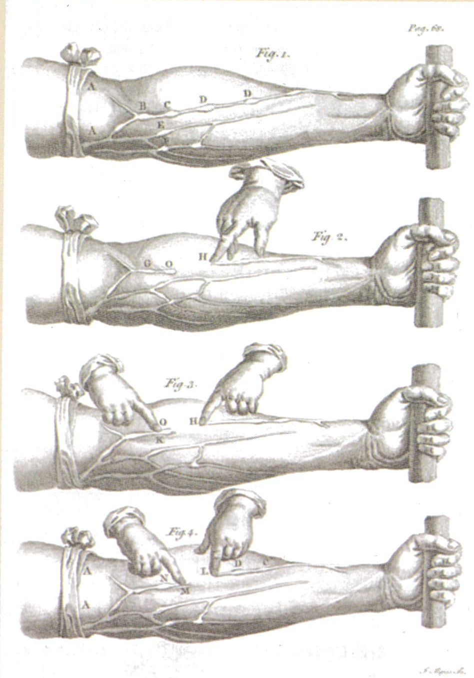
## William Harvey and the circulation of blood

### William Harvey's discovery of the circulation of the blood with the heart acting as the pump.

William Harvey is usually credited with the discovery of the circulation of the blood as he combined earlier discoveries with his own research findings to produce a convincing overall theory for blood flow in the body. He overcame widespread opposition by publishing his results and also by touring Europe to demonstrate experiments that falsified previous theories and provided evidence for his theory. As a result his theory became generally accepted.

Harvey demonstrated that blood flow through the larger vessels is unidirectional, with valves to prevent backflow. He also showed that the rate of flow through major vessels was far too high for blood to be consumed in the body after being pumped out by the heart, as earlier theories proposed. It must therefore return to the heart and be recycled. Harvey showed that the heart pumps blood out in the arteries and it returns in veins. He predicted the presence of numerous fine vessels too small to be seen with contemporary equipment that linked arteries to veins in the tissues of the body.

Blood capillaries are too narrow to be seen with the naked eye or with a hand lens. Microscopes had not been invented by the time that Harvey published his theory about the circulation of blood in 1628. It was not until 1660, after his death, that blood was seen flowing from arteries to veins though capillaries as he had predicted.



▲ Figure 1 Harvey's experiment to demonstrate that blood flow in the veins of the arm is unidirectional

## Overturning ancient theories in science

### Theories are regarded as uncertain: William Harvey overturned theories developed by the ancient Greek philosopher Galen on movement of blood in the body.

During the Renaissance, interest was reawakened in the classical writings of Greece and Rome. This stimulated literature and the arts, but in some ways it hampered progress in science. It became almost impossible to question the doctrines of such writers as Aristotle, Hippocrates, Ptolemy and Galen.

According to Galen, blood is formed in the liver and is pumped to and fro between the liver and the right ventricle of the heart. A little blood passes into the left ventricle, where it meets air from the lungs and becomes "vital spirits". The vital spirits are distributed to the body by the arteries. Some of the vital spirits flow to the brain, to be converted into "animal spirits", which are then distributed by the nerves to the body.

William Harvey was unwilling to accept these doctrines without evidence. He made careful observations and did experiments, from which he deduced that blood circulates through the pulmonary and systemic circulations. He predicted the existence of capillaries, linking arteries and veins, even though the lenses of the time were not powerful enough for him to see them.

The following extract is from Harvey's book *On the Generation of Animals*, published in 1651 when he was 73.

> *And hence it is that without the due admonition of the senses, without frequent observation and reiterated experiment, our mind goes astray after phantoms and appearances. Diligent observation is therefore requisite in every science, and the senses are frequently to be appealed to. We are, I say, to strive after personal experience, not to rely of the experience of others: without which no one can properly become a student of any branch of natural science. I would not have you therefore, gentle reader, to take anything on trust from me concerning the Generation of Animals: I appeal to your own eyes as my witness and judge. The method of pursuing truth commonly pursued at this time therefore is to be held erroneous and almost foolish, in which so many enquire what things others have said, and omit to ask whether the things themselves be actually so or not.*

## Arteries

### Arteries convey blood at high pressure from the ventricles to the tissues of the body.

Arteries are vessels that convey blood from the heart to the tissues of the body. The main pumping chambers of the heart are the ventricles. They have thick strong muscle in their walls that pumps blood into the arteries, reaching a high pressure at the peak of each pumping cycle. The artery walls work with the heart to facilitate and control blood flow. Elastic and muscle tissue in the walls are used to do this.

Elastic tissue contains elastin fibres, which store the energy that stretches them at the peak of each pumping cycle. Their recoil helps propel the blood on down the artery. Contraction of smooth muscle in the artery wall determines the diameter of the lumen and to some extent the rigidity of the arteries, thus controlling the overall flow through them.

Both the elastic and muscular tissues contribute to the toughness of the walls, which have to be strong to withstand the constantly changing and intermittently high blood pressure without bulging outwards (aneurysm) or bursting. The blood's progress along major arteries is thus pulsatile, not continuous. The pulse reflects each heartbeat and can easily be felt in arteries that pass near the body surface, including those in the wrist and the neck.

Each organ of the body is supplied with blood by one or more arteries. For example, each kidney is supplied by a renal artery and the liver by the hepatic artery. The powerful, continuously active muscles of the heart itself are supplied with blood by coronary arteries.

## Artery walls

### Arteries have muscle and elastic fibres in their walls.

The wall of the artery is composed of several layers:

- tunica externa – a tough outer layer of connective tissue
- tunica media – a thick layer containing smooth muscle and elastic fibres made of the protein elastin
- tunica intima – a smooth endothelium forming the lining of the artery.

**Activity**

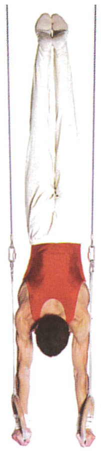
**Discussion questions on William Harvey's methods**

1. William Harvey refused to accept doctrines without evidence. Are there academic contexts where it is reasonable to accept doctrines on the basis of authority rather than evidence gathered from primary sources?
2. Harvey welcomed questions and criticisms of his theories when teaching anatomy classes. Suggest why he might have done this.
3. Can you think of examples of the "phantoms and appearances" that Harvey refers to?
4. Why does Harvey recommend "reiteration" of experiments?
5. Harvey practised as a doctor, but after the publication in 1628 of his work on the circulation of the blood, far fewer patients consulted him. Why might this have been?

## Activity

**Standing on your head**

Pocket valves and vein walls become less efficient with age, causing poor venous return to the heart. Have you ever performed gymnastic moves such as headstands or handstands, or experienced very high g-forces on a ride at an amusement park? Young people can mostly do any of these activities easily but older people may not be able to. What is the explanation?



▲ Figure 5 Which veins in this gymnast will need valves to help with venous return?

▲ Figure 6 Artery and vein in transverse section. The tunica externa and tunica intima are stained more darkly than the tunica media. Clotted blood is visible in both vessels

# Valves in veins

## Valves in veins and the heart ensure circulation of blood by preventing backflow.

Blood pressure in veins is sometimes so low that there is a danger of backflow towards the capillaries and insufficient return of blood to the heart. To maintain circulation, veins contain pocket valves, consisting of three cup-shaped flaps of tissue.

- If blood starts to flow backwards, it gets caught in the flaps of the pocket valve, which fill with blood, blocking the lumen of the vein.
- When blood flows towards the heart, it pushes the flaps to the sides of the vein. The pocket valve therefore opens and blood can flow freely.

These valves allow blood to flow in one direction only and make efficient use of the intermittent and often transient pressures provided by muscular and postural changes. They ensure that blood circulates in the body rather than flowing to and fro.

# Identifying blood vessels

## Identification of blood vessels as arteries, capillaries or veins from the structure of their walls.

Blood vessels can be identified as arteries, capillaries or veins by looking at their structure. Table 1 below gives differences that may be useful.

| | Artery | Capillary | Vein |
|---|---|---|---|
| Diameter | Larger than 10 μm | Around 10 μm | Variable but much larger than 10 μm |
| Relative thickness of wall and diameter of lumen | Relatively thick wall and narrow lumen | Extremely thin wall | Relatively thin wall with variable but often wide lumen |
| Number of layers in wall | Three layers, tunica externa, media and intima. These layers may be sub-divided to form more layers | Only one layer – the tunica intima which is an endothelium consisting of a single layer of very thin cells | Three layers – tunica externa, media and intima |
| Muscle and elastic fibres in the wall | Abundant | None | Small amounts |
| Valves | None | None | Present in many veins |

▲ Table 1

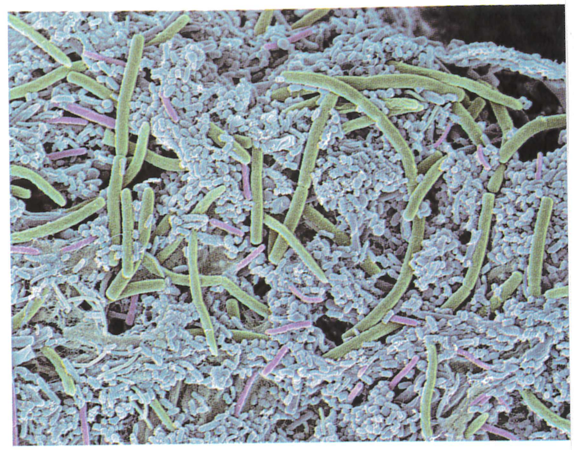
## Skin as a barrier to infection

### The skin and mucous membranes form a primary defence against pathogens that cause infectious disease.

There are many different microbes in the environment that can grow inside the human body and cause a disease. Some microorganisms are opportunistic and although they can invade the body they also commonly live outside it. Others are specialized and can only survive inside a human body. Microbes that cause disease are called pathogens.

The primary defence of the body against pathogens is the skin. Its outermost layer is tough and provides a physical barrier against the entry of pathogens and protection against physical and chemical damage. Sebaceous glands are associated with hair follicles and they secrete a chemical called sebum, which maintains skin moisture and slightly lowers skin pH. The lower pH inhibits the growth of bacteria and fungi.

Mucous membranes are a thinner and softer type of skin that is found in areas such as the nasal passages and other airways, the head of the penis and foreskin and the vagina. The mucus that these areas of skin secrete is a sticky solution of glycoproteins. Mucus acts as a physical barrier; pathogens and harmful particles are trapped in it and either swallowed or expelled. It also has antiseptic properties because of the presence of the anti-bacterial enzyme lysozyme.

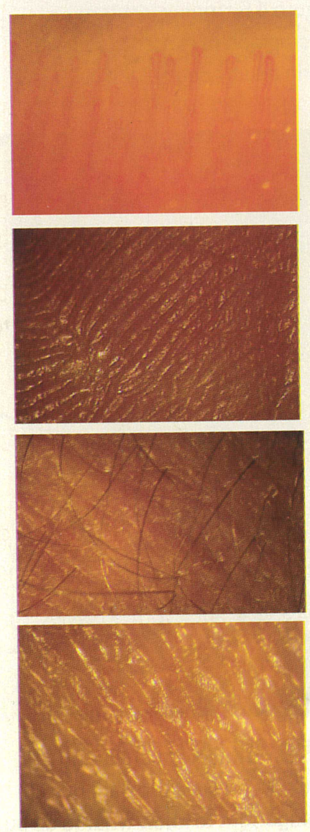


▲ Figure 1 Scanning electron micrograph of bacteria on the surface of teeth. Mucous membranes in the mouth prevent these and other microbes from invading body tissues

**Activity**

**Imaging human skin**

A digital microscope can be used to produce images of the different types of skin covering the human body. Figure 2 shows four images produced in this way.



▲ Figure 2

## Cuts and clots

### Cuts in the skin are sealed by blood clotting.

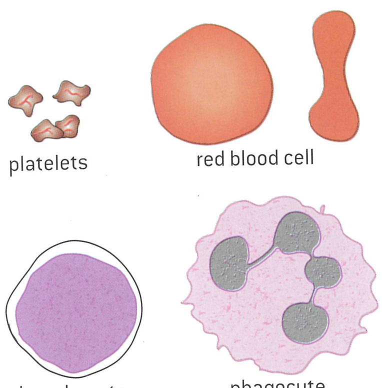
When the skin is cut, blood vessels in it are severed and start to bleed. The bleeding usually stops after a short time because of a process called clotting. The blood emerging from a cut changes from being a liquid to a semi-solid gel. This seals up the wound and prevents further loss of blood and blood pressure. Clotting is also important because cuts breach the barrier to infection provided by the skin. Clots prevent entry of pathogens until new tissue has grown to heal the cut.

## Platelets and blood clotting

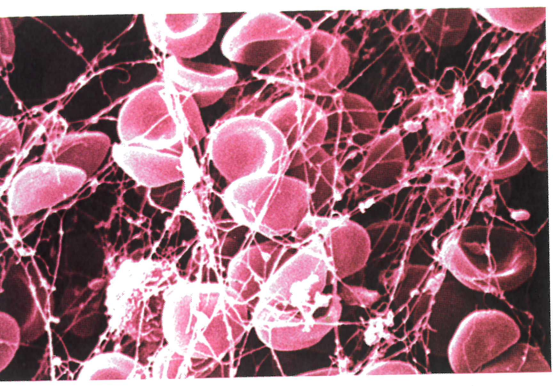
### Clotting factors are released from platelets.

Blood clotting involves a cascade of reactions, each of which produces a catalyst for the next reaction. As a result blood clots very rapidly. It is important that clotting is under strict control, because if it occurs inside blood vessels the resulting clots can cause blockages.

The process of clotting only occurs if platelets release clotting factors. Platelets are cellular fragments that circulate in the blood. They are smaller than either red or white blood cells. When a cut or other injury involving damage to blood vessels occurs, platelets aggregate at the site forming a temporary plug. They then release the clotting factors that trigger off the clotting process.




▲ Figure 3 Cells and cell fragments from blood. Lymphocytes and phagocytes are types of white blood cell



▲ Figure 4 Scanning electron micrograph of clotted blood with fibrin and trapped blood cells

▲ Figure 5 Early intervention during a heart attack can save the patient's life so it is important to know what to do by being trained

## Fibrin production

### The cascade results in the rapid conversion of fibrinogen to fibrin by thrombin.

The cascade of reactions that occurs after the release of clotting factors from platelets quickly results in the production of an enzyme called thrombin. Thrombin in turn converts the soluble protein fibrinogen into the insoluble fibrin. The fibrin forms a mesh in cuts that traps more platelets and also blood cells. The resulting clot is initially a gel, but if exposed to the air it dries to form a hard scab.

Figure 4 shows red blood cells trapped in this fibrous mesh.

## Coronary thrombosis

### Causes and consequences of blood clot formation in coronary arteries.

In patients with coronary heart disease, blood clots sometimes form in the coronary arteries. These arteries branch off from the aorta close to the semilunar valve. They carry blood to the wall of the heart, supplying the oxygen and glucose needed by cardiac muscle fibres for cell respiration. The medical name for a blood clot is a thrombus. Coronary thrombosis is the formation of blood clots in the coronary arteries.

If the coronary arteries become blocked by a blood clot, part of the heart is deprived of oxygen and nutrients. Cardiac muscle cells are then unable to produce sufficient ATP by aerobic respiration and their contractions become irregular and uncoordinated. The wall of the heart makes quivering movements called fibrillation that do not pump blood effectively. This condition can prove fatal unless it resolves naturally or through medical intervention.

Atherosclerosis causes occlusion in the coronary arteries. Where atheroma develops the endothelium of the arteries tends to become damaged and roughened; especially, the artery wall is hardened by deposition of calcium salts. Patches of atheroma sometimes rupture causing a lesion. Coronary occlusion, damage to the capillary epithelium, hardening of arteries and rupture of atheroma all increase the risk of coronary thrombosis.

There are some well-known factors that are correlated with an increased risk of coronary thrombosis and heart attacks:

- smoking
- high blood cholesterol concentration
- high blood pressure
- diabetes
- obesity
- lack of exercise.

Of course correlation does not prove causation, but doctors nonetheless advise patients to avoid these risk factors if possible.

| | | | |
|---|---|---|---|
| Movement of the diaphragm | Diaphragm | The diaphragm contracts and so it moves downwards and pushes the abdomen wall out | The diaphragm relaxes so it can be pushed upwards into a more domed shape |
| | Abdomen wall muscles | Muscles in the abdomen wall relax allowing pressure from the diaphragm to push it out | Muscles in the abdomen wall contract pushing the abdominal organs and diaphragm upwards |
| Movement of the ribcage | External intercostal muscles | The external intercostal muscles contract, pulling the ribcage upwards and outwards | The external intercostal muscles relax and are pulled back into their elongated state. |
| | Internal intercostal muscles | The internal intercostal muscles relax and are pulled back into their elongated state | The internal intercostal muscles contract, pulling the ribcage inwards and downwards |

## Epidemiology

### Obtain evidence for theories: epidemiological studies have contributed to our understanding of the causes of lung cancer.

Epidemiology is the study of the incidence and causes of disease. Most epidemiological studies are observational rather than experimental because it is rarely possible to investigate the causes of disease in human populations by carrying out experiments.

As in other fields of scientific research, theories about the causes of a disease are proposed. To obtain evidence for or against a theory, survey data is collected that allows the association between the disease and its theoretical cause to be tested. For example, to test the theory that smoking causes lung cancer, the smoking habits of people who have developed lung cancer and people who have not are needed. Examples of very large epidemiological surveys that provided strong evidence for a link between smoking and lung cancer are included in sub-topic 1.6.

A correlation between a risk factor and a disease does not prove that the factor causes the disease. There are usually confounding factors which also have an effect on the incidence. They can cause spurious associations between a disease and a factor that does not cause it. For example, an association has repeatedly been found by epidemiologists between leanness and an increased risk of lung cancer. Careful analysis showed that among smokers leanness is not significantly associated with an increased risk. Smoking reduces appetite and so is associated with leanness and of course smoking is a cause of lung cancer. This explains the spurious association between leanness and lung cancer.

To try to compensate for confounding factors it is usually necessary to collect data on many factors apart from the one being investigated. This allows statistical procedures to be carried out to take account of confounding factors and try to isolate the effect of single factors. Age and sex are almost always recorded and sometimes epidemiological surveys include only males or females or only people in a specific age range.

## Causes of lung cancer

### Causes and consequences of lung cancer.

Lung cancer is the most common cancer in the world, both in terms of the number of cases and the number of deaths due to the disease. The general causes of cancer are described in sub-topic 1.6. The specific causes of lung cancer are considered here.

▲ Figure 9 A large tumour (red) is visible in the right lung. The tumour is a bronchial carcinoma

- Smoking causes about 87% of cases. Tobacco smoke contains many mutagenic chemicals. As every cigarette carries a risk, the incidence of lung cancer increases with the number smoked per day and the number of years of smoking.
- Passive smoking causes about 3% of cases. This happens when non-smokers inhale tobacco smoke exhaled by smokers. The number of cases will decline in countries where smoking is banned indoors and in public places.
- Air pollution probably causes about 5% of lung cancers. The sources of air pollution that are most significant are diesel exhaust fumes, nitrogen oxides from all vehicle exhaust fumes and smoke from burning coal, wood or other organic matter.
- Radon gas causes significant numbers of cases in some parts of the world. It is a radioactive gas that leaks out of certain rocks such as granite. It accumulates in badly ventilated buildings and people then inhale it.
- Asbestos, silica and some other solids can cause lung cancer if dust or other particles of them are inhaled. This usually happens on construction sites or in quarries, mines or factories.

The consequences of lung cancer are often very severe. Some of them can be used to help diagnose the disease: difficulties with breathing, persistent coughing, coughing up blood, chest pain, loss of appetite, weight loss and general fatigue.

In many patients the tumour is already large when it is discovered and may also have metastasized, with secondary tumours in the brain or elsewhere. Mortality rates are high. Only 15% of patients with lung cancer survive for more than 5 years. If a tumour is discovered early enough, all or part of the affected lung may be removed surgically. This is usually combined with one or more courses of chemotherapy. Other patients are treated with radiotherapy.

The minority of patients who are cured of lung cancer, but have lost some of their lung tissue, are likely to continue to have pain, breathing difficulties, fatigue and also anxiety about the possible return of the disease.

## Emphysema

### Causes and consequences of emphysema.

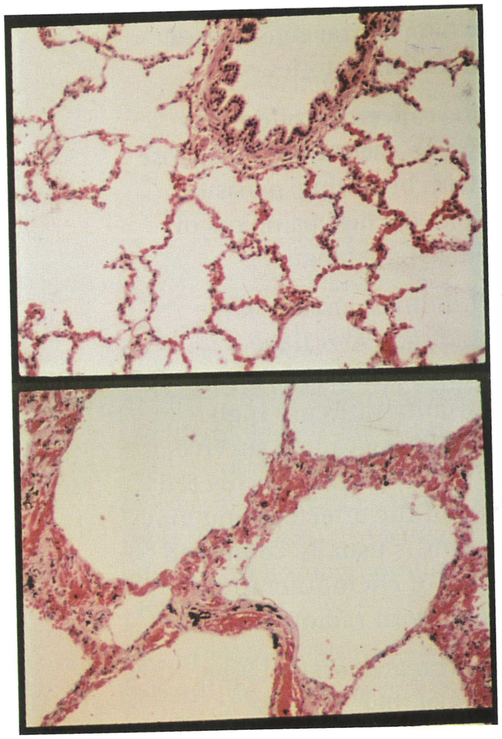
In healthy lung tissue each bronchiole leads to a group of small thin-walled alveoli. In a patient with emphysema these are replaced by a smaller number of larger air sacs with much thicker walls. The total surface area for gas exchange is considerably reduced and the distance over which diffusion of gases occurs is increased, and so gas exchange is therefore much less effective. The lungs also become less elastic, so ventilation is more difficult.

The molecular mechanisms involved are not fully understood, though there is some evidence for these theories:

- Phagocytes inside alveoli normally prevent lung infections by engulfing bacteria and produce elastase, a protein-digesting enzyme, to kill them inside the vesicles formed by endocytosis.
- An enzyme inhibitor called alpha 1-antitrypsin (A1AT) usually prevents elastase and other proteases from digesting lung tissue. In smokers, the number of phagocytes in the lungs increases and they produce more elastase.
- Genetic factors affect the quantity and effectiveness of A1AT produced in the lungs.

In about 30% of smokers digestion of proteins in the alveolus wall by the increased quantity of proteases is not prevented and alveolus walls are weakened and eventually destroyed.

Emphysema is a chronic disease because the damage to alveoli is usually irreversible. It causes low oxygen saturation in the blood and higher than normal carbon dioxide concentrations. As a result the patient lacks energy and may eventually find even tasks such as climbing stairs too onerous. In mild cases there is shortness of breath during vigorous exercise but eventually even mild activity causes it. Ventilation is laboured and tends to be more rapid than normal.



▲ Figure 10 Healthy lung tissue (top) and lung tissue showing emphysema (bottom)

### Data-based questions: Emphysema and gas exchange

Figure 10 shows healthy lung tissue and tissue from a lung with emphysema, at the same magnification. Smoking usually causes emphysema. Breathing polluted air makes the disease worse.

1 a) Place a ruler across each micrograph and count how many times the edge of the ruler crosses a gas exchange surface. Repeat this several times for each micrograph, in such a way that the results are comparable. State your results using suitable units. [3]

b) Explain the conclusions that you draw from the results. [3]

2 Explain why people who have emphysema feel tired all the time. [3]

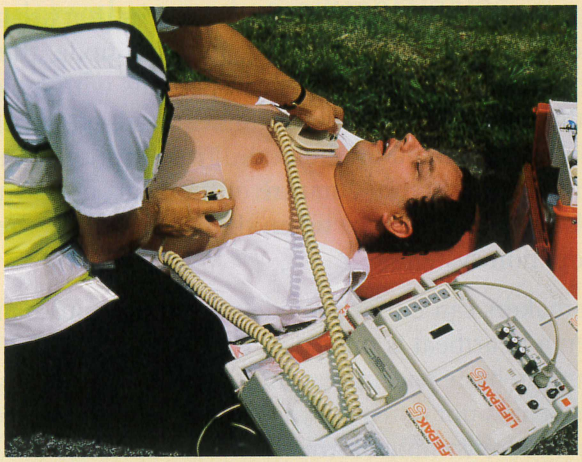
3 Suggest why people with emphysema often have an enlarged and strained right side of the heart. [1]

## Explaining the use of a defibrillator

### Use of defibrillation to treat life-threatening cardiac conditions.

Cardiac arrest occurs when the blood supply to the heart becomes reduced and heart tissues are deprived of oxygen. One of the first negative consequences of this is abnormalities in the cardiac cycle such as ventricular fibrillation. This is essentially the twitching of the ventricles due to rapid and chaotic contraction of individual muscle cells.

When "first responders" reach a scene where a victim is not breathing, they will apply the two paddles of a defibrillator to the chest of the patient, setting up a diagonal line between the two paddles with the heart in the middle. The device will first detect whether fibrillation is happening and if it is, an electric discharge is given off to restore a normal heart rhythm.




▲ Figure 11 First responders applying a defibrillator to the chest of a man who is undergoing cardiac arrest

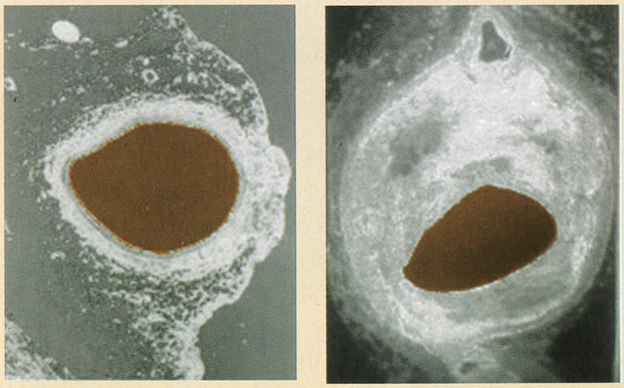
## Hypertension and thrombosis

### Causes and consequences of hypertension and thrombosis.

Atherosclerosis is hardening of the arteries caused by the formation of plaques, or atheromas, on the inner lining of arteries (figure 12). Plaques are areas that are swollen and accumulate a diversity of debris. The plaques often develop because of high circulating levels of lipids and cholesterol. The plaques can reduce the speed at which blood moves through vessels. This can trigger a clot, or thrombosis, which can block the blood flow through the artery and deny the tissue access to oxygen. If this occurs on the surface of the heart, the consequence can be a myocardial infarction, or heart attack.

Greater resistance to the flow of blood can slow the flow of blood. The result is greater pressure on the walls of arteries, also known as hypertension. Hypertension has a number of consequences.

- Damage to the cells that line arteries can cause a cascade of events that ultimately leads to the arteries becoming narrower and stiff.
- Constant high blood pressure can weaken an artery causing a section of the wall to enlarge and form a bulge called an aneurysm. An aneurysm can burst and cause internal bleeding. They can form in any artery in the body but are most common in the aorta.

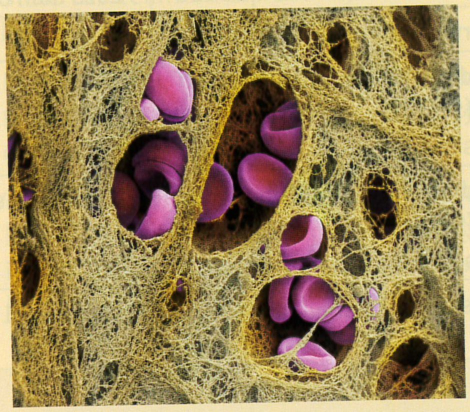


▲ Figure 12 A normal artery (top) can be compared to an artery where a plaque has formed (bottom)

- Chronic high blood pressure can lead to stroke by weakening blood vessels in the brain causing them to narrow, leak or rupture. It can also lead to blood clots in the arteries leading to the brain potentially causing a stroke.
- Chronic high blood pressure is one of the most common causes of kidney failure as it damages both the arteries leading to the kidney and the capillaries within the glomerulus.

There are a number of factors that are correlated with a greater incidence of thrombosis and hypertension.

- Having parents who have experienced heart attacks indicates a genetic precondition to either condition.
- Old age leads to less flexible blood vessels. In children, the normal ranges are lower than for adults.
- Risk in females increases post-menopause correlated with a fall in estrogen levels.
- Males are at greater risk compared with females correlated with lower levels of estrogen.
- Smoking raises blood pressure because nicotine causes vasoconstriction.
- A high-salt diet, excessive amounts of alcohol and stress are also correlated with hypertension.
- Eating too much saturated fat and cholesterol promotes plaque formation.
- Height affects blood pressure.
- Sedentary lifestyle, i.e. a lack of exercise is correlated with obesity and prevents the return of venous blood from the extremities leading to a greater risk of clot formation.



▲ Figure 13 A blood clot (thrombus) in the coronary artery, showing red blood cells (purple) in a fibrin mesh (threads). The coronary artery supplies blood to the heart

## Interpreting blood pressure measurements

### Interpretation of systolic and diastolic blood pressure measurements.

Blood pressure, or more accurately arterial pressure is the pressure that circulating blood puts on the walls of arteries. During each heartbeat, the pressure of blood within arteries varies from a peak during the ventricle systole to a minimum near the beginning of the cardiac cycle when the ventricles are filled with blood and are in systole.

Blood pressure measurements are often quoted in the pressure unit "mm Hg". An example blood pressure would be "120 over 80". The higher number refers to the pressure in the artery caused by ventricular systole and the lower number refers to the pressure in the artery due to ventricular diastole.

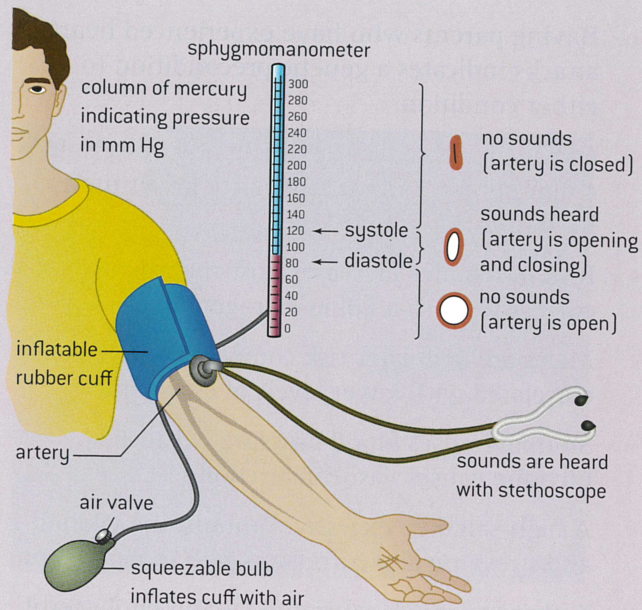
Figure 14 shows a pregnant woman having her blood pressure measured. Monitoring blood pressure during pregnancy is important. High blood pressure during pregnancy is called pre-eclampsia and it can be a life-threatening condition if it is not treated.

To measure blood pressure, a cuff is placed on the bicep and inflated so that it constricts the arm and prevents blood from entering the forearm. The cuff is slowly deflated and the nurse listens for the occurrence of a sound. This occurs when the cuff pressure is lowered below the systolic pressure. The sound is caused by the opening and closing of the artery. The cuff is further deflated until normal blood flow returns and there is no longer a sound. The absence of sound occurs when the cuff pressure is less than the diastolic pressure.

▲ Figure 14

| Blood pressure category | Systolic | Diastolic |
|---|---|---|
| Hypotension (low blood pressure) | 90 or less | 60 or less |
| Normal | Less than 120 | Less than 80 |
| Pre-hypertension | 120–139 | 80–89 |
| High blood pressure (Stage 1 hypertension) | 140–159 | 90–99 |
| High blood pressure (Stage 2 hypertension) | 160 or higher | 100 or higher |
| Hypertension crisis | Higher than 180 | Higher than 110 |

▲ Table 1




▲ Figure 15

## Data relating to coronary heart disease

### Analysis of epidemiological data relating to the incidence of coronary heart disease.

Coronary heart disease (CHD) refers to the damage to the heart as a consequence of reduced blood supply to the tissues of the heart itself. This is often caused by narrowing and hardening of the coronary artery.

Ethnic groups can differ in their predisposition to CHD because of differing diets and lifestyles.

Gender groups, age groups, groups that differ in their level of physical activity, groups with different genotypes, groups with differing medical histories – all can have different probabilities of experiencing CHD. Epidemiology is the study of the patterns, causes and effects of diseases in groups of individuals or populations.

### Data-based questions: Hypertension

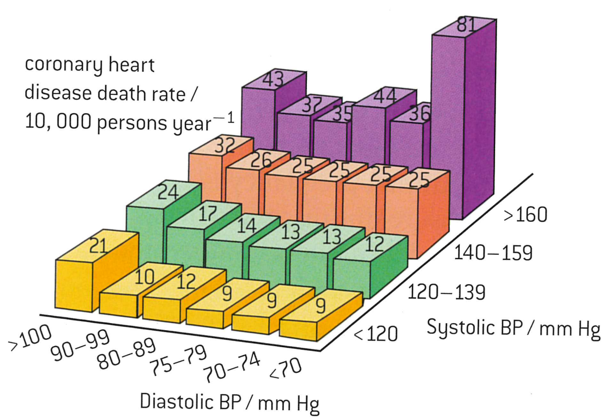
High blood pressure (hypertension) is a major risk factor for coronary heart diseases. In a major study, more than 316,000 males were followed for 12 years to investigate the effects of high blood pressure (BP). Figure 16 shows the relationship between systolic and diastolic blood pressure and the effect on the death rate per 10,000 persons year$^{-1}$.

1 Determine the death rate for a systolic blood pressure between 140 and 159 mmHg and a diastolic blood pressure between 75 and 79 mmHg. [1]

2 Describe the effect of systolic blood pressure and diastolic blood pressure on the death rate. [2]

3 Calculate the minimum difference between systolic and diastolic blood pressure where the death rate is highest. [1]

4 Evaluate the impact of differences between systolic and diastolic pressure on death rate. [3]




▲ Figure 16 The effect of blood pressure on coronary heart disease