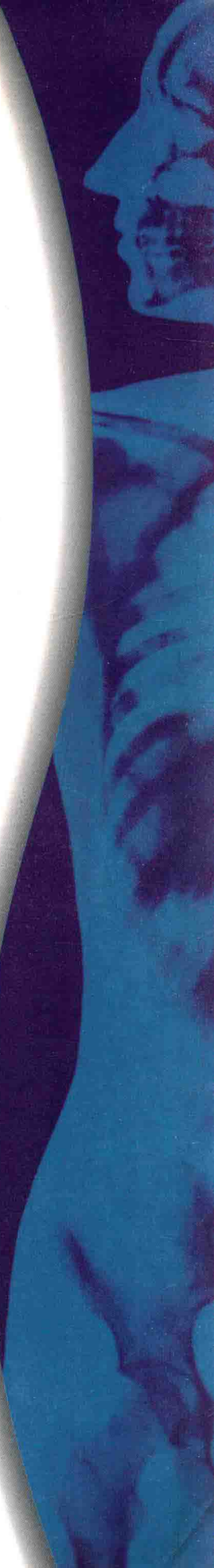
英文原版教材

MASTER MEDICINE

Systematic Pathology
系统病理学

A clinically-orientated core text with self-assessment

PAUL BASS
SUSAN BURROUGHS
CLAIRE WAY



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Systematic Pathology

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For Paulina, Aaron, David and Abraham.
Thanks for all the encouragement
PB

and

For Mark
CW

Commissioning Editor: Timothy Horne
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Using this book

Learning about systemic pathology provides the building blocks for understanding disease processes, which is something that all doctors require in order to practise effectively.

Over the last five years, there have been radical changes to many undergraduate medical courses, with increasing emphasis on communication and clinical skills, ethics, special study modules and interprofessional learning. These are delivered within different curriculum models, such as integrated, graduate entry or problem-based learning. In some curricula, pathology is not taught as an identifiable 'course' and it can be difficult for students to identify the important subject matter that must be learnt.

All the material in this book is core pathology. It is the basis of clinical medicine and is essential for good clinical practice. Much of the detail found in larger textbooks has been eliminated, so if you know and understand the information in this book, you will have an adequate basis for your ward-based and postgraduate studies. Larger textbooks can be used for reference if you wish to study topics in more depth, but it is not necessary to read them from cover to cover. Revision 'crammers' consisting largely of lists are favoured by some, but they encourage simple retention of facts rather than understanding, and they are unlikely to be of use unless you already understand the material.

It is important that you develop the skills of deep learning that will underpin a lifetime of learning. Qualified doctors learn until they retire. Systemic pathology has immediate relevance and importance to clinical medicine and as such is easier to learn than some basic science subjects. The ability to apply pathology knowledge to clinical situations is fundamental to the diagnostic process. The use of clinical examples and case histories in this book is designed to make the subject more interesting, memorable and understandable.

General principles of assessment

Most medical school assessments or exams are of summative type; they are designed to pass or fail and to enable you to move on to the next stage of the course. Formative assessment is a different kind of assessment where the results are used to give feedback to the students about their strengths and weaknesses and about their progress. In this book the self-assessment questions are intended to give you some idea of where there are gaps in your knowledge.

Assessment methods

Multiple choice questions

The multiple choice question (MCQ) is a popular form of assessment in many medical courses because the questions are relatively easy to set and can be marked quickly and efficiently in large numbers by mechanical means. MCQs mainly test knowledge, understanding and reasoning skills. The most valid and useful MCQs are those that use the 'best-matched answer' format.

Some MCQs use negative marking, where points are deducted for wrong answers. This system is designed to prevent guessing. Nevertheless, studies have shown that you are, on average, more likely to be right than wrong if you have a hunch about the right answer, even if you are not sure. An over-cautious approach can result in answering too few questions to pass, so it is probably best to 'play your hunches' if you have to. If there is no negative marking, you should attempt all questions as you have nothing to lose.

Short answer questions

Short answer questions are used to test knowledge, reasoning and understanding and sometimes problem solving. The examiners usually devise a prototype answer and marks are simply awarded for every item or cluster of items required. Start your answer with some kind of definition and go on from there. It is a good idea to use simple diagrams wherever possible. You can then refer to them in your explanation.

No extra points will be given for information that is not strictly relevant, therefore read the question and answer the question that is set. Unless the instructions for the paper indicate that different questions have different weights of marks, spend roughly the same amount of time on each question. There is sometimes a temptation to spend longer on questions that you believe you can answer particularly well, but this is unlikely to compensate fully for a question that is answered badly or not at all because of lack of time. It

may be a good idea to start with the questions about which you feel less confident; as the pressure increases towards the end of the exam you can concentrate on your areas of strength.

Essay

The essay gives you a chance to show how much you understand and your ability to relate one area of knowledge to another. It also tests your ability to organise and present information logically and clearly. Some essays also allow you to develop an argument rather than simply set down facts. It is a communication exercise; marks may be given not just for factual content but for use of English, presentation (including handwriting) and structure of the essay and how the points and arguments are expounded. Use side headings (underlined if necessary) and diagrams. These help to make things clear and will often enable you to communicate your knowledge to the examiner.

It is vital that you read the question carefully and answer only the question that is set. Examiners will not award marks for irrelevant material, so don't waste your time presenting it. Do not spend too long on an essay on a favourite topic, or you will have insufficient time for other questions.

Essays are time consuming to mark and may be subject to marker bias and for this reason are often denigrated. Nevertheless, a well-set and properly marked essay can test a variety of skills, and essay papers are still encountered in many medical schools.

Viva

The viva voce or oral examination is an integral part of many examinations in medicine, both undergraduate and postgraduate. It can be an alarming experience, but it is your opportunity to show the examiners not just how much you can recall but your breadth and depth of understanding.

All students find vivas stressful. Sometimes you will feel as though your mind has gone blank when the examiner asks a question. Don't panic; take a deep breath and think for a second or two before jumping in with the first thing that comes into your head. Try to imagine how you would start the answer if you were writing it down. A simple definition is often a good start. If you do not understand the question then say so and ask for it to be repeated. The viva is a two-way communication process and examiners cannot expect you to give your best if they do not express themselves clearly.

If the question requires an answer listing the causes of a disease, assemble your causes in order of importance. Do not put the most rare one at the top of the list. Common things occur commonly. For example, haemorrhoids or rectal polyps are common causes of rectal bleeding, whereas amoebiasis would be a very rare cause in the UK. It may help to assemble topics in a logical way that demonstrates your understanding of basic principles and also acts as an aide-mémoire so that you don't forget important areas. For example, you can divide causes of intestinal obstruction into factors within the lumen, within the wall and outside the wall. Likewise, an intestinal polyp can be inflammatory, hamartomatous or neoplastic. Neoplasms can be benign or malignant, primary or metastatic.

If you mention a rare disease, the examiner may ask you more about it. This is fine if you know the subject, but not if you don't, so try to keep the conversation to areas in which you are confident. Most examiners try to be empathic and sympathetic. Nevertheless, they are usually trying to determine the limits of your knowledge and understanding, so you will probably be asked some questions that you cannot answer. If you haven't a clue, it is perfectly acceptable to say you don't know so the examiner can move on to a different area.

Spotter

The spotter exam consists of a series of 'stations' at which there will be a specimen, test result or diagram about which you have to answer questions. You are allowed a certain time at each station and then you move on to the next one, usually when a bell rings. More sophisticated versions of the spotter may include a clinical case in which you move through a series of stations which all relate to the one case. For example, a pathology image showing myocardial infarction may be followed by stations with chest X-rays, ECGs or cardiac enzyme results.

Students often feel pressurised during spotter exams and it is a good idea to jot down a précis of the question at a station if you cannot respond, so that if there are a few spare minutes at another easier station, you can go back to the one that you had trouble with.

OSCEs

Pathology is the link between basic science and clinical medicine, and so you may be required to demonstrate pathological knowledge in a wide variety of OSCEs (objective structured clinical examinations). Ensure you are up to date with the regulations for death certification

and asking for autopsy consent, since these may be the focus of an OSCE station.

Using the self-assessment sections in this book

A mixture of assessment methods for you to use have been included in this book. The answers provided will give you some idea of where your knowledge gaps are and will also help you to organise your answers effectively.

There are factual answers to all the MCQs and answers with discussion points for the case histories.

The answers for the OSCE, short answer and viva questions are not comprehensive. Where appropriate, an outline answer has been suggested and a way of approaching the answer to show that you can organise, prioritise and apply your knowledge to different situations.

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Contents

1 Cardiovascular system

Overview

Pathology of the cardiovascular system, the heart and blood vessels, is responsible for a large proportion of deaths in the UK each year, and also causes considerable morbidity through heart failure, stroke and peripheral vascular disease. The major underlying disease processes responsible include atherosclerosis, hypertension and diabetes mellitus. Lifestyle modification can play a significant role in reducing disease risk, particularly in relation to smoking, exercise, body weight and fat consumption. This chapter covers atherosclerosis and its complications, ischaemic heart disease, hypertension, valvular heart disease, cardiomyopathies and congenital heart disease. Many cardiac pathologies result in heart failure, which may initially primarily involve either the left or right ventricle. The basic pathology of vasculitis and vascular tumours is also reviewed.

1.1 Atherosclerosis, aneurysms and ischaemic heart disease

Learning objectives

You should:

- Understand the pathogenesis and clinical consequences of atherosclerosis
- Be able to discuss pathology and complications of myocardial infarction
- Know how lifestyle modifications can reduce the risk of ischaemic heart disease

Atherosclerosis

Atherosclerosis (also called atheroma) is an inflammatory, degenerative disease of large and medium sized arterial vessels. It is characterised by the development of fibrolipid plaques within the intima of the vessel wall. In smaller arteries, including the coronary vessels that supply the myocardium, these plaques can cause severe narrowing (stenosis) of the lumen, with significant impairment of blood flow. The clinical consequences depend on the speed of development of the stenosis, and on whether the affected tissue has any additional source of blood supply (known as collateral supply). In large arteries, such as the abdominal aorta, the inflammatory atherosclerotic process damages the muscular wall causing weakness and dilatation. This is known as aneurysm formation (see Box 1). As the aneurysm enlarges there is an increasing risk of rupture, with resultant catastrophic haemorrhage.

Four major *risk factors* are recognised for atherosclerosis.

1. Smoking
2. Hypercholesterolaemia (raised low density lipoproteins)
3. Hypertension
4. Diabetes mellitus

Minor risk factors include increasing age, male gender, obesity, family history and stress.

Pathogenesis of the fibrolipid atherosclerotic plaque

Atheromatous plaques are probably initiated by injury to the endothelial cells of the arterial intima. An inflammatory response is evoked to the damage, which results in an infiltrate of macrophages, and proliferation of smooth muscle cells from the media of the vessel wall. These smooth muscle cells migrate into the intima and begin to produce collagen. Both the macrophages and the smooth muscle cells may accumulate lipid within their cytoplasm, giving a vacuolated appearance on light microscopy ('foam cells'). Free cholesterol and necrotic inflammatory debris also become incorporated within the plaque lesion.

Figure 1 shows a normal muscular artery and a typical atheromatous plaque with a fibrous tissue cap and a lipid-rich, necrotic centre. It is important to realise that the actual composition of individual plaques varies, and can change over time. Plaques that are particularly rich in lipids may be more unstable and susceptible to rupture or haemorrhage (see later section on ischaemic heart disease). Older plaques can become heavily calcified. The plaque surface is prone to develop superimposed thrombosis, which can rapidly increase the severity of the obstruction to blood flow. At autopsy, it is common to find a recent thrombus complicating an atheromatous coronary artery plaque in patients who died after acute myocardial infarction.

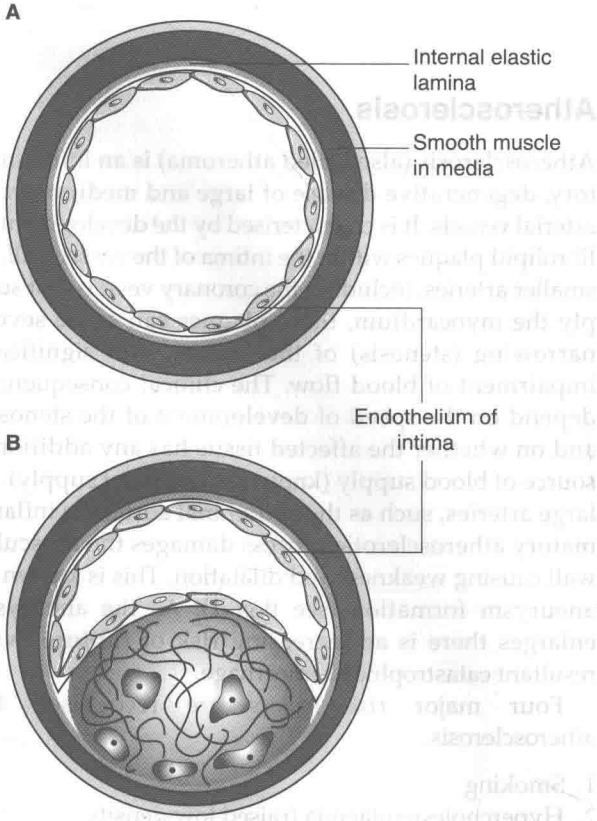

Fig. 1 (**A**) Normal muscular artery structure within intima (endothelium), internal elastic lamina and media. (**B**) An atherosclerotic plaque composed of lipid and fibrous tissue is present in the intima causing internal narrowing (stenosis) of the vessel lumen and thinning of the underlying muscular media.

Clinical complications of atherosclerosis

- **Coronary arteries:** angina, myocardial infarction, heart failure, sudden death (cardiac arrhythmia).
- **Cerebral arteries:** transient ischaemic attacks, stroke.
- **Aorta:** abdominal aneurysm formation (risk of rupture and death) (see Box 1).
- **Mesenteric arteries:** intestinal ischaemia and infarction.
- **Renal arteries:** renal artery stenosis (hypertension, ischaemic kidney).
- **Lower limbs:** intermittent claudication, gangrene.

Aortic dissection

Also called dissecting aneurysm, although this is an inaccurate term as the aorta is not significantly dilated. In aortic dissection, blood tracks into the muscular wall of the blood vessel. The entry point of blood into the aortic media is through an intimal tear, usually within the proximal 10 cm of the ascending aorta. Occasionally, there is a second distal luminal tear, through which blood re-enters the circulation, producing a 'double-barrelled' aorta. More commonly, however, the haemorrhage extends outwards with vessel rupture and catastrophic extamural haemorrhage into:

- the pericardium, causing cardiac tamponade
- the mediastinum, causing haemothorax
- the abdominal cavity (haematoperitoneum).

The dissection can also involve the great vessels of the neck, compromising cerebral blood flow. Dissection of the coronary arteries is a rare cause of acute myocardial ischaemia.

There is a strong association with systemic hypertension and with Marfan's syndrome.

Ischaemic heart disease

Ischaemia is due to lack of oxygen, and in the overwhelming majority of ischaemic heart disease (IHD) cases this is due to reduced blood flow through coronary arteries narrowed or occluded by atherosclerosis. However, the left ventricular myocardium is also at risk

Box 1 Aneurysms

Definition
Abnormal dilatation of a vessel wall, which communicates with the lumen—almost always arterial

Pathogenesis

Inflammation
- Atherosclerotic aneurysm (abdominal aorta, iliac arteries, popliteal arteries)
- Polyarteritis nodosa
- Kawasaki disease (coronary arteries)

Infection (mycotic aneurysm)
- Syphilis
- Direct spread from adjacent infection

Congenital defect
- Berry aneurysm (Circle of Willis, see Chapter 14 Nervous System)

Metabolic
- Diabetes mellitus (retinal capillary microaneurysms)

Hypertension
- Charcot–Bouchard aneurysms (deep white matter of cerebral hemispheres)

Trauma

Complications
- Rupture with haemorrhage (often fatal if aorta or cerebral vessels involved)
- Compression of adjacent structures
- Thrombus formation (vessel occlusion and distal thromboembolism)
- Secondary infection
- Sclerosing periaortitis (dense fibrosis surrounding abdominal aortic aneurysm which can entrap ureters)

of ischaemia when there is pathological hypertrophy, for example in systemic hypertension or aortic valve stenosis. Under these conditions, cardiac perfusion may be insufficient to meet the metabolic needs of the increased muscle mass. Rarely, cardiac ischaemia can result from decreased oxygen-carrying capacity of the blood in severe anaemia (even though the coronary arteries may be normal).

Myocardial infarction

Cell death (necrosis) caused by ischaemia is known as infarction. Cardiac muscle cells cease to function within 30–60 seconds of loss of blood supply. Irreversible cell injury requires at least 20 minutes of anoxia (no oxygen). Cardiac muscle cells do not divide in post-natal life (i.e. they are 'permanent' cells) and infarcted myocardium is eventually replaced by fibrous scar tissue.

Regional (transmural) infarction—is caused by occlusion of a single coronary artery. The arterial blockage results from atherosclerosis complicated by thrombosis or by intraplaque haemorrhage, which rapidly expands the atheromatous plaque (see Fig. 2). The commonest sites for clinically significant coronary atherosclerosis are:

- proximal left anterior descending artery (up to 50%)
- right coronary artery (30%)
- left circumflex artery (up to 20%)
- left main coronary artery.

Regional infarction most frequently affects part of the anterior wall of the left ventricle, or part of the interventricular septum, with extension into the right ventricle in a small proportion of cases. Isolated right ventricular infarction is very uncommon.

The subendocardial region of the myocardium is the muscle area most vulnerable to hypoxia.

Subendocardial infarction—can occur when there is a global decrease in cardiac blood flow due to systemic hypotension ('shock'). Myocardial necrosis is usually limited to the inner third of the muscle but can involve the territory of more than one coronary artery.

Unusual causes of myocardial infarction include coronary artery dissection, arteritis or spasm.

Macroscopic and microscopic changes in myocardial infarction

- Less than 24 hours—microscopic changes only (increased eosinophilic staining of cardiac muscle cells, loss of nuclei, muscle cells become buckled).
- From 24 to 72 hours—infarct becomes apparent macroscopically at autopsy as an area of pallor or yellow discolouration, with a peripheral rim of haemorrhage. Microscopically the dead muscle fibres provoke an inflammatory response, initially consisting of neutrophil polymorphs, followed by macrophages. The infarct becomes soft.
- Up to 2–3 weeks—the dead tissue is removed and replaced by blood vessel proliferation and myofibroblasts (granulation tissue).
- Weeks to months—collagen is produced and the scar becomes progressively less cellular, less vascular and more fibrotic.

Biochemical markers of myocardial infarction

Necrotic cardiac muscle releases enzymes, which can be measured in the serum and are helpful in confirmation of the diagnosis.

- **Heart-specific troponins**—released 2–4 hours after cell death, remaining elevated for up to one week. Troponin T and I are highly specific for myocardial damage.
- **Creatine kinase (CK)**—starts to rise after a few hours of infarction, and falls again within 48 hours. CK is

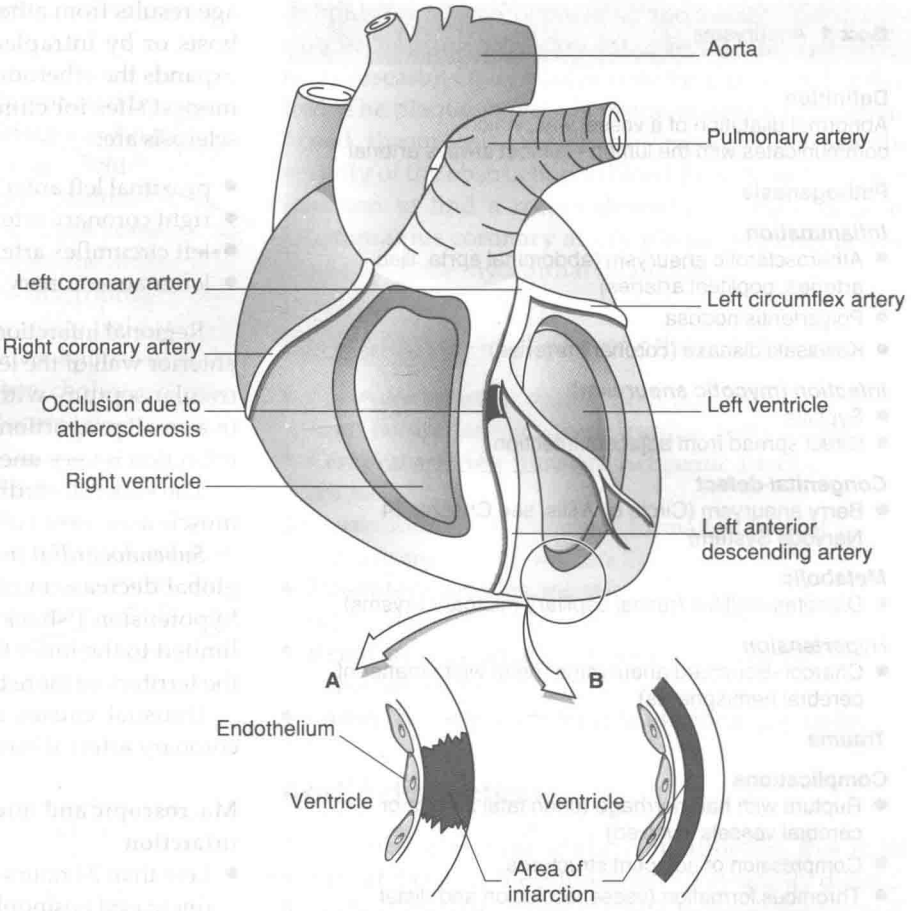

Fig. 2 Major coronary arteries and types of myocardial infarction: (**A**) regional and (**B**) subendocardial.

also released from injured skeletal muscle cells; measurement of the specific cardiac isoenzyme is therefore more diagnostically helpful.

- **Aspartate aminotransferase (AST)**—also non-specific as it is released by damaged liver cells.
- **Lactate dehydrogenase (LDH)**—peaks at 3–6 days and may remain elevated for two weeks. May be useful in patients presenting late after suspicious chest pain.

Complications of myocardial infarction

Immediate

- Arrhythmias
- Acute cardiac failure
- Cardiogenic shock
- Sudden death.

Early

- Infarct rupture (3–7 days).

Later

- Mural thrombosis
- Cardiac aneurysm.

Dressler's syndrome (pericarditis associated with circulating antibodies to heart muscle) occurs from two weeks to two years post infarction.

Reinfarction can occur at any time. Cardiac failure and arrhythmias may also be late complications. The presence of myocardial scarring increases the risk of sudden death from ventricular arrhythmia.

1.2 Hypertension, cardiomyopathies and myocarditis

Learning objectives

You should:

- Know the aetiology, risk factors and complications of hypertension, so as to be able to identify patient risk factors amenable to treatment by lifestyle modification, and to investigate patients appropriately for causes of secondary hypertension
- Understand the term cardiomyopathy, its classification, major causes and complications

Hypertension

Chronically raised systemic blood pressure is a major cause of morbidity and mortality. Hypertension can cause, or significantly contribute to:

- atherosclerosis
- hypertensive heart disease (left ventricular hypertrophy)
- chronic renal failure
- cerebrovascular disease (intracerebral haemorrhage, ruptured Berry aneurysm)
- retinopathy.

'Normal' blood pressure varies within a population and with age, but evidence suggests that a sustained pressure of 140/90 mmHg or greater is associated with increased risk of disease. Persistent diastolic blood pressure in excess of 100 mmHg requires treatment. Very high elevation (e.g. 240/120 mmHg) can result in accelerated disease—'malignant hypertension'.

In approximately 10% of cases, systemic hypertension is secondary to another disease (Box 2). The mechanism of primary hypertension is unclear but the following defects have been found in patients:

- abnormal renal excretion of sodium
- abnormal sodium and calcium metabolism in vascular smooth muscle
- abnormalities of renin–angiotensin mechanism, probably in part related to polymorphisms in key genes.

Family history, obesity and excessive alcohol intake are further associated factors. The aetiology of essential hypertension is complex and clearly involves a combination of genetic and environmental factors. Modest, but clinically significant, reductions in blood pressure may be achieved by weight loss, regular physical exercise, moderation of alcohol intake and possibly by reduction of salt in the diet.

Blood-vessel changes are similar in both primary and secondary hypertension, with homogenous thickening of arteriolar walls and narrowing of the vascular lumen ('hyaline arteriosclerosis'). Marked cellular proliferation ('onion skinning') and blood-vessel necrosis may occur in malignant hypertension. Hypertensive heart disease is characterised by concentric hypertrophy of the left ventricle.

Box 2 Secondary hypertension

Renal disease
- Glomerulonephritis
- Polycystic kidney disease
- Renal artery stenosis
- Chronic pyelonephritis
- Renal cell carcinoma

Endocrine disease
- Adrenal cortical tumours
- Cushing's disease
- Phaeochromocytoma
- Diabetes mellitus
- Acromegaly

Coarctation of the aorta

Iatrogenic
- Steroid therapy

Note that hypertension can be either a cause or a consequence of chronic renal impairment

Cardiomyopathy

Cardiomyopathy is defined as heart-muscle disease not caused by ischaemic, hypertensive, valvular or congenital heart disease. Although uncommon, cardiomyopathies are an important cause of cardiac failure and sudden death in young adults. The aetiology of specific cardiomyopathies is shown in Box 3. Ninety per cent are of the dilated type.

Hypertrophic cardiomyopathy (HOCM)—is characterised by asymmetrical left ventricular hypertrophy (as opposed to the concentric hypertrophy seen in hypertensive heart disease and aortic valve stenosis). The interventricular septum is particularly thickened. Microscopically, the cardiac muscle cells are enlarged and haphazardly organised (myocyte disarray). There is often fibrosis between muscle cells. Many cases show autosomal dominant inheritance. Genetic defects include cardiac myosin genes on chromosome 14. Complications of hypertrophic cardiomyopathy include:

- atrial fibrillation
- atrial thrombus and systemic embolism
- infective endocarditis of the mitral valve
- cardiac failure
- sudden death.

Box 3 Cardiomyopathy

Genetic
- Hypertrophic cardiomyopathy (HOCM)
- Haemochromatosis

Post-infectious
- Dilated cardiomyopathy (many cases are probably caused by viral infection)

Toxic
- Alcoholic cardiomyopathy
- Drug induced (chemotherapy agents—adriamycin commonest)

Metabolic
- Amyloid heart disease

Idiopathic

Dilated cardiomyopathy—is characterised by dilatation of all four cardiac chambers with progressive cardiac failure. The heart is typically enlarged (2–3 times normal weight) and flabby at autopsy. Mural thrombi may be present. The microscopic findings are not specific, but there is often patchy ventricular fibrosis. Cardiomyopathy caused by alcohol, chemotherapy agents and haemochromatosis is of the dilated type.

Restrictive cardiomyopathy—describes a condition of 'stiff' ventricles, which fail to relax, impeding diastolic filling. The ventricles are of normal size but the atria are dilated. Microscopically there is non-specific myocardial scarring. Causes include radiation fibrosis and cardiac involvement by amyloid (see Box 4).

Myocarditis

Myocarditis is inflammation of the heart muscle. It may be asymptomatic, or cause:

- acute cardiac failure
- sudden death
- chronic cardiac failure (usually due to dilated cardiomyopathy).

Acute myocarditis may be suggested at autopsy by a pale, flabby heart, but histological examination is necessary for diagnosis. Microscopically there is multifocal myocardial chronic inflammation associated with cardiac muscle-cell death. The aetiology of myocarditis is shown in Box 5.

Box 4 Amyloid

Definition
An abnormal extracellular accumulation of protein with specific physical and chemical properties (including β-pleated sheet conformation on X-ray crystallography).

Demonstration
On light microscopy, amyloid appears pink in tissue sections stained with Congo Red. When sections are viewed with polarised light, the amyloid changes colour to bright green. Amyloid fibrils can also be recognised on electron microscopy.

All forms of amyloid contain a glycoprotein (P component) as a minor constituent. The major amyloid protein varies and is reflected in the disease classification.

Classification
- AL amyloid (light chains of immunoglobulins—multiple myeloma)
- AA amyloid (serum amyloid A protein—long-standing chronic inflammation)
- Haemodialysis associated amyloid (β_2-microglobulin)
- Hereditary amyloidosis (serum amyloid A protein or transthyretin)
- Localised cardiac amyloid (transthyretin)
- Isolated atrial amyloid (atrial natriuretic factor)
- Endocrine-associated amyloid (calcitonin in medullary carcinoma of thyroid)

Box 5 Causes of myocarditis

Infection
- Viral (Coxsackie, ECHO)
- Bacterial (meningococcus)
- Fungal (Candida)
- Parasitic (Chagas' disease, toxoplasmosis)

Immune-mediated
- Post-infective (including rheumatic fever)
- Systemic lupus erythematosus
- Transplant rejection

Idiopathic
- Sarcoidosis

1.3 Congenital heart disease

Learning objectives

You should:

- Know the commonest types of congenital heart disease and the aetiological factors that may cause congenital cardiac defects
- Understand what is meant by cyanotic congenital heart defects

Congenital heart disease—describes abnormalities of the heart and major vessels present at birth. The incidence in live-born infants is approximately 1 in 200. The common lesions include:

- isolated defects in cardiac chamber walls—atrial septal defect, ventricular septal defect
- persistence of embryonic structures—patent foramen ovale, patent ductus arteriosus
- stenosing lesions ('narrowings')—aortic valve stenosis, pulmonary stenosis, coarctation of the aorta
- transposition of the great arteries
- complex anomalies—Fallot's tetralogy.

The aetiology is unknown in many cases but there is evidence of genetic predisposition. A small percentage of cases are associated with chromosome abnormalities, particularly Turner's syndrome (45XO syndrome), with coarctation of the aorta, and Down's syndrome (trisomy 21), with atrial and ventricular septal defects. Intrauterine infection with rubella may cause multiple

congenital cardiac defects. Atrial septal defects are a feature of fetal alcohol syndrome.

Some congenital heart defects, such as small atrial septal defects, may be clinically inconsequential or present only in later adult life.

Abnormal connections between the cardiac chambers permit shunting of blood from one side of the circulation to the other. In post-natal life, atrial and ventricular septal defects usually cause shunting of blood from the left side of the heart (high pressure) to the right side (low pressure). This increases the work of the right ventricle (pressure and volume overload) and can lead to right ventricular hypertrophy and pulmonary hypertension. Structural narrowing of pulmonary arteries occurs in response to chronically raised pulmonary vascular pressure, and the flow of blood through the shunt may be reversed (i.e. it becomes a right-to-left shunt, known as Eisenmenger's syndrome).

Some congenital cardiac defects cause right-to-left blood shunts from their onset. Deoxygenated blood bypasses the lungs and passes directly from the right heart into the systemic circulation. If the shunt is large enough, cyanosis will be clinically apparent as blue discolouration of the skin and nail beds.

Cyanotic congenital heart defects include:

Fallot's tetralogy

- Ventricular septal defect.
- Outflow obstruction to the right ventricle.
- Aorta overriding the ventricular septal defect.
- Right ventricular hypertrophy.

Transposition of the great vessels

- The aorta emerges from the right ventricle and the pulmonary artery arises from the left ventricle. To be compatible with post-natal life, there must also be either an atrial or ventricular septal defect.

1.4 Valvular heart disease

Learning objectives

You should:

- Understand the pathological causes and pathophysiological consequences of stenosis and incompetence of all the cardiac valves, but particularly the mitral and aortic valves
- Understand the pathology of infective endocarditis, so as to be able to identify patients at risk and, when appropriate, ensure prophylactic treatment is given

Valvular stenosis and incompetence

Damage to the cardiac valves can result in stenosis (narrowing of the valve orifice with obstruction to blood flow) or incompetence (regurgitation of blood back through a leaking valve). Valve disease can be congenital (see Section 1.3) or acquired. In non-congenital cases the clinically significant lesions almost always affect the mitral or aortic valves.

Abnormal movement of deformed valves and abnormal blood flow causes characteristic murmurs and added sounds on cardiac auscultation.

Rheumatic heart disease

Rheumatic heart disease (RHD) is a major cause of acquired mitral valve disease. The incidence has dramatically decreased in the UK over recent decades but is still relatively common in Third World countries. The initiating event is usually a pharyngeal infection by Group A β-haemolytic streptococci, followed several weeks later by rheumatic fever (RF), an immunologically mediated multisystem disorder. RF results from the cross-reaction of antistreptococcal antibodies with normal host tissues—direct bacterial infection does not occur. During acute RF there is often a pancarditis with inflammation of pericardium, myocardium and endocardium. Myocarditis can occasionally cause acute heart failure, arrhythmias and death. However, it is recurrent attacks of RF that produce the most significant cardiac lesions. Repeated acute inflammation of the endocardium covering heart valves leads to fibrosis and deformity. Valve leaflets become thickened and fused, resulting in 'fishmouth' or 'buttonhole' mitral valve stenosis. The aortic valve may also be affected. Complications include:

- atrial fibrillation
- valvular and atrial thrombus formation with systemic embolism
- cardiac failure
- infective endocarditis.

Mitral valve prolapse

Mitral valve prolapse, also known as 'floppy mitral valve', is a common condition involving approximately 5% of adults. Young females and Marfan's syndrome patients are particularly affected. One or both mitral valve leaflets are enlarged and prolapse into the left atrium during systole. The condition is usually incidental but occasionally can cause mitral regurgitation, infective endocarditis, valvular thrombosis or arrhythmias.

Infective endocarditis (IE)

Infection of the endocardium or vascular endothelium can occur in:

Table 1 Causes and consequences of valvular heart disease

Valve lesion	Causes	Consequences
Mitral stenosis	Rheumatic heart disease	Increased left atrial pressure; left atrial dilatation, atrial fibrillation Increased pulmonary venous pressure, leading to pulmonary hypertension and right ventricular hypertrophy
Mitral incompetence	Rheumatic heart disease Infective endocarditis Left ventricular dilatation Papillary muscle ischaemia, fibrosis or rupture Mitral valve prolapse Leaking prosthetic valve	Left atrial dilatation Left ventricular hypertrophy, due to volume overload (Acute mitral incompetence caused by rupture of necrotic papillary muscle in myocardial infarction can result in acute cardiac failure)
Aortic stenosis	Senile calcification of normal valve Calcification of congenitally bicuspid valve Rheumatic heart disease	Left ventricular hypertrophy, due to pressure overload (increased gradient across stenotic valve); ischaemia of hypertrophic ventricular myocardium (angina, arrhythmias, cardiac failure, sudden death)
Aortic incompetence	Rheumatic heart disease Infective endocarditis Leaking prosthetic valve Aortic root dilatation (aortic dissection, arthritis, Marfan's syndrome, syphilis)	Left ventricular hypertrophy, due to volume overload; left ventricular failure

- previously damaged heart valves (e.g. RHD, calcific aortic stenosis)
- congenital heart disease
- prosthetic heart valves or vascular tissue
- normal heart valves (uncommon causes, acute severe endocarditis).

IE is usually a chronic/subacute illness caused by low-virulence organisms colonising abnormal tissue. Normal heart valves can be infected by high virulence bacteria or fungi, especially in IV drug abusers or the immunosuppressed (AIDS, diabetes, alcoholics, transplant recipients).

Common pathogenetic bacteria in IE include:

- *Streptococcus viridans*—normal flora of upper respiratory tract; low virulence.
- *Streptococcus faecalis*—normal flora of perineum and gut; low virulence.
- *Staphylococcus aureus*—can be member of normal mucocutaneous flora; high virulence.
- *Staphylococcus epidermidis*—normal skin flora; low virulence.

Other organisms include *Coxiella*, *E. coli*, *Chlamydia* and *Candida*.

Colonisation occurs following transient bacteraemia (bacteria floating in the bloodstream, distinct from septicaemia, which is clinical illness caused by bacteria multiplying in the blood). Such bacteraemia may result from dental work, endoscopy, surgery or established infection elsewhere in the body. Organisms may be introduced in prosthetic material or by intravascular catheters such as central venous pressure (CVP) lines. Patients known to have damaged or prosthetic heart valves are at risk of developing IE after episodes of transient bacteraemia with low virulence organisms, and so require prophylactic antibiotic therapy prior to undergoing any procedure that might seed organisms into the bloodstream.

Layers of microorganisms and fibrinous inflammatory debris build up at the site of colonisation, forming

Box 6 Infective endocarditis: clinical notes

Acute endocarditis
Typically presents with fever and acute valvular incompetence. In IV drug abusers the tricuspid valve is often affected (organisms are injected directly into arm or leg veins). Blood cultures will often be positive for the causative virulent organism. Early antibiotic treatment is necessary and emergency valve replacement may be indicated if valve destruction has caused cardiac failure.

Subacute endocarditis
May give rise to non-specific chronic symptoms of malaise, fatigue, weight loss and anorexia. There is often a fluctuating pyrexia and a heart murmur (particularly a regurgitant or changing murmur). Extracardiac clinical features frequently reflect embolisation of cardiac vegetations, immune complex deposition or sepsis, and include:

- Splinter haemorrhages in the nails
- Petechial haemorrhages in the skin and conjunctivae
- Glomerulonephritis
- Cerebral infarction (or history of transient ischaemic attacks)
- Finger clubbing
- Splenomegaly
- Disseminated abscesses or infarcts