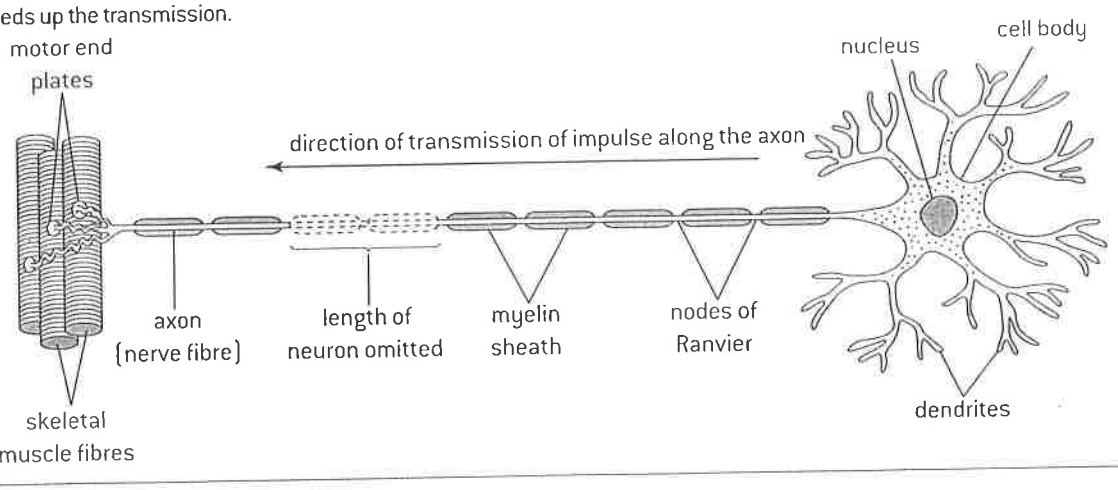
Neurons and synapses

STRUCTURE AND FUNCTION OF NEURONS

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

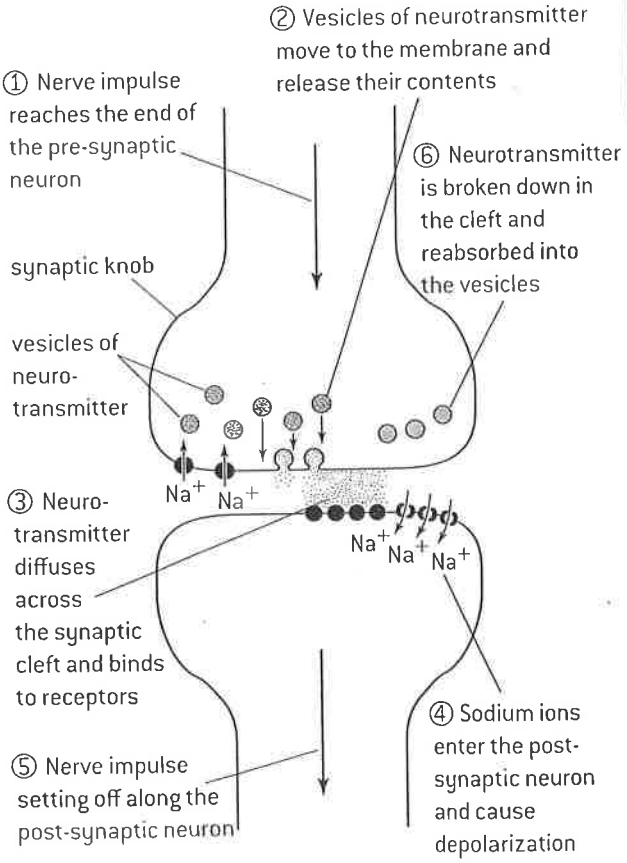


SYNAPSES

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

Many synapses function in the following way.

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



CHOLINERGIC SYNAPSES

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

NEONICOTINOID PESTICIDES

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

Nerve impulses

RESTING POTENTIALS

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

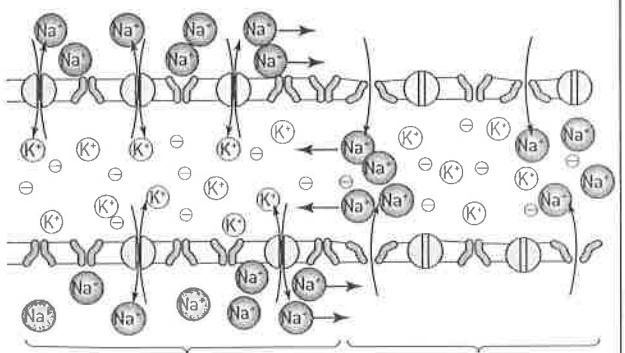
ACTION POTENTIALS

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

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

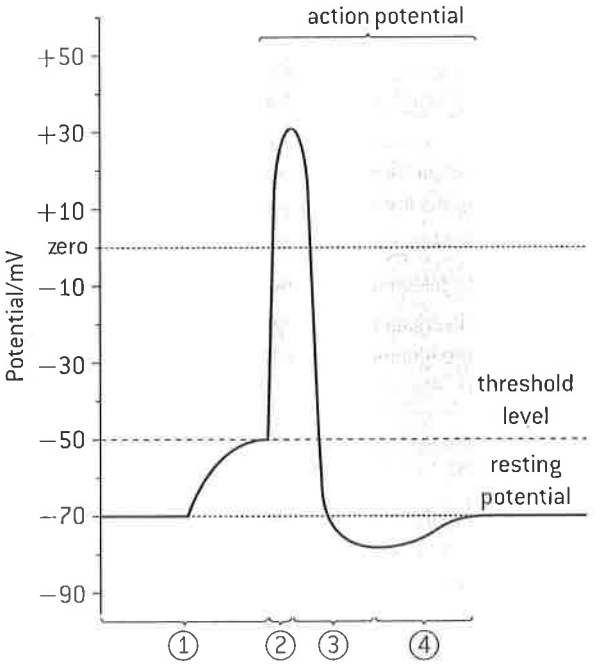
PROPAGATION OF NERVE IMPULSES

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



OSCILLOSCOPE TRACES

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



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

MEMORY AND LEARNING

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

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

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

Research into reproduction

IN VITRO FERTILIZATION

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

1. **Down-regulation**

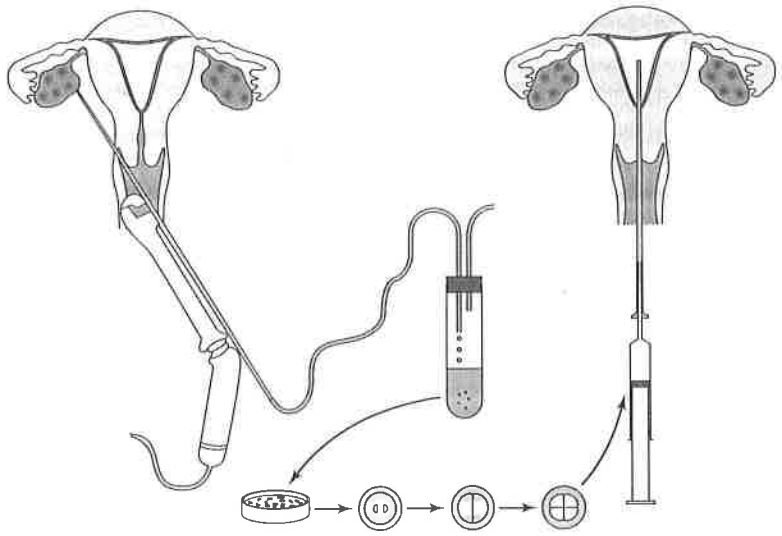
The woman takes a drug each day, usually as a nasal spray, to stop her pituitary gland secreting FSH or LH. Secretion of estrogen and progesterone therefore also stops. This suspends the normal menstrual cycle and allows doctors to control the timing and amount of egg production in the woman's ovaries.

2. **Artificial doses of hormones**

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

3. **Egg retrieval and fertilization**

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



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

4. **Establishing a pregnancy**

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

HARVEY AND THE DISCOVERY OF SEXUAL REPRODUCTION

William Harvey's discovery of the circulation of blood in the 17th century shows that he was a brilliant research scientist and yet he made little progress in another area that interested him very much: reproduction in humans and other animals. He was taught the 'seed and soil' theory of Aristotle, according to which the male produces a seed, which forms an egg when it mixes with menstrual blood. The egg develops into a fetus inside the mother.

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

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

Harvey was understandably reluctant to publish his research into sexual reproduction, but he did eventually do so in 1651 when he was 73 years old in his work *Exercitationes de Generatione Animalium*. He knew that he had not solved the mystery of sexual reproduction. He was unlucky in his choice of experimental animal because embryos in the deer that he used remain microscopically small for an unusually long period.

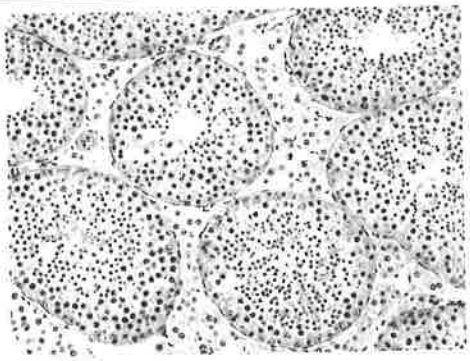
Scientific research has often been hampered for a time by deficiencies in apparatus, with discoveries only being made following improvements. This will continue into the future and we can look forward to further transformations in our understanding of the natural world as new techniques and technology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

Spermatogenesis

STAGES IN GAMETOGENESIS

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

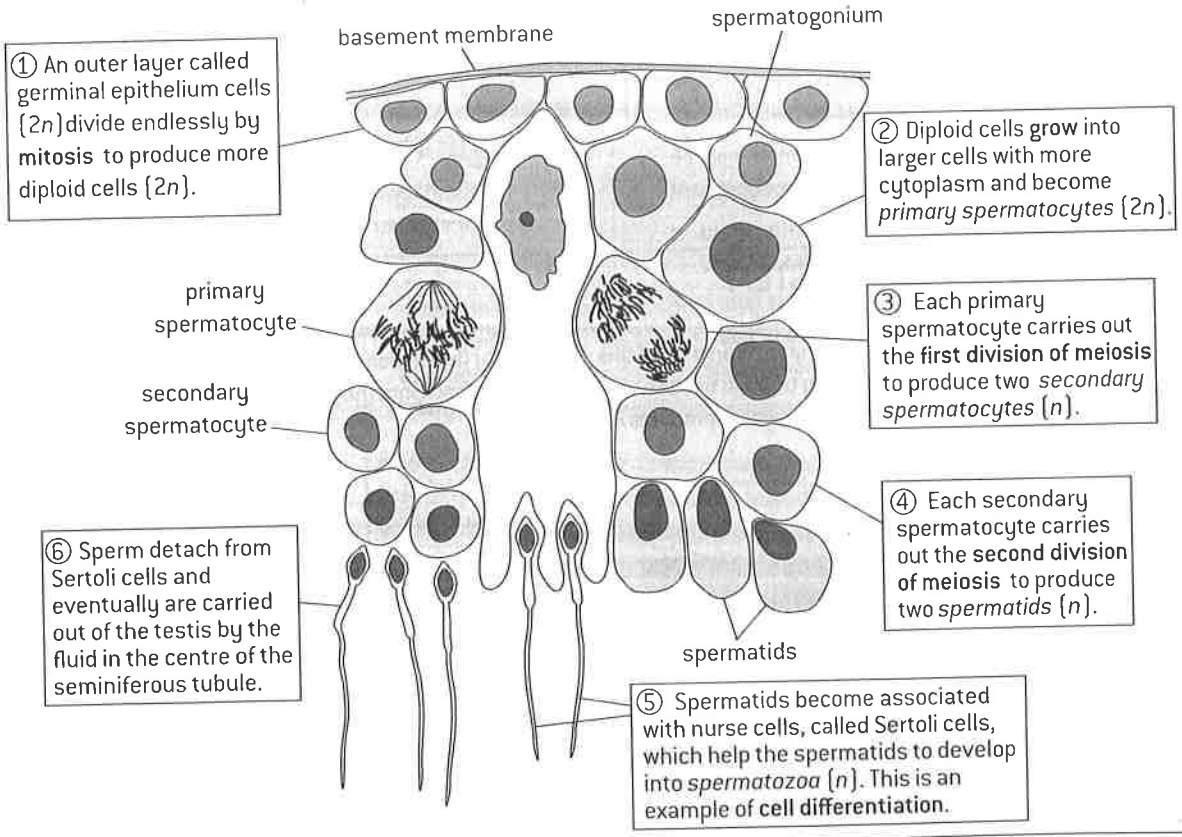
- mitosis to generate large numbers of diploid cells
- cell growth so the cells have enough resources to undergo two divisions of meiosis
- meiosis to produce haploid cells
- differentiation so the haploid cells develop into gametes with structures needed for fertilization.



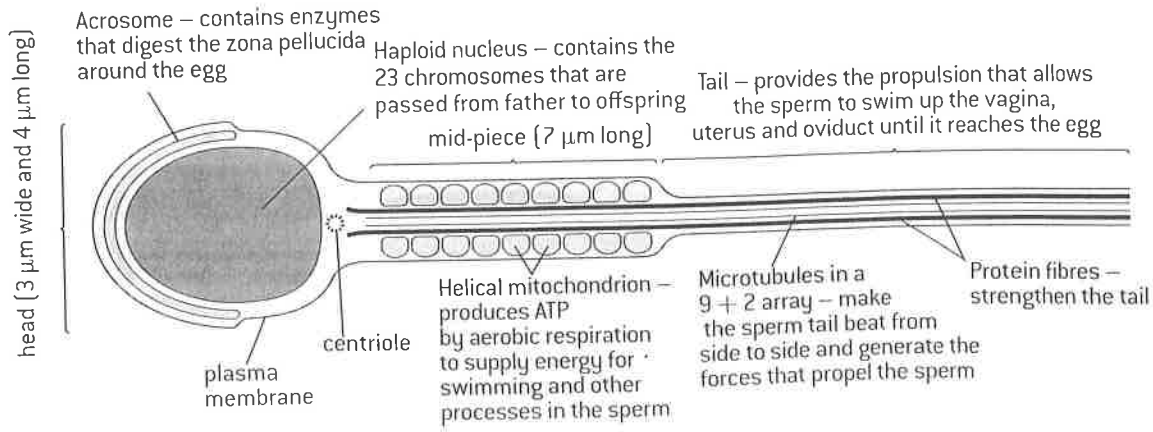
The micrograph (left) shows the testis tissue. Most of it is seminiferous tubules. The tubule walls produce sperm.

STAGES IN SPERMATOGENESIS

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



STRUCTURE OF HUMAN SPERM



Oogenesis

STAGES IN OOGENESIS

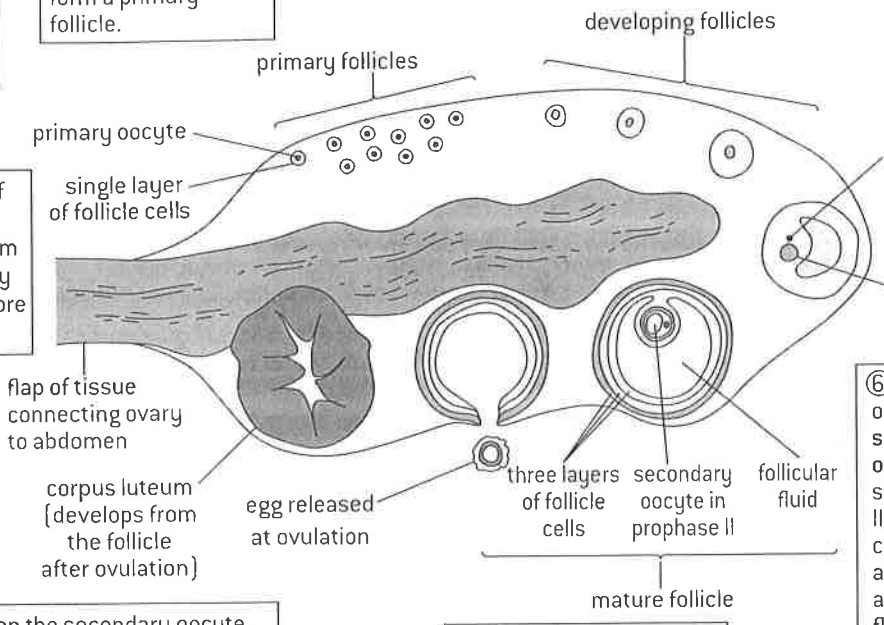
① In the ovaries of a female fetus, germinal epithelium cells ($2n$) divide by **mitosis** to form more diploid cells ($2n$).

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

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

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

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

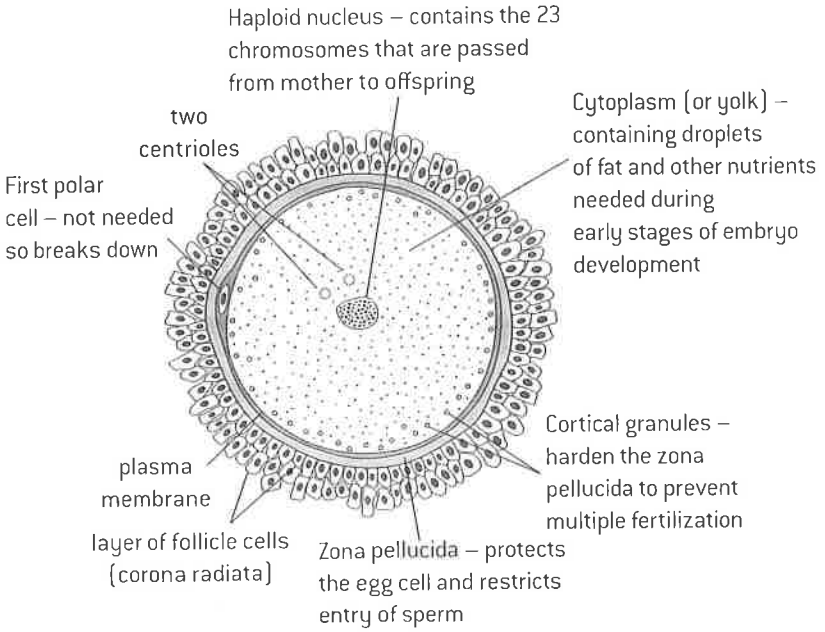


⑥ The secondary oocyte starts the **second division of meiosis** but stops in prophase II. The follicle cells meanwhile are proliferating and follicular fluid is forming.

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

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

STRUCTURE OF A MATURE HUMAN EGG



Diameter of egg cell = 110 μm

COMPARING OOGENESIS AND SPERMATOGENESIS

There are some significant differences between spermatogenesis and oogenesis:

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

Fertilization

INTERNAL AND EXTERNAL FERTILIZATION

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

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

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

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

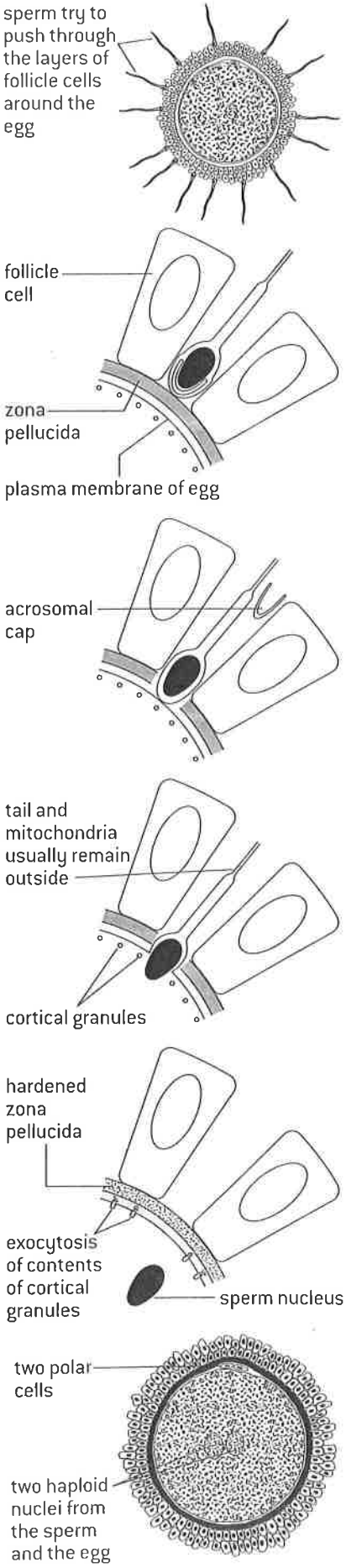
AVOIDING POLYSPERMY

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

DECLINING MALE FERTILITY

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

STAGES IN THE FERTILIZATION OF A HUMAN EGG



1. **Arrival of sperm**

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

2. **Binding**

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

3. **Acrosome reaction**

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

4. **Fusion**

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

5. **Cortical reaction**

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

6. **Mitosis**

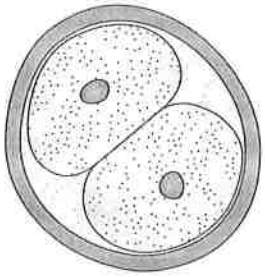
   The nuclei from the sperm and egg do not fuse together. Instead, both nuclei carry out mitosis, using the same centrioles and spindle of microtubules. A two-cell embryo is produced.

Pregnancy and childbirth

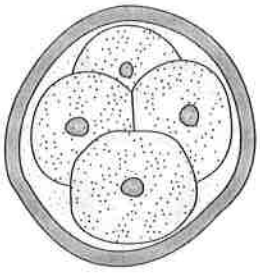
EARLY EMBRYO DEVELOPMENT AND IMPLANTATION

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

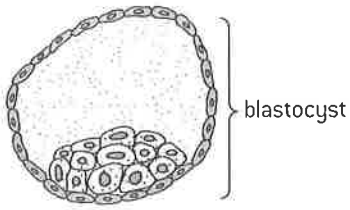
The zygote produced by fertilization in the oviduct is a new human individual. It starts to divide by mitosis to form a 2-cell embryo, then a 4-cell embryo (right) and so on until a hollow ball of cells called a **blastocyst** is formed. While these early stages in the development of the embryo are happening,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



2-cell embryo

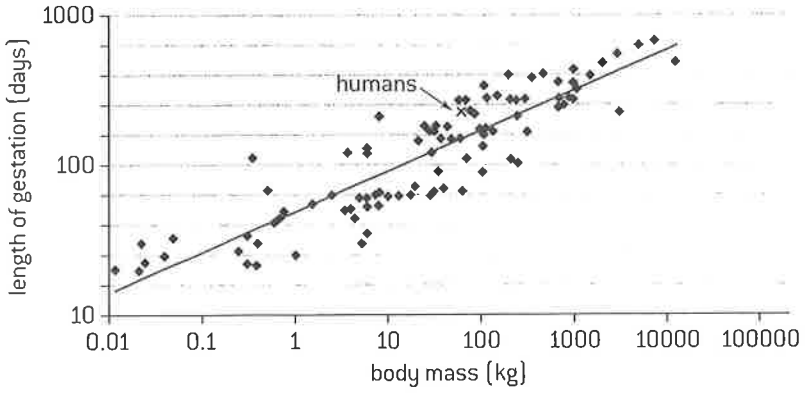


4-cell embryo



ANIMAL SIZE AND DURATION OF GESTATION

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



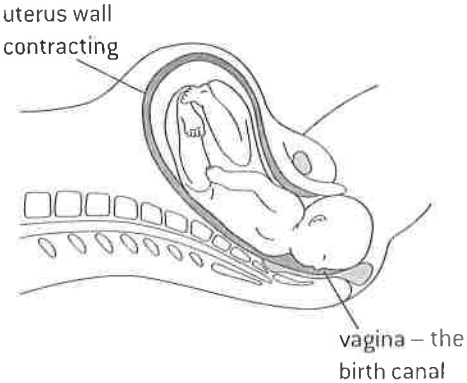
HORMONAL CONTROL OF PREGNANCY

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

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

HORMONAL CONTROL OF CHILDBIRTH

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

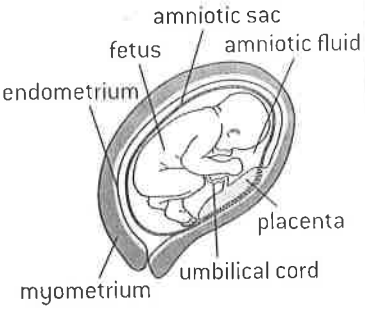


While the muscle in the wall of the uterus is contracting, the cervix relaxes and becomes wider. The amniotic sac bursts and the amniotic fluid is released. Finally, often after many hours of contractions, the baby is pushed out through the cervix and the vagina. The umbilical cord is cut and the baby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

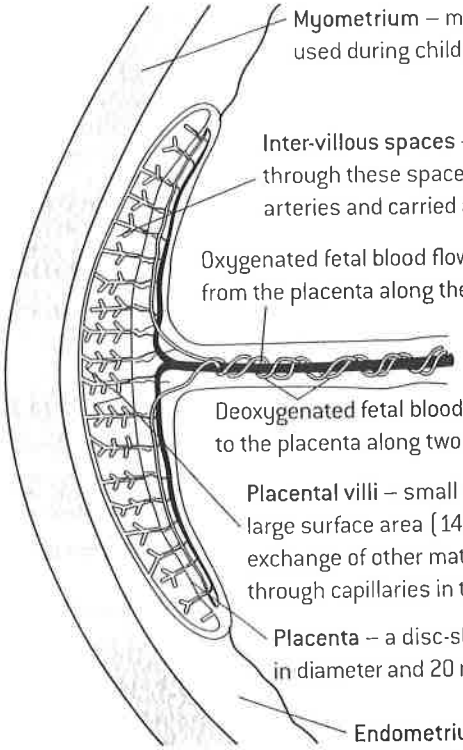
Structure and function of the placenta

FUNCTION OF THE PLACENTA

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



STRUCTURE OF THE PLACENTA



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

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

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

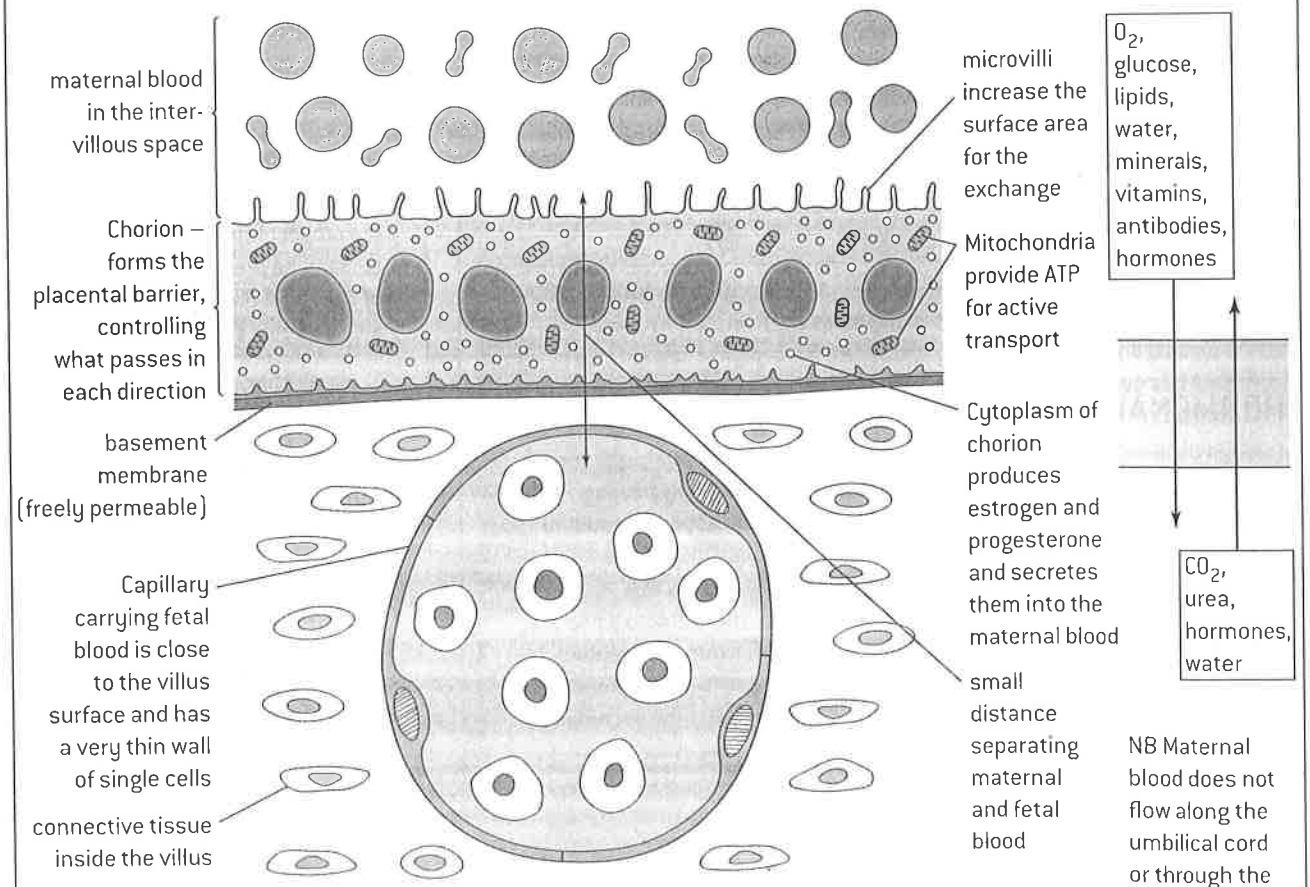
Deoxygenated fetal blood flows from the fetus to the placenta along two umbilical arteries.

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

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

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

EXCHANGE OF MATERIALS ACROSS THE PLACENTA



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