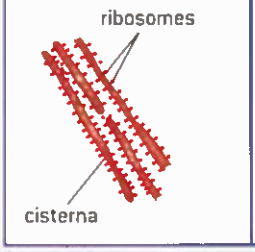
- Enzymes and substrates for a particular process can be much more concentrated than if they were spread throughout the cytoplasm.
- Substances that could cause damage to the cell can be kept inside the membrane of an organelle. For example, the digestive enzymes of a lysosome could digest and kill a cell, if they were not safely stored inside the lysosome membrane.
- Conditions such as pH can be maintained at an ideal level for a particular process, which may be different to the levels needed for other processes in a cell.
- Organelles with their contents can be moved around within the cell.

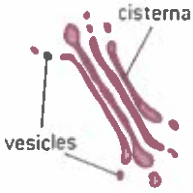
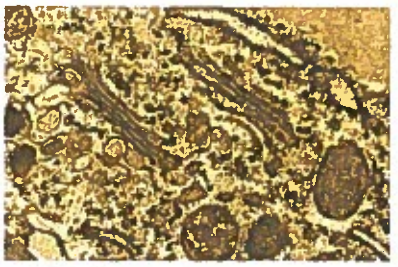
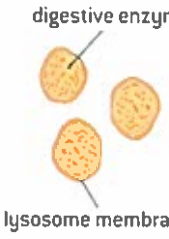
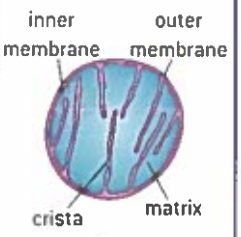
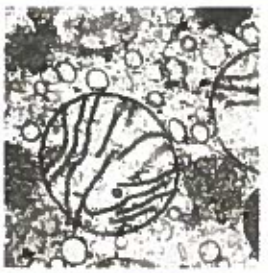
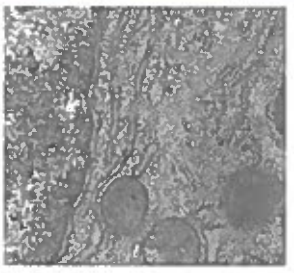
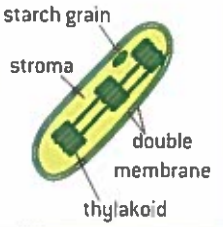
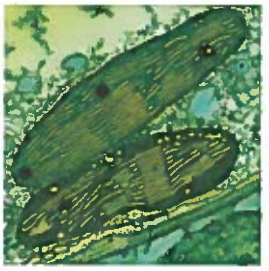
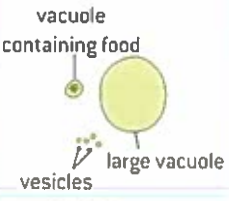
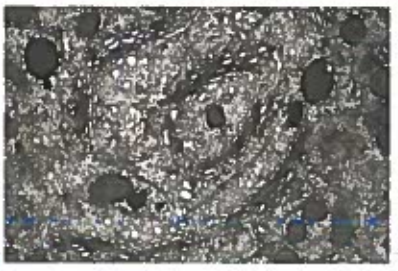
Drawing eukaryotic cells

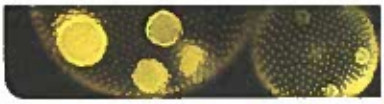
Draw the ultrastructure of eukaryotic cells based on electron micrographs.

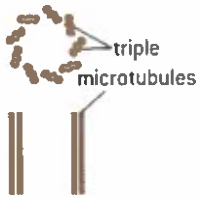
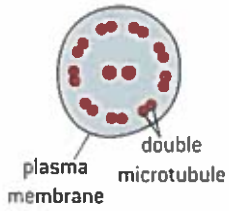
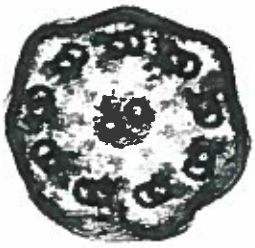
The ultrastructure of eukaryotic cells is very complex and it is often best to draw only part of a cell. Your drawing is an interpretation of the structure, so you need to understand the structure of the organelles that might be present.

The table below contains an electron micrograph of each of the commonly occurring organelles, with a drawing of the structure. Brief notes on recognition features and the function of each organelle are included.

Nucleus  		The nuclear membrane is double and has pores through it. The nucleus contains the chromosomes, consisting of DNA associated with histone proteins. Uncoiled chromosomes are spread through the nucleus and are called chromatin. There are often densely staining areas of chromatin around the edge of the nucleus. The nucleus is where DNA is replicated and transcribed to form mRNA, which is exported via the nuclear pores to the cytoplasm.
Rough endoplasmic reticulum  		The rER consists of flattened membrane sacs, called cisternae. Attached to the outside of these cisternae are ribosomes. They are larger than in prokaryotes and are classified as 80S. The main function of the rER is to synthesize protein for secretion from the cell. Protein synthesized by the ribosomes of the rER passes into its cisternae and is then carried by vesicles, which bud off and are moved to the Golgi apparatus.

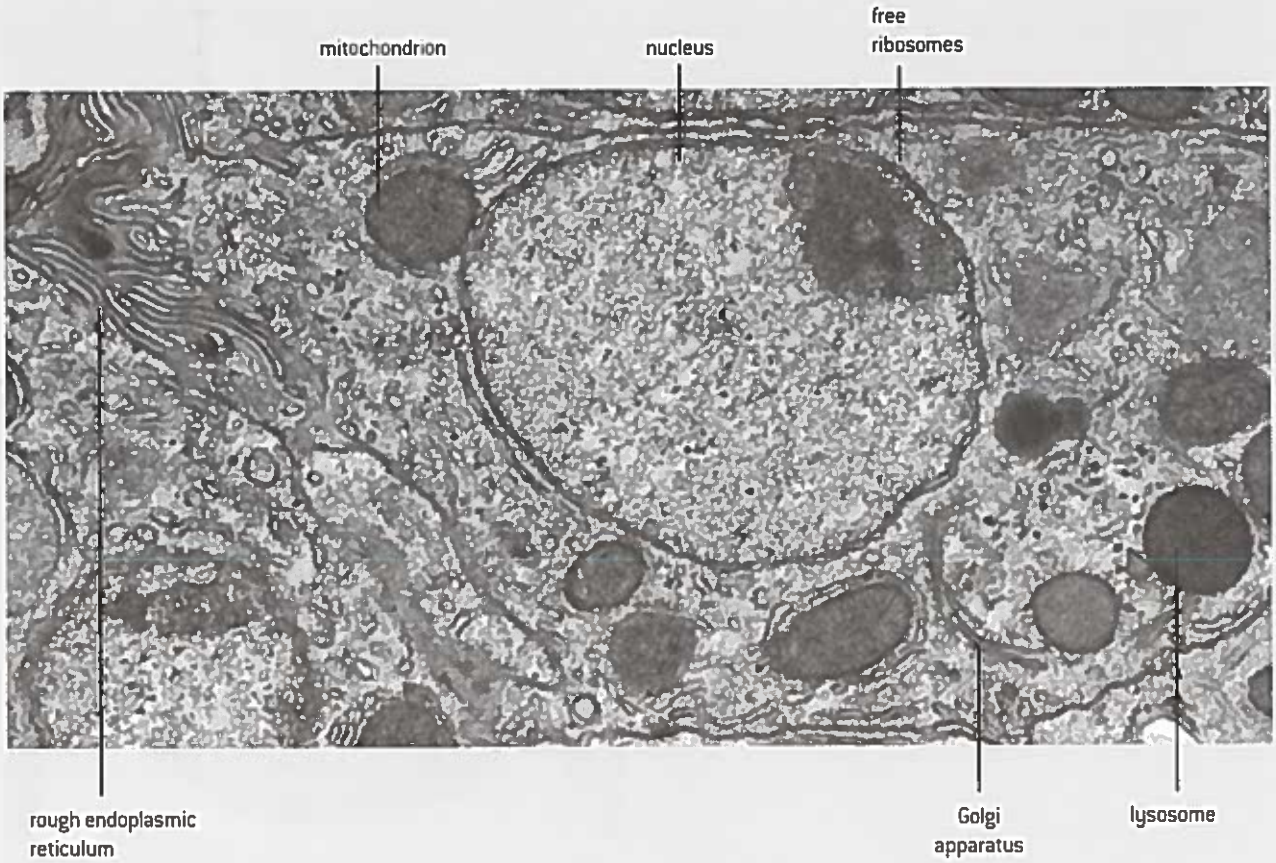
Golgi apparatus 		This organelle consists of flattened membrane sacs called cisternae, like rER. However the cisternae are not as long, are often curved, do not have attached ribosomes and have many vesicles nearby. The Golgi apparatus processes proteins brought in vesicles from the rER. Most of these proteins are then carried in vesicles to the plasma membrane for secretion.
Lysosome 		These are approximately spherical with a single membrane. They are formed from Golgi vesicles. They contain high concentrations of protein, which makes them densely staining in electron micrographs. They contain digestive enzymes, which can be used to break down ingested food in vesicles or break down organelles in the cell or even the whole cell.
Mitochondrion 		A double membrane surrounds mitochondria, with the inner of these membranes invaginated to form structures called cristae. The fluid inside is called the matrix. The shape of mitochondria is variable but is usually spherical or ovoid. They produce ATP for the cell by aerobic cell respiration. Fat is digested here if it is being used as an energy source in the cell.
Free ribosomes 		These appear as dark granules in the cytoplasm and are not surrounded by a membrane. They have the same size as ribosomes attached to the rER – about 20nm in diameter, and known as 80S. Free ribosomes synthesize protein, releasing it to work in the cytoplasm, as enzymes or in other ways. Ribosomes are constructed in a region of the nucleus called the nucleolus.
Chloroplast 		A double membrane surrounds the chloroplast. Inside are stacks of thylakoids, which are flattened sacs of membrane. The shape of chloroplasts is variable but is usually spherical or ovoid. They produce glucose and a wide variety of other organic compounds by photosynthesis. Starch grains may be present inside chloroplasts if they have been photosynthesizing rapidly.
Vacuoles and vesicles 		These are organelles that consist simply of a single membrane with fluid inside. Many plant cells have large vacuoles that occupy more than half of the cell volume. Some animals absorb foods from outside and digest them inside vacuoles. Some unicellular organisms use vacuoles to expel excess water. Vesicles are very small vacuoles used to transport materials inside the cell.



Microtubules and centrioles 		In the cytoplasm of cells there are small cylindrical fibres called microtubules that have a variety of roles, including moving chromosomes during cell division. Animal cells have structures called centrioles, which consist of two groups of nine triple microtubules. Centrioles form an anchor point for microtubules during cell division and also for microtubules inside cilia and flagella.
Cilia and flagella 		These are whip-like structures projecting from the cell surface. They contain a ring of nine double microtubules plus two central ones. Flagella are larger and usually only one is present, as in a sperm. Cilia are smaller and many are present. Cilia and flagella can be used for locomotion. Cilia can be also be used to create a current in the fluid next to the cell.

The electron micrograph below shows a liver cell with labels to identify some of the organelles that are present.

- Using your understanding of these organelles, draw the whole cell to show its ultrastructure.



▲ Figure 3 Electron micrograph of part of a liver cell

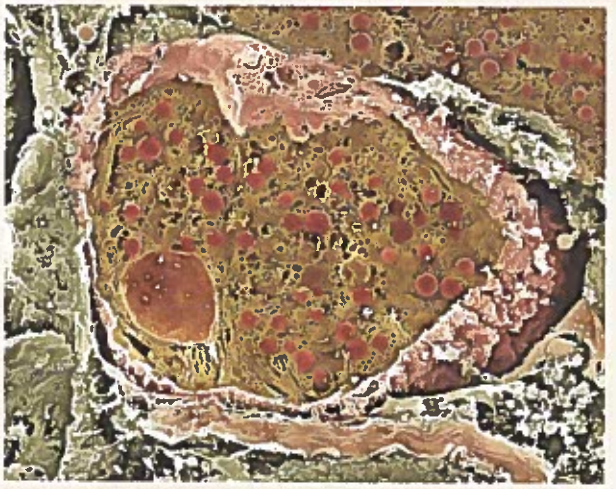
Exocrine gland cells of the pancreas

The structure and function of organelles within exocrine gland cells of the pancreas.

Gland cells secrete substances – they release them through their plasma membrane. There are two types of gland cells in the pancreas. Endocrine cells secrete hormones into the bloodstream. Exocrine gland cells in the pancreas secrete digestive enzymes into a duct that carries them to the small intestine where they digest foods.

Enzymes are proteins, so the exocrine gland cells have organelles needed to synthesize proteins in large quantities, process them to make them ready for secretion, transport them to the plasma membrane and then release them. The electron micrograph on the right shows these organelles:

- plasma membrane
- mitochondrion
- nucleus
- rough ER
- Golgi apparatus
- vesicles
- lysosomes



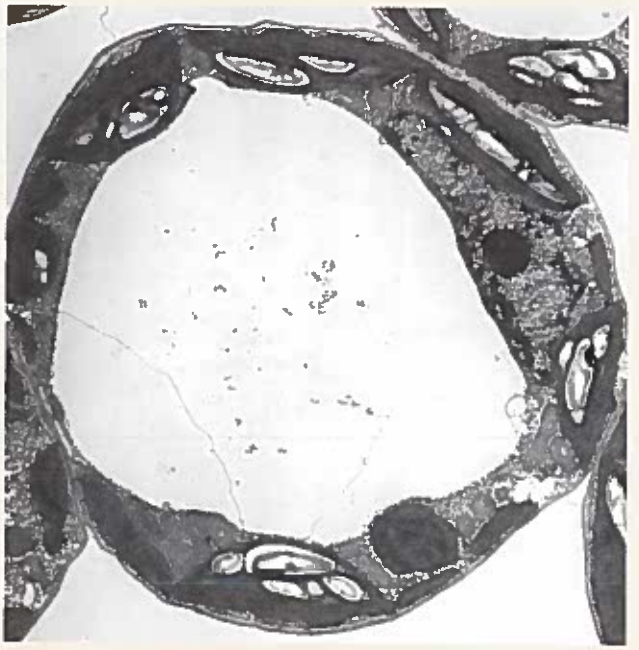
▲ Figure 4 Electron micrograph of pancreas cell

Palisade mesophyll cells

The structure and function of organelles within palisade mesophyll cells of the leaf.

The function of the leaf is photosynthesis – producing organic compounds from carbon dioxide and other simple inorganic compounds, using light energy. The cell type that carries out most photosynthesis in the leaf is palisade mesophyll. The shape of these cells is roughly cylindrical. Like all living plant cells the cell is surrounded by a cell wall, with a plasma membrane inside it. The electron micrograph on the right shows the organelles that a palisade mesophyll cell contains:

- cell wall
- plasma membrane
- chloroplasts
- mitochondrion
- vacuole
- nucleus



▲ Figure 5 Electron micrograph of palisade mesophyll cell