chapter 14:

DISORDERS OF THE CARDIOVASCULAR SYSTEM

OBJECTIVES

After studying this chapter you should be able to:

- outline the structure of the heart and circulatory system;
- describe the general functioning of the heart;
- list the major types of heart diseases and their causes;
- review some of the methods for detecting and investigating heart disease;
- discuss the role of cholesterol and apolipoproteins in atherosclerosis;
- explain the use of antithrombolytic therapy;
- describe the major peripheral vascular diseases.

14.1 INTRODUCTION

The cardiovascular system comprises the heart, with its covering pericardium, and blood vessels, that is, arteries, arterioles, capillaries, venules and veins, which enclose and distribute blood to the tissues.

The heart is a muscular pump weighing about 500 g in an adult and is the strongest muscle in the body. It can contract for over a hundred years nonstop, beating about 100 000 times a day at a rate of about 70 beats min^{-1}, to pump blood (*Chapter 13*)) around the body. This supplies, for example, oxygen and nutrients to the tissues and removes their waste products. However, in such a complicated system many things can go wrong. In the developed countries, heart disease is responsible for about half of the annual deaths. Much of this is due to lifestyle, for example smoking, poor diets and excess weight. In developing countries rheumatic heart disease is more of a problem but this has decreased in the developed countries.

14.2 THE HEART AND CIRCULATORY SYSTEMS

The heart (*Figure 14.1 (A)* and *(B)*) is a hollow, four-chambered, muscular organ situated approximately in the center of the chest. A smooth layer called the **endocardium** lines the inside of the chambers. The wall of the heart or **myocardium** is rich in cardiac muscle tissue arranged into three layers. The inner layer is circular and thicker in the wall of the left ventricle than in the right. The outer layers of muscle spiral around the ventricles and extend to the fibrous attachments of the four valve rings. On contraction they tend to pull the chamber of the ventricle towards the valve rings. The exterior of the heart is a tough, fibrous layer that is partly covered by fat. The heart is enclosed by a double membrane system called the pericardium.

Internally, the heart is centrally divided by a septum that prevents oxygenated and deoxygenated blood from mixing. Each side is subdivided into an upper chamber or **atrium,** which collects blood and passes it to a lower chamber or **ventricle** that ejects blood. Each of the heart's ventricles has a one-way inlet valve and a one-way outlet valve (*Figure 14.1 (B)*). The tricuspid valve opens from the right atrium to the right ventricle and the pulmonary valve opens from this ventricle into the pulmonary arteries. The mitral valve separates the left atrium and ventricle and the aortic valve opens from the ventricle into the aorta. All these valves ensure that blood flows only in one direction.

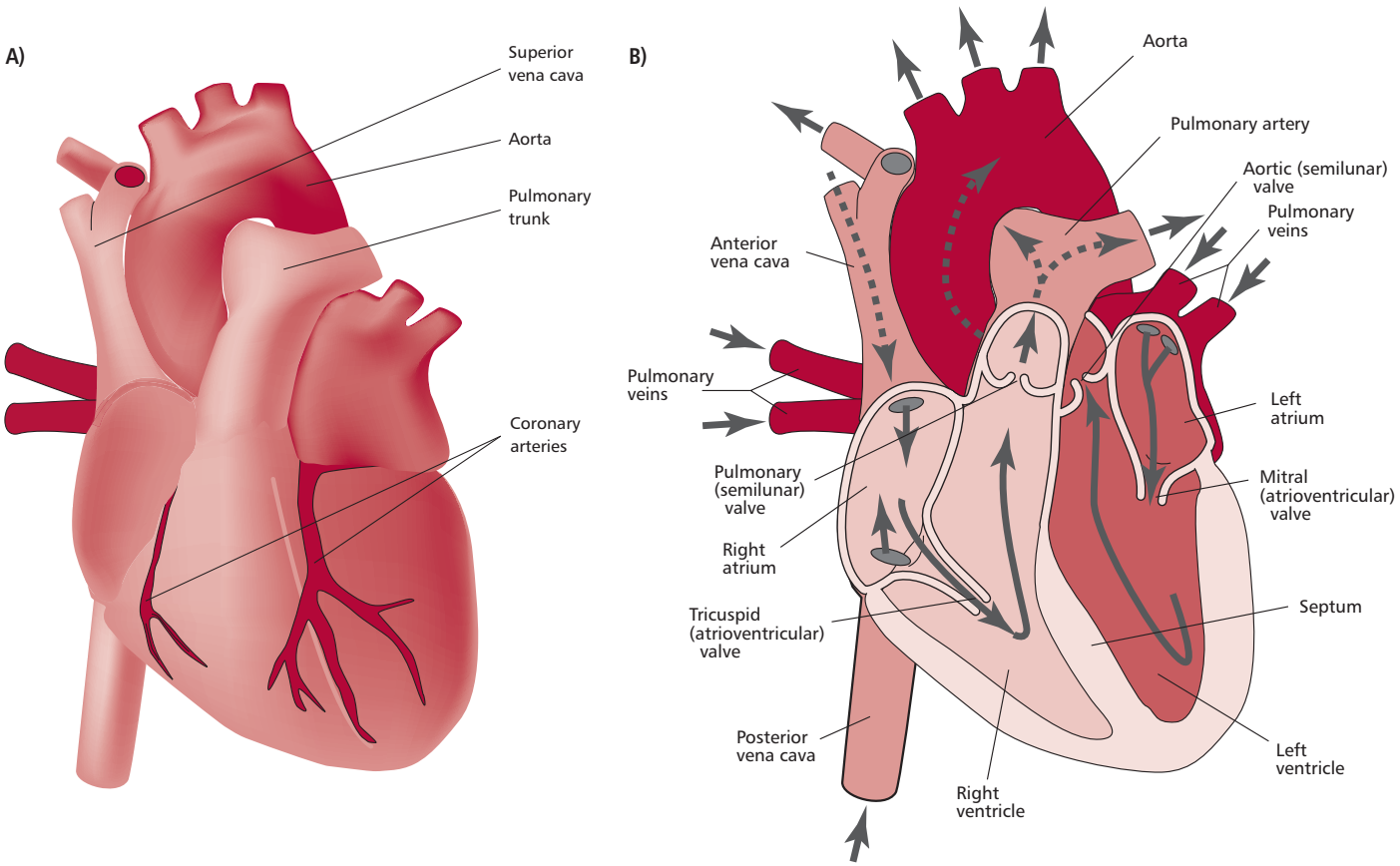

Figure 14.1 Structure of the heart. (A) Overall view of the heart showing the major blood vessels. (B) A cutaway view from the same perspective showing the heart valves and the direction of blood flow.

The flow of blood through the pulmonary and systemic circulations is illustrated in *Figure 14.2*. Oxygen-depleted blood from the body flows through the two largest veins, the venae cavae, into the right atrium. When this chamber is full it propels the blood into the right ventricle and when this is full it pumps blood through the pulmonary valve into the pulmonary artery, which takes it to the lungs. As the blood flows through the network of capillaries that surround the lung alveoli it absorbs oxygen and gives up its carbon dioxide (*Chapter 9*). The resulting oxygen-enriched blood flows through the pulmonary veins into the left atrium of the heart. The complete circuit between the right side of the heart, the lungs and the left atrium is called the **pulmonary circulation**. When the left atrium is full, it sends the oxygen-rich blood into the left ventricle, which, in turn, propels the blood into the **aorta**, which is the largest artery in the body. From there it flows to all the tissues of the body, with the exception of the lungs, in the **systemic circulation**. The major arteries to the head, neck and arms branch off from the aorta (*Section 14.3*) and there are also smaller vessels, the coronary arteries that supply the heart itself with blood. The aorta arches over the

Margin Note 14.1 Heart sounds

Listening to the heart with a stethoscope ('ausculation') reveals the distinctive sounds caused by the opening and closing of the heart's valves and the flow of blood. If there are abnormalities of the valves and heart structures then these may cause turbulent flow of the blood that creates characteristic sounds called **murmurs**. Typically the murmur is caused by blood flowing through narrowed or leaking valves. However, not all heart diseases cause murmurs and not all murmurs indicate heart disease. For example, pregnant women usually have heart murmurs because of the increase in blood flow. In infants and young children, harmless murmurs are commonly caused by the rapid flow of blood through the smaller sized heart structures.

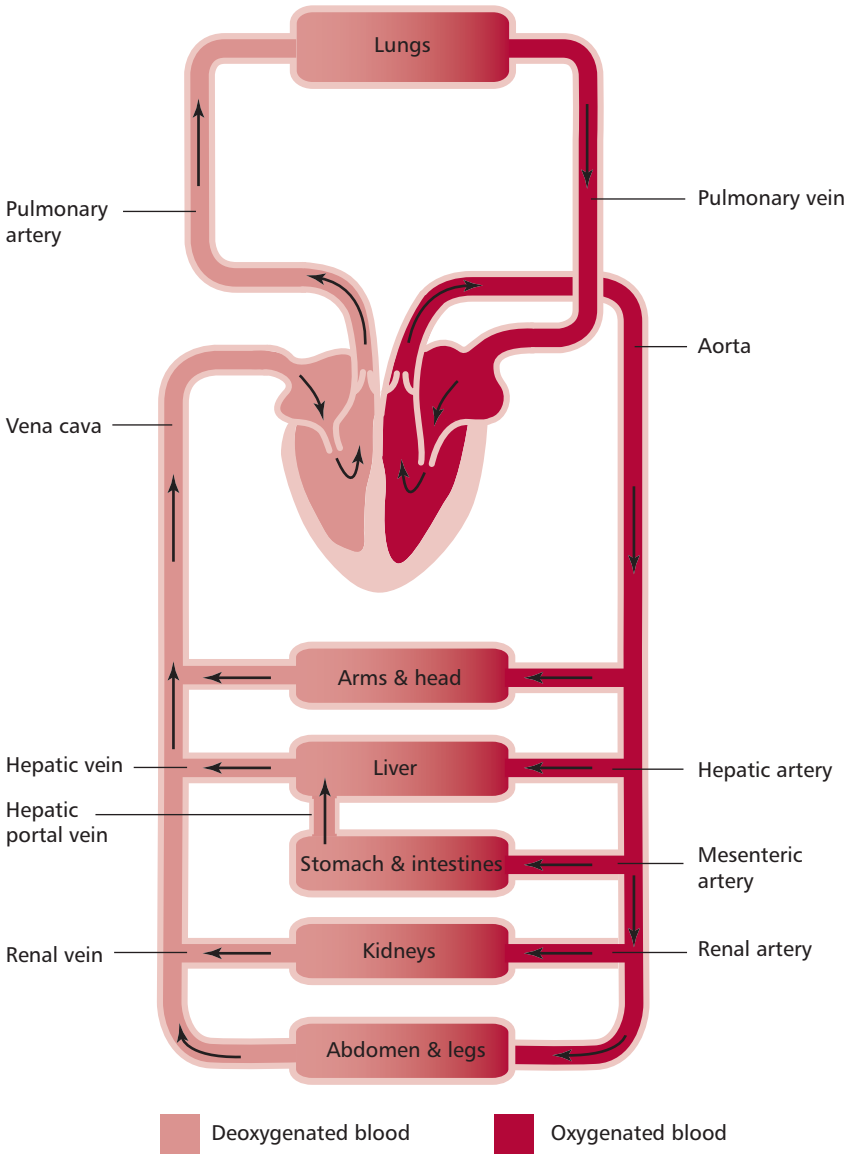

Figure 14.2 Schematic illustrating the pulmonary and systemic circulations. See text for details.

heart and then goes downwards carrying blood to the abdomen and legs. In the capillaries of the tissues, oxygen is exchanged for carbon dioxide and nutrients and hormones, for example, supplied to the tissues. The blood then returns to the heart through the veins (*Figure 14.2*).

To work efficiently, the four chambers of the heart must beat in a coordinated way, with the atria and then the ventricles contracting simultaneously (*Figure 14.3*). A given chamber of the heart contracts when an electrical impulse moves across it. Each signal originates in a small bundle of specialized cells in the right atrium called the **sinoatrial** or **SA node** (*Figure 14.4*). This is the natural **pacemaker** that ensures the heart beats regularly by generating impulses at a given rate. Although it produces a natural rate, this can be modified by emotional and physical reactions and by hormones, especially adrenaline and noradrenaline (*Chapter 7*), which speed up the heart rate, enabling it to respond to varying demands. The electrical impulses generated by the SA node travel throughout the right and left atria causing the heart muscle to contract (*Figure 14.4*) and arrive at the **atrioventricular** or **AV** node situated between the atria and the ventricles. This node delays the transmission of the impulse to allow the atria to contract completely and the ventricles to fill with as much blood as possible. The phase of relaxation of the ventricles is called **diastole**. After passing through the AV node, the impulse travels through the **bundle of His**. This is a group of modified cardiac muscle fibers, called **Purkinje fibers**, that divides into two branches that serves the left and right ventricles respectively (*Figure 14.4*). The fibers spread over the surface of the ventricles in an orderly arrangement and thus initiate **systole** or ventricular

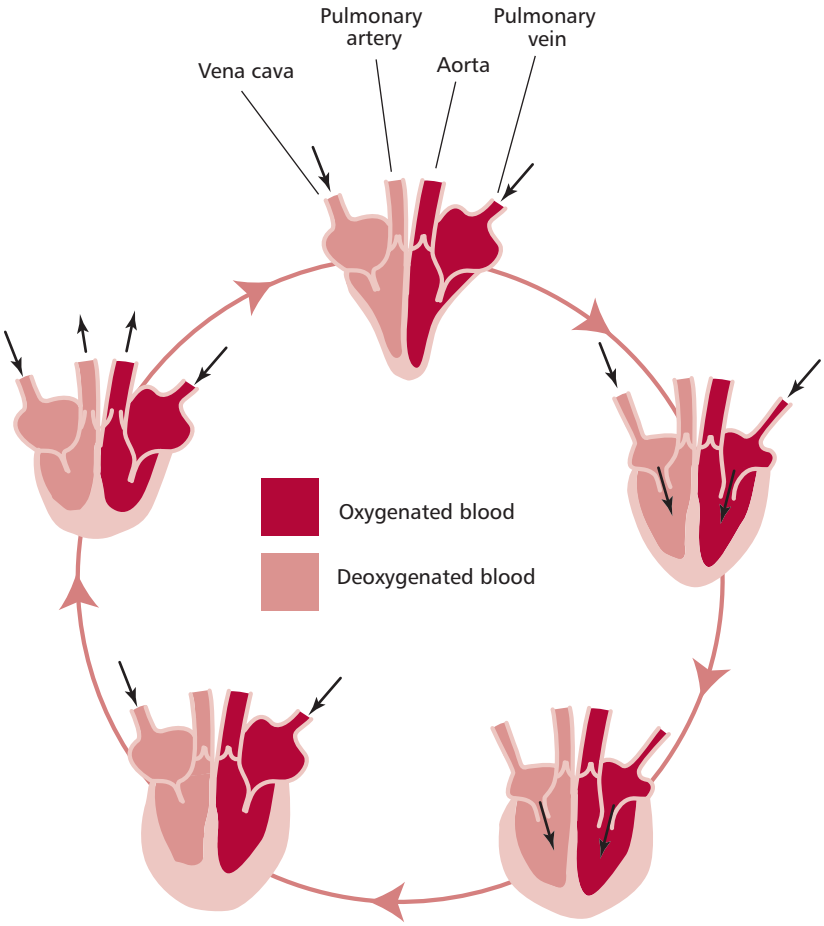

Figure 14.3 Diagrammatic representation of the contractions and relaxation of the heart chambers during one cardiac cycle. Start at the top and observe oxygenated and deoxygenated blood entering the heart, its passage from the atria to the ventricles and finally its expulsion from the ventricles as the cycle starts again.

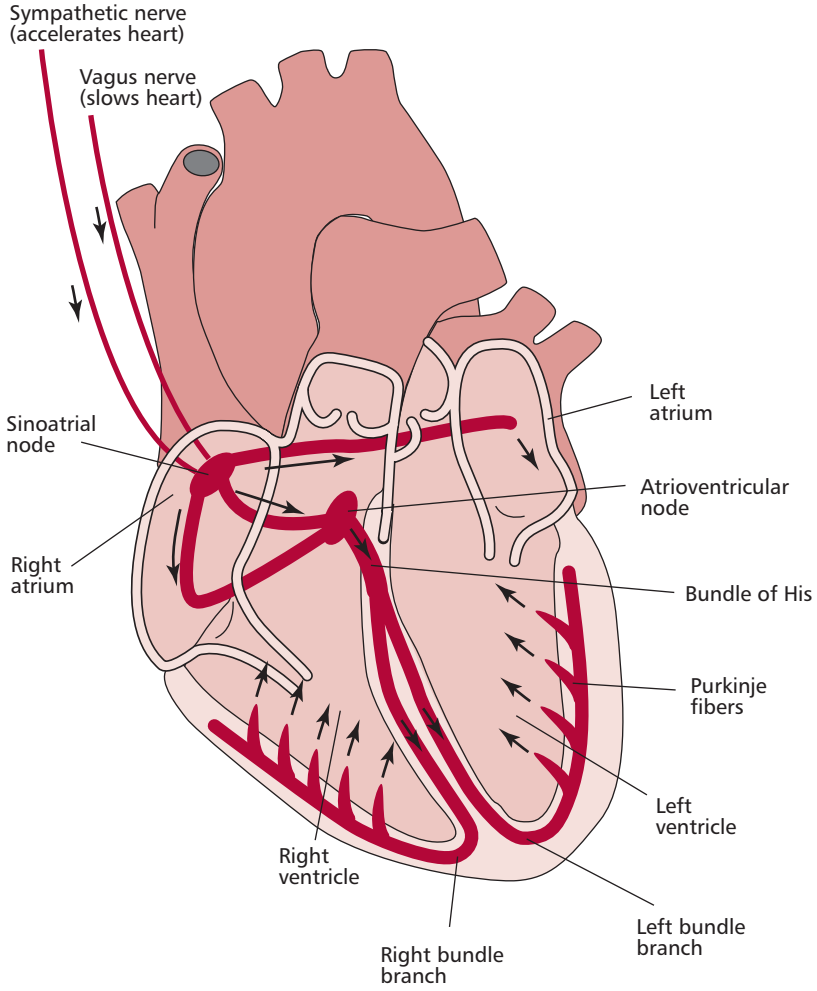

Figure 14.4 The SA and AV nodes and the control of the heart rate. See text for details.

contraction. Both ventricles contract together in a wringing fashion so that blood is squeezed out from their bases, pumping blood from the heart. These coordinated actions keep the four chambers of the heart working in the appropriate sequence. When things go wrong people may have to have artificial pacemakers fitted.

The part of the nervous system that regulates the heart rate automatically is, not surprisingly, the autonomic nervous system and consists of the sympathetic and the parasympathetic fibers of the vagus nerve (*Figure 14.4*). The sympathetic system increases the heart rate and the parasympathetic system slows it down.

The pericardium is a thin, flexible, two-layered bag that surrounds the heart. It contains just sufficient lubricating fluid between the two layers so that they slide easily over each other as the heart beats. It keeps the heart in position and prevents it overfilling with blood.

14.3 BLOOD VESSELS

The blood vessels comprise arteries, arterioles, capillaries, venules and veins (*Figures 14.5 and 14.6*). Arteries are strong and flexible and carry blood away from the heart. They are subjected to the highest pressure (*Section 14.4*), and their resilience helps to maintain blood pressure while the heart is in between

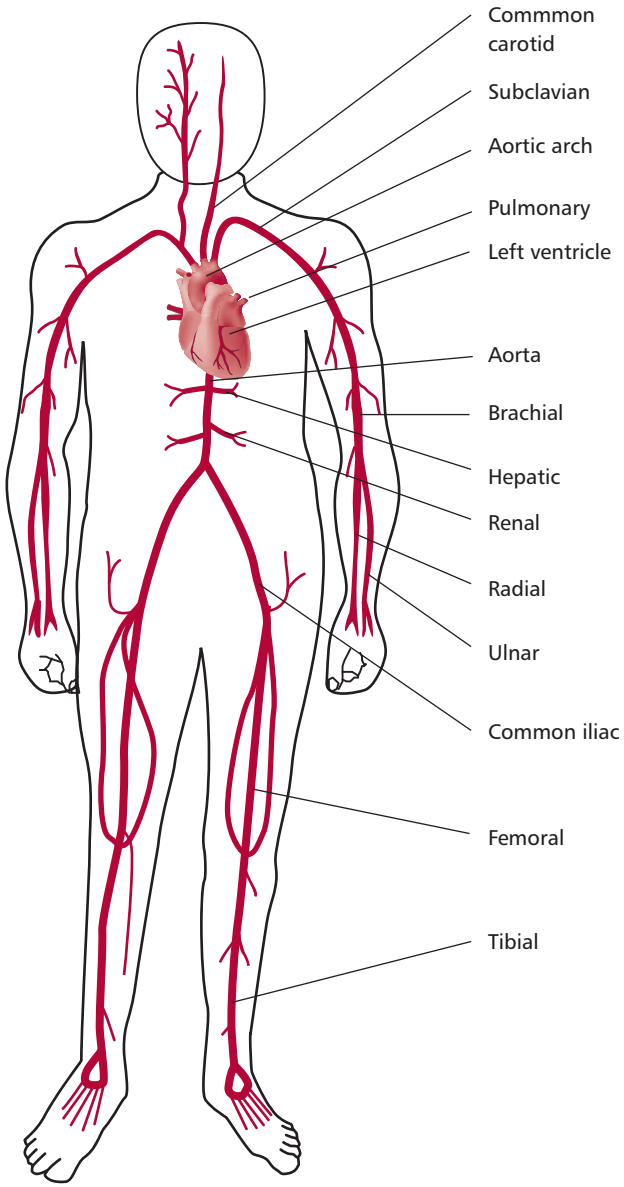

Figure 14.5 Schematic showing the main arteries of the body.

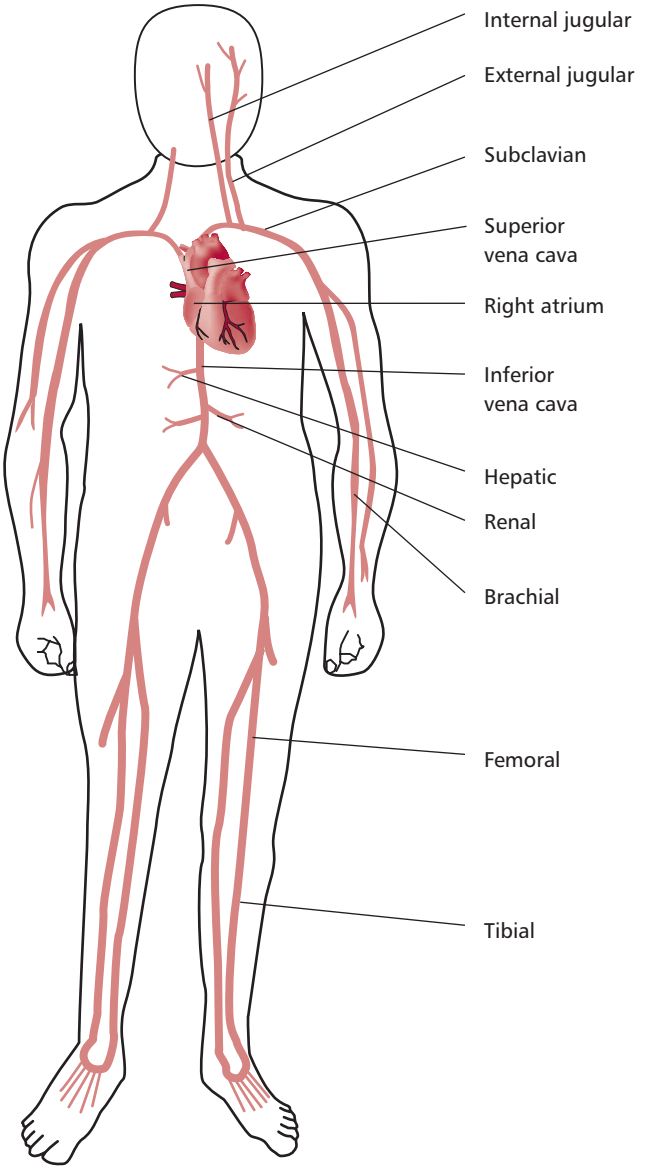

Figure 14.6 Schematic showing the main veins of the body.

beats. The smaller arteries and arterioles have muscular walls and their diameters can be adjusted to regulate blood flow to a particular region of the body. Capillaries are thin-walled vessels that allow oxygen, nutrients and other materials, for example hormones, to diffuse from the blood to the tissues and waste products to pass from the tissues into the blood. The capillaries are links between the arteries and arterioles and the venules and veins. Veins are, in general, larger in diameter than arteries but have much thinner walls. They transport blood back to the heart but at much lower pressures and speeds than is found in arteries.

ARTERIES

Arteries are elastic tubes with circular cross-sections (*Figures 14.7 (A)* and *(B)*). They are built up from three layers called tunics. The tunica intima is

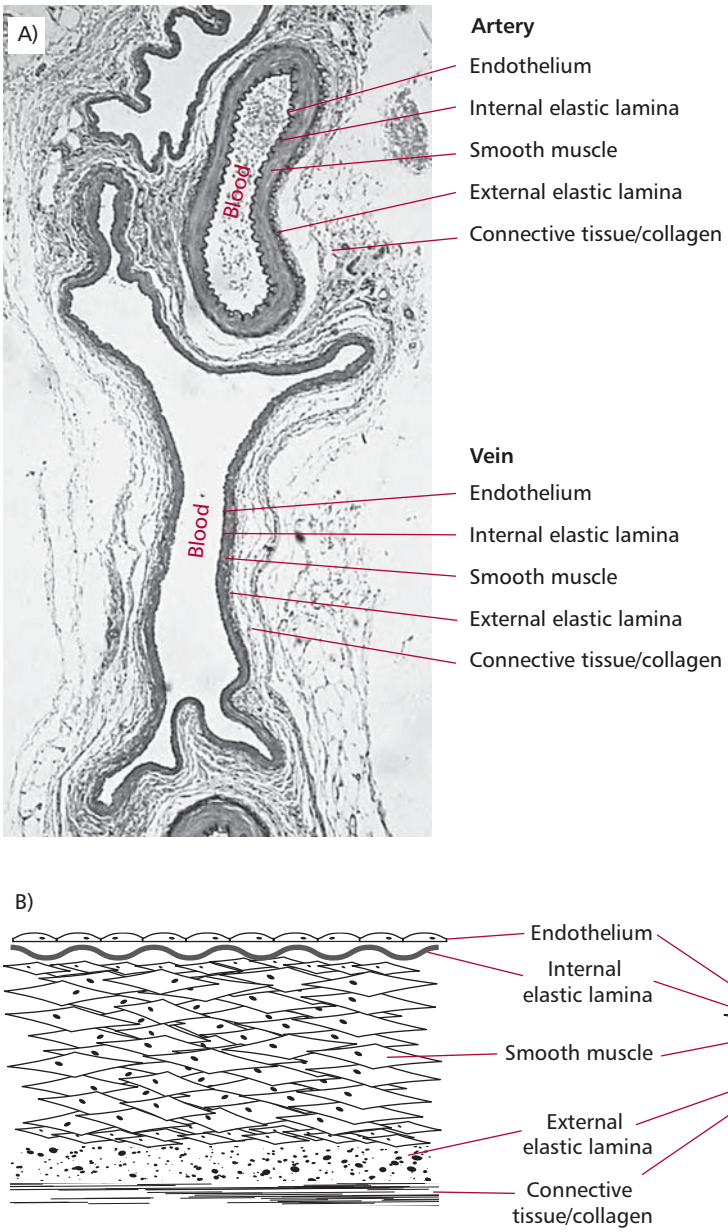

Figure 14.7 (A) Photomicrograph showing the cross sections of an artery and a vein. Schematics illustrating the layers in the walls of (B) an artery and (C) a vein.

the layer of endothelial cells that provides a smooth, low friction innermost surface. This layer is in direct contact with the blood, and damage to it leads to serious clinical problems. The tunica media is a relatively thick middle layer composed of smooth muscle and elastic fibers, which are arranged both lengthways and circumferentially. The amount of elastic material varies with the vessel. Closer to the heart, the aorta and large branches contain larger amounts because they have to accommodate the stroke volume. In contrast, the pulmonary artery has rather thin walls. The smooth muscle is under autonomic nervous control that regulates the diameter of the vessel. The fibrous components limit the amount of stretch under a surge of pressure. The tunica adventitia is the outer covering fibrous layer composed of tough collagenous material.

Arteries branch repeatedly in order to supply all parts of the body. The diameter of the aorta is about 25 mm, and that of a medium-sized artery about 4 mm.

When their diameter is less than 0.1 mm, they are called arterioles. Junctions between the branches are called anastomoses and these may occur between arteries and arterioles.

The pulmonary arteries distribute the output of the right ventricle to the lungs. They are shorter, have thinner walls and contain blood at a lower pressure than systemic arteries. Arteries also have a storage function since the output of the ventricles is discontinuous as the heart beats. For example, the aorta stores up blood during systole and its elastic recoil propels it on during diastole. This means that the discontinuous blood flow from the heart is converted to a more continuous flow through the peripheral circulation, conserving energy and reducing the pressure that the smaller arteries have to withstand.

VEINS

The veins form a blood collecting system that returns blood from the periphery to the heart. In general, veins have the same pattern of distribution as the arteries and frequently run alongside them (*Figure 14.6*). The blood collected from the systemic circuit is eventually delivered to the right atrium of the heart. However, the venous drainage from the stomach, spleen and intestine is carried by the hepatic portal vein to the liver (*Chapter 11*). Blood from the liver is then returned to the heart in the hepatic vein.

Veins, like arteries, have walls composed of three layers but they contain considerably less muscle and elastic tissues and their walls are much thinner (*Figure 14.7 (A)* and *(C)*). The internal lining is the same endothelium as in the arteries. Veins are much more easily distended than arteries and are also more easily collapsed because they are less able to withstand high pressures. At intervals, especially along the lengths of long veins, the endothelial lining forms cup-shaped valves, rather similar to the semilunar valves in the heart. These allow blood to flow in only one direction, which is back towards the heart, and also prevent its back flow under gravity. In addition, during muscular activity especially in the legs, the compression and relaxation of the muscular tissue surrounding the veins forms a 'muscle pump' that expedites the transport of blood back to the heart. In general, the blood flow through veins is less discontinuous than it is in arteries.

CAPILLARIES

The arterioles supply beds of capillaries found deep in the tissues and these eventually deliver their blood to the venules, and hence to the veins for return to the heart. Capillaries have internal diameters about the same as that of erythrocytes, about 7 μm.Their walls are composed of a single layer of endothelial cells on a basement membrane (*Figure 14.8*) and so they lack muscle and elastic tissues. The capillary network is the site where gases are exchanged, nutrients and other biomolecules are delivered and waste products removed. The flow of blood through capillaries is relatively slow compared with that in arteries and veins and this allows adequate exchanges to take place.

14.4 BLOOD PRESSURE

The blood pressure is the hydrostatic force that the blood exerts against the wall of a blood vessel and that propels blood around the body. It is determined partly by cardiac output and partly by the peripheral resistance. As already stated, it is greater in arteries than in veins and is highest in the arteries when the heart contracts (systole). This is called the systolic pressure. When the heart contracts blood enters the arteries faster than it can leave through the capillaries so the vessels stretch under the pressure. This bulging of the arteries is the **pulse** that can be felt at a number of sites in the body. During diastole,

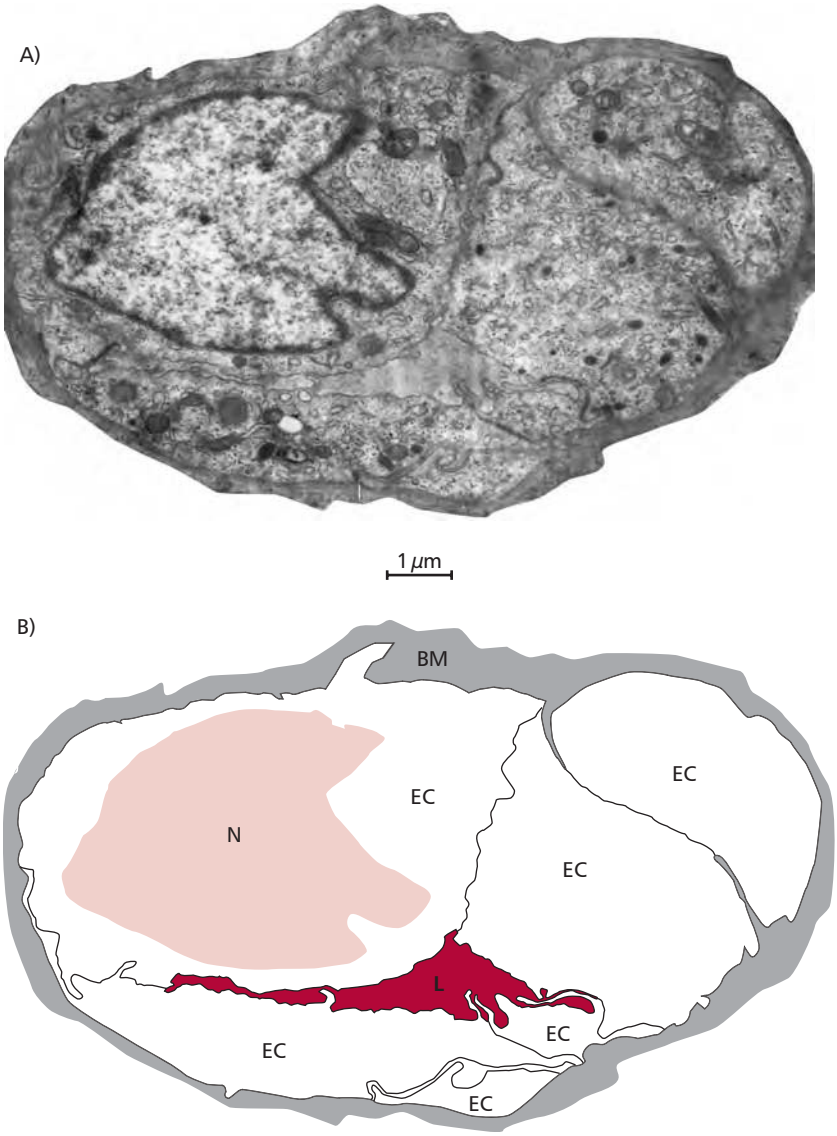

Figure 14.8 An electron micrograph of (A) a capillary and (B) its tracing. BM, basement membrane; EC, endothelial cell; L, lumen; N, nucleus of endothelial cell. Courtesy of Dr P. Kumar, School of Biology, Chemistry and Health Science, Manchester Metropolitan University, UK.

the artery walls snap back, but the heart contracts again before enough blood has flowed into the capillary bed to relieve the pressure. This is the peripheral resistance. As a result, there is still a substantial blood pressure even during diastole, the diastolic pressure, and so blood flows into the arterioles more or less continuously.

Typically, at rest the systolic pressure is about 120 mmHg and the diastolic pressure approximately 70 mmHg. Blood pressure can be measured using a manual sphygmomanometer combined with a stethoscope (*Figure 14.9 (A)* and *Box 14.1*) or with an automatic electronic one (*Figure 14.9 (B)*). Blood pressure is not constant because as demands on the circulatory system change, regulatory mechanisms ensure that adequate blood flow is maintained. Thus, during heavy exercise the arterioles in the working muscles dilate to allow increased delivery of oxygen to the muscles. This of course decreases the peripheral resistance, which, by itself, would cause a fall in blood pressure. However, the cardiac output is increased to counteract this effect.

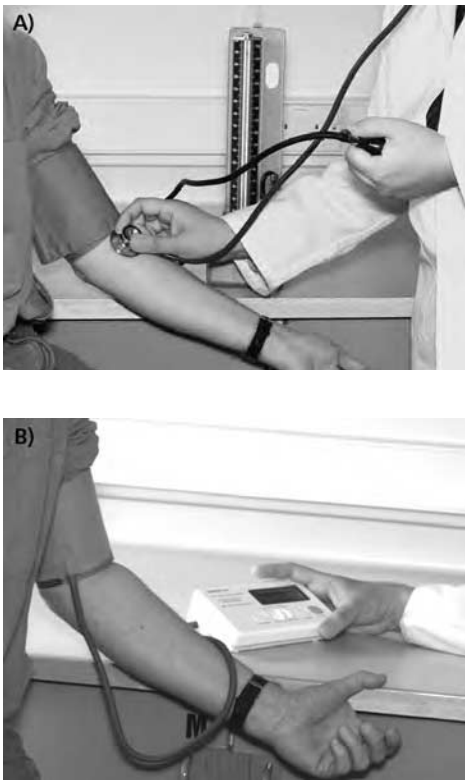

Figure 14.9 Measuring blood pressure using (A) a manual sphygmomanometer and a stethoscope (*Box 14.1*) and (B) electronic sphygmomanometer.

BOX 14.1 Measuring blood pressure

Traditionally, blood pressure is measured using a manual sphygmomanometer and stethoscope (Greek, *sphygmos*, pulse), as illustrated in *Figure 14.10 (A)–(D).* There are also electronic instruments that can be used (*Figure 14.9 (B)*). With a sphygmomanometer, an inflatable cuff connected to a pressure gauge, in this case a mercury manometer, is placed around the upper arm over the brachial artery and inflated (*Figure 14.10 (B)*). A stethoscope is placed on the skin above the brachial artery so that blood sounds may be heard. When the pressure in the cuff is greater than the systolic pressure the arteries are compressed and no brachial pulse can be heard. The cuff pressure is then slowly reduced and when it falls to that of the systolic pressure, clear sounds (**Korotkoff sounds**) can be heard due to the turbulence generated as the blood flows through the partially occluded artery (*Figure 14.10 (B)–(C)*). As the pressure further reduces the sounds become suddenly muffled and then disappear completely. The pressure at this point is generally taken as the diastolic pressure (*Figure 14.10 (D)*).

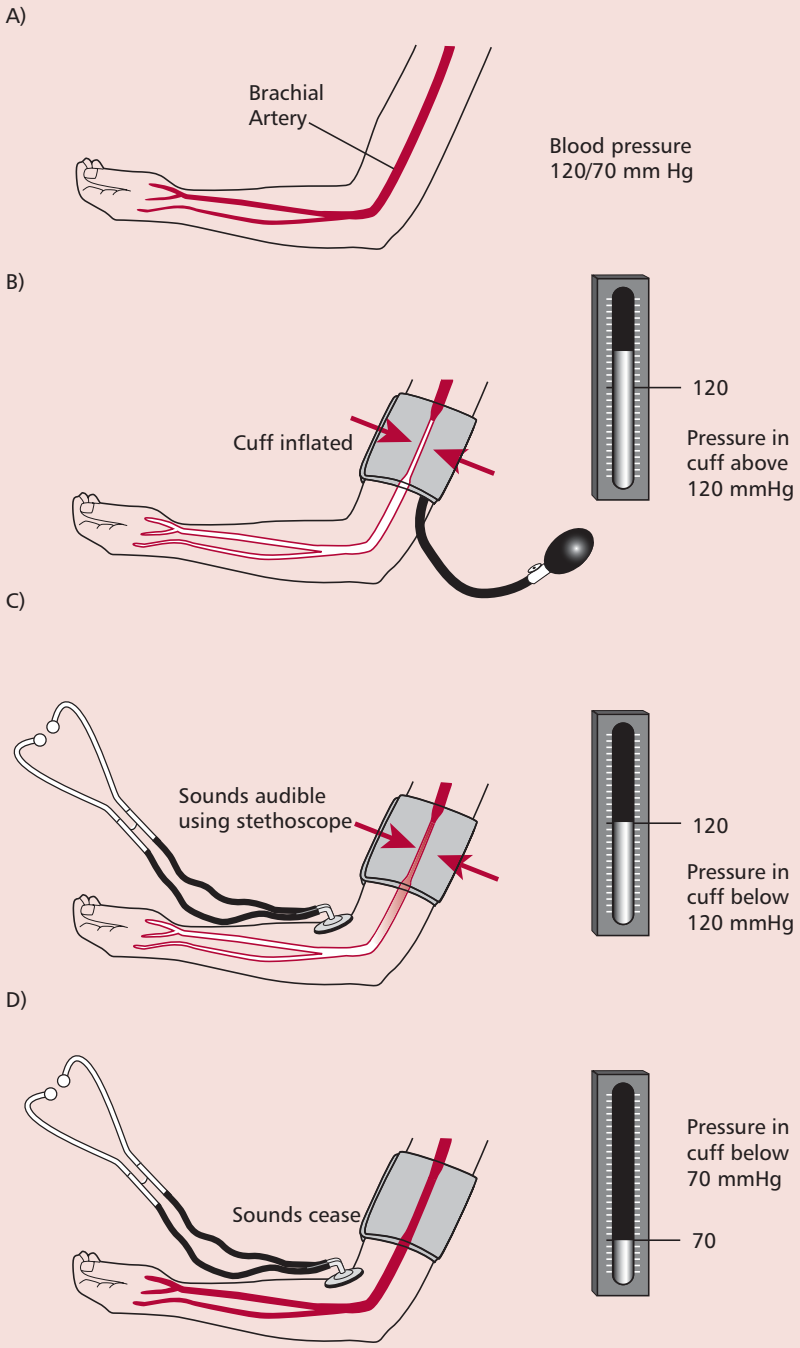

Figure 14.10 Panels (A) to (D) schematically show the use of a manual sphygmomanometer and stethoscope to measure blood pressure. See text for details.

14.5 INVESTIGATING CARDIAC FUNCTION IN HEALTH AND DISEASE

Clinicians need to be able to diagnose cardiovascular problems and to monitor their treatment. Obviously, noninvasive methods are to be preferred as far as possible for the comfort of the patient.

THE ELECTROCARDIOGRAM (ECG)

The spread of depolarization and repolarization through the muscle mass of the heart is accompanied by measurable electrical potentials, which may be recorded through electrodes placed on the skin. The record of these potentials is called an **electrocardiogram** (**ECG**) and represents the aggregate or resultant electrical activity associated with the action potentials of millions of individual cells, each of which has an amplitude and direction. Recording a patient's ECG is a way of investigating the electrical activity of the heart and when the pattern is abnormal it is invaluable in diagnosing a variety of heart complaints. The test is quick, simple and painless, and provides information on the heart rhythm and underlying cardiac morphology.

An ECG is recorded by placing electrodes, these days usually disposable, self-adhesive ones, on the chest and limbs. In practice the ECG is recorded simultaneously from six electrodes connected to the limbs and six to the chest that measure the direction and flow of electric currents during each heartbeat. The results are recorded (*Figure 14.11 (A)*), with each trace representing a particular 'view' of the heart's electrical activity; these views are referred to as leads. The spikes and troughs on the graph correspond to specific events in the cycle of a heartbeat and these are lettered alphabetically (*Figure 14.11 (B)*). Modern ECG instruments have a built-in computer that analyzes the recordings and produces a printout of the analysis.

In the normal ECG waveform, the first deflection is caused by atrial depolarization and is a low-amplitude slow deflection called a P wave. The following QRS complex results from ventricular depolarization, and as can be seen in *Figure 14.11 (B)*, it is sharper and larger in amplitude than the P wave. The T wave is another slow, low-amplitude wave resulting from ventricular repolarization. Atrial repolarization is not usually seen because it is low voltage and is hidden by the QRS complex. The PR interval is the time from the start of the P wave to the start of the QRS complex and represents the time taken for activation to pass from the SA node, through the atrium to the AV node. The QRS complex is a measure of the time associated with impulses passing through the His-Purkinje system and the subsequent contractions of the ventricles. The QT interval begins at the start of the QRS complex and finishes at the end of the T wave and this represents the time taken to depolarize and repolarize the ventricular myocardium. The ST segment is the time between the end of the QRS complex and the start of the T wave. At this point all the cells of the normal heart are depolarized.

The print out from an ECG examination can help the cardiologist to identify a number of heart problems including abnormal rhythms, inadequate blood supply to the heart and excessive thickening of the heart muscle (hypertrophy). For example, a heightened P wave indicates an enlarged atrium; a deeper than normal Q wave may indicate a myocardial infarction (*Section 14.14*) and a heightened R wave usually indicates a thickening of the ventricular wall. If the ST segment is raised above the horizontal it may indicate acute myocardial infarction or, if it is below the horizontal, it can imply high blood K^+ concentrations (*Chapter 8*) or cardiac ischemia (*Section 14.9*). Any deviation from the normal rate or sequence of the ECG is referred to as a cardiac arrhythmia. If the sinoatrial (SA) node is damaged the heart rate may slow to 40–50 beats per min and if damage occurs to both the SA and AV nodes it may fall to 20–40 beats per min and the patient will require a pacemaker.

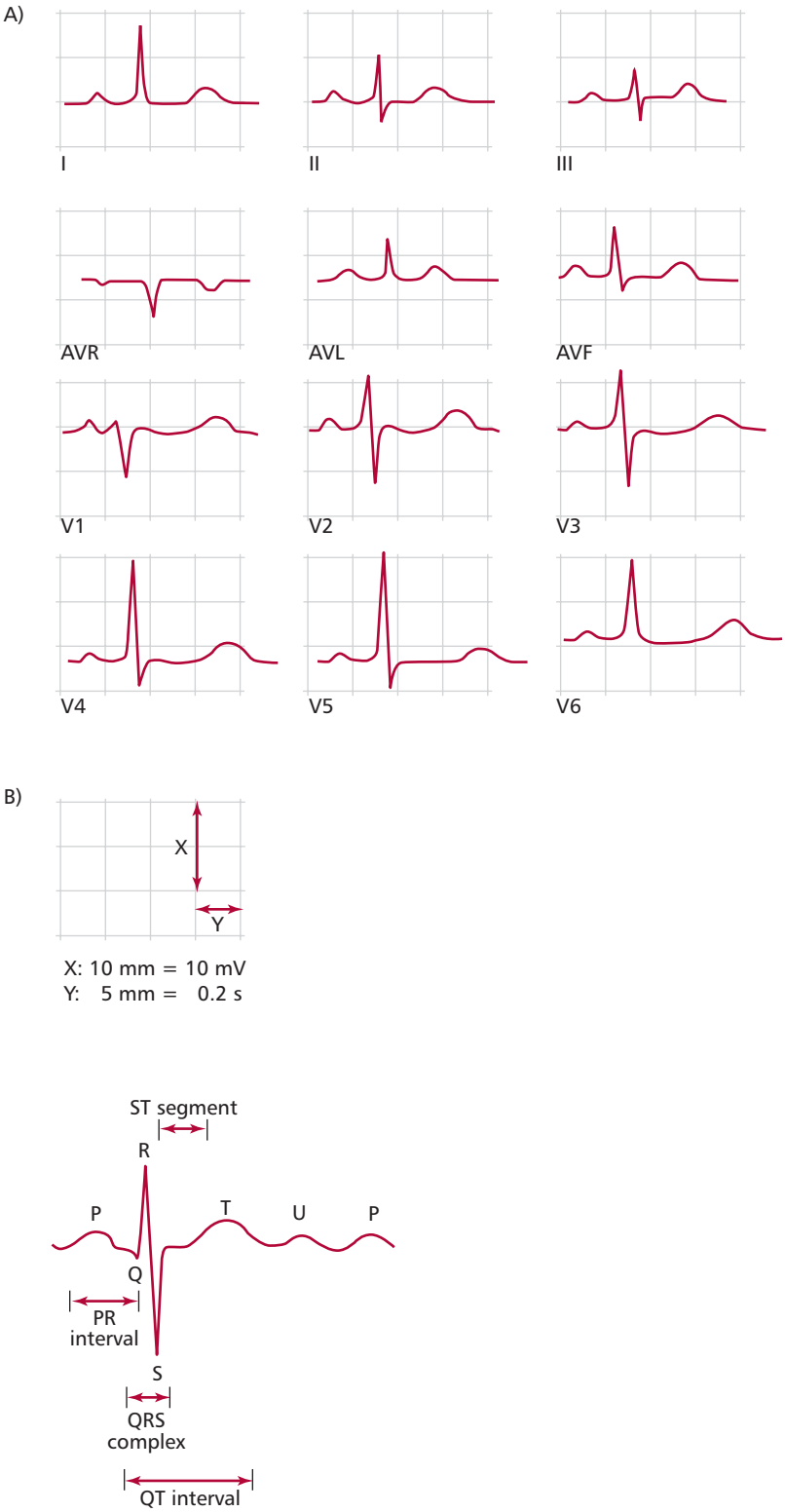

Figure 14.11 Electrocardiogram arising from (A) the 12 leads and (B) explanation of the parts of the wave observable in the graphs. See text for details.

In addition to the basic technique, the cardiac response may be recorded during exercise as the patient walks or runs on a treadmill and this can give further clinical information. In other situations, the ECG may be recorded over 24 h using a portable ECG machine to monitor intermittent arrhythmias (*Section 14.7*).

ECHOCARDIOGRAPHY

Echocardiography uses high-frequency ultrasound to map the heart and study its various functions. It is one of the most widely used diagnostic techniques, is painless and does not use X-rays and can indicate the extent of cardiac damage. Ultrasound waves from a probe at wavelengths of 1 mm or less (corresponding to frequencies of around 2 MHz) are generated in short bursts of a few microseconds. When the probe is pressed against the body the emitted pulses encounter the interfaces between the various body tissues. In crossing each interface some sound energy is reflected and is detected by a transducer in the probe and recorded as an echo. The time delays for the echoes to return are analyzed by a computer to produce a video picture on a screen with a moving image of the heart and blood vessels (*Figure 14.12*). This allows the cardiologist to see if the heart valves are functioning properly, for example whether they leak when closed and if blood is flowing normally. Abnormal connections between blood vessels of heart chambers are also revealed, as well as contractibility of muscle walls.

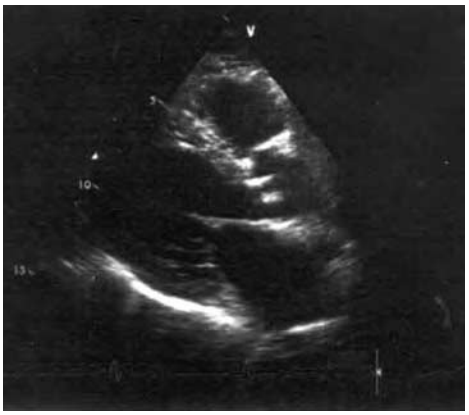

Figure 14.12 Echocardiography uses ultrasound waves that are reflected from the interfaces between the various tissues and analyzed to produce the type of image shown.

CARDIAC CATHETERIZATION (ANGIOGRAPHY)

Cardiac catheterization is a further method for investigating heart function and abnormalities. However, it is an invasive technique and involves a certain amount of discomfort for the patient. Under local anesthetic, a thin plastic tube is inserted into a vein or artery in an arm or leg (groin) and advanced into the major vessels and heart chambers. The catheter can be used to measure pressure, take a view of the inside of the heart or to take blood samples to measure oxygen and lactate concentrations. Dyes which are X-ray opaque can be injected into the catheter allowing moving X-ray pictures to be made that can show up anatomical abnormalities or abnormal blood flow. The coronary arteries can also be investigated by catheterization to check for coronary artery disease.

ANGIOGRAPHY AND RADIOGRAPHIC VISUALIZATION

A chest X-ray taken from the back also enables the size of the heart in relation to the lungs and the major blood vessels to be assessed. It may also reveal areas of calcium deposition, which are a sign of tissue damage and death.

EXERCISE STRESS TEST

The exercise stress test measures oxygen uptake, CO_2 production, heart rate and lung ventilation during progressively more strenuous treadmill or cycle ergometer exercises. It can detect lung and heart diseases in their early stage and also be used to assess fitness. Patients with lung disease stop exercising before achieving their maximal predicted heart rate. Also, their levels of ventilation are disproportionately high for a given oxygen uptake. Thus the more expensive and complicated equipment can differentiate breathlessness due to lung or to heart disease. For patients who cannot physically exercise, stress test measurements can be obtained using the dobutamine stress test. Dobutamine is an inotropic drug that increases the heart rate, hence giving increasing doses makes the heart work harder.

14.6 ENDOCARDITIS

Endocarditis is an inflammation of the endocardium, the interior lining of the heart and its valves. It most often results from bacterial infection that may originate from bacteria in the blood or as a result of heart surgery. The bacteria in the blood may enter from a skin wound or even from small injuries occurring when chewing food or brushing the teeth. Injecting drug users and patients with prolonged catheter use are also at risk. Abnormal or damaged valves are more susceptible than normal ones, and people with artificial valves are at risk. Bacteria and blood clots can accumulate on the valves (called **vegetation**) and can then break loose and block vessels elsewhere in the body causing strokes, heart attacks (*Section 14.14*) pulmonary embolisms or infecting the area where they lodge.

Acute infective endocarditis has a rapid onset and can be life threatening, unlike subacute infective endocarditis which develops slowly over weeks and months. In the acute form, the symptoms are usually the sudden onset of a high fever, a fast heart rate and tiredness. There can be extensive valve damage as well as the blood clot damage elsewhere in the body. Individuals may go into shock and be subject to renal failure. Prompt diagnosis and hospitalization are vital. The subacute form is associated with mild fever, tiredness, weight loss, sweating and a low erythrocyte count. However, because the symptoms of the subacute form are more vague, damage may occur before the condition is recognized; it is just as life threatening as the acute form.

Patients with heart valve abnormalities or artificial valves are more susceptible to endocarditis, as mentioned above. If they are about to undergo medical or dental procedures, they must inform their surgeon or dentist and be given antibiotics prior to invasive treatments. If endocarditis occurs and is identified, the treatment usually consists of at least two weeks of high-dose, intravenous antibiotics. However, heart surgery may also be necessary to repair or replace damaged valves.

14.7 ABNORMAL HEART RHYTHMS

The normal heart rate is between 60 and 100 beats per min but much lower rates may be encountered and are quite normal in young adults who are physically fit. As has been mentioned, the rate also responds to exercise or inactivity and also to pain and anger. An inappropriately fast heartbeat is called **tachycardia** and an abnormally low rate **bradycardia**. Abnormal rhythms are frequently encountered and can be regular or irregular. The contractions of the heart muscle fibers and therefore heartbeat is controlled by electrical discharges that flow through the heart along distinct pathways at controlled speeds (*Section 14.2* and *Figure 14.4*). If disturbances occur with the flow of the electrical discharge then **arrhythmias** in these contractions can occur. These range from the harmless to the life threatening. For example, minor arrhythmias can be caused by excessive alcohol consumption, smoking, stress or exercise. Thyroid hormones also affect the heart rate and an over- or under-active thyroid gland (*Chapter 7*) may affect the rate and rhythm of the heart. Some of the drugs used to treat lung disease or high blood pressure can have similar effects.

The commonest causes of arrhythmia are heart disease, especially coronary heart disease, heart failure or abnormal valve function. In many cases patients are aware of an abnormal heartbeat and this is referred to as **palpitations**. This awareness may be disturbing but there are many possible causes of arrhythmias and they are often not the result of an underlying disease.

However, when they are, it is the nature and severity of the disease that is more important than the arrhythmia itself. If brought to the attention of a clinician, he or she will want to know if they are fast or slow, regular or irregular, whether they make the person feel dizzy, light-headed or even lose consciousness, whether they occur at rest or during exercise and are they accompanied by a shortness of breath or chest pain.

An ECG is, of course, helpful in diagnosis but the arrhythmias may only occur over a short period. Consequently a portable monitor may be placed on the patient to record them over 24 h. The prognosis and treatment will depend on whether the arrhythmias start in the pacemaker, the atria or the ventricles. Most arrhythmias are harmless and do not interfere with the heart's pumping action. However, antiarrhythmic drugs are available if the patient is anxious or if the arrhythmias cause intolerable symptoms or pose a risk. Sometimes it is necessary to fit the patient with an artificial pacemaker that is programmed to replace the heart's own pacemaker. These are usually implanted surgically under the skin of the chest and are wired to the heart. Most commonly they are used to correct abnormally slow heart rates. Sometimes an externally applied electric shock to the heart, called cardioversion, electroversion, or defibrillation, can correct an abnormal arrhythmia. Arrhythmias caused by coronary artery disease may be controlled by drugs, pacemakers or by surgery (*see below*). After a coronary infarction, some people have life-threatening episodes of ventricular tachycardia that may be triggered in an injured area of heart muscle that may have to be removed during open heart surgery.

ATRIAL FIBRILLATION AND FLUTTER

Atrial fibrillation and flutter are rapid electrical discharges which make the atria contract rapidly but each contraction may not conduct to the ventricles. This causes the ventricles to contract less efficiently and irregularly, producing a condition that may be sporadic or persistent. During the fibrillation or flutter, the atrial walls simply quiver and blood is not pumped into the ventricles properly. The consequence is that inadequate amounts of blood are pumped from the heart, blood pressure falls and heart failure may occur. The diminished pumping ability may make the patient feel weak, faint and short of breath. Sometimes, especially with elderly patients, there is chest pain and heart failure. If the atria do not contract completely, blood may stagnate in the atria and clot. If pieces of clot or emboli break off they may move and block an artery elsewhere in the body. If this is in the brain it may cause an embolism or stroke (*Section 14.16*).

The treatment for atrial fibrillation is to correct the disorder that causes the abnormal rhythm, restoring it to normal, and to slow the rate at which the ventricles contract so as to improve the pumping efficiency. The latter can often be achieved with digoxin but a β-blocker, such as propanolol, or other drugs may also be required. Frequently a normal rhythm has to be restored by antiarrhythmic drugs or cardioversion. In these conditions blood can pool in the ventricles and clot, hence anticoagulant drugs may be used when atrial fibrillation is present.

VENTRICULAR TACHYCARDIA

Sustained ventricular tachycardia, with a ventricular rate of at least 120 beats per min, occurs in various heart diseases that damage the ventricles. Most often it occurs over weeks or months after a heart attack (*Margin Note 14.2*). It is characterized by palpitations and will usually require emergency treatment because the blood pressure falls and heart failure may follow. Cardioversion is needed immediately.

Margin Note 14.2 Heart attack or myocardial infarction

A heart attack is a **myocardial infarction**. It is a severe medical emergency during which some or all of the blood supply to the heart muscle through the coronary arteries is cut off. If this continues for more than a few minutes the heart tissue dies with serious clinical consequences or death of the individual. The term heart attack is sometimes used loosely for other heart conditions: strictly it should only be applied to myocardial infarctions.

VENTRICULAR FIBRILLATION

Ventricular fibrillation is a form of cardiac arrest. It is similar to atrial fibrillation, but the prognosis is very serious and potentially fatal if not treated immediately. It is the product of an uncoordinated series of rapid but ineffective contractions throughout the ventricles. These, in turn, arise from multiple chaotic electrical impulses. Its commonest cause is an insufficient flow of blood to the heart muscle because of coronary heart disease or a heart attack. Given that blood is not pumped from the heart, it can lead to unconsciousness in seconds and, if untreated, the patient usually has convulsions and develops irreversible brain damage because of oxygen starvation. Ventricular fibrillation needs to be treated as a medical emergency. Cardiopulmonary resuscitation must be started within the minimum time possible, usually three minutes. This should be followed by cardioversion also as soon as possible. Subsequently drugs are needed to restore and maintain the normal heart rhythm.

HEART BLOCK

Heart block describes a delay in electrical conduction through the AV node. There are various degrees of seriousness; the least may not require treatment but the most serious may require the fitting of an artificial pacemaker. First-degree heart block is common in well-trained athletes, teenagers, and young adults, but it may also be caused by rheumatic fever (*Box 14.2*) or by certain drugs. At the other extreme in third-degree heart block, electrical impulses from the atria to the ventricles are completely blocked. The ventricles beat very slowly and the pumping ability of the heart is compromized. Fainting, dizziness and sudden heart failure are common.

BOX 14.2 Rheumatic fever

Rheumatic fever occurs mostly in children and young adults and is caused by infection with group A Streptococci. It is now much less common in the developed countries than was previously the case: for example 10% of children in the 1920s compared with about 0.01% now. This is mainly due to the use of antibiotics (*Chapter 3*). Rheumatic fever is thought to result from an autoimmune reaction triggered by the bacteria rather than any bacterial toxin. The skin, joints and the central nervous system and all the layers of the heart may be affected. The disease presents with fever, joint pains, malaise, loss of appetite and a characteristic fleeting polyarthritis affecting the larger joints, such as knee, elbows, ankles, which become swollen, red and tender. Effects on the heart include new or changed murmurs, cardiac enlargement or failure and pericardial effusion.

INVESTIGATION

There will usually be nonspecific indicators of inflammation, such as the erythrocyte sedimentation rate and C-reactive protein (*Chapter 13*), both of which may be elevated. Throat swabs should be cultured for group A *Streptococcus* and there may be serological changes indicative of a recent streptococcal infection.

TREATMENT

If patients have fever, active arthritis or active carditis, they should be completely bed rested. Residual streptococcal infection should be eradicated with a single intramuscular injection of benzathine penicillin or four daily oral doses of phenoxymethyl penicillin for a week. Salicylate and steroids may also be given if carditis is present. Recurrence is common. More than half of those with acute rheumatic fever with **carditis**, a general inflammation of the heart, will develop conditions after 10–20 years that affect the mitral and aortic valves.

14.8 CARDIAC FAILURE

Cardiac failure is the inability of the heart to maintain an adequate cardiac output, that is pump a volume of blood per minute sufficient to meet the demands of the body. The heart does not stop beating as is often thought, but its diminished ability imposes severe demands. It is a serious condition but commoner in older people. The incidence is about one in a hundred for individuals over 65 years, and irrespective of the cause, the prognosis is poor. Approximately 50% of patients will die within two years, although new drug treatments are improving mortality and morbidity.

There are many possible causes of heart failure and, indeed, any disease that affects the heart and circulatory system can lead to heart failure. The commonest of these is coronary artery disease that limits the flow of blood, and hence oxygen and nutrients to the heart muscle and can lead to heart attack. Bacterial and viral infections (*Chapter 2*) can also damage the heart muscle, as can diabetes, an overactive thyroid (*Chapter 7*) and obesity (*Chapter 10*). Obstruction of the heart valves or heart valves that leak increases its workload and this eventually weakens the contractions. Similarly, a narrowed aortic valve means that the heart has to work harder because it has to force blood through a smaller exit, again imposing an extra metabolic burden. High blood pressure (*Section 14.17*) also means that the heart has to work too hard. Diseases that affect electrical conduction in the heart can result in an abnormal heartbeat that reduces the pumping efficiency. Other causes are also known. Although the increased workload initially results in enlargement, or hypertrophy, of the heart muscle so that it can contract with greater force, eventually the heart malfunctions making the heart failure worse.

Heart failure results in tiredness and weakness during physical activities because the skeletal muscles are starved of blood. The disease may be on one side of the heart or the other, but the condition usually affects the whole heart. Nevertheless, there are characteristic symptoms depending on which side is affected. Thus right-sided disease tends to cause a build-up of blood flowing into the right side of the heart, which leads to swelling of the feet, ankles, legs and liver. In contrast, left-sided disease increases fluid in the lungs (pulmonary edema) causing, in turn, shortness of breath. At first this is only experienced during exertion but it gradually increases in severity so that the breathlessness occurs even at rest. If this happens at night, the patient may wake up gasping for breath and may find it better to sleep in a sitting position. Cardiac failure gradually worsens with time if the underlying disease is not treated, although patients may continue to live for many years.

INVESTIGATION

The symptoms described above are usually sufficient for an initial diagnosis of heart failure, which would be confirmed by a weak and rapid pulse, lowered blood pressure and abnormal heart sounds. However, its underlying cause must also be identified. In many cases taking a clinical history and examining the patients will be sufficient. General diagnostic tests include chest X-ray to demonstrate an enlarged heart and fluid accumulation in the lungs, ECG, echocardiography, blood tests, for example full blood count, liver function, urea and electrolytes (*Chapters 8, 11* and *13*), and analysis of cardiac enzymes in acute heart failure to diagnose myocardial infarction (*Box 14.4*) will then usually be carried out. Functional tests may also be performed, including exercise testing, ECG monitoring and angiography at rest and under stress.

TREATMENT

The treatment for heart failure is focused on relieving the symptoms, retarding the progression of the disease and aiming to improve the chances

Margin Note 14.3 ACE inhibitors

Angiotensin converting enzyme (ACE) inhibitors are used to treat chronic heart failure and high blood pressure. The drugs block the conversion of angiotensin I to angiotensin II which is both a vasoconstrictor and the most important stimulus for the release of aldosterone (*Chapter 8*) from the adrenal cortex. Angiotensin converting enzyme inhibitors are therefore effective antihypertensives. Their effect is to lower the systemic vascular resistance, venous pressure and reduce levels of circulating catecholamines, thus improving myocardial performance. The first ACE inhibitor used was captopril but a number of other drugs are now available. The way in which they work is well understood. If the flow of blood through the kidneys is low they release renin which converts angiotensinogen to angiotensin I. Subsequently ACE converts angiotensin I into angiotensin II. Among its other effects on blood vessels, angiotensin II causes the division of heart muscle cells and fibrosis that can make heart failure more serious in the long run. Giving ACE inhibitors reduces or eliminates these effects. Angiotensin converting enzyme inhibitors are used routinely postmyocardial infarction, to maintain good cardiac action and prevent heart failure.

of survival. This means that any factor aggravating the failure should be identified and treated. The precise cause of failure should be identified and if possible corrected. Patients should be nursed in a comfortable, upright position.

CHRONIC HEART FAILURE

In chronic heart failure, the circulation at rest is adequate but there is an inadequate reserve to pursue daily activities. Its treatment depends upon the underlying disease to be dealt with. For example, heart surgery can correct narrowed or leaking heart valves, and bypass surgery can correct blocked coronary arteries. If the disease is caused by an infection the condition may be improved by antibiotics without surgery. Additionally, there are many things a patient can be advised to do to help the condition, including giving up smoking, eating less salt, reducing excessive weight and controlling alcohol consumption.

The best treatment for heart failure is to prevent it happening in the first place or by reversing its underlying cause as soon as possible. Nevertheless, there is still much that can be done. For example, if reducing the salt intake does not lower fluid retention then diuretics may be prescribed. A reduction in the amount of body fluid reduces the volume of blood to be pumped and so alleviates the strain on the heart. Digoxin may be given to increase the power of each heart contraction and will slow a rate that is too rapid. Vasodilatory drugs may be prescribed to expand blood vessels, lowering the blood pressure. Some of the older drugs dilate arteries more than veins or *vice versa*. However, the ACE inhibitors (angiotensin converting enzyme inhibitors (*Margin Note 14.3*)) dilate both arteries and veins are, perhaps, the most commonly used. These improve the symptoms and prolong life. A heart transplant is perhaps the ultimate possibility but there are never enough good hearts to go round!

ACUTE HEART FAILURE

In acute heart failure, the hemodynamic derangement is so severe that it results in symptoms even at rest. If fluid suddenly accumulates in the lungs the condition is known as acute pulmonary edema and the person has to gasp for breath and emergency treatment is required. Oxygen is given by a facemask and together with intravenous diuretics may result in a rapid and dramatic improvement. Glyceryltrinitrate may be given intravenously or placed under the tongue and this leads to dilation of the veins, reducing the amount of blood flowing through the lungs. It may be necessary to insert a tube into the patient's airway to help breathing. The treatment for acute heart failure is essentially as for the chronic condition described above.

14.9 ISCHEMIC HEART DISEASE

Myocardial ischemia, meaning a lack of oxygen to the myocardium, is the result of an imbalance between the demand of the myocardium for oxygen

and the amount supplied. There are several possible causes of this condition. Firstly, the blood flow through the coronary arteries may be reduced because of mechanical blockages, such as atheroma (plaque), thrombosis (a clot), spasm, ostial stenosis, arteritis or any sort of blockage (an embolism) due to, for example, tumor cells or an air bubble. Secondly, a decreased flow of oxygenated blood to the myocardium because of anemia (*Chapter 13*), **hypotension** (low blood pressure) or carbon monoxide poisoning (*Chapter 12*). Thirdly, an increased demand for oxygen caused by exercise or myocardial hypertrophy that requires an increase in cardiac output. Note that in the last two scenarios, the coronary arteries may be healthy. The commonest cause of ischemic heart disease is coronary atheroma, which obstructs the flow of blood through the coronary arteries.

14.10 CARDIOMYOPATHIES

Cardiomyopathy is a progressive disorder that impairs the function of the ventricular muscle walls. It may come about as a result of a number of diseases or may have no identifiable cause.

DILATED CONGESTIVE CARDIOMYOPATHY

Dilated congestive cardiomyopathy is not a single condition but a group of heart disorders in which the ventricles have enlarged but are still not able to pump enough blood to meet the needs of the body. Heart failure may result. The commonest cause of the defect in developed countries is widespread coronary artery disease, which leads to an inadequate blood supply to the heart muscle. This causes damage and the undamaged muscle then stretches in compensation. If this is inadequate to meet body needs, then dilated congestive cardiomyopathy develops. Its symptoms are shortness of breath on exertion and a rapid onset of tiredness due to the weakening of the heart's pumping action. The heart rate speeds up so blood pressure is normal or low, but fluid is retained in the legs, abdomen and lungs. Enlargement of the heart can mean that the valves do not close properly, leading to leakage, and this improper closing may be heard as murmurs using a stethoscope. The stretching may also increase the potential for arrhythmias. Electrocardiography or magnetic resonance imaging (MRI, *see Chapter 18*) may be used to confirm the initial diagnosis.

About 70% of people with the condition die within five years from the onset of symptoms and the prognosis declines as the heart walls become thinner with reduced contractibility. Men tend to survive only half as long as women and blacks half as long as whites. In about half of the cases there is sudden death. Treating the underlying cause, for example reducing alcohol abuse can prolong life. When there is coronary artery disease there may be angina (*Section 14.13*), which is treated with glyceryltrinitrate, β-blockers or calcium channel blockers. There may also be pooling of blood in the swollen heart that can cause clots to form and therefore the patient is given anticoagulants (*Chapter 13* and *Box 14.3*).

BOX 14.3 Anticoagulant therapy

Venous thromboembolism is a common problem after surgery, especially in patients who are elderly, have malignancies or have a previous history of thrombosis. There is also a high incidence in patients confined to bed after trauma or a variety of heart diseases. Its prevention and treatment includes the use of anticoagulants, such as heparin, warfarin and aspirin.

HEPARIN

Heparin is a mixture of polysaccharides prepared from pig gastric mucosa. It potentiates the formation of irreversible complexes between antithrombin III (AT-III), a potent inhibitor of coagulation and several coagulation factors, for example thrombin, and factors XIIa, XIa, Xa, IXa and VIIa (*Chapter 13*). Its injection has an immediate effect on blood coagulation, but its action is quite short-lived. Bleeding complications of heparin treatment occasionally occur and are treated by giving the positively charged protein, protamine. Low M_r heparins, produced by chemical degradation of standard heparin, have somewhat different properties. They have a longer half-life than heparin and so can be given as a once or twice daily subcutaneous injection (preferred) or as a continuous infusion or six-hourly injection, as is required with regular heparin. They also seem to cause less inhibition of platelet function and thus there is a reduced risk of causing bleeding.

Myocarditis, which is an acute inflammation of the heart muscle, occurs as a result of a viral infection, most often coxsackie virus B, hence it is sometimes called viral cardiomyopathy. It may weaken the heart muscle, producing a condition similar to dilated congestive cardiomyopathy. A number of chronic hormonal disorders (*Chapter 7*) including diabetes and thyroid disease can also produce cardiomyopathy, as can prolonged alcohol abuse (*Chapter 12*).

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is a group of conditions in which the ventricular walls thicken. It may occur as a birth defect, in adults with acromegaly or in people with pheochromocytoma, a tumor of the adrenal gland (*Chapter 7*). The heart becomes thicker and stiffer than normal and more resistant to filling with blood from the lungs, leading to a backpressure on the lung veins causing a pulmonary edema. The patient therefore becomes chronically short of breath, with symptoms that include faintness, chest pains and palpitations brought on by irregular heartbeats; the heart sounds through a stethoscope are usually characteristic. Younger patients tended to die suddenly of hypertrophic cardiomyopathy but with better and earlier diagnosis and drug therapies this is now less of a problem.

The main treatments are administering β-blockers and calcium channel blockers. Surgery to remove some of the heart muscle may improve the outflow of blood but this is only undertaken when the patient is incapacitated despite drug therapy.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy is the least common of the cardiomyopathies. It has many features in common with hypertrophic cardiomyopathy. The replacement of heart muscle tissue with scar tissue or its infiltration with abnormal material, such as white blood cells, amyloidosis and sarcoidosis (*Margin Notes 14.4* and *14.5*) can all lead to the condition, although its cause is frequently unknown. The major symptoms are shortness of breath and an edematous swelling of the tissues. About 70% of individuals with the disease die within about five years of the symptoms commencing. In most cases therapy is unsatisfactory. The use of diuretics, which are normally given to treat heart failure and reduce the amount of fluid accumulating in the tissues, may actually reduce the amount of blood entering the heart and worsen the condition.

Margin Note 14.4 Amyloidosis 

There are several forms of this disease in which amyloid, an unusual form of protein that is not normally present in the body, accumulates in various tissues. One type of amyloidosis affects the heart and is associated with normal aging, but what causes the build up of the amyloid protein is not known with any certainty. The condition may not need treatment and, in any case, treatments are not usually very successful. A patient with heart problems may be given a heart transplant, but the transplanted organ itself may be affected later.

ORAL ANTICOAGULANTS

Oral anticoagulants work by interfering with vitamin K metabolism (*Chapters 10* and *13*). Vitamin K is a cofactor required for the formation of γ-carboxyglutamate residues in prothrombin. The coumarin anticoagulant, warfarin, is most frequently used because of its low incidence of side effects other than promoting bleeding. However, many drugs interact with warfarin. Tricyclic antidepressants, clofibrate, aspirin, and alcohol increase the anticoagulant effect of warfarin, while other drugs such as rifampicin and barbiturates decrease this effect. Contraindications include pregnancy, peptic ulcers, severe liver and renal disease and preexisting hemostatic disease.

ASPIRIN

Low doses of aspirin inhibits platelet aggregation by blocking cyclooxygenase activity irreversibly thus altering the balance between the complex fatty acids, prostacyclin and thromboxane A_2 which is required for platelet activation. Clinical trials have confirmed that long-term treatment with aspirin greatly reduces the risk of myocardial infarction (and death) in patients with angina.

14.11 HEART VALVE DISORDERS

Major problems encountered with heart valves include an improper closing of the valves leading to leakage (**regurgitation**) or failure to open fully (**stenosis**). These conditions interfere with the heart's capacity to pump blood. If the mitral valve leaks, then regurgitation occurs each time the ventricle contracts. As blood is pumped into the aorta some leaks back into the left atrium increasing the volume and the pressure in that compartment. This, in turn, increases the blood pressure in the vessels leading from the lungs to the heart resulting in a pulmonary edema. Rheumatic fever was once the commonest cause of mitral valve regurgitation (*Box 14.2*) and heart attacks that damage the structures supporting the valve is its commonest cause. However, in countries where there is poor preventive medicine, rheumatic fever is still common. Repair or replacement of the valve is required if the regurgitation is severe.

The aortic valve may also become leaky, and the most common causes were rheumatic fever and syphilis but this is now rare because of the use of antibiotics. In contrast, aortic valve stenosis is mainly a disease of the elderly (over 60 years) and is the result of the valve becoming calcified. The left ventricle wall thickens as the heart strains to pump sufficient blood through the narrow opening and the enlarged heart muscle requires extra oxygen and nutrients from the coronary arteries. Eventually the output of blood from the heart becomes insufficient for the body's needs and the resulting heart failure causes shortness of breath and fatigue. The treatment is to replace the aortic valve, preferably before the left ventricle becomes irreparably damaged.

Problems can also occur with the tricuspid valve. However, regurgitation usually requires little treatment. Stenosis of the tricuspid valve is rare, again, because the damage was mainly associated with rheumatic fever.

Margin Note 14.5 Sarcoidosis

In sarcoidosis, abnormal collections of inflammatory cells called granulomas, commonly appear in lymph nodes, lungs, liver, eyes and skin, but can also occur in the spleen, bones, joints, skeletal muscles, heart and nervous system. The cause of the disease is unknown but seems to result from an abnormal response of the immune system. In some instances there are no symptoms, while in others there can be fever, weight loss and aching joints. Often the condition clears up spontaneously and the granulomas may eventually disappear or become scar tissue. In other cases, there may be permanent damage, such as lung scarring. Most people do not need treatment but corticosteroids may be used to suppress severe symptoms, such as shortness of breath or severe skin lesions.

14.12 HEART TUMORS

Heart tumors (*Chapter 17*) may be asymptomatic or precipitate life-threatening crises, such as sudden heart failure, sudden onset of irregular heartbeat or a sudden drop in blood pressure caused by bleeding into the pericardium. They are relatively uncommon and are difficult to diagnose.

14.13 ATHEROSCLEROSIS OR ARTERIOSCLEROSIS

Atherosclerosis or **arteriosclerosis** refers to the simultaneous development of an **atheroma** in an artery and the sclerosis of its wall. An atheroma (from the Greek word for porridge) is a hard yellow plaque that gradually builds up on the inside of medium-sized arteries. The plaque consists of a necrotic (dead) core rich in cholesterol, surrounded by fibrous tissue. Sclerosis (from the Greek word for hard) means an abnormal hardening or fibrosis, which is the formation of excess fibrous material within a tissue. Sufferers may experience a sudden heart attack or stroke, but this belies the fact that in most cases the arteries of the victims have gradually become blocked by atherosclerosis.

Initially atheromatous plaques start at the site in an artery where the smooth muscle layer has thickened and been infiltrated with fibrous connective tissue (fibrosis) when cholesterol and other lipids have been deposited, and may become calcified. This condition is commonly referred to as hardening of the arteries. During the course of the disease, the affected artery expands as the plaque becomes larger so as to allow a more or less normal flow of blood. However, as the plaque increases in size this becomes less possible and the lumen of the artery becomes narrower and a ballooning of the arterial wall causes it to weaken. Also, there is more likelihood of an embolus becoming trapped in the narrowed artery making the blockage worse. Healthy arteries are lined with endothelial cells, but the rough lining of a plaque-damaged artery seems to encourage the adhesion of platelets which means they are common sites for the formation of a clot (thrombus).

The progresses of atheromatous disease means the arteries become increasingly occluded and the threat of a heart attack or stroke increases. Some patients may receive warning in the form of chest pains if, for example, a coronary artery is partially blocked. The condition known as angina pectoris (*see below*) is a signal that the heart is not receiving sufficient oxygen. This is most likely to occur when the heart is working hard because of physical or emotional stress. However, for many people there are no symptoms and they are completely unaware of their condition until the catastrophic event occurs. Some individuals have an inherited tendency to develop hypertension (*Section 14.17*), which promotes atherosclerosis and increases the risk of heart attack or stroke and can cause chronic damage to the endothelium lining the arteries promoting atherosclerosis.

ANGINA

Angina pectoris is caused by myocardial ischemia. It presents as a crushing or squeezing pain in the chest and the discomfort may radiate into the neck, jaw, arms (especially the left) and sometimes into the back. There may also be shortness of breath, abdominal pain, nausea and dizziness. Myocardial oxygen demand relates to the heart rate, left ventricular contractility and systolic wall stress. The demand for oxygen is increased by exercise, hypertension (*Section 14.17*) and left ventricular dilation, which may happen in chronic heart failure.

Several types of angina are recognized. Stable angina occurs when atherosclerotic plaques block one or more of the coronary arteries. Under resting conditions, cardiac oxygen demand is quite low and is satisfied even by the diminished blood flow. However, when exertion or emotional stresses increase this oxygen demand, ischemia develops on the inner part of the myocardial wall. However, the response to exercise is variable: some patients may have excellent exercise tolerance one day and then develop angina with minimal exertion the next. In addition to causing pain, the ischemia causes a decline in the output of ATP and creatine phosphate and hence contractility is

impaired. Stable angina is normally relieved by a short rest or by administering glyceryltrinitrate. The latter dilates the arteries, increasing blood, and therefore oxygen, supplies to the muscle leading to less pain.

Variant angina is an intensely painful, transient spasm caused by a blockage of one of the coronary arteries. It is relatively uncommon, but can occur at rest. It is exacerbated by smoking and by cocaine use. About one-third of patients show no evidence of atherosclerotic lesions.

Ischemic heart disease and stable angina can be distinguished from other conditions that cause chest pain on the basis of their characteristic symptoms and by a number of types of diagnostic tests, for example the ECG, exercise stress test and by using coronary angiography to obtain a direct radiographic visualization, as described earlier.

The management of angina is designed to control the symptoms and reduce any underlying risk factors. The drugs used include the nitrovasodilators, for example glyceryltrinitrate, β-adrenoceptor blockers, calcium channel antagonists, as well as drugs that inhibit platelet aggregation and thrombosis (*Margin Note 14.6* and *Chapter 13*). In the case of stable angina, mortality is 2 to 4% a year if only one coronary artery is diseased but increases with the number of diseased arteries.

The other main variant of angina is the so-called unstable angina, which is a dangerous condition, often heralding an impending myocardial infarction (*Section 14.14*). In general, the symptoms resemble those of stable angina but are more intense and persistent, often lasting 30 min, and the pain is often resistant to glyceryltrinitrate treatment. The attacks may be frequent, becoming progressively more severe and prolonged, may be brought on by minimal exertion (or even during sleep) or may occur several days after a myocardial infarction. The episodes are preceded by a fall in coronary blood flow, which is thought to be the result of the periodic development of coronary thrombosis and vasoconstriction. These are triggered by coronary arterial disease. The thrombosis may be promoted by the turbulent blood flow associated with atherosclerotic plaques: there may also be damage to the endothelial lining of the blood vessels.

An ECG is taken to help in the diagnosis but, in addition, serum levels of C-reactive protein and amyloid-A protein may be increased; these are classic markers of inflammation. Unstable angina is a medical emergency and treatment usually begins with aggressive drug therapy to control the symptoms and prevent further episodes, and to try to reverse coronary vasospasm. Platelet glycoproteins IIIA and IIb (Tirofiban and ReoPro) are now used in unstable angina to stabilize the clot in the narrowed coronary artery, which is causing the pain, prior to angiography and possibly angioplasty and stenting. Angioplasty is a procedure similar to angiography (*Section 14.5*) but the catheter delivers a small inflatable balloon to the narrowed portion of the coronary artery. When the balloon is inflated it opens the restricted section of the artery. Stents are very small, coated spring-like structures that are deployed, by cardiac catheters into the narrowed section following angioplasty. They act like miniature struts to maintain the opening of the vessel.

Urgent revascularization needs to be considered for patients at high risk, or unsuitable for angioplasty/stenting due to significant coronary arterial disease. In a coronary artery bypass grafting a length of healthy 'surplus' blood vessel, such as the saphenous vein from the leg (*Figure 14.13*), is obtained and pieces of it are inserted between the aorta and the coronary arteries distal to any stenosis (narrowing). The left internal mammary artery may also be used. A bypass improves survival in patients with severe atherosclerotic disease in all the major coronary arteries.

Margin Note 14.6 Thrombolysis

Thrombolysis is the dissolution of a blood clot blocking an artery. Fibrinolysis occurs when the inactive zymogen, plasminogen, is converted to the fibrin-dissolving active enzyme plasmin by endothelium-derived **tissue** plasminogen activator (t-PA). Plasmin also inactivates fibrinogen and coagulation factors V and VIII (*Chapter 13*).

Streptokinase is a bacterial protein that binds to a molecule of plasminogen. The resulting complex cleaves other molecules of plasminogen to produce more plasmin, which dissolves the fibrin. It can cause hemorrhage and also it can only be used once since it may cause the patient to produce antibodies with the danger of an allergic reaction. Tissue plasminogen activator is now produced commercially by recombinant DNA methods and marketed as tenecteplase and alteplase. Tenecteplase is now the thrombolytic of choice. It binds to fibrin and this has a greater effect on clot-associated plasminogen than on plasma plasminogen. It has the advantage that it is cleared from the plasma in a few minutes and is nonantigenic. Urokinase (u-PA) is another endogenous plasminogen activator with properties similar to those of t-PA.

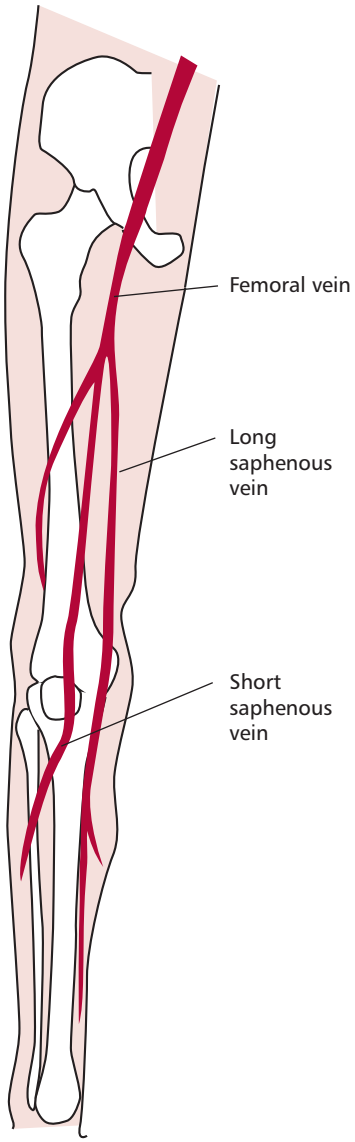

Figure 14.13 Schematic to show the saphenous veins of the leg.

CHOLESTEROL AND LIPOPROTEINS

Aside from any inherited tendency to develop hypertension (*Section 14.17*), there are a number of nongenetic factors that correlate with an increased risk of cardiovascular disease. These include smoking, lack of exercise, a diet containing too much and inappropriate fat types (*Chapter 10*); all lead to an abnormal concentration of cholesterol in the blood. Homocysteine is known to be raised in certain genetic conditions and coronary heart disease and is suspected to have a role in increasing cholesterol levels. Homocysteine concentrations can be lowered by treatments with folate and vitamin B_{12} with a subsequent reduction in blood cholesterol.

Cholesterol is essential because it forms part of the plasma membrane of cells and is used in the biosynthesis of bile salts and steroid hormones. However, atherosclerosis is largely due to problems with cholesterol. The body can synthesize it but it is also obtained from the diet. Cholesterol is practically insoluble in plasma and, like triacylglycerols, is transported in the blood in **lipoprotein particles**. It is an imbalance between the different types of lipoprotein particles that leads to clinical problems.

Plasma lipoprotein particles consist of a core of triacylglycerols and cholesterol esters surrounded by phospholipids, proteins and free cholesterol (*Figure 14.14*). They are classified by their densities, the greater the proportion of triacylglycerol the lower the density (*Table 14.1*). There are several different types of lipoproteins in lipoprotein particles, called apolipoprotein-A and –B, -C, -D and -E, usually abbreviated to apoA, apoB, apoC, apoD and apoE.

The transport of cholesterol round the body is a complicated process (*Figure 14.15*). There is some cholesterol in the chylomicrons derived from the diet, but the liver exports the cholesterol obtained from the diet or synthesized, together with triacylglycerols it synthesized from dietary carbohydrate,

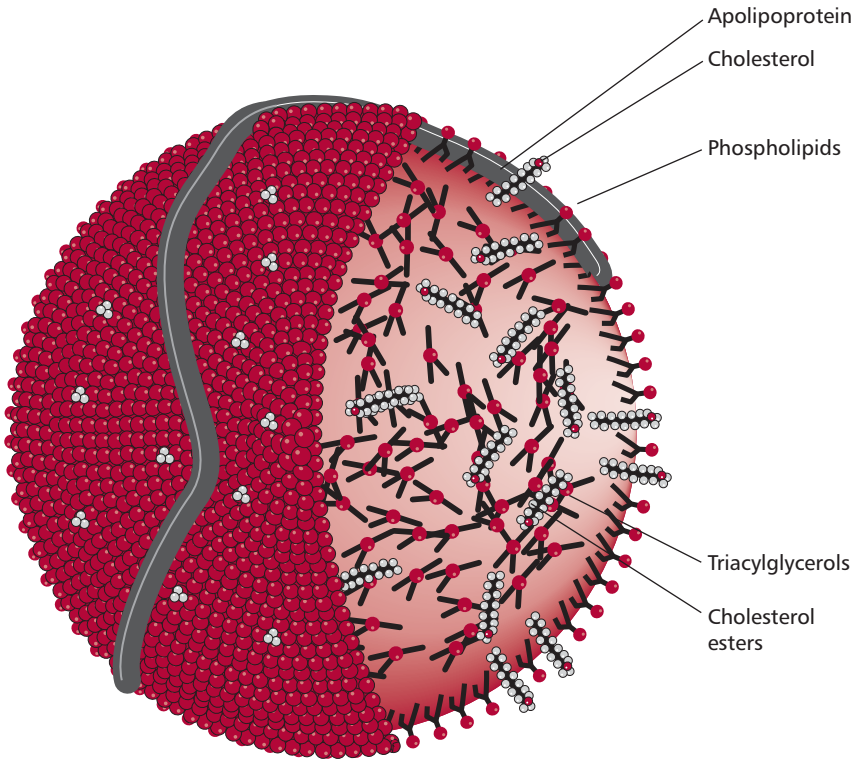

Figure 14.14 Schematic of a generalized lipoprotein particle.

	Chylomicrons	VLDL	LDL	HDL
Density / g cm^{-3}	0.93	<1.006	1.019-1.063	1.063-1.21
Protein / %	2	9	20	45
Phospholipid / %	8	20	20	25
Free cholesterol / %	1	7	10	5
Triacylglycerols / %	85	55	10	8
Cholesteryl esters / %	2	10	35	15
Apolipoproteins	B-48, C, E	A, B-100, C, E	B-100	A, C, D, E

Table 14.1 Composition of lipoprotein particles

in the form of very low density lipoproteins (VLDL). These contain the apolipoprotein, B-100, but the major lipids are triacylglycerols, with less than 20% free cholesterol and cholesteryl esters (*Table 14.1*). A primary determinant of the amount of VLDL secreted is the amount of free fatty acids entering the liver. Further, if saturated fatty acids predominate, the VLDL particles are smaller but more numerous than if polyunsaturated fatty acids are in excess. A high carbohydrate diet also substantially increases the concentration of plasma VLDL particles. Newly secreted VLDL particles undergo a series of changes in the plasma. They acquire apoC and apoE proteins from high density lipoproteins (HDL, *see below*). The catalyzed hydrolysis of triacylglycerols by lipoprotein lipase of the endothelial cells of capillaries allows the fatty acids and glycerol to be taken up by tissues. The reduced triacylglycerol content increases the density of the VLDL so that they become low density lipoproteins (LDL), and these particles are the principal carriers of cholesterol in the plasma. Low density lipoprotein particles serve as the major source of cholesterol for most of the tissues. Although most cells can synthesize cholesterol, the bulk of synthesis occurs in the liver and intestinal enterocytes.

The concentration of LDL in the plasma correlates positively with the incidence of coronary heart disease. Hence LDL is often referred to as 'bad' cholesterol. However, it is only 'bad' in excess, and when combined with other risk factors. High density lipoproteins are secreted by the liver, but they are also formed by modifications to chylomicrons and VLDL. High density lipoproteins (*Table 14.1*) can pick up cholesterol from tissues, essentially the opposite function to that of LDL. The particles probably acquire cholesterol from the cell surface membranes and convert it enzymatically to cholesteryl esters. Consequently HDL may be considered 'good' cholesterol.

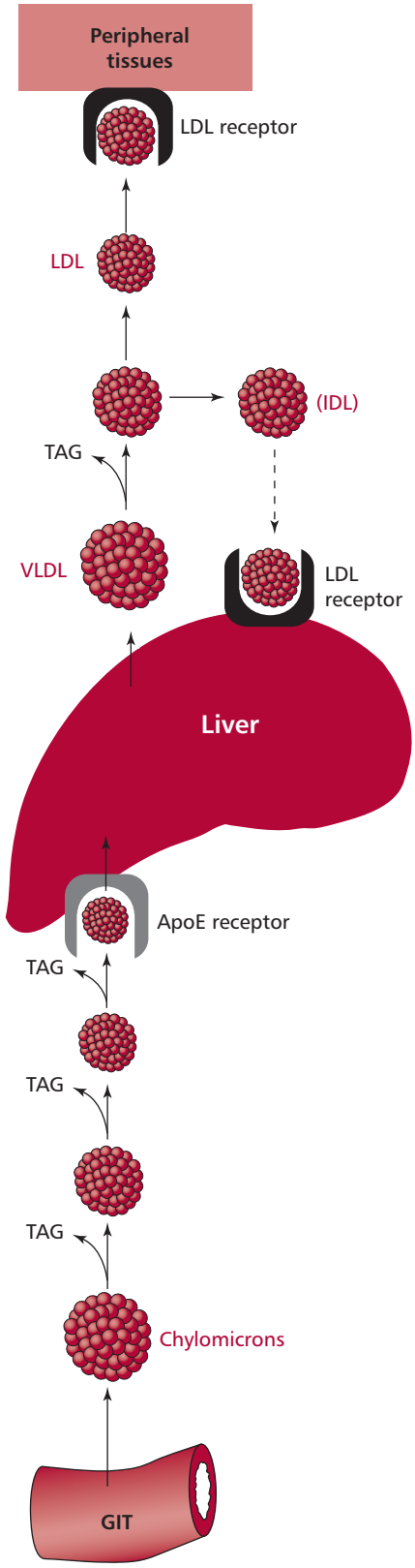

Figure 14.15 **Schematic illustrating the transport of cholesterol. IDL, intermediate density lipoprotein particle; LDL, low density lipoprotein particle; VLDL, very low density lipoprotein particle; TAG, triacylglycerols.** See text for details.

Margin Note 14.7 Tangier disease

The removal of cholesterol from cells uses a transporter protein that hydrolyzes ATP in an active transport process. The rare autosomal recessive disease called Tangier disease is associated with mutations in the gene encoding this transporter, and leads to an accumulation of cholesterol esters in the tissues and an almost complete absence of cholesterol in HDL particles. The name 'Tangier' comes from an island off the coast of Virginia, USA, where inbreeding amongst the families that lived there in isolation made it relatively common. The outlook for sufferers of this mutation is premature coronary heart disease.

Measuring serum cholesterol

It is necessary to know the concentration of LDL cholesterol in serum (*Table 14.2*) to assess risks to a person, diagnose an ailment and monitor the progress of a patient. However, until recently this could only be determined by a rather complicated laboratory technique not available for routine clinical use. An empirical formula (the Friedewald Formula) was used to derive the LDL cholesterol concentration from the HDL cholesterol and the triacylglycerol levels. However, this formula is inaccurate and sometime fails completely, such as when serum triacylglycerol concentrations are high. A newer test is the LDL Direct method that isolates LDL cholesterol using an immunological assay. It is more accurate, does not require the patient to fast and is not affected by high concentrations of triacylglycerols in the serum.

Lipid component	Concentration
Total cholesterol / mmol dm^{-3}	<5.2
LDL cholesterol / mmol dm^{-3}	<3.6
HDL cholesterol / mmol dm^{-3}	
Female	>1.2
Male	>0.9
Triacylglycerols / mmol dm^{-3}	0.4 – 1.8

Table 14.2 Desirable concentrations of cholesterol, lipoproteins and triacylglycerols in adults

Familial hypercholesterolemia

The circulating LDL particles are recognized by protein receptors on the surfaces of liver cells and removed from the plasma by endocytosis into the cells. Here their various components are metabolized, stored or recycled. The disease, **familial hypercholesterolemia**, is an autosomal dominant condition that affects heterozygotes, with a frequency of one in 500. It is associated with a defective receptor on the liver cells. This disease has been intensively investigated and a great deal is known about it. For the sufferers, the problems are whitish-yellow deposits largely of cholesterol on the tendons called **xanthomas**, and opaque fatty deposits around the periphery of the cornea called **corneal arcuses** and an onset of coronary heart disease before the age of 10 years in homozygotes. The blood cholesterol concentrations in homozygotes are between 15 and 30 mmol dm^{-3} compared with normal values of about 5.0.

14.14 MYOCARDIAL INFARCTION

An **infarction** is the death of a section of tissue because its blood supply has been cut off; an **infarct** is the segment of tissue affected. In general, if one artery is blocked neighboring arteries with communicating branches can compensate and tissue death is limited. Infarction occurs in places where small arteries do not communicate with one another, such as in the kidney, or where all the arteries together supply only enough blood for the whole organ, such as in the brain; or where alternative arteries are also blocked and cannot take over. The latter is what happens to the coronary vessels in many middle-aged hearts, particularly in the developed world. Thus myocardial infarction almost always occurs in patients with atheroma in the coronary arteries resulting from sudden coronary thrombosis, usually at the site of a fissure or rupture of the surface of an atheromatous plaque. There may be hemorrhage into the plaque with local coronary spasms. Irreparable damage can begin after only 20 min of occlusion. After about six h, the site of infarction of the myocardium is pale and swollen and after 24 h necrotic tissue appears

deep red owing to the hemorrhage. Subsequently an inflammatory reaction develops and the infarcted tissue turns gray in color.

Myocardial infarction is the commonest cause of death in the UK but surprisingly was hardly known before 1910. Patients present with severe intermittent chest pain that is similar in character to the angina that can occur on exertion, but usually occurring at rest and lasting several hours. Sometimes, however, the pain is less severe and may be mistaken for indigestion. The episodes of pain may become more frequent, but about 20% of patients have no pain. If there is pain, the onset is usually, but not always, sudden. The patient may feel restless and there is often sweating, nausea and vomiting. The most recognizable pain is in the middle of the chest that may spread to the back, jaw or left arm. The condition, once recognized, is a medical emergency. Half of the deaths occur in the first three to four h after the symptoms begin, so the sooner treatment begins the better the chances of survival.

PLASMA ENZYMES IN MYOCARDIAL INFARCTION

The diagnosis of myocardial infarction is usually made on the basis of the clinical symptoms and ECG findings, and is confirmed by the characteristic changes in plasma enzyme activities (*Box 14.4*). The enzyme activities that are of the greatest value are creatine kinase (CK), lactate dehydrogenase (LDH) and aspartate transaminase (AST, previously known as GOT, glutamate oxaloacetate transaminase). Plasma enzyme activities are increased in about 95% of cases of myocardial infarction and sometimes increase to high levels. The degree of increase gives a rough estimation of the size of the infarct but is of little prognostic value. A second and subsequent rise after their return to normal may indicate extension of the damage. All tend to show normal serum activities until at least four h after the onset of chest pain due to the infarction and so blood samples should not be taken until after this time. If the initial serum CK activity is approximately normal, a second blood sample should be taken four to six h later. An increase in plasma CK activity supports the diagnosis of an infarction. The sequence of changes in plasma AST activity after a myocardial infarction are similar to those for CK but the increases are significantly less.

TREATMENT

Usually the patient is given an aspirin to chew, which should improve the chances of survival by reducing the clot in a coronary artery. A β-blocker may also be given to slow the heart rate and reduce its workload. Oxygen may be given through a facemask to deliver more oxygen to the heart. Blood clots in an artery can often be cleared by intravenous thrombolytic therapy (*Box 14.3* and *Margin Note 14.6*). The indication for thrombolytic treatment is usually based on the clinical presentation and the ECG picture rather than on the activities of plasma enzymes. Treatment must be given within 6 h of the start of the heart attack to be effective. After 6 h it is likely that some of the damage will be permanent and the patient could be compromized and some may die. Most patients who survive for a few days after the attack can expect a full recovery but about 10% will die within a year. The majority of deaths occur in the next three to four months in patients who continue to have angina, arrhythmias and subsequent heart failure.

CORONARY BYPASS SURGERY

In individuals who have angina and coronary arterial disease that is not too widespread, coronary bypass surgery is a possible treatment that improves exercise tolerance, reduces symptoms and decreases the number of drugs that are needed. Bypass surgery involves grafting arteries or veins taken from the leg to take blood from the aorta past the obstructed region, replacing the role of the coronary arteries in supplying blood to the heart muscle. Such a graft often works well for up to 10 years or more.

BOX 14.4 Diagnostic value of various plasma markers in heart disease

The activities of a number of enzymes in blood samples are used in diagnosing and monitoring some types of heart damage and some other diseases (*Figure 14.16*). The activities of these enzymes in a patient depend on the rate of their release into the plasma from damaged cells and on the extent of cell damage. Other factors that need to be considered include the rate of cell proliferation and the rate of clearance of enzymes from the circulation. The rate at which damage is occurring is also important. Thus acute cell damage in viral hepatitis may lead to high activities in plasma but these will fall as the condition resolves. In contrast, in advanced cirrhosis of the liver, the rate of cell damage may be low and consequently the plasma enzyme levels may only be a little above normal.

Aspartate transaminase (AST, formerly glutamate oxaloacetate transaminase, GOT) is present in high concentrations in cardiac and skeletal muscle tissues, liver, kidney and erythrocytes. Damage to any of these tissues will increase the plasma level. In myocardial infarction there may be a 10- to 100-fold increase on the upper reference limit. The level will also increase after cardiac surgery.

Lactate dehydrogenase (LDH) is widely distributed in the tissues of the body and is a relatively nonspecific marker of tissue damage. The plasma activity may increase some five-fold above the upper reference limit in myocardial infarction. There are five isoenzymes of LDH (LDH_1–LDH_5) and estimation of the relative levels of their activities may help to identify which tissue is damaged. Thus increase in the activities of LDH_1 and LDH_2 occurs predominantly after myocardial infarction, although the levels of all the isoenzymes may be increased. In contrast the level of LDH_5 is characteristically elevated after damage to liver or muscle tissue.

Creatine kinase (CK) is abundant in the cells of cardiac and skeletal muscle and in brain. Consequently, a marked rise in its plasma activity occurs after myocardial infarction but, since the enzyme is present in so many tissues, this by itself may not be all that helpful. However, the enzyme consists of combinations of two distinct subunits called M and B respectively, which combine to form dimers characteristic of the tissue in which they are found. Thus the isoenzyme, MM is predominant in cardiac and skeletal muscle, whereas the BB isoenzyme is characteristic of brain and smooth muscle. The third isoenzyme, MB, accounts for about 35% of the cardiac muscle activity but less than 5% of that in skeletal muscle. The concentration of this isoenzyme in plasma is always high after myocardial infarction.

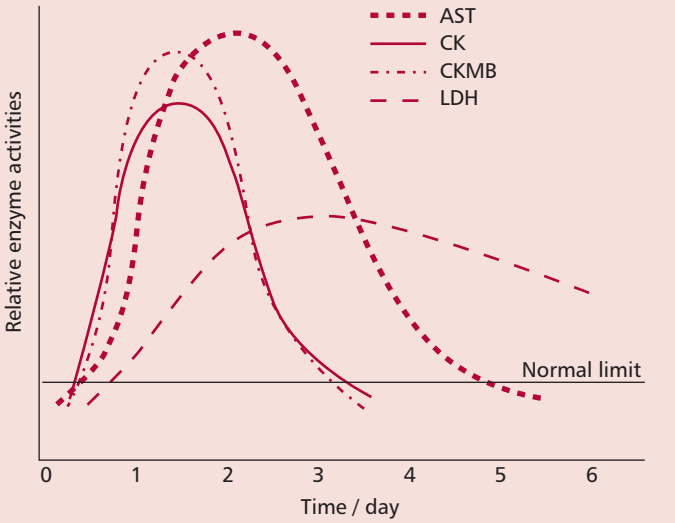

Figure 14.16 Increases in the activities of blood enzyme markers for a myocardial infarction. See text for details.

The triple marker blood test more easily distinguishes between cardiac and skeletal or other muscle damage. The triple marker consists of three components, which are myoglobin, troponin I and CKMB. All three are cardiac specific and therefore more reliable. Myoglobin is released from damaged cardiac muscle and peaks by six h. Troponin I is evident after six h and peaks at 12 to 16 h and remains in the system for two to four weeks. Creatine kinase MB is evident after 12 h and is the cardiac isoform of CK and therefore more accurate than total CK activity. The triple marker blood test is especially valuable when there are no or nonspecific ECG changes and can assist in clinical decision making.

14.15 PERICARDIAL DISEASES

The pericardium can become inflamed producing acute or chronic **pericarditis**. However, the pericardium is not absolutely essential to life and can be removed without significantly affecting the functioning of the heart.

Acute pericarditis has a sudden and often painful onset. There are also characteristic heart sounds. Symptoms include fever and chest pain that

typically extends to the left shoulder and down the left arm. The inflammation causes fluid and blood components, such as fibrin, erythrocytes and leukocytes, to pour into the pericardial space. The inflammation may be caused by a viral infection, in which case the condition may be painful but short-lived and have no lasting effects, or result from a number of other causes, for example cancer, heart attack, AIDS, kidney failure, heart surgery and the side effects of certain drugs, some of which are life-threatening. The treatment for acute pericarditis is to hospitalize the patient and treat with antiinflammatory drugs, such as aspirin or ibuprofen that also reduce the pain. Further treatment depends on the underlying cause. Individuals with cancer that has invaded the pericardium rarely survive longer than 12–18 months.

The chronic form of the disease develops gradually and is long-lasting. Usually the cause is unknown, but cancer and a reduced thyroid function have been implicated.

14.16 DISORDERS OF ARTERIES AND VEINS

A number of clinical disorders are associated with arteries and veins. These include peripheral arterial disease, arterial aneurysms and dissections, strokes, varicose veins and deep vein thromboses.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease can affect the abdominal aorta and its major branches including the arteries to the legs. Obstruction can be sudden or gradual. Most patients with peripheral arterial disease have atherosclerosis that gradually narrows the arteries. Partial occlusion can also result from a blood clot resulting in a sudden decrease in the oxygen supply. A sudden, complete obstruction normally results from a clot lodging in a narrowed artery. Emergency surgery or the use of thrombolytic drugs may be needed to remove the obstruction.

ANEURYSMS

An **aneurysm** is a round or tube-like bulge that usually develops in weak areas of an arterial wall. There are many reasons for the development of aneurysms, but high blood pressure and cigarette smoking increase the risks. Also, a blood clot may form in the aneurysm. If an aneurysm occurs in the aorta, an aortic aneurysm, rupture, hemorrhage and separation of the layers of the wall (called **dissection**, *see below*) can occur with disastrous results. Such conditions can be immediately fatal although most take years to develop. Aortic aneurysm can develop anywhere along its length but over 70% of them occur in the segment that run through the abdomen. An individual with abdominal aortic aneurysm usually becomes aware of a pulsing sensation in the abdomen, with a deep penetrating pain mainly in the back. The aneurysm may rupture, with severe internal bleeding, and the patient will typically go into severe shock (*Section 14.17*). Aortic rupture is frequently fatal. The treatment of ruptured aneurysms involves surgical repair, which is extremely risky. However, many patients are diagnosed early during a routine examination, and then surgery to insert a synthetic graft can be used to repair the aneurysm with a good chance of success.

AORTIC DISSECTION

In an aortic dissection the inner lining of the vessel wall tears allowing blood to surge through the tear, splitting the middle layer and creating a new channel. The condition usually results from a deterioration of the arterial wall caused,

in most cases, by high blood pressure, but it can also be a consequence of certain hereditary conditions. The clinical picture includes stroke, heart attack, sudden abdominal pain, nerve damage and an inability to move a limb. Treatment in intensive care is required. Drugs are given to reduce the heart rate and lower the blood pressure. Thereafter a decision needs to be taken as to whether to carry out surgery to replace the portion of damaged blood vessel with a synthetic graft. Untreated, about 75% of patients die within two weeks, but following treatment several years of life are possible in the majority of cases even though the death rate from surgery is 15% or more.

STROKE

If the blood supply to the brain is disrupted for any length of time the brain cells can be permanently damaged or die due to the lack of oxygen and this is called a **cerebrovascular accident** (CVA) or **stroke** (*Figure 14.17*). Brain cells are also damaged if bleeding into the brain occurs. Therefore strokes can be either ischemic or hemorrhagic. In ischemic stroke the blood supply to part of the brain is cut off either because of atherosclerosis or a clot blocking a blood vessel. In hemorrhagic stroke, a blood vessel bursts, preventing normal flow of blood and allowing it to leak into an area of the brain and destroy it.

In the developed world, strokes are the most common cause of disabling neurological damage resulting, typically, in a loss of speech and/or loss of motor function on one side of the body. High blood pressure and atherosclerosis are the major risk factors. The incidence is falling because the importance of controlling high blood pressure and dealing with inappropriate blood cholesterol levels has been recognized. Clinicians can usually diagnose a stroke from the clinical history of events and a physical examination. Computerized tomography scans and MRI (*Chapter 18*) are used for differential diagnoses.

Many people who have had a stroke recover some or all of their normal functions but others may be mentally and physically devastated, unable to speak or move normally. About 20% of people who have had a stroke die in hospital and the older the patient the greater the risk of this happening. Since each area of the brain is served by specific blood vessels, the area where the cerebrovascular accident occurs decides which part of the body becomes disabled. The loss of function is greatest just after the stroke and some function may return subsequently. This is because although some brain cells die, others may recover and take over a given function at least partially. The immediate treatment is to give oxygen to try to prevent further damage. Anticoagulants may be given if the stroke is ischemic but these are of little use

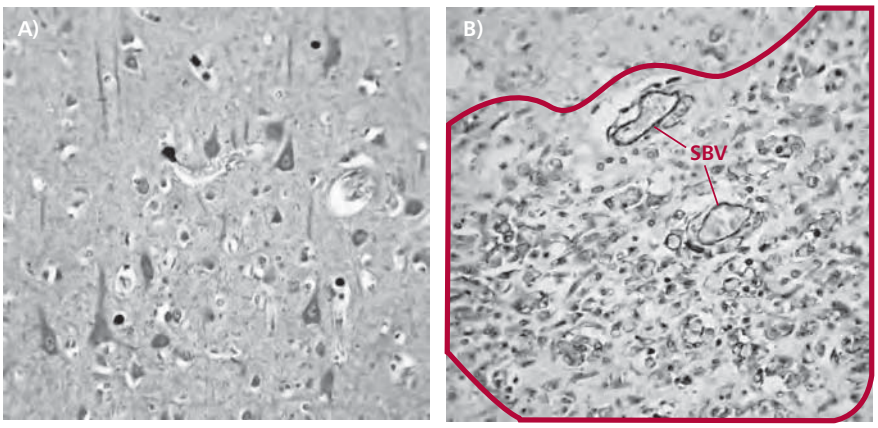

Figure14.17 Photomicrographs showing (A) normal brain tissue with the nuclei of numerous neurones prominent. (B) Brain tissue following an ischemic stroke. The area of damaged (infarcted) tissue is enclosed. Note the surviving blood vessels (SBV).

once the stroke is completed. Surgery is not normally of much use since the brain cells are already dead. For the survivors, a long period of rehabilitation may be required.

VARICOSE VEINS

Varicose veins are enlarged superficial veins, which occur particularly in the legs (*Figure 14.18*). The cause(s) of this condition is(are) not precisely known, but is probably due to a weakness in the walls of the veins which may be inherited. Over time, the veins lose their elasticity and they stretch and become wider. They may take on a tortuous, snake-like appearance, and cause bulges in the skin over them. The widening causes the valve cusps to separate (*Figure 14.19*) and as a result the veins fill with blood when the person stands and the veins bulge even more. As well as being unsightly, the legs feel tired and the veins ache, and after removing socks or stockings the legs may itch. There may be other complications and minor injuries may cause an ulcer that fails to heal. Varicose veins are common during pregnancy but these usually improve during the two to three weeks following delivery. Hypertension and obesity may have parts to play in the propensity for varicose veins.

Treatment for varicose veins

Varicose veins cannot be cured, but the symptoms may be relieved in various ways. Elevating the legs on a stool when sitting down and wearing elasticated stockings compress the veins and prevent them hurting, but these are not cures. They may be treated surgically by either stripping or by injection therapy. Stripping involves removing as many of the varicose veins as possible. The superficial veins play a less important role than the deep veins in returning blood to the heart and their removal does not impair the circulation significantly. Two incisions are made; one in the groin and one at the ankle while the patient is under general anesthetic. The saphenous vein (*Figure 14.13*) is then removed by threading a flexible wire through the vein, which is pulled to remove the entire vein. However, surgery does not remove the tendency to develop new varicose veins. Injection therapy involves sealing the veins by injecting an irritant solution that causes a thrombus to form so that no blood flows. Healing of the thrombus causes scar tissue, which can block the vein. However, the thrombus may dissolve allowing the vein to re-open. Injection therapy was popular but has fallen into disrepute, probably because of poor techniques with resulting complications. The more modern techniques, if carried out carefully, seem to be successful.

DEEP VEIN THROMBOSIS

Deep vein thrombosis is blood clotting in the deep veins. Like varicose veins, they primarily affect the legs. They are potentially dangerous. All or part of the clot or thrombus can break loose and lodge in a narrow artery in the lung obstructing blood flow, causing a pulmonary embolism. In serious cases this can result in blockage of all or nearly all of the blood travelling from the right side of the heart to the lungs rapidly causing death. Such serious consequences are not common but it is impossible to predict what will happen once a thrombus has formed. It is believed that the possible causes of this condition are an increased tendency of the blood to clot, which can happen with some cancers (*Chapter 17*) and very occasionally with oral contraceptives; slowing of the blood movement in the veins, as may also occur in prolonged bed rest or, sitting on a long flight and some types of injury or major surgery. The condition is difficult to diagnose until the thrombus moves. Deep vein thrombosis may be prevented to some extent by flexing and extending the ankles from time to time and by wearing elastic stockings. Anticoagulant therapy may also be appropriate in some cases.

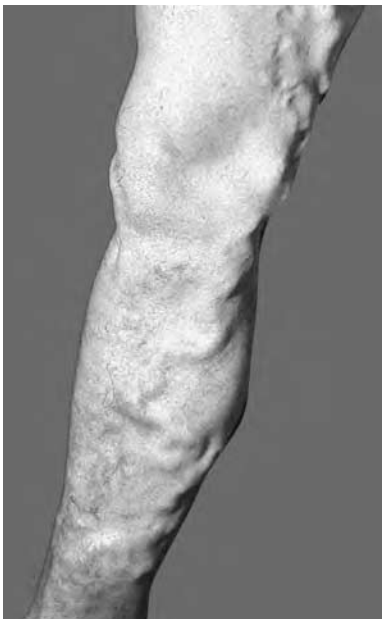

Figure 14.18 Picture showing external appearance of varicose veins of the long saphenous system of the thigh and calf. Courtesy of J. Guy, The Royal College of Surgeons of Edinburgh, Scotland.

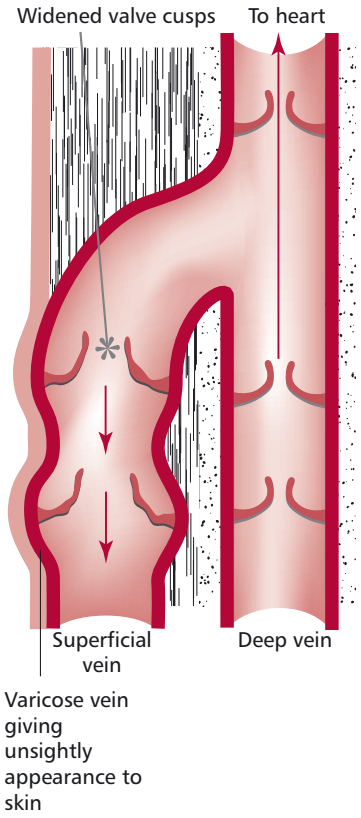

Figure 14.19 Schematic to show the widening of the valve cusps in varicose veins.

14.17 CLINICAL PROBLEMS ASSOCIATED WITH BLOOD PRESSURE

The blood pressure of any individual varies with their age, sex, physical activity and emotional state. For example, the normal upper limits at age 20 are 150/90 mmHg, which can increase to 160/95 and 170/95 at 40 and 60 years of age. If these pressures are found consistently then they are abnormally high. Blood pressure also varies with ethnic origin. American blacks, for example, are much more likely to have high blood pressure than whites.

The three major factors that determine the blood pressure are the amount of blood pumped by the heart, the volume of blood in the blood vessels and the elasticity of the blood vessels. Thus the more blood pumped by the heart, the higher the pressure. If the heart beats more slowly or its contractions are weakened, such as may happen after myocardial infarction (*Section 14.14*), then less blood will be pumped. Equally, a rapid heartbeat can result in inefficient pumping. The greater the volume of blood in circulation, the more likely the blood pressure is to be high. Conversely, a loss of blood by bleeding or as a result of dehydration will have the opposite effect. The smaller the capacity of the blood vessels, the higher will be the resulting blood pressure. Consequently, a dilation of the blood vessels will lower the blood pressure.

Sensors in the neck and chest continually monitor the blood pressure and trigger physiological changes if the blood pressure changes (*Chapter 8*). The actions taken might be to modify and strengthen the heartbeat, to regulate the kidneys to alter the amount of water excreted which, in turn, changes the volume of blood circulating or to constrict or dilate the blood vessels. However, these compensatory mechanisms have limits, for example if too much blood is lost as a result of bleeding there is little that can be done. Action must be taken to stop the bleeding and to transfuse blood or fluid to make up the volume. Furthermore, these compensatory mechanisms may themselves fail in certain conditions.

LOW BLOOD PRESSURE (HYPOTENSION)

Clearly the heart must pump hard enough so that the blood pressure is maintained. Pressures below 100/60 mmHg at any age are abnormally low. If an individual's blood pressure is too low it can lead to dizziness and fainting. Fainting or **syncope** is the result of a temporary inadequacy of oxygen and nutrients and is usually associated with a temporary decrease in blood flow. This can happen in people with an abnormal heart rhythm when they suddenly begin to exercise or the heart rate is too slow. However, there are many other possible causes of fainting including anemia, hypoglycemia, **hypocapnia** (a lower than usual concentration of CO_2 in the blood) or hyperventilation. The latter may be caused by anxiety. Usually lying flat is all that is needed for the individual to regain consciousness but checks should be performed to eliminate more serious conditions and this may mean, for example, an ECG examination.

SHOCK

If the blood pressure falls too low to sustain life, the body is said to have gone into **shock**. This is more severe and prolonged than in fainting, since if body cells are deprived of oxygen and nutrients for any length of time then they quickly become irreversibly damaged and die. Shock may result from low blood volume, inadequate pumping by the heart or excessive vasodilation as can occur in extreme allergic reactions (*Chapter 5*). Low blood volume may

be the result of bleeding following serious trauma. Inadequate pumping by the heart may be the result of a heart attack, pulmonary embolism, the failure of a heart valve or an irregular heartbeat or drug toxicity. Head injuries, liver failure, poisoning, severe bacterial infections or drug reactions may all lead to excessive blood vessel dilation.

Unless treated promptly, shock is usually fatal. When shock results from a sudden loss of blood for example in an accident or a hemorrhage the first person on the scene should aim to stop the bleeding, keep the victim warm and raise the legs slightly to improve the return of blood to the heart. Emergency personnel may provide mechanically assisted breathing, if it has stopped, and fluid or blood to increase the blood volume. Other treatments will depend on the cause of the shock.

HIGH BLOOD PRESSURE (HYPERTENSION)

Hypertension refers simply to the condition where a person has a blood pressure that is higher than that which is regarded as normal, regardless of its cause. High blood pressure is defined as a systolic pressure at rest of 140 mmHg or greater and a diastolic pressure of 90 mmHg or greater, or both of these. In fact both are usually elevated in hypertension. It does not usually cause symptoms, at least for many years, and often tends to go undetected unless the person's blood pressure happens to be measured for some other reason. Nevertheless, it is sometimes referred to as the 'silent killer' because there tend to be no symptoms until some vital organ is damaged. Mortality and morbidity rise continuously with increasing blood pressure. However, the risk is not linear and rises more steeply at higher pressures.

Initially an abnormal heart sound indicating hypertension may be detected using a stethoscope. A diagnosis of hypertension can be made on the basis of an elevated blood pressure reading of 140/90 mmHg or more when measured several times. A single reading on a given day is unreliable. Obviously the higher the values, the more serious the condition must be considered. It is possible to judge the seriousness of the condition by examining the arterioles at the back of the eye to determine the degree of damage to the retina, as hypertension is known to cause retinopathy. In addition, ECG and echocardiography can detect an enlargement of the heart brought on by the increased workload. Kidney damage may be detected by urine analyses.

The cause of hypertension can be identified in less than 10% of patients. These are usually kidney disease, a hormonal disorder or the use of oral contraceptives. Thus in most cases the primary cause cannot be identified and this form is referred to as essential hypertension. Many factors are probably responsible. For example, in older people the larger arteries lose their flexibility and become stiffer. Consequently when the heart pumps blood they cannot expand and the pressure increases. If the kidneys malfunction such that the urinary output is decreased, more fluid will be added to the system. Obesity, stress, a sedentary lifestyle, excessive amounts of alcohol and too much salt in the diet can also contribute.

Untreated hypertension increases the chances of a person developing heart diseases, such as cardiac failure or myocardial infarction (*Section 14.14*), kidney failure (*Chapter 8*), or a stroke (*see above*). Stopping smoking, reducing weight, salt intake and cholesterol levels reduces the risk. In general, patients do not have to restrict their activities as long as their blood pressure is controlled. Various drugs are available as part of a treatment program. These include diuretics to help the kidneys eliminate water and salt, adrenergic blockers to block the effects of the sympathetic nervous system and ACE inhibitors (*Margin Note 14.3*) which lower the blood pressure by stimulating arterial dilation.

CASE STUDY 14.1

Jim, a 52- year-old man, has suffered from angina over the past 18 months. He has also been suffering from lethargy, constipation and loss of concentration. His serum specimen was analyzed and yielded the following results (reference ranges are given in parentheses).

TSH	>100 mU dm^{-3}	(0.35 – 4.1 mU dm^{-3})
Cholesterol	12.8 mmol dm^{-3}	(<5.2 mmol dm^{-3})
Triacylglycerols	1.4 mmol dm^{-3}	(0.5 – 0.9 mmol dm^{-3})

Question

Explain these results.

CASE STUDY 14.2

Ted is a 60-year-old accountant with a past history of myocardial infarction. He was admitted to the hospital about 3 h after developing acute chest pain, fainting with a heavy fall. The results for his ECG were equivocal. His serum enzymes were measured on admission and after 24 and 48 h and give the following activities:

Enzyme	admission	24 h	48 h	reference range
CK	1160	570	190	<90 U dm^{-3}
AST	90	45	25	<37 U dm^{-3}

Question

Has Ted suffered a myocardial infarction?

CASE STUDY 14.3

Roger, a 37-year-old bank manager, has corneal arcus and xanthomata. He had normal blood pressure and weight and is a nonsmoker. However, he had family history of myocardial infarction, as his father died following one at the age of 40. A blood specimen was taken and analyzed for its lipid content (reference ranges are given in parentheses).

Cholesterol	16.8 mmol dm^{-3}	(<5.2 mmol dm^{-3})
Triacylglycerols	2.1 mmol dm^{-3}	(0.4–1.8 mmol dm^{-3})
LDL Cholesterol	14.2 mmol dm^{-3}	(<3.6 mmol dm^{-3})
HDL Cholesterol	1.3 mmol dm^{-3}	(>1.2 mmol dm^{-3})

Questions

(a) How do you account for this abnormal lipid profile?

(b) How should Roger be treated?

14.18 SUMMARY

The cardiovascular system comprises the heart and the blood vessels that supply the organs and tissues of the body with, for example oxygen and nutrients, and remove CO_2 and other wastes. The heart pumps blood through the pulmonary circulation that oxygenates the blood, and the systemic circulation around the rest of the body. The heart pumps nonstop for millions of beats during a person's lifetime. However, there are a number of conditions that can cause serious clinical problems. These can be investigated by listening to the heart sounds using a stethoscope, by measuring its electrical activities by an ECG, as well as studying its function by echocardiography. The rhythm of the heart beat may be faulty and this may require correction, including the insertion of an artificial pacemaker. The valves may function inappropriately due to calcification or other diseases and may need to be replaced. Clinical problems are also associated with blood vessels. These may become partially or completely blocked because of atherosclerosis. When this happens to the coronary arteries, bypass surgery with a grafted blood vessel may be required. Atherosclerosis, caused by high levels of cholesterol in the blood, leads to

inappropriate changes in the plasma lipoproteins. A change of diet and drugs may help this condition. The blood pressure may be excessively high in some individuals. This can be dangerous and lead to heart failure and stroke. Here again, drugs may be used to alleviate the condition. Heart failure needs to be treated promptly otherwise permanent disability or death may occur. The peripheral blood vessels can also become diseased. For example, the veins returning blood to the heart may develop faulty valves leading to varicose veins.

QUESTIONS

1. Which of the following is the odd one out?
   (a) endocardium;
   (b) bundle of His;
   (c) mitral valve;
   (d) pericardium;
   (e) semilunar valve.

2. Hypertension is a risk factor for which of the following?
   (a) asthma;
   (b) cerebral hemorrhage;
   (c) narrowing of the aorta;
   (d) a high blood cholesterol level;
   (e) venous thrombosis.

3. The lesions found in atherosclerosis
   (a) are initiated as a response to damage to the venous endothelium;
   (b) can develop at sites of intact endothelium;
   (c) do not contain smooth muscle cells;
   (d) do not contain macrophages;
   (e) do not contain thrombi.

4. Arrange the two following lists into their most appropriate pairings:

Blood pressure	tricuspid valve
Bundle of His	pacemaker
Coronary arteries	ventricular tachycardia
Pericardial diseases	sphygmomanometer
Palpitations	Purkinje fibers
Right ventricle	tenecteplase
SA node	lowered blood pressure
Thrombolysis	myocardium infarction
Vasodilation	familial hypercholesterolemia
Xanthoma	aspirin, ibuprofen

5. Account for the development of hypertrophic cardiomyopathy in some patients with pheochromocytoma. You may find it helpful to consult *Chapter 7.*

6. Barry, a 55-year-old, was admitted to hospital with severe chest pain, which had been present for the past 30 min. He had a previous history of angina. Which serum markers should be measured for this patient on admission?

7. If a patient is found to have high VLDL levels in the blood, what change in diet could help to lower the concentration?

8. Suggest why chylomicrons are not taken up by LDL receptors.

FURTHER READING

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Useful web sites:

'Target Heart Diseases' is a free booklet produced by the Association of the British Pharmaceutical Industry (ABPI) copies of which are available from the ABPI, 12 Whitehall, London SW1A 2DY or from their website: www.abpi.org.uk

Cox, D and Dougall, H (2001) What's so difficult about ECGs – a bundle of what? – a series of articles for medical students about understanding ECGs, available on www.studentbmj.com