CONTENTS

8 Circulatory system

INTRODUCTION

The circulatory system mediates continuous movement of all body fluids, its principal functions being the transport of oxygen and nutrients to the tissues as well as transport of carbon dioxide and metabolic waste products from the tissues. The circulatory system is also involved in temperature regulation and the distribution of molecules (e.g. hormones) and cells (e.g. those of the immune system). The circulatory system has two functional components: the ***blood vascular system*** and the ***lymph vascular system***.

The blood circulatory system comprises a circuit of vessels through which blood flow is initiated by continuous action of a central muscular pump, the ***heart***. The ***arterial system*** provides a distribution network to the peripheral ***microcirculation***, the ***capillaries*** and ***postcapillary venules***, the main sites of interchange of gas and metabolite molecules between the tissues and the blood. The ***venous system*** carries blood from the capillary system back to the heart.

The lymph vascular system is a network of draining vessels for returning excess extravascular fluid, the ***lymph***, to the blood circulatory system and for transporting lymph to the lymph nodes for immunological screening (see Ch. 14). The lymphatic system has no central pump but there is an intrinsic pumping system effected by contractile smooth muscle fibres in the lymph vessel walls, combined with a valve system preventing backflow.

The whole circulatory system has a common basic structure:

- An inner lining, the ***tunica intima***, comprising a single layer of extremely flattened epithelial cells called ***endothelial cells*** supported by a basement membrane and delicate collagenous tissue.
- An intermediate predominantly muscular layer, the ***tunica media***.
- An outer supporting tissue layer called the ***tunica adventitia***.

The tissues of the thick walls of large vessels (e.g. aorta) cannot be sustained by diffusion of oxygen and nutrients from their lumina, and are supplied by small arteries (***vasa vasorum***) which run in the tunica adventitia and send arterioles and capillaries into the tunica media.

The muscular content exhibits the greatest variation from one part of the system to another. For example, it is totally absent in capillaries but comprises almost the whole mass of the heart. Blood flow is predominantly influenced by variation in activity of the muscular tissue.

THE HEART

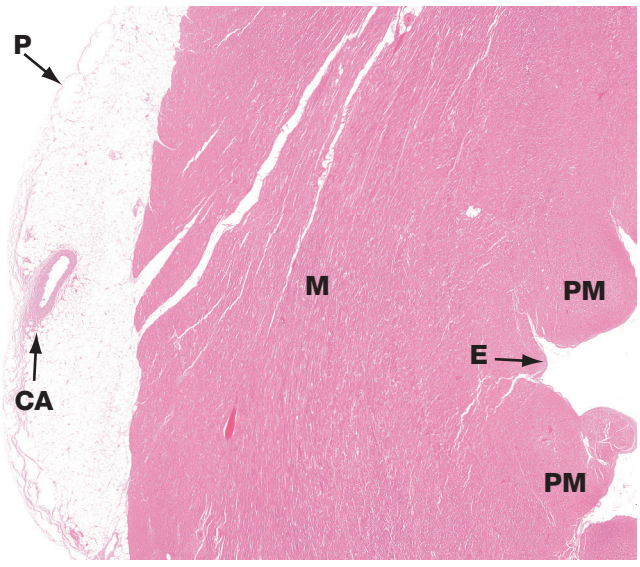

FIG. 8.1 Heart: left ventricular wall
H&E (LP)

Fig. 8.1 is a low-power micrograph showing the three basic layers of the heart wall, in this case the ***left ventricle***.

The tunica intima equivalent of the heart is the ***endocardium*** **E**, normally a thin layer in a ventricle. This is lined by a single layer of flattened endothelial cells, as is the case elsewhere in the circulatory system.

The tunica media equivalent is the ***myocardium*** **M**, made up of cardiac-type muscle (see Ch. 6). In the left ventricle, this layer is very prominent due to its role in pumping oxygenated blood throughout the systemic circulation, but it is less thick in the right ventricle and in the atria which operate at much lower pressures. Note the origins of the ***papillary muscles*** **PM**, extensions of the myocardium which protrude into the left ventricular cavity and provide attachment points of the ***chordae tendinae*** which tether the cusps of the atrio-ventricular valves.

The equivalent of the tunica adventitia is the ***epicardium*** or ***visceral pericardium*** **P**, usually a thin layer but, in some areas, as shown here, containing adipose tissue (see Fig. 8.2a). The ***coronary arteries*** **CA**, run within the epicardial fat.

The myocardium: changes in health and disease

The segment of left ventricular wall illustrated above is composed almost entirely of cardiac muscle. As indicated, the thickness of the myocardium differs in the different chambers of the heart, reflecting differences in their functional requirements. Myocardial thickness also differs between individuals, both in health and in various disease states.

Hypertrophy of the heart muscle may occur due to the effects of long-standing physical exertion and training, as in athletes, or it may occur in pathological states. High blood pressure (***hypertension***) leads to the heart muscle pumping against increased resistance and this commonly causes marked thickening of the left ventricular wall. Less commonly but importantly, there are inherited forms of cardiac hypertrophy such as hypertrophic cardiomyopathy (see e-Fig. 8.1). This disorder is an important cause of sudden unexpected cardiac death, especially in young athletes.

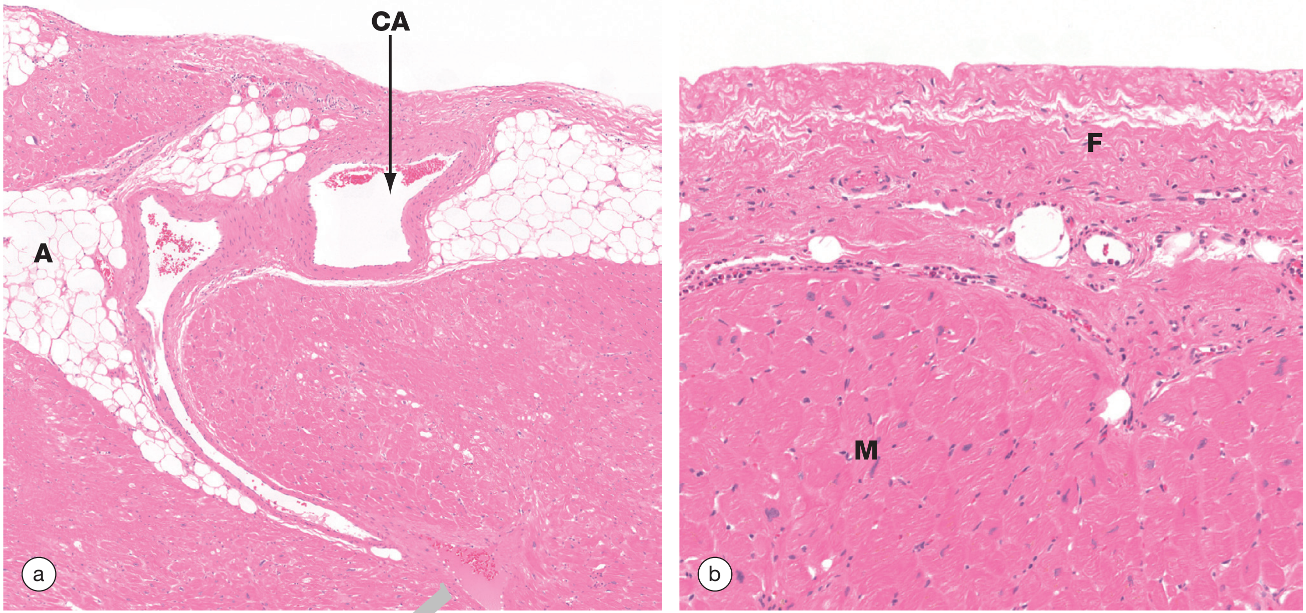

FIG. 8.2 Heart: epicardium (visceral pericardium)
(a) H&E (MP) (b) H&E (HP)

The constant layer of the epicardium is a dense sheet of fibrocollagenous tissue **F** which also contains elastic fibres. On its outer surface, there is a flat monolayer of mesothelial cells (not clearly seen here). These cells are responsible for secretion of lubricating fluid. Fig. 8.2a shows an area where the epicardium contains a large branch of the ***coronary artery*** **CA**, with a smaller branch penetrating the myocardium **M**. Note that in areas containing artery branches, there is a variable layer of adipose tissue **A**. Fig. 8.2b shows the appearance of the epicardium over most of the heart surface, where the fibrocollagenous layer **F** lies directly on the myocardium **M** without significant intervening adipose tissue.

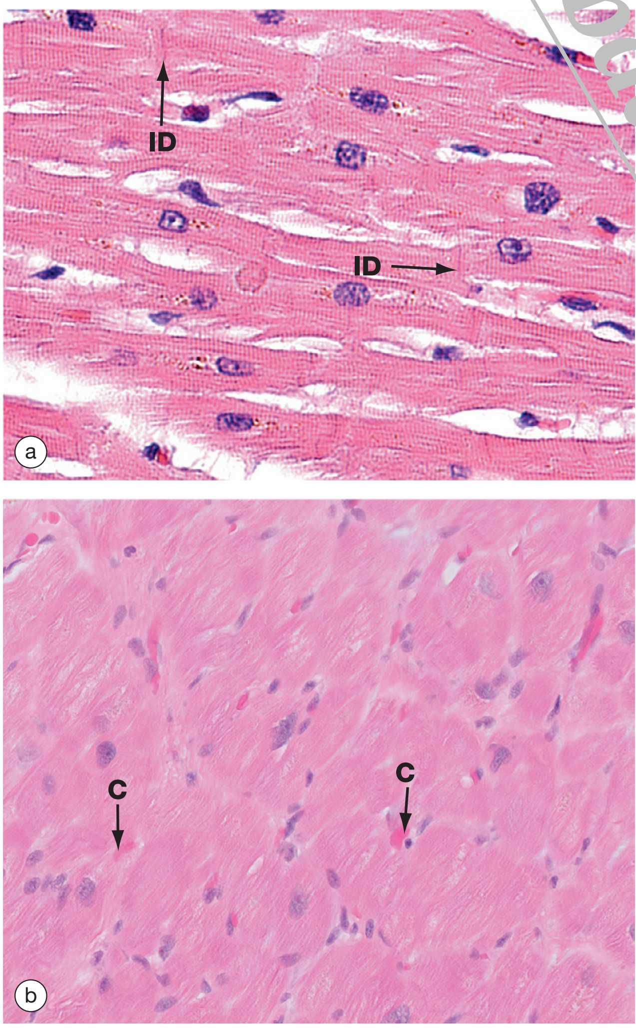

FIG. 8.3 Myocardium
(a) H&E, LS (HP) (b) H&E, TS (HP)

In longitudinal section (Fig. 8.3a), cardiac muscle fibres form an interconnecting network, joined to each other by ***intercalated discs*** **ID**. These specialised intercellular junctions provide both mechanical and electrophysiological coupling, allowing the cardiac myocytes to act as a functional syncytium. The cells possess central nuclei and regular cytoplasmic cross-striations. The intercalated discs and cross-striations can be clearly seen using special methods such as the immunohistochemical technique for α-B crystallin and in thin resin sections stained with toluidine blue (see Fig. 6.24).

In transverse section in Fig. 8.3b, the extensive and intimate capillary network **C** between the myocardial fibres is easily seen. The vessels in this section are distended with red blood cells (see also Fig. 6.21). This high level of vascularity is a reflection of the high and constant oxygen demand of the myocardium, particularly in the left ventricle which is shown in these two pictures. Further structural details of the cardiac muscle of the myocardium are given in Ch. 6.

Myocarditis

Myocarditis is an uncommon inflammatory disorder affecting the cardiac muscle. Its causes are diverse, but viral forms are the most frequent. The diagnosis requires the combination of interstitial inflammation (inflammation between myocytes) and myocyte damage (known as the ***Dallas criteria***). Myocarditis can be classified by the predominance of inflammatory cells seen on microscopy. A lymphocytic myocarditis is the typical pattern seen in viral myocarditis (see e-Fig. 8.2a). An eosinophilic myocarditis can be seen in the setting of hypersensitivity. Other rarer types of myocarditis include giant cell myocarditis (see e-Fig. 8.2b). Sarcoidosis, a systemic granulomatous condition, is a cause of granulomatous myocarditis (see e-Fig. 8.2c).

A adipose tissue **C** capillary **CA** coronary artery **E** endocardium **F** fibrocollagenous pericardium **ID** intercalated disc **M** myocardium **P** pericardium **PM** papillary muscle

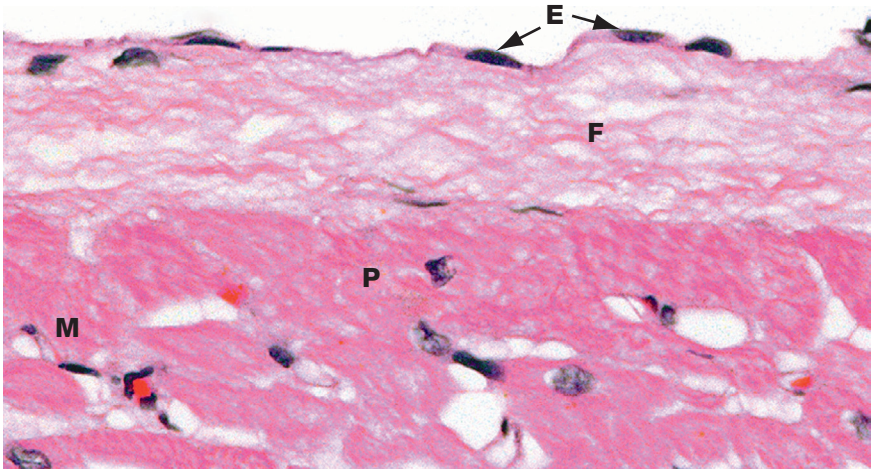

FIG. 8.4 Endocardium
H&E (HP)

The ***endocardium*** (Fig. 8.4) has a surface layer of flattened endothelial cells **E**. The endothelium is supported by a layer of fibrous connective tissue **F** containing variable amounts of elastic tissue. This merges into the collagen fibres surrounding adjacent cardiac muscle cells **M**, as well as the larger ***Purkinje fibres*** **P** (see Fig. 8.6).

The endocardium shown here is from the wall of the left ventricle. The endocardium of the atria is much thicker than this and includes more elastic fibres.

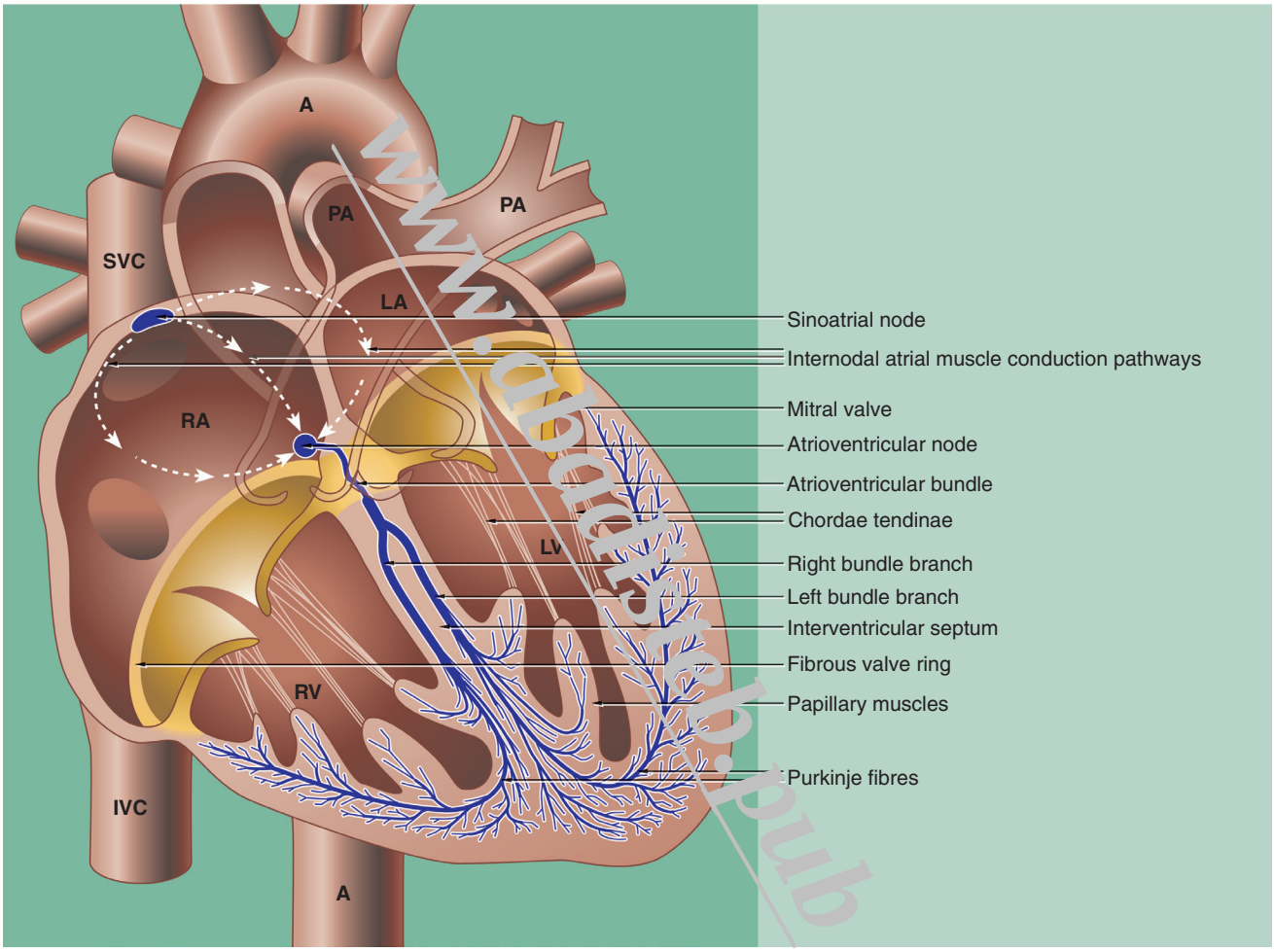

FIG. 8.5 The conducting system of the heart

The co-ordinated contraction of the heart is largely effected by a specialised ***conducting system*** of modified cardiac muscle fibres (Fig. 8.5). The initial impulse originates spontaneously in the ***sinoatrial node***, situated in the right atrial wall near the entry of the superior vena cava **SVC**. The impulse rate is controlled by the autonomic nervous system.

The impulse passes through the muscle of the atria **RA** and **LA**, causing them to contract, and reaches the ***atrioventricular node*** in the medial wall of the right atrium just above the tricuspid valve ring at the base of the interatrial septum. Both the sinoatrial and atrioventricular nodes are irregular meshworks of very small specialised myocardial fibres, with electrochemical stimuli being transmitted via ***gap junctions***. The nodal fibres are embedded in collagenous fibrous tissue which contains blood vessels and many autonomic nerve fibres.

From the atrioventricular node, the impulse is passed along a specialised bundle of conducting fibres, the ***atrioventricular bundle (of His)***, which initially divides into right and left bundle branches that then (halfway down the interventricular septum) become ***Purkinje fibres*** which run immediately beneath the endocardium before penetrating the myocardium (see Figs 8.4 and 8.6).

A aorta **BB** bundle branch **E** endothelial cell **En** endocardium **F** fibrous connective tissue **IVC** inferior vena cava **LA** left atrium **LF** lamina fibrosa **LV** left ventricle **M** cardiac myocytes **P** Purkinje fibre **PA** pulmonary artery **RA** right atrium **RV** right ventricle **SVC** superior vena cava **VR** valve ring

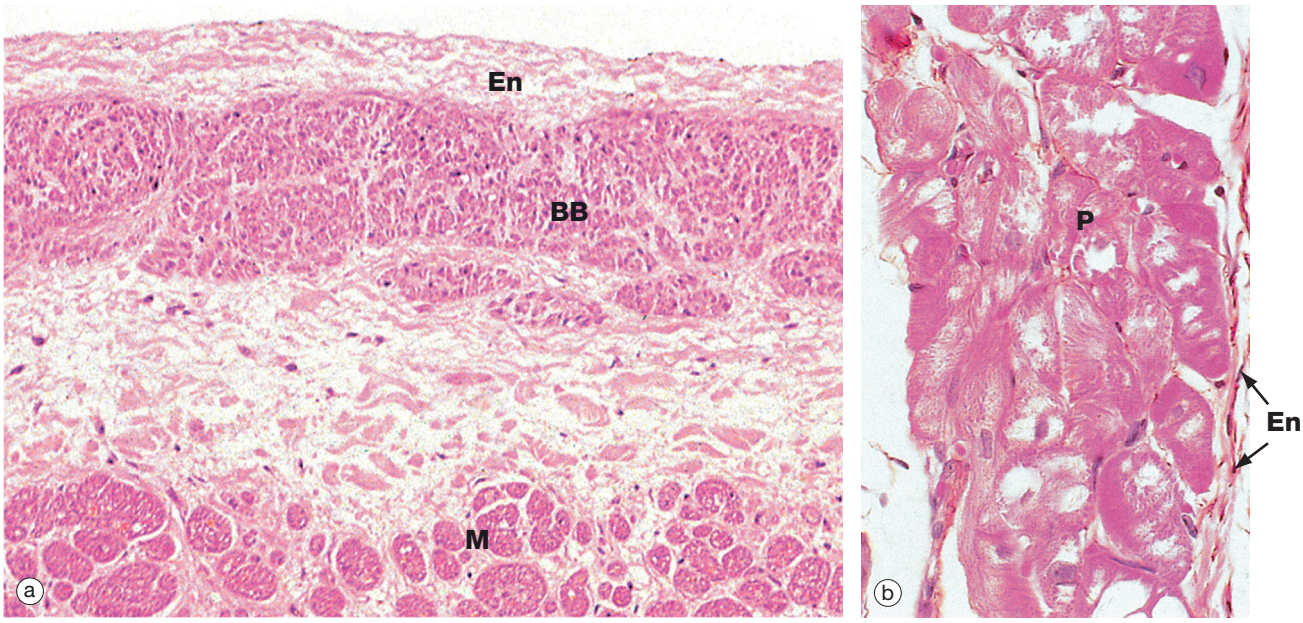

FIG. 8.6 Heart
(a) Bundle branch, H&E (MP) (b) Purkinje fibres, H&E (HP)

Fig. 8.6a shows the left branch bundle of conducting fibres **BB** running in the interventricular septum, just beneath the endocardium **En** lining the left ventricular cavity. At this level, the conducting fibres are separated from the myocardial fibres **M** of the septum by a layer of fibrous tissue. The conducting fibres are specialised cardiac muscle fibres and contain comparatively few myofibrils, which are mainly located beneath the cell membrane, but abundant glycogen granules and mitochondria. This makes the fibres paler staining than normal myocardial fibres by most stains.

Fig. 8.6b shows the distal extension of the branch bundle, with the ***Purkinje fibres*** **P** beneath the thin endocardium **En**. These fibres are larger than cardiac muscle fibres and have a pale-staining central area with most of the red-staining myofibrils around the periphery of the cell. Unlike myocardial fibres, Purkinje and other conducting fibres have no T tubule system and connect with each other by desmosomes and gap junctions, rather than intercalated discs.

Common disorders of the myocardium

The myocardial cells have a high energy demand and therefore a high and constant oxygen requirement. When there is a reduction of blood flow to the myocardium caused by ***atherosclerosis*** of the epicardial coronary arteries (e-Fig. 8.3a), the cardiac myocytes supplied by the artery can die (***necrosis***). The patient develops ***angina*** (a characteristic crushing central chest pain on exertion, disappearing on rest). With increasingly severe ischaemia of the myocardium, the angina symptoms appear with minimal or no exertion.

Histologically, the dead muscle fibres are replaced by collagenous fibrous tissue (***replacement fibrosis***) (e-Fig. 8.3b) and remaining muscle fibres enlarge and increase their work rate (***hypertrophy***) to compensate (e-Fig. 8.3c).

When a coronary artery suddenly becomes completely occluded (e.g. by ***thrombosis***), a substantial mass of the heart muscle cells dies. For example, the muscle comprising the entire anterior wall of the left ventricle and the anterior part of the interventricular septum dies if the left anterior descending coronary artery is blocked. This is called ***myocardial infarction***, commonly referred to as a 'heart attack'. Death of some of the conducting bundles of Purkinje fibres can also lead to potentially fatal abnormalities of cardiac rhythm (***arrhythmia***). When the area of infarction heals, the large areas of replacement fibrosis are strong but not contractile, so the patient may suffer from persistent left ***heart failure*** as the heart cannot adequately pump blood from the left ventricle to the systemic circulation.

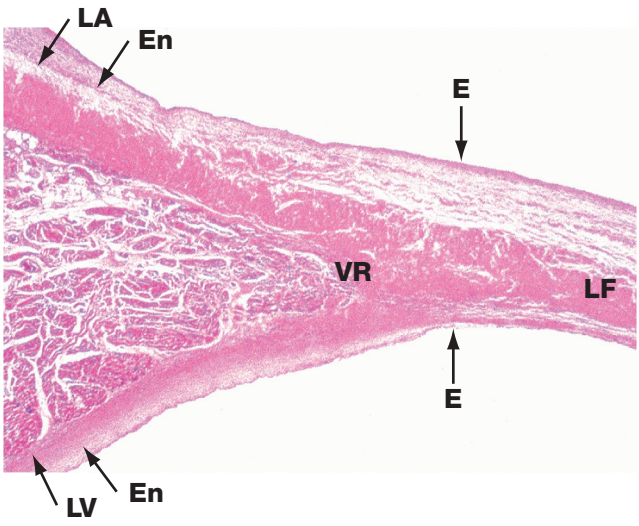

FIG. 8.7 Heart valve
H&E (LP)

The heart valves consist of leaflets of fibroelastic tissue. The surfaces are covered by a thin layer of endothelium **E** which is continuous with that lining the heart chambers and great vessels. This low-power image in Fig. 8.7 shows the left atrioventricular valve (the ***mitral valve***), arising at the junction of the walls of the left atrium **LA** and left ventricle **LV**.

The fibroelastic layer of the endocardium **En** condenses to form the ***valve ring*** **VR**, and from this arises the central fibroelastic sheet of the valve, the ***lamina fibrosa*** **LF**.

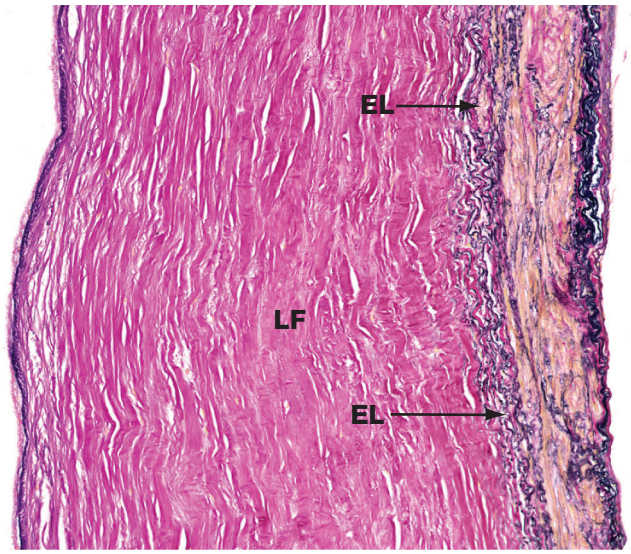

FIG. 8.8 Heart valve
Elastic van Gieson (LP)

The valves are sheets of fibroelastic tissue covered on both sides by endocardium (Fig. 8.8). There is a dense central plate of collagen (the ***lamina fibrosa*** **LF**) containing scattered elastic fibres (black in this stain) as shown in the micrograph at low magnification. In the left atrioventricular valves (as here), there is a distinct elastic lamina (**EL**) towards the atrial surface and the collagen (red staining here) is particularly prominent on the ventricular surface where the chordae tendinae are attached.

Common disorders of heart valves

The aortic valve normally has three cusps but occasionally there are only two (bicuspid) due to a developmental anomaly. Bicuspid aortic valves are particularly prone to develop fibrous thickening, within which calcium salts are deposited to make fibrocalcific nodules. These severely distort the cusps, which also tend to fuse. This disease, called ***calcific aortic valve disease*** (see e-Fig. 8.4a), interferes with valve function, reducing flow of blood through the valve during systole (***aortic stenosis***) and allowing blood to leak back from the aorta into the left ventricle during diastole (***aortic regurgitation***).

Thrombosis may occur on the free edges of heart valves and, if there is subsequent ***bacteraemia***, they may become infected (***valvitis*** or ***endocarditis***) (see e-Fig. 8.4b). Depending on the bacterium involved, the infected thrombus may erode the valve, leading to severe valve failure, or fragments of the thrombus may break off and pass in the circulation to distant sites where they may block arteries (***embolism***).

THE ARTERIAL SYSTEM

The function of the arterial system is to distribute blood from the heart to capillary beds throughout the body. The cyclical pumping action of the heart produces a pulsatile blood flow in the arterial system. With each contraction of the ventricles (***systole***), blood is forced into the arterial system causing expansion of the arterial walls; subsequent recoil of the arterial walls assists in maintenance of arterial blood pressure between ventricular beats (***diastole***). This expansion and recoil is a function of elastic tissue within the walls of the arteries.

The flow of blood to various organs and tissues may be regulated by varying the diameter of the distributing vessels. This function is performed by the circumferentially disposed smooth muscle of vessel walls and is principally under the control of the sympathetic nervous system and adrenal medullary hormones.

The walls of the arterial vessels conform to the general three-layered structure of the circulatory system but are characterised by the presence of considerable elastin and the smooth muscle wall is thick relative to the diameter of the lumen. There are three main types of vessel in the arterial system:

- **Elastic arteries**. These comprise the major distribution vessels and include the aorta, the innominate (brachiocephalic trunk), common carotid and subclavian arteries and most of the large pulmonary arterial vessels.
- **Muscular arteries**. These are the main distributing branches of the arterial tree, such as the radial, femoral, coronary and cerebral arteries.
- **Arterioles**. These are the terminal branches of the arterial tree which supply the capillary beds.

There is a gradual transition in structure and function between the three types of arterial vessel rather than an abrupt demarcation. In general, the amount of elastic tissue decreases as the vessels become smaller and the smooth muscle component assumes relatively greater prominence.

Common disorders of arteries

Elastic and muscular arteries develop ***atherosclerosis*** in which lipid material infiltrates the tunica intima and accumulates in macrophages. This stimulates the proliferation of intimal fibroblasts and myointimal cells, with collagen deposition to produce a ***plaque*** which thickens the intima. If severe and in a small-diameter artery, this intimal thickening can severely reduce the artery lumen and limit the blood flow. These plaques commonly rupture, leading to aggregation of platelets and fibrin. This forms a ***thrombus*** (see e-Fig. 8.5) which narrows the vessel lumen leading to infarction.

A further consequence of severe atheroma in elastic arteries is that the muscle cells in the tunica media are replaced by non-contractile and non-elastic collagen, leading to a weakness in the artery wall, which may bulge and rupture (***aneurysm***).

A tunica adventitia **EEL** external elastic lamina **EL** elastic lamina **I** tunica intima **IEL** internal elastic lamina
LF lamina fibrosa **M** tunica media **VV** vasa vasorum

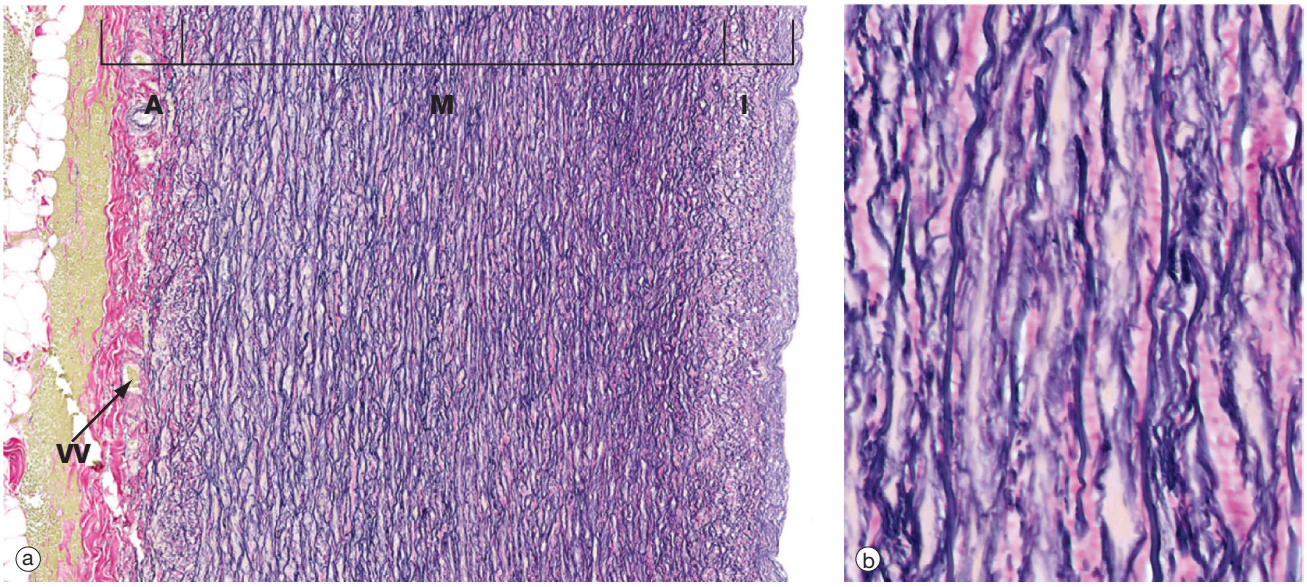

FIG. 8.9 Elastic artery: aorta
(a) Elastic van Gieson (LP) (b) Elastic van Gieson (HP)

The highly elastic nature of the aortic wall is demonstrated in these preparations in which the elastic fibres are stained brownish-black. In Fig. 8.9a, the three basic layers of the wall can be seen: the narrow ***tunica intima*** **I**, the broad ***tunica media*** **M** and the ***tunica adventitia*** **A**.

The tunica intima consists of a single layer of flattened endothelial cells (not seen at this magnification) supported by a layer of collagenous tissue rich in elastin disposed in the form of both fibres and discontinuous sheets. The subendothelial supporting tissue contains scattered fibroblasts and other cells with ultrastructural features akin to smooth muscle cells and known as ***myointimal cells***. Both cell types are probably involved in elaboration of the extracellular constituents. The myointimal cells are not invested by basement membrane and are thus not epithelial (myoepithelial) in nature. With increasing age, the myointimal cells accumulate lipid and the intima progressively thickens. If this process continues, ***atherosclerosis*** will develop.

The tunica media is particularly broad and extremely elastic. At high magnification in Fig. 8.9b, it is seen to consist of concentric fenestrated sheets of elastin (stained black) separated by collagenous tissue and smooth muscle fibres. As seen in Fig. 8.9a, the collagenous tunica adventitia (stained red) contains small ***vasa vasorum*** **VV** which also penetrate the outer half of the tunica media.

Blood flow within elastic arteries is highly pulsatile. With advancing age, the arterial system becomes less elastic, thereby increasing peripheral resistance and thus arterial blood pressure.

Aneurysms

An ***aneurysm*** is an abnormal and permanent dilatation of the wall of an artery. Various types of aneurysm can occur, and these can be classified in several different ways: according to morphology (shape) into ***saccular*** and ***fusiform*** types, according to aetiology (cause) into congenital, acquired, atherosclerotic, mycotic, etc., or by the nature of the aneurysmal wall into true or false aneurysms. The wall of a true aneurysm includes all of the normal layers of the vessel wall, whilst a false aneurysm is deficient in one or more of these layers and essentially represents a protrusion at a site of weakness or deficiency in the vessel wall.

Atherosclerotic aneurysms are common in developed cultures and most often affect the abdominal aorta (see e-Fig. 8.6a). These aneurysms are acquired and are usually fusiform in shape.

Rupture of such aneurysms can occur when the wall becomes attenuated due to increasing dilatation. Catastrophic and rapidly fatal haemorrhage can occur unless immediate treatment is available. If such aneurysms are identified before acute presentation with haemorrhage, planned operative repair can be performed. This approach dramatically reduces morbidity and mortality when compared against attempted repair after bleeding has occurred. Some patients can be treated by minimally invasive radiological techniques instead of open surgery.

An ***acute dissection*** (see e-Fig. 8.6b) can be caused by weakening of the aortic wall due to longstanding hypertension or inherited connective tissue disease affecting the aorta, such as Marfan syndrome.

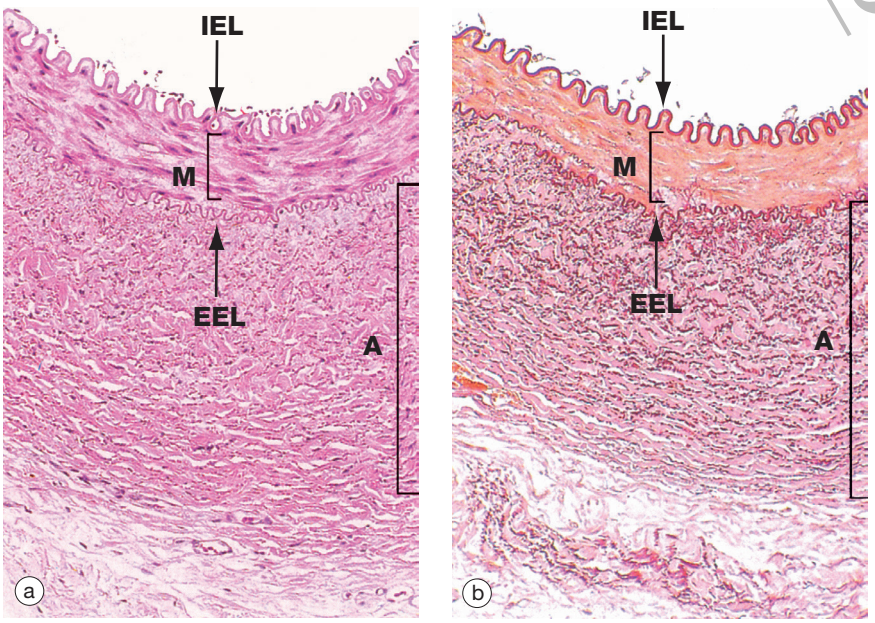

FIG. 8.10 Muscular artery
(a) H&E (MP) (b) Elastic van Gieson (MP)

In muscular arteries, as shown in Figs 8.10a and b, the elastic tissue is largely concentrated as two well-defined elastic sheets. One sheet is the ***internal elastic lamina*** **IEL** between the tunica intima and the tunica media. The less prominent and more variable ***external elastic lamina*** **EEL** lies between the tunica media **M** and the adventitia. The tunica intima is usually a very thin layer, not visible at low magnification, and the tunica media **M** is composed of concentrically arranged smooth muscle fibres with scanty elastic fibres between them. The tunica adventitia **A** is of variable thickness and is composed of collagen and a variable amount of elastic tissue. In larger muscular arteries, this layer may contain prominent vasa vasorum.

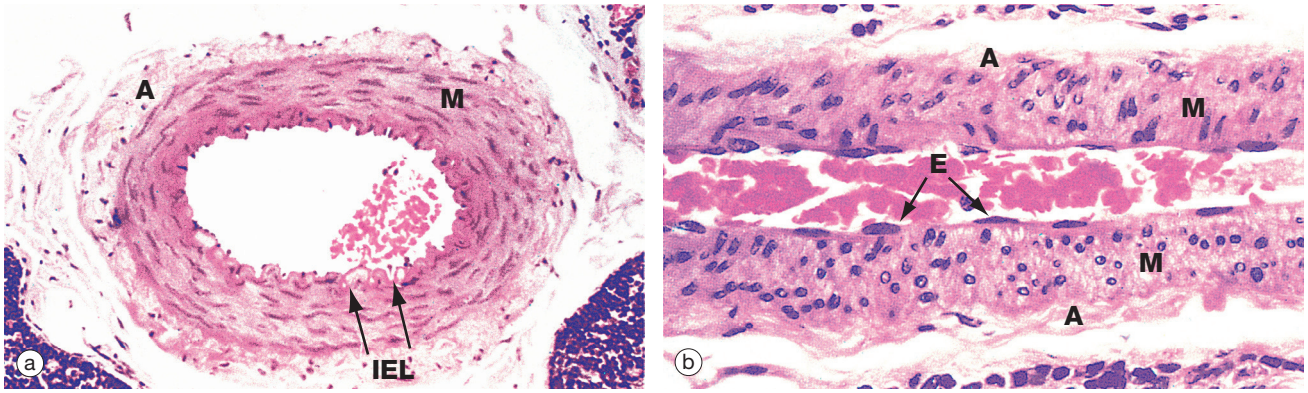

FIG. 8.11 Small muscular artery
(a) H&E, TS (MP) (b) H&E, LS (HP)

The diameter of a small muscular artery is approximately 0.5 to 2 mm and a thin but distinct internal elastic lamina is present, but there is usually little or no external elastic lamina. The tunica media has 3 to 10 concentric layers of smooth muscle cells and contains almost no elastic fibres. Fig. 8.11a shows an artery in transverse section. The distinction between the tunica media **M** and adventitia **A** is obvious. The internal elastic lamina **IEL** can just be distinguished as a densely staining wavy line. Fig. 8.11b is a smaller artery at higher magnification. The nuclei of the intimal endothelial cells **E** are visible, but the elastic lamina has largely disappeared.

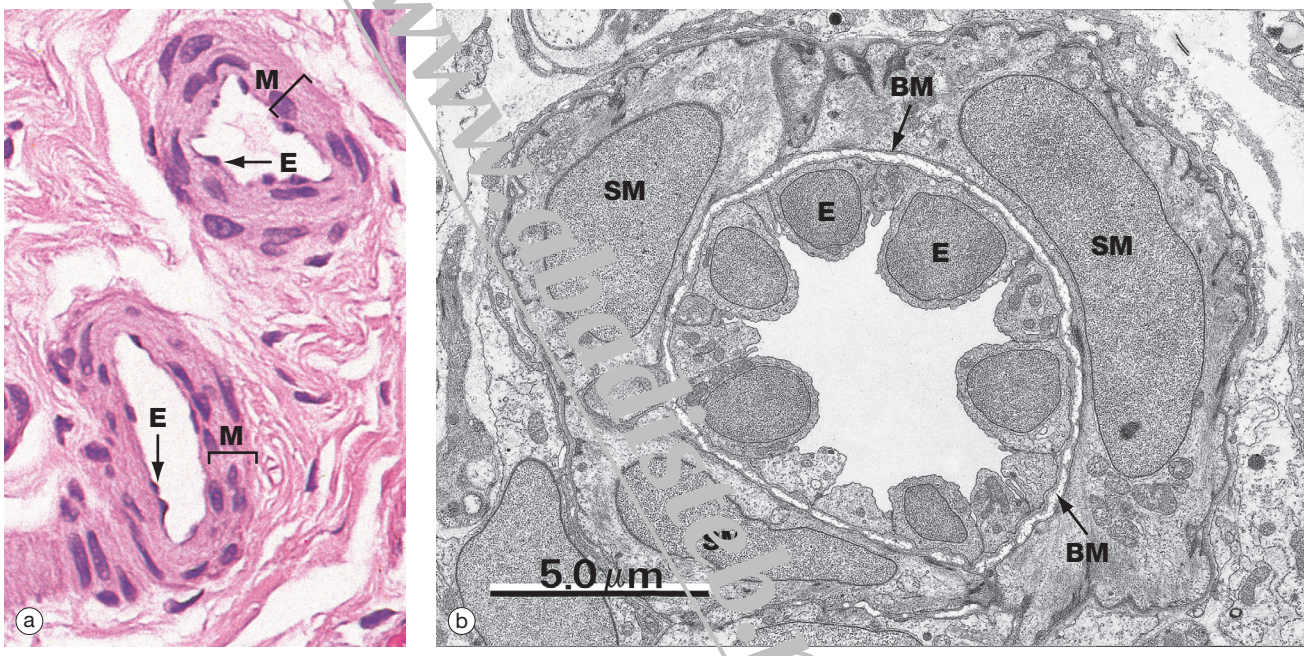

FIG. 8.12 Arterioles
(a) Large arteriole H&E, TS (MP) (b) Small arteriole, EM ×5250, TS

Small muscular arteries merge into large arterioles, which eventually become small arterioles. These transitions are gradual with no sharp demarcations and involve loss of the internal elastic lamina and progressive reduction of the number of muscle layers in the media. Fig. 8.12a shows two large arterioles, with a thin intima lined by endothelial cells **E** and a tunica media **M** comprising only 2 to 3 layers of muscle. The adventitia is thin and merges imperceptibly with surrounding supporting collagenous fibrous tissue.

Fig. 8.12b is an electron micrograph of a small arteriole, with a single layer of smooth muscle cells **SM** separated from endothelium **E** by basement membrane **BM**. The endothelium is prominent because the arteriole is constricted.

THE MICROCIRCULATION

The ***microcirculation*** is that part of the circulatory system concerned with the exchange of gases, fluids, nutrients and metabolic waste products. Exchange occurs mainly within the capillaries, extremely thin-walled vessels forming an interconnected network. Blood flow within the capillary bed is controlled by the ***arterioles*** and muscular sphincters at the arteriolar–capillary junctions called ***precapillary sphincters***. The capillaries drain into a series of vessels of increasing diameter, namely ***postcapillary venules***, ***collecting venules*** and ***small muscular venules*** which make up the venous component of the microcirculation.

A tunica adventitia **At** arteriole **BM** basement membrane **BMp** pericyte basement membrane **C** capillary
E endothelial cell **F** collagen fibrils **IEL** internal elastic lamina **M** tunica media **Ma** metarteriole **MF** marginal fold
P pericyte **S** arteriovenous shunt **SM** smooth muscle cell **V** venule

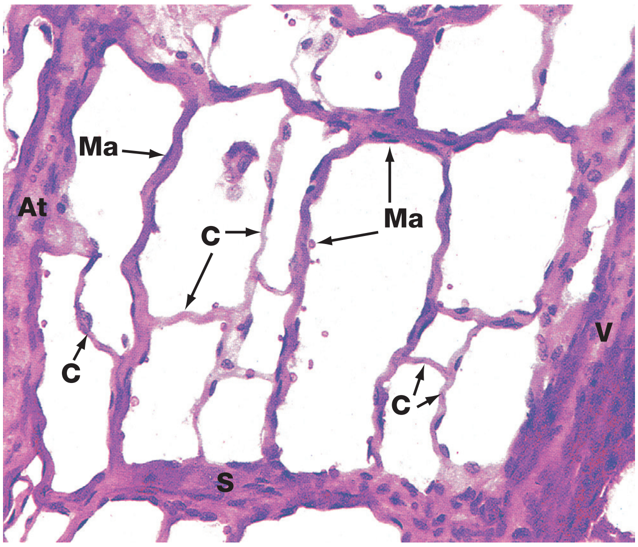

FIG. 8.13 The microcirculation, mesenteric spread
H&E (MP)

Fig. 8.13 demonstrates a network of anastomosing capillaries between an arteriole **At** and a venule **V**. The capillary network comprises small-diameter capillaries **C** with a single layer of endothelial cells and basement membrane, as well as larger-diameter capillaries known as ***metarterioles*** **Ma**. These are characterised by a discontinuous outer layer of smooth muscle cells. Small capillaries arise from both arterioles and metarterioles.

At the origin of each capillary, there is a sphincter mechanism, the ***precapillary sphincter***, which is involved in regulation of blood flow. There is also a direct wide-diameter link between the arteriole and venule, an ***arteriovenous shunt*** **S**. Metarterioles also form direct communications between arterioles and venules. Contraction of the smooth muscle of shunts and metarterioles directs blood through the network of small capillaries. Thus arterioles, metarterioles, precapillary sphincters and arteriovenous shunts regulate blood flow in the microcirculation. The smooth muscle activity of these vessels is modulated by the autonomic nervous system and by circulating hormones (e.g. adrenal catecholamines).

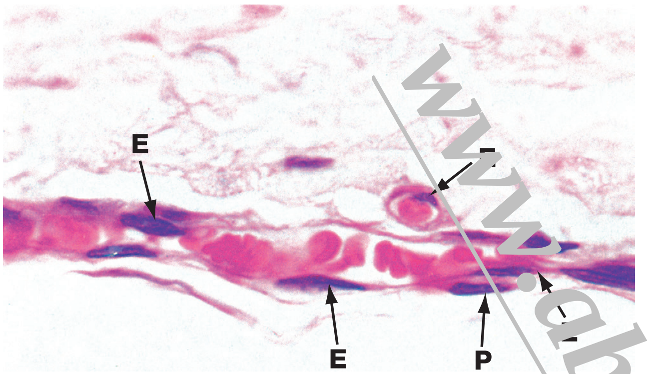

FIG. 8.14 Capillaries
H&E (HP)

The vessels seen in Fig. 8.14 in longitudinal and transverse section illustrate the characteristic features of capillaries. A single layer of flattened endothelial cells lines the capillary lumen. The thin layer of cytoplasm is difficult to resolve by light microscopy.

The flattened endothelial cell nuclei **E** bulge into the capillary lumen. In longitudinal section, the nuclei appear elongated, whereas in transverse section they appear more rounded.

Muscular and adventitial layers are absent. Occasional flattened cells called ***pericytes*** **P** embrace the capillary endothelial cells and may have a contractile function. Note that the diameter of capillaries is similar to that of the red blood cells contained within them.

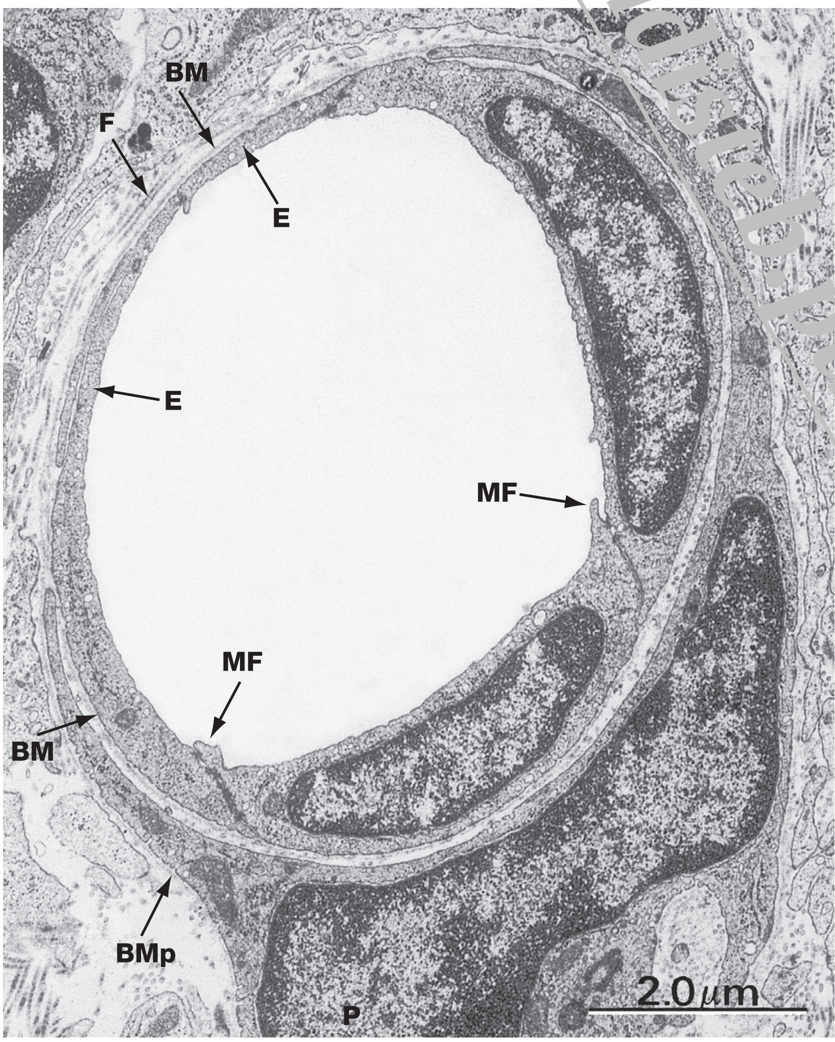

FIG. 8.15 Capillary, continuous endothelium type
EM ×12 000

This electron micrograph (Fig. 8.15) illustrates the ultrastructure of capillaries of the continuous endothelium type, the type found in most tissues. Endothelial cells **E** encircle the capillary lumen, their plasma membranes approximating one another very closely and bound together by scattered tight junctions of the fascia occludens type (see Fig. 5.11). Small cytoplasmic flaps called ***marginal folds*** **MF** extend across the intercellular junctions at the luminal surface. The capillary endothelium is supported by a thin ***basement membrane*** **BM** and adjacent collagen fibrils **F**. A pericyte **P** embraces the capillary and is supported by its own basement membrane **BMp**.

Exchange between the lumen of the continuous-type capillary and the surrounding tissues is believed to occur in three ways. ***Passive diffusion*** through the endothelial cell cytoplasm mediates exchange of gases, ions and low molecular weight metabolites. Proteins and some lipids are transported by ***pinocytotic vesicles*** (see Ch. 1). White blood cells pass through the intercellular space between the endothelial cells, in some way negotiating the endothelial intercellular junctions. Some researchers maintain that the intercellular spaces also permit molecular transport. In capillaries of the continuous endothelial type, the basement membrane is thought to present little barrier to exchange between capillaries and surrounding tissues.