PasTest
Dedicated to your success

THE NO.1 BEST SELLER FROM PasTest

Essential Revision Notes for MRCP

Fourth Edition

Philip A Kalra

Essential Revision Notes for MRCP Fourth Edition

Dedication

To my wife, Marian, and children, Michael, Gabriella and Alicia, who will always inspire

Essential Revision Notes for MRCP Fourth Edition

edited by

Philip A Kalra MA MB BChir FRCP MD
Consultant and Honorary Professor of Nephrology,
Salford Royal NHS Foundation Trust and The University of Manchester

Egerton Court
Parkgate Estate
Knutsford
Cheshire WA16 8DX
Telephone: 01565 755226

First published 1999
Reprinted 1999
Revised edition 2002
Reprinted 2003
Second edition 2004
Third edition 2009
Reprinted 2009
Fourth edition 2014

ISBN: 1 905 635 92 4

978 1 905635 92 4
ePub ISBN: 978 1 909491 97 7
Mobi ISBN: 978 1 909491 96 0

A catalogue record for this book is available from the British Library.

Original design and typesetting by EDITEXT, Derbyshire (01457 857622).
Fourth edition text prepared by Keytec Typesetting Ltd, Bridport, Dorset
Printed and bound in the UK by Page Bros (Norwich) Ltd.

Contents

Contributors to Fourth Edition

Emma Burkitt Wright MBChB PhD MRCP(UK)
Specialist Registrar and Honorary Clinical Research Fellow, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals Foundation Trust and University of Manchester, *Chapter 7 Genetics*

Louise Byrd MBBS, MRCOG, Dip RCR/RCOG Cert. Medical Education
Consultant in High Risk Obstetrics and Maternal Medicine with special interest in Medical Education, Central Manchester Foundation Trust, Manchester, *Chapter 12 Maternal Medicine*

Justin E R Davies BSc, MBBS, PhD, MRCP
Senior Research Fellow and Consultant Cardiologist, Imperial College London, *Chapter 1 Cardiology*

James Galloway MBChB, MRCP, MSc, PhD, CHP
Clinical Lecturer / Honorary Consultant Rheumatologist, Department of Rheumatology, King's College Hospital, London, *Chapter 10 Immunology*

Sumithra Giritharan MBChB MRCP(UK)
Specialist Registrar, Department of Diabetes and Endocrinology, Salford Royal NHS Foundation Trust, Manchester, *Chapter 4 Endocrinology*

Ben Goorney MBChB FRCP
Consultant Genito-Urinary Physician, Department of Genito-Urinary Medicine, Hope Hospital, Salford, *Chapter 8 Genito-Urinary Medicine and AIDS*

Heather Green BSc, MBChB (Hons), MRCP(UK), Certificate in Respiratory Medicine
Respiratory Registrar/Research Fellow in Cystic Fibrosis, Manchester Adult Cystic Fibrosis Centre, University Hospital of South Manchester, Manchester, *Chapter 19 Respiratory Medicine*

Matthew Jones MD MRCP
Consultant Neurologist and Clinical Teaching Fellow, Department of Neurology, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, *Chapter 16 Neurology*

Philip A Kalra MA MB BChir FRCP MD
Consultant and Honorary Professor of Nephrology, Salford Royal NHS Foundation Trust and University of Manchester, *Chapter 15 Nephrology*

Eirini Koutoumanou BSc MSc
Senior Teaching Fellow, UCL Institute of Child Health, Population, Policy, Practice Programme, London, *Chapter 21 Statistics*

Tara Kearney MB BS, BSc(Hons), FRCP, MD
Consultant Endocrinologist, Salford Royal Foundation NHS Trust, Manchester, *Chapter 4 Endocrinology*

Mohit Kumar MBChB MRCP
Specialist Trainee, Department of Diabetes, Endocrinology and Weight Management, Salford Royal Foundation Trust, Salford Manchester, *Chapter 4 Endocrinology*

Simon Lal BSc MBChB PhD FRCP
Consultant Gastroenterologist, Salford Royal NHS Foundation Trust, Salford, *Chapter 6 Gastroenterology*

Michael McMahon BSc MBChB FRCP
Consultant Physician and Rheumatologist, Department of Rheumatology, Dumfries and Galloway Royal Infirmary, Dumfries, *Chapter 20 Rheumatology*

Sukhjinder S Nijjer BSc (Hons) MBChB (Hons) MRCP(UK)
Cardiology Registrar, Hammersmith Hospital and the International Centre for Circulatory Health, Imperial College London, *Chapter 1 Cardiology*

Keith Patterson FRCP FRCPath
Consultant Haematologist, London, *Chapter 9 Haematology*

James Ritchie MBChB, MRCP PhD
Clinical Research Fellow, Department of Renal Medicine, Salford Royal Hospital, Salford, Manchester, *Chapter 5 Epidemiology*

Helen Robertshaw BSc(Hons) MBBS FRCP
Consultant in Dermatology, Royal Bournemouth and Christchurch Hospitals, Bournemouth, *Chapter 3 Dermatology*

David Rog BMedSci (Hons), BMBS, FRCP, MD
Consultant Neurologist and Honorary Lecturer, Department of Neurology, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, *Chapter 16 Neurology*

Liz Sampson MBChB MRCPsych MD MSc
Clinical Senior Lecturer In Old Age Psychiatry, Division of Psychiatry, University College London. Consultant in Liaison Psychiatry, Barnet Enfield and Haringey Mental Health Trust London, *Chapter 18 Psychiatry*

Kirk W Siddals BSc PhD
Research Fellow, Vascular Research, Salford Royal Hospital, Manchester, *Chapter 14 Molecular*

Medicine

Smeeta Sinha MBChB PhD MRCP FRCP
Consultant and Honorary Senior Lecturer in Nephrology, Salford Royal NHS Foundation Trust, Salford, *Chapter 13 Metabolic Diseases*

Katherine Smyth MBChB MRCP FRCOpth
Consultant Ophthalmologist, Royal Bolton Hospital, Bolton, *Chapter 17 Ophthalmology*

Clare L van Halsema MBChB MSc MD MRCP DTM&H Dip HIV Med
Specialist Registrar in Infectious Diseases, Department of Infectious Diseases and Tropical Medicine, North Manchester General Hospital, Manchester, *Chapter 11 Infectious Diseases and Tropical Medicine*

Dipesh H Vasant MB ChB, MRCP(UK)
Clinical Research Fellow and Specialist Registrar in Gastroenterology and Medicine, The University of Manchester Clinical Sciences Building, Salford Royal NHS Trust, *Chapter 6 Gastroenterology*

Stephen Waring PhD FRCP (Edin) FRCP FBPharmacolS
Consultant in Acute Medicine & Toxicology, Acute Medical Unit, York Teaching Hospital NHS Foundation Trust, York, *Chapter 2 Clinical Pharmacology, Toxicology and Poisoning*

Contributors to Third Edition

Emma Burkitt Wright MBCh MPhil MRCP(UK)
Academic Clinical Fellow, Medical Genetics Research Group and University of Manchester, St Mary's Hospital, Manchester *Genetics*

Louise Byrd MRCOG
Specialist Registrar in Obstetrics and Gynaecology, North West Region *Maternal Medicine*

Colin M Dayan MA MBBS FRCP PhD
Consultant Senior Lecturer in Medicine, Head of Clinical Research, URCN, Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol *Endocrinology*

Ben Goorney MBChB FRCP
Consultant Genito-Urinary Physician, Department of Genito-Urinary Medicine, Hope Hospital, Salford *Genito-urinary Medicine and AIDS*

Philip A Kalra MA MB BChir FRCP MD
Consultant Nephrologist and Honorary Reader, Hope Hospital, Salford *Nephrology*

Mike McMahon BSc MBChB FRCP
Consultant Physician and Rheumatologist, Department of Rheumatology, Dumfries and Galloway Royal Infirmary, Dumfries *Immunology & Rheumatology*

John Paisey DM MRCP
Consultant Cardiac Electrophysiologist, Royal Bournemouth Hospital, Bournemouth *Cardiology*

Keith Patterson FRCP FRCPath
Consultant Haematologist, Department of Haematology, University College London Hospitals, London *Haematology*

Jaypal Ramesh MRCP(UK)
Consultant Gastroenterologist, University Hospital of South Manchester, NHS Foundation Trust, Manchester *Gastroenterology*

Geraint Rees BA BMBCh MRCP PhD
Wellcome Senior Clinical Fellow, Institute of Cognitive Neuroscience, University College London *Neurology*

Helen Robertshaw BSc(Hons) MBBS MRCP

Specialist Registrar in Dermatology, Southampton University Hospitals Trust, Southampton *Dermatology*

Liz Sampson MBChB MRCPsych MD
Lecturer in Old Age Psychiatry, Royal Free and University College Medical School, University College London *Psychiatry*

Kirk W Siddals BSc PhD
Research Fellow, Vascular Research, Salford Royal Hospital, Stott Lane, Salford *Molecular Medicine*

Smeeta Sinha MBChB MRCP
Specialist Registrar Nephrology, Salford Royal NHS Foundation Trust, Salford, Manchester *Metabolic Diseases*

Katherine Smyth MBChB MRCP FRCOpth
Consultant Opthalmologist, Royal Bolton Hosptial, Bolton *Ophthalmology*

Clare L van Halsema MBChB MRCP DTM&H
Specialist Registrar in Infectious Diseases, Monsall Unit, Department of Infectious Diseases and Tropical Medicine, North Manchester General Hospital, Manchester *Infectious Diseases*

Angie Wade MSc PhD CStat ILTM
Senior Lecturer in Medical Statistics, Institute of Child Health and Great Ormond Street Hospital, London *Statistics*

Deborah A Wales MBChB MRCP FRCA
Consultant Respiratory Physician, Nevill Hall Hospital, Brecon Road, Abergavenny, Monmouthshire *Respiratory Medicine*

GaryWhitlock BHB MBChB MPH(Hons) PhDFAFPHM
Clinical Research Fellow, Clinical Trial Service Unit, University of Oxford *Epidemiology*

Stephen Waring MRCP(UK)
Consultant Physician in Acute Medicine and Toxicology, The Royal Infirmary of Edinburgh *Clinical Pharmacology*

Permissions

The following have been reproduced with kind permission from BMJ Publishing Group Ltd.

Cardiology

Fig 1.5 – Radionuclide myocardial perfusion imaging. Left panel shows the gamma camera. Right panel shows a reversible inferolateral perfusion defect: left column stress, right column rest.

Fig 1.6 – Mechanism for atrioventricular nodal re-entry tachycardia

Fig 1.7 – Mechanism for atrioventricular re-entry tachycardia

Maternal Medicine

Table 12.4 – Specific renal diseases and pregnancy

Neurology

Figure 16.2 – Demonstrating how the ‘shape’ of three common neurological conditions – seizures, transient ischaemic attacks and migraine – and their positive and negative neurological features in the history help to differentiate them.

The following images in this book have been reproduced with kind permission from Science Photo Library.

Immunology

Fig 10.3 – Angioedema on the tongue

Preface to the Fourth Edition

I am delighted that 'Essential Revision Notes for MRCP' has retained it's place as one of the key texts for preparation for the MRCP over a period now extending beyond 15 years. In this latest edition there has been a significant revision of the text in all of the chapters by experts in the subject, and the material has been brought right up to date with coverage of the latest clinical developments in the subject areas.

We continue to use the same successful style of layout within the Essential Revision Notes (ERN) with emphasis upon 'user-friendliness' with succinct text, bullet points and tables. The double-column format enhances readability and revision. The aim is to provide the practising physician with accessible, concise and up-to-date core knowledge across all of the subspecialties of medicine. For candidates who are preparing for the MRCP, it fills a unique gap between large detailed textbooks of medicine and those smaller texts which concentrate specifically on how to pass the examinations. However, many physicians use the ERN as a career-long companion to be used as a concise source of reference long after they have successfully collected their exam certificates.

A special thanks goes to our skilled team of contributing authors for their outstanding efforts which have ensured that this new edition maintains the standard set by previous editions. I am also particularly grateful to Cathy Dickens, who has been a key contributor to the ERN effort since it's initiation in 1998, and to Brad Fallon, for co-ordinating the book production process at PasTest.

Philip A Kalra
Consultant and Honorary Professor of Nephrology
Salford Royal NHS Foundation Trust and University of Manchester

Chapter 1
Cardiology

CONTENTS

Appendix II

Summary of further trials in cardiology

Cardiology

1.1 INTRODUCTION

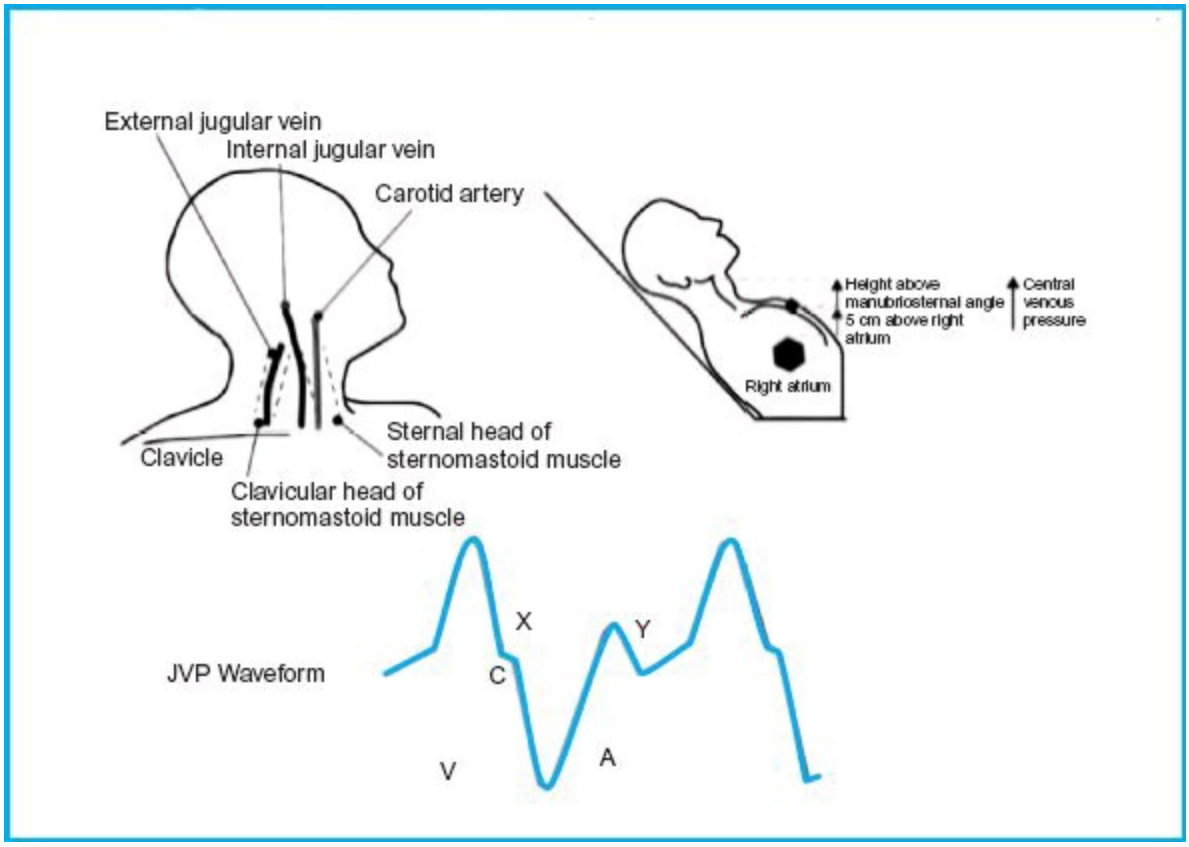
Patients with cardiovascular disease form a large part of clinical work and accordingly have prominence in the MRCP examination. Ischaemic heart disease, valvular disease and arrhythmic disorders have the largest preponderance of questions. Many of the conditions have overlapping causes and cardiac pathophysiology is such that one condition can lead to another. Understanding the pathophysiology will allow clinicians to unpick diagnoses, understand the diseases and answer examination questions more effectively.

1.2 CLINICAL EXAMINATION

1.2.1 Jugular venous pressure

This is an essential clinical sign that reflects patient filling status and is essential to detect for correct fluid management. The jugular venous pressure (JVP) reflects right atrial pressure, and in healthy individuals at 45° is 3 cm in vertical height above the sternal angle (the angle of Louis, the manubriosternal junction). Inspiration generates negative intrathoracic pressure and a suction of venous blood towards the heart, causing the JVP to fall (Figure 1.1).

Figure 1.1 The location and wave-form of the jugular venous pressure (JVP). The JVP must be assessed with the patient at 45°



Normal waves in the JVP

The a wave
Due to atrial contraction – actively push up superior vena cava (SVC) and into the right ventricle (may cause an audible S4).

The c wave
An invisible flicker in the *x* descent due to closure of the tricuspid valve, before the start of ventricular systole.

The *x* descent
Downward movement of the heart causes atrial stretch and a drop in pressure.

The v wave
Due to passive filling of blood into the atrium against a closed tricuspid valve.

The *y* descent
Opening of the tricuspid valve with passive movement of blood from the right atrium to the right ventricle (causing an S3 when audible).

Causes of a raised JVP

1. Raised JVP with normal waveform:
   - Heart failure – biventricular or isolated right heart failure
   - Fluid overload of any cause
   - Severe bradycardia.

   Raised JVP upon inspiration and drops with expiration: **Kussmaul's sign** is the opposite of what occurs in health and implies that the right heart chambers cannot increase in size to

2. accommodate increased venous return. This can be due to pericardial disease (constriction) or fluid in the pericardial space (pericardial effusion and cardiac tamponade).

3. Raised JVP with loss of normal pulsations: SVC syndrome is obstruction caused by mediastinal malignancy, such as bronchogenic malignancy, which causes head, neck and/or arm swelling.

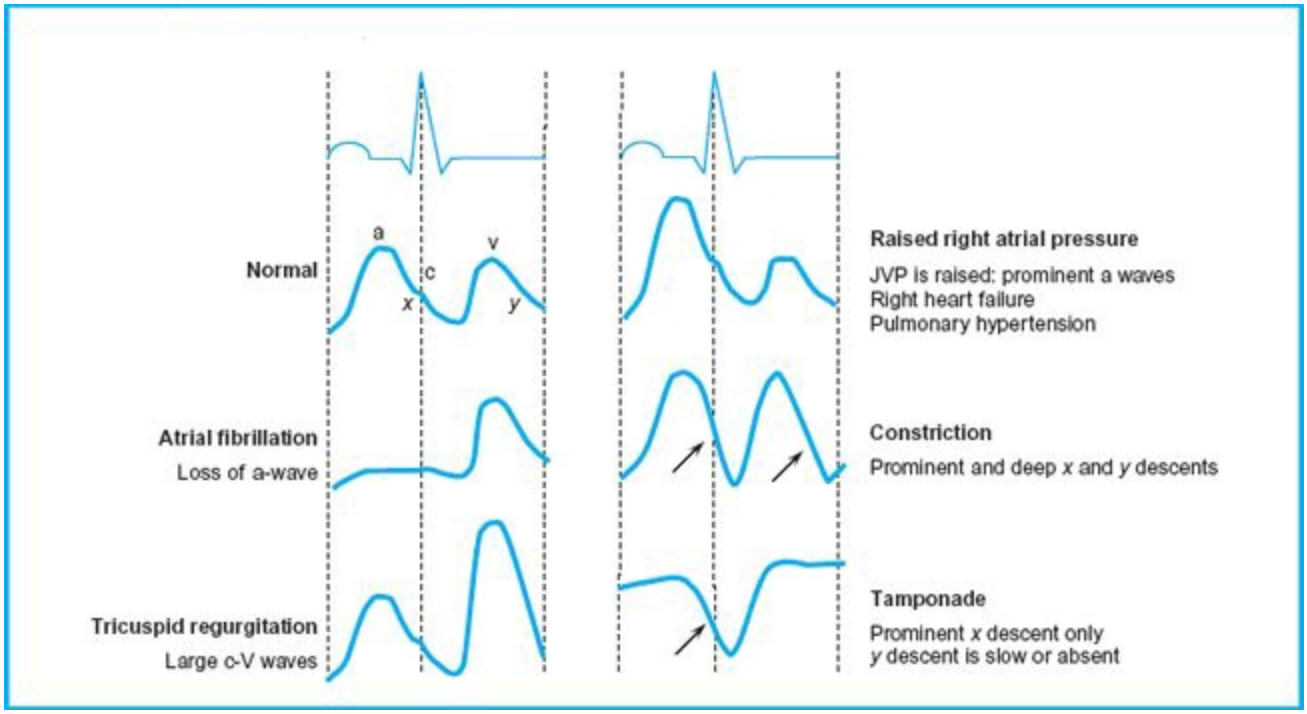
Pathological waves in the JVP

This is a common source of MRCP Part 1 questions. See Table 1.1 and Figure 1.2 for these waves.

Table 1.1 Pathological waves in the jugular venous pressure (JVP)

a waves	Absent	Atrial fibrillation – no co-ordinated contraction
	Large	Tricuspid stenosis, right heart failure, pulmonary hypertension
	Cannon	Caused by atrioventricular dissociation – allowing the atria and ventricles to contract at same time: Atrial flutter and atrial tachycardias Third-degree ('complete') heart block Ventricular tachycardia and ventricular ectopics
v waves	Giant	Tricuspid regurgitation – technically a giant 'c-V' wave
x descent	Steep	Tamponade and cardiac constriction
		If steep *x* descent only, then tamponade
y descent	Steep	Cardiac constriction
	Slow	Tricuspid stenosis

Figure 1.2 Different JVP morphologies can reflect different disease states



1.2.2 Arterial pulse associations

The radial arterial pulse is suitable for assessing the rate and rhythm, and whether it is collapsing. The central arterial pulses, preferably the carotid, are used to assess the character.

Absent radial pulse

- Iatrogenic: post-catheterisation or arterial line
- Blalock–Taussig shunt for congenital heart disease, eg tetralogy of Fallot
- Aortic dissection with subclavian involvement
- Trauma
- Takayasu's arteritis
- Peripheral arterial embolus.

Pathological pulse characters

- **Collapsing**: aortic regurgitation, arteriovenous fistula, patent ductus arteriosus (PDA) or other large extracardiac shunt
- **Slow rising**: aortic stenosis (delayed percussion wave)
- **Bisferiens**: a double shudder due to mixed aortic valve disease with significant regurgitation (tidal wave second impulse)
- **Jerky**: hypertrophic obstructive cardiomyopathy
- **Alternans**: occurs in severe left ventricular dysfunction. The ejection fraction is reduced meaning the end-diastolic volume is elevated. This may sufficiently stretch the myocytes (Frank–Starling physiology) to improve the the ejection fraction of the next heart beat. This leads to pulses that alternate from weak to strong
- **Paradoxical (pulsus paradoxus):** an excessive reduction in the pulse with inspiration (drop in

- systolic BP >10 mmHg) occurs with left ventricular compression, tamponade, constrictive pericarditis or severe asthma as venous return is compromised.

1.2.3 Cardiac apex

The cardiac apex pulsation reflects the ventricle striking the chest wall during isovolumetric contractions, and gives an indication of the position of the left ventricle and it size. It is typically palpable in the fifth intercostal space in the midclavicular line.

Absent apical impulse

- Obesity/emphysema
- Right pneumonectomy with displacement
- Pericardial effusion or constriction
- Dextrocardia (palpable on right side of chest)

Pathological apical impulse

- **Heaving**: left ventricular hypertrophy (LVH) (and all its causes), sometimes associated with palpable fourth heart sound
- **Thrusting/hyperdynamic**: high left ventricular volume (eg in mitral regurgitation, aortic regurgitation, PDA, ventricular septal defect)
- **Tapping**: palpable first heart sound in mitral stenosis
- **Displaced and diffuse/dyskinetic**: left ventricular impairment and dilatation (eg dilated cardiomyopathy, myocardial infarction [MI])
- **Double impulse**: with dyskinesia is due to left ventricular aneurysm; without dyskinesia in hypertrophic cardiomyopathy (HCM)
- **Pericardial knock**: constrictive pericarditis
- **Parasternal heave**: due to right ventricular hypertrophy (eg atrial septal defect [ASD], pulmonary hypertension, chronic obstructive pulmonary disease [COPD], pulmonary stenosis)
- **Palpable third heart sound**: due to heart failure and severe mitral regurgitation.

1.2.4 Heart sounds

Abnormalities of first heart sounds are given in Table 1.2 and of second heart sounds in Table 1.3.

Third heart sound (S3)

Due to the passive filling of the ventricles on opening of the atrioventricular (AV) valves, audible in normal children and young adults. Pathological in cases of rapid left ventricular filling (eg mitral regurgitation, ventricular septal defect [VSD], congestive cardiac failure and constrictive pericarditis).

Table 1.2 Abnormalities of the first heart sound (S1): closure of mitral and tricuspid valves

Loud	Soft	Split	Variable
Mobile mitral stenosis	Immobile mitral stenosis	RBBB	Atrial fibrillation
Hyperdynamic states	Hypodynamic states	LBBB	Complete heart block
Tachycardic states	Mitral regurgitation	VT	
Left-to-right shunts	Poor ventricular function	Inspiration	
Short PR interval	Long PR interval	Ebstein's anomaly	

LBBB, left bundle-branch block; RBBB, right bundle-branch block; VT, ventricular tachycardia.

Table 1.3 Abnormalities of the second heart sound (S2): closure of aortic then pulmonary valves (<0.05 s apart)

Intensity	Splitting	
Loud*:** Systemic hypertension (loud A2) Pulmonary hypertension (loud P2) Tachycardic states ASD (loud P2) ***Soft or absent: Severe aortic stenosis	***Fixed*:** ASD ***Widely split:*** RBBB Pulmonary stenosis Deep inspiration Mitral regurgitation	***Single S2:*** Severe pulmonary stenosis/aortic stenosis Hypertension Large VSD Tetralogy of Fallot Eisenmenger's syndrome Pulmonary atresia Elderly ***Reversed split S2:*** LBBB Right ventricular pacing PDA Aortic stenosis

A2, aortic second sound; ASD, atrial septal defect; LBBB, left bundle-branch block; P2, pulmonary second sound; PDA, patent ductus arteriosus; RBBB, right bundle-branch block; VSD, ventricular septal defect.

Fourth heart sound (S4)

Due to the atrial contraction that fills a stiff left ventricle, such as in LVH, amyloid, HCM and left

ventricular ischaemia. It is absent in atrial fibrillation.

Causes of valvular clicks

- **Aortic ejection**: aortic stenosis, bicuspid aortic valve
- **Pulmonary ejection**: pulmonary stenosis
- **Mid-systolic**: mitral valve prolapse.

Opening snap

In mitral stenosis an opening snap (OS) can be present and occurs after S2 in early diastole. The closer it is to S2 the greater the severity of mitral stenosis. It is absent when the mitral cusps become immobile due to calcification, as in very severe mitral stenosis.

1.3 CARDIAC INVESTIGATIONS

1.3.1 Electrocardiography

Both the axis and sizes of QRS vectors give important information. Axes are defined as:

- −30° to +90°: normal
- −30° to −90°: left axis
- +90° to +180°: right axis
- −90° to −180°: indeterminate.

Tip: if the QRS is positive in leads 1 and aVF the axis is normal.

The causes of common abnormalities are given in the box below. Electrocardiography (ECG) strips illustrating typical changes in common disease states are shown in Figure 1.3.

Causes of common abnormalities in the ECG

- **Causes of left axis deviation**
  - Left bundle-branch block (LBBB)
  - Left anterior hemi-block (LAHB)
  - LVH
  - Primum ASD
  - Cardiomyopathies
  - Tricuspid atresia
- **Low-voltage ECG**
  - Pulmonary emphysema
  - Pericardial effusion
  - Myxoedema

- Severe obesity
- Incorrect calibration
- Cardiomyopathies
- Global ischaemia
- Amyloid

- **Causes of right axis deviation**
  - Infancy
  - Right bundle-branch block (RBBB)
  - Right ventricular hypertrophy (eg lung disease, pulmonary embolism, large secundum ASD, severe pulmonary stenosis, tetralogy of Fallot)
- **Abnormalities of ECGs in athletes**
  - Sinus arrhythmia
  - Sinus bradycardia
  - First-degree heart block
  - Wenckebach's phenomenon
  - Junctional rhythm

Clinical diagnoses that can be made from the ECG of an asymptomatic patient

- Atrial fibrillation
- Complete heart block
- HCM
- ASDs (with RBBB)
- Long QT and Brugada's syndromes
- Wolff–Parkinson–White (WPW) syndrome (δ waves)
- Arrhythmogenic right ventricular dysplasia (cardiomyopathy).

Short PR interval

This is rarely <0.12 s; the most common causes are those of pre-excitation involving accessory pathways or of tracts bypassing the slow region of the AV node; there are other causes.

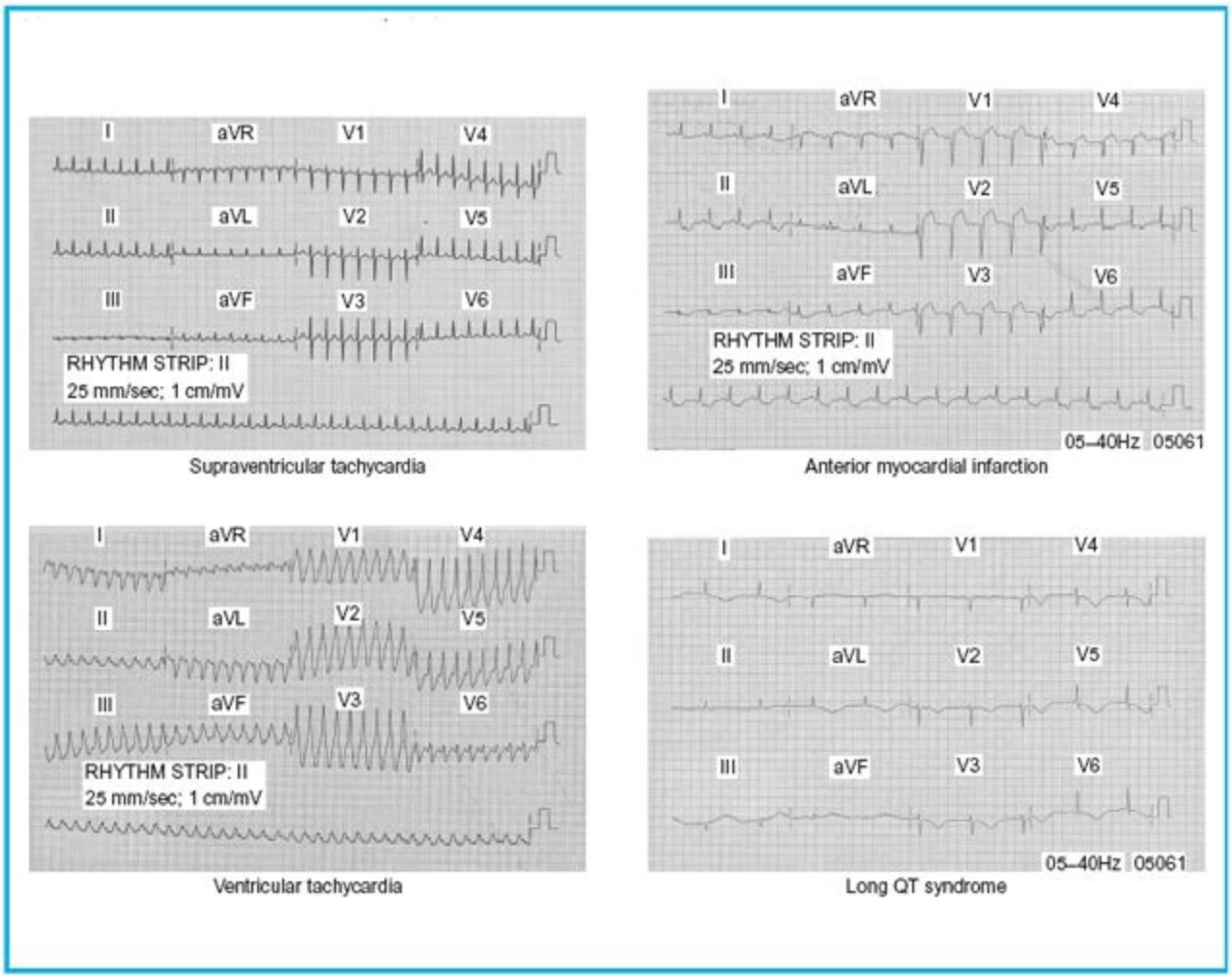
- **Pre-excitation**
  - WPW syndrome
  - Lown–Ganong–Levine syndrome (short PR syndrome)
- **Other**
  - Ventricular extrasystole falling after P wave
  - AV junctional rhythm (but P wave will usually be negative)
  - Low atrial rhythm
  - Coronary sinus escape rhythm

- Normal variant (especially in young people)

Causes of tall R waves inV1

It is easy to spot tall R waves in V1. This lead largely faces the posterior wall of the left ventricle and the mass of the right ventricle. As the overall vector is predominantly towards the bulkier left ventricle in normal situations, the QRS is usually negative in V1. This balance can be reversed in the following situations:

Figure 1.3 ECG strips demonstrating typical changes in common disease states



- Right ventricular hypertrophy (myriad causes)
- RBBB
- Posterior infarction
- Dextrocardia
- WPW syndrome with left ventricular pathway insertion (often referred to as type A)
- HCM (septal mass greater than posterior wall).

Posterior infarctions are easily missed because the rest of the ECG can be normal. Recognition of positive tall R waves in V1 can be the only sign with a typical history; there may be subtle ST depression in V1–V3. Performing a posterior ECG with leads placed over the back will reveal ST elevation.

Bundle-branch block and ST-segment abnormalities

Complete bundle-branch block is a failure or delay of impulse conduction to one ventricle from the AV node, requiring conduction via the other bundle, and then transmission within the ventricular myocardium; this results in abnormal prolongation of QRS duration (>120 ms) and abnormalities of the normally isoelectric ST segment. In contrast to RBBB, LBBB is always pathological.

During the hyperacute and acute phases of cerebral events, including ischaemic stroke and haemorrhage, marked ST changes may be observed on the ECG and there may even be an associated rise in cardiac troponin. These changes result from abnormal autonomic discharges due to intense sympathetic nervous activation, with consequent myocytolysis, which accounts for troponin leak.

- **Causes of LBBB**
  - Ischaemic heart disease (recent or old MI)
  - Hypertension
  - LVH
  - Aortic valve disease
  - Cardiomyopathy
  - Myocarditis
  - Post-valve replacement
  - Right ventricular pacemaker
  - Tachycardia with aberrancy or concealed conduction
  - Ventricular ectopy
- **Causes of RBBB**
  - Normal in young people
  - Right ventricular strain (eg pulmonary embolus)
  - ASD
  - Ischaemic heart disease
  - Myocarditis
  - Idiopathic
  - Tachycardia with aberrancy or concealed conduction
  - Ventricular ectopy
- **Causes of ST elevation**
  - Early repolarisation
  - Acute MI
  - Pericarditis (saddle shaped)
  - Ventricular aneurysm
  - Coronary artery spasm
  - During angioplasty
  - Non-standard ECG acquisition settings (eg on monitor)
- **Other ST–T wave changes (not elevation)**

• Ischaemia:	ST depression, T inversion and peaking
• Digoxin therapy:	downsloping ST depression
• Hypertrophy:	ST depression, T inversion
• Post-tachycardia:	ST depression, T inversion
• Hyperventilation:	ST depression, T inversion and peaking
• Oesophageal/upper abdominal irritation:	ST depression, T inversion
• Cardiac contusion:	ST depression, T inversion
• Mitral valve prolapse:	T-wave inversion
• Acute cerebral event (eg subarachnoid haemorrhage):	ST depression, T inversion
• Electrolyte abnormalities	

Q waves can be permanent (reflecting myocardial necrosis) or transient (suggesting failure of myocardial function, but not necrosis).

- **Permanent Q waves**
  - Transmural infarction
  - LBBB
  - WPW syndrome
  - HCM
  - Idiopathic cardiomyopathy
  - Amyloid heart disease
  - Neoplastic infiltration
  - Friedreich's ataxia
  - Dextrocardia
  - Sarcoidosis
  - Progressive muscular dystrophy
  - Myocarditis (may resolve)
- **Transient Q waves**
  - Coronary spasm
  - Hypoxia
  - Hyperkalaemia
  - Cardiac contusion
  - Hypothermia

Potassium and ECG changes

There is a reasonable correlation between plasma potassium and ECG changes.

- **Hyperkalaemia**
  - Tall T waves
  - Prolonged PR interval
  - Flattened/absent P waves
- **Very severe hyperkalaemia**
  - Wide QRS
  - Sine wave pattern
  - Ventricular tachycardia/ventricular fibrillation/asystole
- **Hypokalaemia**
  - Flat T waves, occasionally inverted
  - Prolonged PR interval
  - ST depression
  - Tall U waves

ECG changes after coronary artery bypass surgery

- U waves (hypothermia)
- Saddle-shaped ST elevation (pericarditis)
- PR-segment depression (pericarditis)
- Low-voltage ECG in chest leads (pericardial effusion)
- Changing electrical alternans (alternating ECG axis – cardiac tamponade)
- S1Q3T3 (pulmonary embolus)
- Atrial fibrillation
- Q waves
- ST-segment and T-wave changes.

ECG techniques for prolonged monitoring

- **Holter monitoring**: the ECG is monitored in one or more leads for 24–72 h. The patient is encouraged to keep a diary in order to correlate symptoms with ECG changes
- **External recorders**: the patient keeps a monitor with them for a period of days or weeks. At the onset of symptoms the monitor is placed to the chest and this records the ECG
- **Wearable loop recorders**: the patient wears a monitor for several days or weeks. The device records the ECG constantly on a self-erasing loop. At the time of symptoms, the patient activates the recorder and a trace spanning some several seconds before a period of symptoms to several minutes afterwards is stored
- **Implantable loop recorders**: a loop recorder is implanted subcutaneously in the pre-pectoral region. The recorder is activated by the patient or according to pre-programmed parameters. Again the ECG data from several seconds before symptoms to several minutes after are stored; data are uploaded by telemetry. The battery life of the implantable loop recorder varies between 18–36 months.

1.3.2 Echocardiography

Principles of the technique

Sound waves emitted by a transducer are reflected back differentially by tissues of variable acoustic properties. Moving structures (including fluid structures) reflect sound back as a function of their own velocity. The signal-to-noise ratio is improved by minimising the distance and number of acoustic structures between the transducer and the object being recorded.

M-mode: named after appearance of the mitral valve on this modality, this is a longitudinal beam that achieves high temporal resolution for a given location. It allows calculations of left atrial (LA) size, aortic root, left ventricular (LV) outflow tract (LVOT), and ventricular end-systolic and end-diastolic dimensions. These are typically made in the parasternal long-axis view.

Doppler measurements: the Doppler phenomenon is used to measure the velocity of blood flow for estimation of pressure gradients across valve abnormalities. Velocities can be measured along the length of the Doppler beam (continuous-wave Doppler, useful for aortic stenosis assessment), or at a specific location (pulsed-wave Doppler, useful for LV filling patterns or for measuring the velocity of myocardial tissue movement).

Two-dimensional echocardiography: the piezoelectric crystals in the probe head are activated in sequence to reconstruct a two-dimensional image of the heart. This allows identification of anatomy and structural abnormalities, eg enlarged structures, abnormal valves or abnormal communications between chambers. Newer probes can produce three-dimensional images to better visualise defects.

Colour Doppler: this applies Doppler to assess the average velocities of blood within a region of interest. Movement of blood can be coded red (moving towards transducer) or blue (moving away from transducer) known as the BART convention (**b**lue = **a**way **r**ed = **t**oward). This helps identify and quantify valvular regurgitation.

Diagnostic uses of echocardiography

Conventional echocardiography is used in the diagnosis of:

- Pericardial effusion and tamponade
- Valvular disease (including large vegetations)
- HCM, dilated cardiomyopathy, LV mass and function
- Cardiac tumours and intracardiac thrombus
- Congenital heart disease (eg PDA, coarctation of the aorta)
- Right ventricular function and pressure.

Stress echo is used in the diagnosis of myocardial viability and ischaemia, to help risk stratify patients and consider them for further investigations such as coronary angiography. Resting images are acquired and then stress is induced, by either intravenous dobutamine infusion or exercise performed on a bike or treadmill. Stress images are then acquired in the long-axis and short-axis views at moderate and peak heart rates and compared with resting images, typically arranged in a grid for ease of comparison. Contrast may be required for optimal myocardial definition – it appears bright. Regional wall motion abnormalities such as hypokinesia, dyskinesia and akinesia are defined

in a 16- or 17-segment model of the left ventricle. Patients should avoid β blockers before stress echocardiography, because these will attenuate peak heart rate response.

Standard contrast echo is used in the diagnosis of right-to-left shunts, particularly for patent foramen ovale (PFO) but also ASD and ventricular septal defect (VSD). Agitated saline or Gelofusine is injected into the venous system and the patient is asked to undergo Valsalva's manoeuvre to encourage increased right-sided pressure. Bubbles may then be observed crossing from the right atrium to the left ventricle through a PFO or ASD.

Transpulmonary contrast echo is used to improve discrimination between the blood pool and the endocardium to help definition in those individuals whose characteristics lead to poor image quality. It is also used to diagnose LV thrombus and other specific conditions (eg the congenital failure of muscle fibre alignment [known as non-compaction] and apical hypertrophy).

Tissue Doppler imaging is a new technique that applies Doppler principles to analyse the velocity of myocardial motion. Specifically, the movement of a given cardiac wall can be interrogated by manually selecting the region of interest on the echo machine. Each wall will have a unique pattern of velocities, from which many different calculations can be made, most commonly to estimate cardiac function and pressures. Values will vary according to the site, and the age and function of the heart. Tissue Doppler differs from conventional Doppler, which focuses on the velocity of blood, and is used to assess blood flow across valves and the rate of ventricular filling.

Transoesophageal echocardiography (TOE) is performed under general anaesthesia or in sedated patients with local anaesthetic applied to the oropharynx. The probe is passed into the oesophagus, meaning that it is closer to the cardiac structures, improving image quality. It is indicated in the diagnosis of aortic dissection (when a CT aortogram is delayed), suspected atrial thrombus (before cardioversion of atrial arrhythmia), assessment of vegetations or abscesses in endocarditis, prosthetic valve dysfunction or leakage, and the intraoperative assessment of LV function or success of valvular repair. It may also be indicated when transthoracic images are suboptimal.

Three-dimensional echocardiography has increasing clinical application in better understanding structural anatomy. This is particularly useful for planning therapy to valvular heart disease, whether it is surgical or percutaneous replacement. Often imaging is performed during the procedure to guide valve placement. It has particular usefulness in congenital heart disease. It can be performed using either transthoracic or transoeophageal approaches.

Intravascular ultrasonography (IVUS) is performed by placing a small probe mounted on a catheter on an intracoronary wire during coronary angioplasty. It provides high-resolution imaging of coronary arteries for measurement of stenosis severity and plaque characteristics, and assessment of the success of stent deployment.

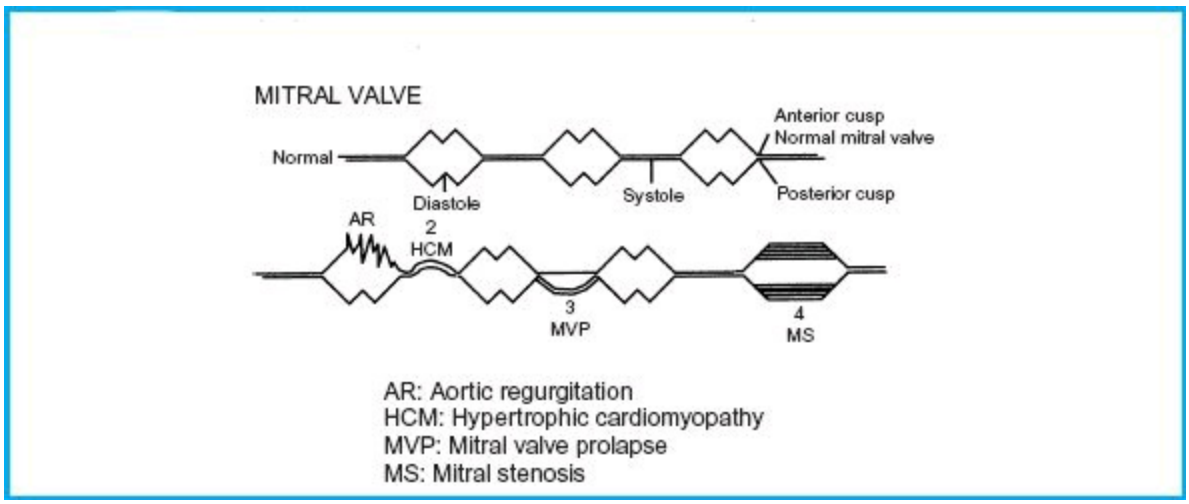
Intracardiac ultrasonography images the heart chambers from within; it is used mainly in those with congenital heart disease and in electrophysiological procedures.

Classic M-mode patterns

Due to improvements in real-time image quality. M-mode imaging is now used less in clinical practice; it does, however, allow interpretable traces to be printed as still images, and these still occasionally feature in exams. Particular M-mode patterns that have been used in past MRCP exams include:

- **Aortic regurgitation**: fluttering of the anterior mitral leaflet is seen
- **HCM**: systolic anterior motion (SAM) of the mitral valve leaflets and asymmetrical septal hypertrophy (Figure 1.4)
- **Mitral valve prolapse**: one or both leaflets prolapse during systole
- **Mitral stenosis**: the opening profile of the cusps is flat and multiple echoes are seen when there is calcification of the cusps.

Figure 1.4 Classic valvular disease patterns seen with M-mode echocardiography



1.3.3 Nuclear cardiology: myocardial perfusion imaging (Figure 1.5)

Perfusion tracers such as thallium or technetium can be used to gauge myocardial blood flow, both at rest and during exercise- or drug-induced stress. Tracer uptake is detected using tomograms and displayed in a colour scale in standard views.

Lack of uptake may be:

- **Physiological**: due to lung or breast tissue absorption
- **Pathological**: reflecting ischaemia, infarction or other conditions in which perfusion abnormalities also occur (eg HCM or amyloidosis).

Pathological perfusion defects are categorised as fixed (scar) and reversible (viable but ischaemic tissue).

MPI can be used to:

- Detect infarction
- Investigate atypical chest pains
- Assess ventricular function
- Determine prognosis and detect myocardium that may be 're-awakened' from hibernation with an improved blood supply (eg after coronary artery bypass grafting [CABG]).

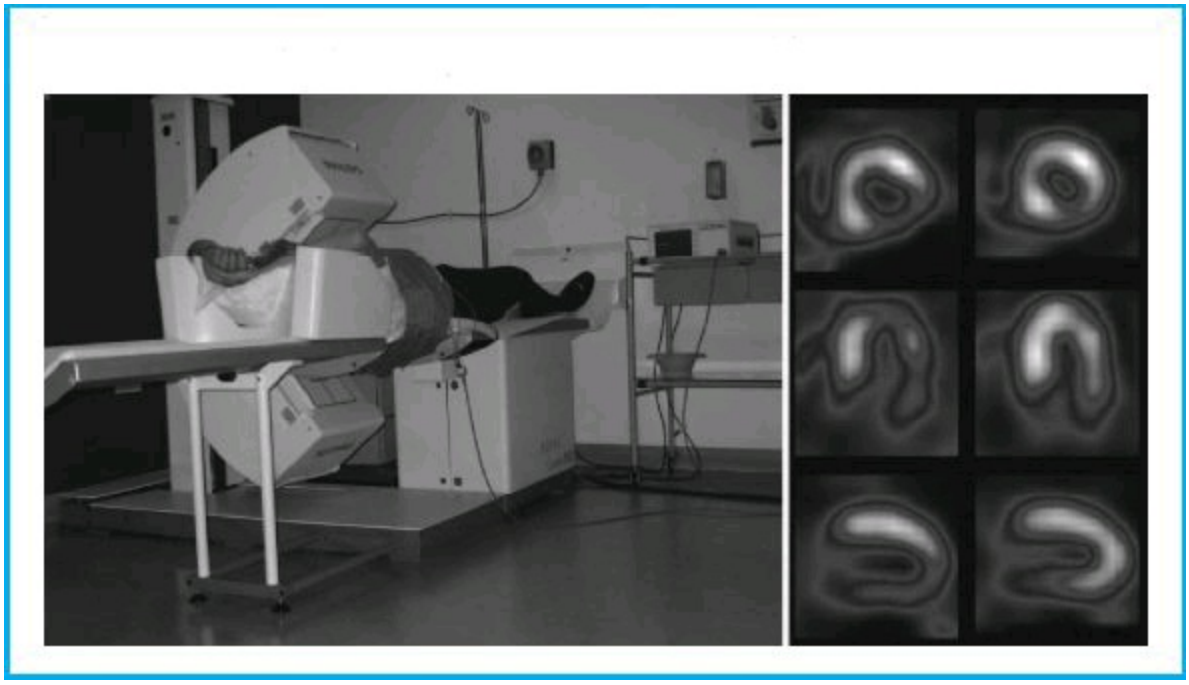
1.3.4 Cardiac catheterisation

Coronary and ventricular angiography

Direct injection of radio-opaque contrast into the coronary arteries allows high-resolution assessment of restrictive lesions and demonstrates any anomalies. Left ventriculography provides a measure of ventricular systolic function.

Angiography is typically performed via the femoral artery or radial artery through a sheath that allows insertion of specifically designed catheters that intubate the coronary vessels. Contrast can be hand injected or injected by automated pumps. Imaging is acquired by fluoroscopy. The contrast provides an image of the vessel lumen but the other parts of the vessel are poorly visualised. The lumen is carefully assessed for narrowings or stenoses, which represent coronary atherosclerotic lesions that limit blood flow. Multiple different radiographic views are required to view each vessel, because stenoses can be hidden in different projections.

Figure 1.5 Radionuclide myocardial perfusion imaging. Left panel shows the gamma camera. Right panel shows a reversible inferolateral perfusion defect: left column stress, right column rest.



The severity of a stenosis can be gauged visually, reported as a percentage of the vessel, or measured objectively using quantitative coronary angiography (QCA), which uses computer-aided edge detection of coronary vessels. IVUS and optical coherence tomography (OCT) are intracoronary tools used to visualise the stenosis severity and estimate the lumen area occupied by atherosclerotic plaque. Functional, or physiological, lesion severity can be detected using a wire with a tiny pressure sensor on it placed distal to a stenosis to estimate the degree of pressure drop in comparison to the aortic pressure.

Percutaneous coronary intervention (PCI) can be performed immediately after coronary angiography or at a later occasion. It involves the treatment of stenoses using balloon inflation and stent deployment. Intervention is most commonly performed for the treatment of coronary obstruction in acute coronary syndrome. Other indications include primary PCI (PPCI) for acute treatment of an MI or in symptomatic stable angina where there is evidence of cardiac ischaemia.

Complications of cardiac catheterisation

Complications are uncommon (approximately 1%, including minor complications); these include contrast allergy, local haemorrhage from puncture sites with subsequent occurrence of thrombosis, retroperitoneal haemorrhage, false aneurysm formation (which can be compressed or injected) or arteriovenous malformation. Vasovagal reactions are common. Other complications are:

- **Coronary dissection**: (particularly the right coronary artery in women) and aortic dissection or ventricular perforation
- **Air or atheroma embolism**: in the coronary or other arterial circulations, with consequent ischaemia or strokes
- **Ventricular dysrhythmias**: can even cause death in the setting of left main stem disease
- Mistaken cannulation and contrast injection into the conus branch of the right coronary artery can cause ventricular fibrillation
- Overall mortality rates are quoted at <1/1000 cases.

1.3.5 Exercise stress testing

This is used in the investigation of coronary artery disease, exertion-induced arrhythmias, and the assessment of cardiac workload and conduction abnormalities. Exercise tests also give diagnostic and prognostic information post-infarction, and generate patient confidence in rehabilitation after an MI. Diagnostic sensitivity is improved if the test is conducted with the patient having discontinued antianginal (especially rate-limiting) medication.

The main contraindications to exercise testing include those conditions where fatal ischaemia or arrhythmias may be provoked, or where exertion may severely and acutely impair cardiac function. These include the following:

- Severe aortic stenosis or HCM with marked outflow obstruction
- Acute myocarditis or pericarditis
- Pyrexial or coryzal illness
- Severe left main stem disease
- Untreated congestive cardiac failure
- Unstable angina
- Dissecting aneurysm
- Ongoing tachy- or bradyarrhythmias
- Untreated severe hypertension.

Indicators of a positive exercise test result

The presence of each factor is additive in the overall positive prediction of coronary artery disease:

- Development of anginal symptoms
- A fall in BP of >15 mmHg or failure to increase BP with exercise
- Arrhythmia development (particularly ventricular)
- Poor workload capacity (may indicate poor left ventricular function)
- Failure to achieve target heart rate (allowing for β blockers)

- >1-mm down-sloping or planar ST-segment depression, 80 ms after the J point
- ST-segment elevation
- Failure to achieve 9 min of the Bruce protocol due to any of the points listed.

Exercise tests have **low specificity** in the following situations (often as a result of resting ST-segment abnormalities):

- Ischaemia in young women with atypical chest pains
- Atrial fibrillation
- LBBB
- WPW syndrome
- LVH
- Digoxin or β-blocker therapy
- Anaemia
- Hyperventilation
- Biochemical abnormalities such as hypokalaemia.

1.3.6 24-hour ambulatory blood pressure monitoring

The limited availability and relative expense of ambulatory BP monitoring prevent its use in all hypertensive patients. Specific areas of usefulness include the following situations:

- Assessing for 'white coat' hypertension
- Borderline hypertensive cases who may not need treatment
- Evaluation of hypotensive symptoms
- Identifying episodic hypertension (eg in phaeochromocytoma)
- Assessing drug compliance and effects (particularly in resistant cases)
- Nocturnal BP dipper status (non-dippers are at higher risk).

1.3.7 Computed tomography

Computed tomography (CT) has applications in anatomical (coronary arteries, chamber dimension, pericardium) and functional (contractility, ischaemia, viability) assessments of the heart.

CT coronary angiography has gained considerable attraction in the identification of coronary artery disease, particularly in chest pain clinics and in some emergency departments following guidance from the National Institute for Health and Care Excellence (NICE). Calcium scores can be calculated quickly, with higher scores being more predictive of coronary obstruction. More detailed scanning allows coronary arteries to be identified and followed in two-dimensional cross-sections, as well as in three-dimensional reconstructions. This enables identification of lesions that appear obstructive. Increased speed, better ECG gating and higher-resolution scanners have meant that coronary arteries can be assessed with relatively low levels of radiation.

The negative predictive value is higher than the positive predictive value; entirely normal scans are typically normal on invasive coronary angiography, whereas those with apparently more important

disease may or may not have findings requiring action on invasive assessment. As such, CT coronary angiography is typically used when patients have a low pre-test likelihood of coronary disease, a negative effectively excluding the condition.

CT pulmonary angiography (CTPA) is the gold standard investigation for:

- Pulmonary thromboembolic disease
- Anatomical assessment of the pericardium (eg in suspected constriction)
- Anomalous coronary artery origins (reliable imaging of the proximal third of major coronary arteries)
- Extramyocardial mediastinal masses
- Chamber dimensions
- Myocardial function, perfusion and ischaemia.

1.3.8 Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) is the gold standard technique for assessment of myocardial function, ischaemia, perfusion and viability, cardiac chamber anatomy and imaging of the great vessels. It has a useful adjunctive role in pericardial/mediastinal imaging. Limitations include its contraindication in patients with certain implanted devices (eg pacemakers) and time (consequently also cost), as a full functional study can take about 45 min. The contrast used (gadolinium), although not directly nephrotoxic, is subject to increased risk of metabolic toxicity in renally impaired individuals.

Chief indications for cardiac MRI:

- Myocardial ischaemia and viability assessment
- Differential diagnosis of structural heart disease (congenital and acquired)
- Chamber anatomy definition
- Initial diagnosis and serial follow-up of great vessel pathology (especially aortopathy)
- Pericardial and mediastinal structural assessment.

1.4 VALVULAR DISEASE AND ENDOCARDITIS

1.4.1 Murmurs

Benign flow murmurs: soft, short systolic murmurs heard along the left sternal edge to the pulmonary area, without any other cardiac auscultatory, ECG or chest radiograph abnormalities. Thirty per cent of children may have an innocent flow murmur.

Cervical venous hum: continuous when upright and is reduced by lying; occurs with a hyperdynamic circulation or with jugular vein compression.

Large arteriovenous fistula of the arm: may cause a harsh flow murmur across the upper mediastinum.

Effect of posture on murmurs: standing significantly increases the murmurs of mitral valve prolapse

and HCM only. Squatting and passive leg raising increase cardiac afterload and therefore decrease the murmur of HCM and mitra valve prolapse, while increasing most other murmurs such as VSD, aortic, mitral and pulmonary regurgitation, and aortic stenosis.

Effect of respiration on murmurs: inspiration accentuates right-sided murmurs by increasing venous return, whereas held expiration accentuates left-sided murmurs. The strain phase of Valsalva's manoeuvre reduces venous return, stroke volume and arterial pressure, decreasing all valvular murmurs but increasing the murmur of HCM and mitral valve prolapse.

Classification of murmurs

- **Mid-/late systolic murmurs**
  - Innocent murmur
  - Aortic stenosis or sclerosis
  - Coarctation of the aorta
  - Pulmonary stenosis
  - HCM
  - Papillary muscle dysfunction
  - ASD (due to high pulmonary flow)
  - Mitral valve prolapse
- **Mid-diastolic murmurs**
  - Mitral stenosis or 'Austin Flint' murmur due to aortic regurgitant jet
  - Carey Coombs murmur (rheumatic fever)
  - High AV flow states (ASD, VSD, PDA, anaemia, mitral regurgitation, tricuspid regurgitation)
  - Atrial tumours (particularly if causing AV flow disturbance)
- **Continuous murmurs**
  - PDA
  - Ruptured sinus of Valsalva's aneurysm
  - ASD
  - Large arteriovenous fistula
  - Anomalous left coronary artery
  - Intercostal arteriovenous fistula
  - ASD with mitral stenosis
  - Bronchial collaterals

1.4.2 Mitral stenosis

Mitral stenosis (MS) is the thickening of the mitral leaflets that may occur at the cusps, commissures

or chordal level, to cause an obstruction of blood flow from the left atrium to the left ventricle. Two-thirds of patients presenting with this are women. The most common cause remains chronic rheumatic heart disease, which involves a sustained inflammatory reaction against the valve and valvular apparatus, due to antibody cross-reactivity to a streptococcal illness. Rarer causes include congenital disease, carcinoid, systemic lupus erythematosus (SLE) and mucopolysaccharidoses (glycoprotein deposits on cusps). Rheumatic heart disease originating in the UK is now exceptionally rare.

A normal mitral valve has a valve area of 4–6 cm^2: MS is diagnosed when the valve area is $\leq 2cm^2$: It is considered severe when $\leq 1cm^2$; symptoms are invariable and increased pulmonary pressures lead to pulmonary oedema, when heart rates increase, and pulmonary hypertension. Atrial fibrillation is invariable and increases thromboembolic stroke risk by 17×; anticoagulation is essential.

Treatment can be percutaneous (balloon valvuloplasty) or surgical (limited mitral valvotomy – now rarely performed in developed nations – or open valve replacement).

Features of severe MS

- **Symptoms**
  - Dyspnoea with minimal activity
  - Haemoptysis
  - Dysphagia (due to left atrium enlargement)
  - Palpitations due to atrial fibrillation
- **Chest radiograph**
  - Left atrial or right ventricular enlargement
  - Splaying of subcarinal angle (>90°)
  - Pulmonary congestion or hypertension
  - Pulmonary haemosiderosis
- **Echocardiogram**
  - Doming of leaflets
  - Heavily calcified cusps
  - Direct orifice area >1.0 cm^2
- **Signs**
  - Low pulse pressure
  - Soft first heart sound
  - Long diastolic murmur and apical thrill (rare)
  - Very early opening snap, ie closer to S2 (lost if valves immobile)
  - Right ventricular heave or loud P2
  - Pulmonary regurgitation (Graham Steell murmur)
  - Tricuspid regurgitation
- **Cardiac catheterisation**

  Pulmonary capillary wedge end diastole to left ventricular end-diastolic pressure (LVEDP)

- gradient >15 mmHg
- LA pressures >25 mmHg
- Elevated right ventricular (RV) and pulmonary artery (P)A pressures
- High pulmonary vascular resistance
- Cardiac output <2.5 L/min per m^2 with exercise

Mitral balloon valvuloplasty

Valvuloplasty using an Inoue balloon requires either a trans-septal or a retrograde approach, and is used only in suitable cases where echocardiography shows the following:

- The mitral leaflet tips and valvular chordae are not heavily thickened, distorted or calcified
- The mitral cusps are mobile at the base
- There is minimal or no mitral regurgitation
- There is no left atrial thrombus seen on TOE.

1.4.3 Mitral regurgitation

The full structure of the mitral valve includes the annulus, cusps, chordae and papillary musculature, and abnormalities of any of these can cause regurgitation. The presence of symptoms and increasing left ventricular dilatation are indicators for surgery in the chronic setting. Surgical mortality rates are 2–7% for valvular replacements in patients with New York Heart Association (NYHA) grade II–III symptoms. Various techniques have revolutionised mitral valve surgery, transforming outcomes from being no better than medical therapy with replacement to almost normal with repair. In skilled surgical hands the repair is tailored to the precise anatomical abnormality.

Functional mitral regurgitation (MR) is a term used to describe MR that is caused by stretching of the annulus secondary to ventricular dilatation.

Main causes of MR

- Myxomatous degeneration
- Functional, secondary to ventricular dilatation
- Mitral valve prolapse
- Ischaemic papillary muscle rupture
- Congenital heart diseases
- Collagen disorders
- Rheumatic heart disease
- Endocarditis

Indicators of the severity of MR

- Small-volume pulse
- Left ventricular enlargement due to overload
- Presence of S3
- Atrial fibrillation
- Mid-diastolic flow murmur
- Precordial thrill, signs of pulmonary hypertension or congestion (cardiac failure).

Signs of predominant MR in mixed mitral valve disease

- Soft S1; S3 present
- Displaced and hyperdynamic apex (LV enlargement)
- ECG showing LVH and left axis deviation.

Mitral valve prolapse

This condition occurs in 5% of the population and is commonly over-diagnosed (depending on the echocardiography criteria applied). The patients are usually female and may present with chest pains, palpitations or fatigue, although it is often detected incidentally in asymptomatic patients. Squatting increases the click and standing increases the murmur, but the condition may be diagnosed in the absence of the murmur by echocardiography. Often there is myxomatous degeneration and redundant valve tissue due to deposition of acid mucopolysaccharide material. Mitral valve prolapse is usually eminently suitable for mitral valve repair, although this should be undertaken only if the severity of the regurgitation associated with the condition justifies it (see above). Several conditions are associated with mitral valve prolapse (see below), and patients with the condition are prone to certain sequelae.

Sequelae of mitral valve prolapse:

- Embolic phenomena
- Rupture of mitral valve chordae
- Dysrhythmias with QT prolongation
- Sudden death
- Cardiac neurosis.

Conditions associated with mitral valve prolapse

- Coronary artery disease
- Polycystic kidney disease
- Cardiomyopathy – dilated cardiomyopathy/HCM
- Secundum ASD
- WPW syndrome
- PDA
- Marfan's syndrome
- Pseudoxanthoma elasticum

- Osteogenesis imperfecta
- Myocarditis
- SLE; polyarteritis nodosa
- Muscular dystrophy
- Left atrial myxoma

1.4.4 Aortic regurgitation

Aortic regurgitation (AR) can occur due to disruption of the aortic valve or the aortic root. Either can occur acutely or chronically. Acute causes, including aortic dissection or valve rupture from endocarditis, present with acute decompensation and profound heart failure. Chronic causes allow time for the left ventricle to accommodate, with gradual enlargement of end-diastolic volumes. There are many echocardiographic criteria used to assess the severity of AR and none is ideal; they are usually used in combination with symptoms and LV dimensions.

Causes of AR

- **Valve inflammation**
  - Chronic rheumatic
  - Infective endocarditis
  - Rheumatoid arthritis; SLE
  - Hurler's syndrome
- **Aortitis**
  - Syphilis
  - Ankylosing spondylitis
  - Reiter's syndrome
  - Psoriatic arthropathy
- **Aortic dissection/trauma**
- **Hypertension**
- **Bicuspid aortic valve**
- **Ruptured sinus of Valsalva's aneurysm**
- **VSD with prolapse of (right) coronary cusp**
- **Disorders of collagen**
  - Marfan's syndrome (aortic aneurysm)
  - Hurler's syndrome
  - Pseudoxanthoma elasticum

Eponymous signs associated with AR

- Quincke's sign – nail-bed fluctuation of capillary flow
- Corrigan's pulse – (waterhammer); collapsing radial pulse
- Corrigan's sign – visible carotid pulsation
- De Musset's sign – head nodding with each systole
- Duroziez's sign – audible femoral bruits with diastolic flow (indicating moderate severity)
- Traube's sign – 'pistol shots' (systolic auscultatory finding of the femoral arteries)
- Austin Flint murmur – functional mitral diastolic flow murmur
- Argyll Robertson pupils – aetiological connection with syphilitic aortitis
- Müller's sign – pulsation of the uvula

Indications for surgery

Acute severe AR will not be tolerated for long by a normal ventricle and therefore requires prompt surgery, except in the case of infection, where delay for antibiotic therapy is preferable (if haemodynamic stability allows). At 10 years, 50% of patients with moderate chronic AR are alive, but once symptoms occur deterioration is rapid.

Features of AR indicative of the need for surgery

- **Symptoms of dyspnoea/LV failure**
  - Reducing exercise tolerance
- **Rupture of sinus of Valsalva's aneurysm**
- **Infective endocarditis not responsive to medical treatment**
- **Enlarging aortic root diameter in Marfan's syndrome with AR**
- **Enlarging heart**
  - End-systolic diameter >55 mm at echo
  - Pulse pressure >100 mmHg
  - Diastolic pressure <40 mmHg
  - Lengthening diastolic murmur
  - ECG: lateral lead T-wave inversion

Bicuspid valves

The aortic valve is typically trileaflet, but can be congenitally bicuspid in 0.5–1% of the population. This abnormal valve has early onset degeneration with aortic stenosis presenting many years sooner than typical (40–50s versus 60–70s). In cases of biscuspid disease aortic regurgitation is more common. Bicuspid valves are also associated with an aortopathy and aortic root dilatation, which itself can lead to aortic regurgitation.

1.4.5 Aortic stenosis

Aortic stenosis (AS) is generally caused by senile degeneration and thickening of normally thin pliable leaflets. A normal valve area is >2cm^2 and severe AS typically has a valve area ≤1 cm^2, with a mean pressure gradient of >40 mmHg on transthoracic echocardiography. The pressure gradient is dependent not only on the severity of the stenosis, but also on the speed that blood is pushed across the valve. This means that the pressure gradient can be reduced when LV function is impaired, or in MS or significant AR. In these cases, the dimensionless index, a ratio of aortic and LVOT velocities, can be useful (1 is normal, 0.25 severe).

- **Causes of AS**: may be congenital bicuspid valve, degenerative calcification (common in elderly people) and post-rheumatic disease
- **Subvalvular**: causes of aortic gradients include HCM and subaortic membranous stenosis, whereas supravalvular stenosis is due to aortic coarctation, or Williams' syndrome (with elfin facies, learning disability, hypercalcaemia)
- **Sudden death**: may occur in AS or subvalvular stenosis due to ventricular tachycardia. The vulnerability to ventricular tachycardia is due to LVH
- **Complete heart block**: may be due to calcification involving the upper ventricular septal tissue housing the conducting tissue. This can also occur post-operatively (after valve replacement) due to trauma
- **Calcified emboli**: can arise in severe calcific AS
- **All symptomatic patients should be considered for surgery**: surgical mortality rate for AS is predominantly related to the absence (2–8%) or presence (10–25%) of LV failure
- **There is a strong association with ischaemic heart disease**: 50% of AS patients have important coronary disease. Concomitant CABG should be considered at the time of valve replacement.

Indicators of severe AS

- Symptoms of syncope or LV failure
- Signs of LV failure
- Absent A2
- Paradoxically split A2
- Presence of precordial thrill
- S4
- Slow-rising pulse with narrow pulse pressure
- Late peaking of long murmur
- Valve area >0.5 cm^2 on echocardiography

1.4.6 Tricuspid regurgitation

Tricuspid regurgitation (TR) is typically an inaudible murmur due to the low pressure in the right heart, but may have low frequency pansystolic murmur if right ventricular pressures are elevated. Other signs may be more prominent with an elevated JVP and giant c-V waves; a pulsatile liver edge may be palpable and peripheral oedema is invariable.

Causes of severe TR include the following:

- Functional, due to right ventricular dilatation (commonly coexists with significant MR)
- Infection: the tricuspid valve is vulnerable to infection introduced by venous cannulation (iatrogenic or through intravenous drug abuse)
- Carcinoid (nodular hepatomegaly and telangiectasia)
- Post-rheumatic
- Ebstein's anomaly: tricuspid valve dysplasia with a more apical position to the valve. Patients have cyanosis and there is an association with pulmonary atresia or ASD and, less commonly, congenitally corrected transposition.

1.4.7 Prosthetic valves

Valve prostheses may be metal or tissue. Mechanical valves are more durable but tissue valves do not require full lifelong anticoagulation. All valve replacements have a residual transvalvular gradient across them; for mechanical valves this can cause loud murmurs, eg an aortic valve replacement may still have a loud AS ejection systolic murmur.

Mechanical valves

There are many different types of mechanical valves. Common ones are:

- **Ball & Cage valve**: e.g Starr–Edwards: ball and cage – ejection systolic murmur (ESM) in the aortic area and an opening sound in the mitral position are normal. These are the original mechanical valves, first implanted in 1961, and modified versions are still available
- **Single tilting disc**: Bjork–Shiley was the first, involving a single graphite disc coated in pyrolite carbon which tilts between struts of metal housing. A variation designed in the 1980s was prone to strut fracture with catastrophic embolisation and is now no longer manufactured. A modern variant includes the Medtronic Hall valve
- **Bileaflet valves**: two semicircular leaflets that open, creating a central and two peripheral orifices. Now the most commonly used valve type with many different manufacturers, including St Jude and the Sorin Carbomedics valve.

Tissue valves

- **Allografts**: porcine or bovine three-cusp valve – 3 months' anticoagulation sometimes recommended until tissue endothelialisation. No need for long-term anticoagulation if patient is in sinus rhythm
- **Homografts**: usually cadaveric and, again, need no long-term anticoagulation.

Infection of prosthetic valves

- Mortality rate is still as high as 60% depending on the organism
- Within 6 months of implantation, it is usually due to colonisation by *Staphylococcus epidermidis*
- Septal abscesses may cause PR-interval lengthening
- Valvular sounds may be muffled by vegetations; new murmurs may occur
- Mild haemolysis can occur, and is detected by the presence of urobilinogen in the urine
- Dehiscence is an ominous feature requiring urgent intervention.

Anticoagulation in pregnancy

Warfarin may cause fetal haemorrhage and has a teratogenicity risk of 5–30%. This risk is dose dependent and abnormalities include chondrodysplasia, mental impairment, optic atrophy and nasal hypoplasia. The risk of spontaneous abortion may be increased. There is no agreed consensus on the ideal strategy: warfarin, unfractionated heparin and low-molecular-weight heparin all have advocates and detractors.

1.4.8 Infective endocarditis

Clinical presentation

Commonly presents with non-specific symptoms of malaise, tiredness and infective-type symptoms. Heart failure secondary to valvular regurgitation or heart block may also occur, as may an incidental presentation in the context of another primary infection.

Signs of infective endocarditis

As well as cardiac murmurs detected at auscultation, there are several other characteristic features of infective endocarditis:

- Systemic signs of fever and arthropathy
- Hands and feet: splinter haemorrhages, Osler's nodes (painful), Janeway's lesions (painless) and clubbing (late); needle-track signs may occur in arm or groin
- Retinopathy: Roth's spots
- Hepatosplenomegaly
- Signs of arterial embolisation (eg stroke or digital ischaemia)
- Vasculitic rash
- *Streptococcus viridans* (α-haemolytic group) are still the most common organisms, occurring in 50% of cases
- Marantic (metastatic-related) and SLE-related (Libman–Sacks) endocarditis are causes of non-infective endocarditis
- Almost any pathogenic organism may be implicated, particularly in immunocompromised patients.

See also Section 1.4.7 on 'Prosthetic valves' and Table 1.4.

Table 1.4 Infective endocarditis

Groups affected by endocarditis	Percentage of all cases of endocarditis
Chronic rheumatic disease	30
No previous valve disease	40
Intravenous drug abuse	10
Congenital defects	10
Prosthetic	10

Management of infective endocarditis

The aim of treatment is to sterilise the valve medically (usually 4–6 weeks of intravenous antibiotics), then assess whether the valvular damage sustained (eg degree of incompetence) or the risk of recurrence (eg if prosthetic valves) mandates surgical replacement. Earlier operations are undertaken only if clinically necessary as outcomes are poorer.

- **Poor prognostic factors in endocarditis**
  - Prosthetic valve
  - *Staphylococcus aureus* infection
  - Culture-negative endocarditis
  - Depletion of complement levels
- **Indications for surgery**
  - Cardiac failure or haemodynamic compromise
  - Extensive valve incompetence
  - Large vegetations
  - Septic emboli
  - Septal abscess
  - Fungal infection
  - Antibiotic-resistant endocarditis
  - Failure to respond to medical therapy

Antibiotic prophylaxis

The conditions listed in the next box are associated with an increased risk of endocarditis.

- Acquired valvular heart disease with stenosis or regurgitation
- Valve replacement
- Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated ASD, fully repaired VSD or fully repaired PDA, and

closure devices that are judged to be endothelialised
- Previous infective endocarditis
- HCM

Antibiotic and chlorhexidine mouthwash prophylaxis is no longer recommended for dental procedures, endoscopies or obstetric procedures.

Patients should be made aware of non-medical riskprone activities (eg intravenous drug use, piercings) and the symptoms of possible endocarditis.

1.5 CONGENITAL HEART DISEASE

Causes of congenital acyanotic heart disease[a]

- **With shunts**
  - Aortic coarctation (with VSD or PDA)
  - VSD
  - ASD
  - PDA
  - Partial anomalous venous drainage (with ASD)
- **Without shunts**
  - Congenital AS
  - Aortic coarctation

[a] Associated shunts

Causes of cyanotic heart disease

- With shunts
  - Tetralogy of Fallot (VSD)
  - Severe Ebstein's anomaly (ASD)
  - Complete transposition of great vessels (ASD, VSD/PDA)
- Without shunts
  - Tricuspid atresia
  - Severe pulmonary stenosis
  - Pulmonary atresia
  - Hypoplastic left heart

1.5.1 Atrial septal defect

In ASDs, the interatrial septum may be defective or absent, allowing mixing of oxygenated and deoxygenated blood and shunting at the atrial level. The size of shunting and reduction in oxygenation will depend upon the size of the defect.

ASDs are the most common congenital defects found in adulthood. Rarely, they may present as stroke in young people, due to paradoxical embolus that originated in the venous system and reached the cerebral circulation via right-to-left shunting. Fixed splitting of the second heart sound is the hallmark of an uncorrected ASD. There may be a left parasternal heave and a pulmonary ESM due to increased blood flow. There are three main subtypes:

- **Secundum** (70%): central fossa ovalis defects often associated with mitral valve prolapse (10–20% of cases). ECG shows incomplete or complete RBBB with right axis deviation. Note that a PFO (slit-like deficiency in the fossa ovalis) occurs in up to 25% of the population, but this does not allow equalisation of atrial pressures, unlike ASD
- **Primum** (15%): sited above the AV valves, often associated with varying degrees of MR and TR and occasionally a VSD, and thus usually picked up earlier in childhood. ECG shows RBBB, left axis deviation and first-degree heart block. Associated with Down's, Klinefelter's and Noonan's syndromes
- **Sinus venosus** (15%): defect in the upper septum, often associated with anomalous pulmonary venous drainage directly into the right atrium.

Surgical closure is recommended with pulmonary: systolic flow ratios >1.5 : 1. Closure of secundum defects may be performed via cardiac catheterisation.

Holt–Oram syndrome (triphalangeal thumb with ASD): a rare syndrome (autosomal dominant with incomplete penetration). It is associated with absence (or reduction anomalies) of the upper arm.

Lutembacher's syndrome: a rare combination of an ASD with mitral stenosis (the latter is probably rheumatic in origin).

Investigations forASDs

Right atrial and right ventricular dilatation may be seen on any imaging technique, as may pulmonary artery conus enlargement. Other characteristic features are:

- **Chest radiograph**: pulmonary plethora
- **Echocardiogram**: paradoxical septal motion, septal defect and right-to-left flow of contrast during venous injection with Valsalva's manoeuvre
- **Catheterisation**: pulmonary hypertension – raised right ventricular pressures and step-up in oxygen saturation between various parts of the right circulation (eg SVC to high right atrium).

Treatment of ASD

There is no specific medical therapy for ASDs; they are managed by either closure (percutaneous or surgical) or clinical and echocardiographic follow-up.

Indications for closure:

- Symptoms (dyspnoea)
- Systemic embolism (typically stroke)
- Chamber dilatation
- Elevated right heart pressures
- Significant left-to-right shunt
- Systemic embolism (typically stroke).

Patent foramen ovale

A PFO is a channel within the interatrial septum, which is typically covered by a flap that opens to allow right-to-left communication when right-sided pressures elevate, such as when coughing or sneezing, or during Valsalva's manoeuvre. During fetal development and while the placenta provides oxygenation, the interatrial septum allows communication through the foramen ovale.

Upon birth, the reduction in resistance in lungs lowers right-sided pressure, and the septum primum shuts, sealing the foraman ovale. In a quarter of adults, this closure is incomplete allowing venous embolic material to cross into the arterial circulation. There may be a history of headaches, migraine or paradoxical embolism. Stroke may occur in young patients. PFOs are visualised on echocardiography using bubble contrast, by injecting agitated saline into a peripheral vein, which is then seen under echocardiography travelling from the right to the left atrium during Valsalva's manoeuvre. Debate continues about the value of closing PFOs, which can be performed either percutaneously or surgically, but it may be considered according to the clinical scenario, and particularly after stroke in a young patient.

1.5.2 Ventricular septal defect

The ventricular septum is made of two parts with a superior membranous component, which contains the AV node (AVN), and an inferior muscular component. Defects can occur in either. Most defects are small, requiring only conservative observation. VSDs are the most common isolated congenital heart defect (2/1000 births; 30% of all congenital defects). Membranous VSDs can be more complicated due to the AVN and proximity of the aortic apparatus. Spontaneous closure is more common in muscular defects but either can be closed by a percutaneous or surgical approach.

Indications for closure

- Significant left-to-right shunt
- Associated with other defect requiring cardiotomy
- Elevated right heart pressure causing pulmonary hypertension
- Endocarditis
- Membranous VSD causing AR

- Large defects allow significant left-to-right shunt, causing elevated right heart pressures and consequent pulmonary hypertension
- Parasternal thrill and pansystolic murmur are present. The murmur may be ejection systolic in very small or very large defects. With large defects the aortic component of the second sound is obscured, or even a single/palpable S2 is heard; a mitral diastolic murmur may occur. The apex beat is typically hyperdynamic.

Once Eisenmenger's complex develops, the thrill and left sternal edge (LSE) murmur abate and signs are of pulmonary hypertension regurgitation and right ventricular failure. Surgery should occur earlier to avoid this situation, otherwise a combined heart/lung transplantation would be required.

- **Other cardiac associations of VSD**
  - PDA (10%)
  - AR (5%)
  - Pulmonary stenosis
  - ASD
  - Tetralogy of Fallot
  - Coarctation of the aorta
- **Types of VSD**
  - Muscular
  - Membranous
  - AV defect
  - Infundibular
  - Into the right atrium (Gerbode's defect)

1.5.3 Patent ductus arteriosus

PDA is common in premature babies, particularly female infants born at high altitude, and also if maternal rubella occurs in the first trimester. The connection occurs between the pulmonary trunk and the descending aorta, usually just distal to the origin of the left subclavian artery. PDA often occurs with other abnormalities.

Key features of PDA

- A characteristic left subclavicular thrill
- Enlarged left heart and apical heave
- Continuous 'machinery' murmur
- Wide pulse pressure and bounding pulse

Signs of pulmonary hypertension and Eisenmenger's syndrome develop in about 5% of cases. Indometacin closes the duct in about 90% of babies whereas intravenous prostaglandin E_1 (PGE_1) may reverse the natural closure (useful when PDA is associated with coarctation or hypoplastic left heart syndrome, and in complete transposition of the great vessels, because it will help to maintain flow between the systemic and pulmonary circulations). The PDA may also be closed thoracoscopically or percutaneously.

1.5.4 Coarctation of the aorta

Coarctation is an aortopathy, a disease of the aorta, in which there is severe narrowing at the site of the regressed ductus arteriosus, which connects the aorta to the pulmonary artery in utero. If severe, aortic blood flow is impaired, causing heart failure and metabolic acidosis; it is life-threatening in early life. PGE_1 can keep the ductus arteriosus patent to allow right-to-left shunting to the descending aorta while awaiting surgery.

Milder coarctation may present beyond infancy with hypertension, leg cramps, muscle weakness and neurological changes. Pulses distal to the obstruction are diminished and delayed with lower blood pressure in the legs. Collateral development can be significant and audible posteriorly, and may cause 'notching' of ribs on chest radiographs. Barium swallows may demonstrate oesophageal compression from the post-stenotic dilatation of the aorta. Echocardiography may be sufficient but MRI is definitive.

Treatment can be surgical or percutaneous. End-to-end anastomosis is the preferred surgical technique but re-stenosis can occur. Balloon dilatation of the coarctation is typically focused on recurrent coarctation after surgery.

Complications may occur despite repair with 30% of patients with surgically corrected coarctation remaining significantly hypertensive with end-organ harm. Heart failure, re-coarctation at a new site in the aorta and aneurysm formation at the site of repair are other complications. Berry aneurysms and bicuspid aortic valves should be sought as there are strong associations with coarctation.

Associations of coarctation

- **Cardiac**
  - Bicuspid aortic valve (and thus AS ± AR) in 10–20%
  - PDA
  - VSD
  - Mitral valve disease
- **Non-cardiac**
  - Berry aneurysms (circle of Willis)
  - Turner's syndrome
  - Renal abnormalities
- **Signs of coarctation**
  - Hypertension

- Radiofemoral delay of arterial pulse
- Absent femoral pulses
- Mid-systolic or continuous murmur (infraclavicular)
- Subscapular bruits
- Rib notching on chest radiograph
- Post-stenotic aortic dilatation on chest radiograph

1.5.5 Eisenmenger syndrome

Eisenmenger syndrome refers to any untreated congenital cardiac defect with intracardiac communication that leads to severe irreversible pulmonary hypertension, reversal of left-to-right shunts, and cyanosis. Long-standing left-to-right shunts (eg in large VSDs, ASDs or PDAs) cause remodelling of the pulmonary microvasculature, with obstruction and pulmonary blood flow and raised pressures. This causes shunts to reverse, sending deoxygenated blood into the systemic circulation, which is evident as cyanosis. Signs of development include:

- Clubbing and central cyanosis
- Decrease of original pansystolic (left-to-right) murmur
- Decreasing intensity of tricuspid/pulmonary flow murmurs
- Single S2 with louder intensity, palpable P2; right ventricular heave
- Appearance of Graham Steell murmur due to pulmonary regurgitation
- Pansystolic murmur and v waves due to TR

Eisenmenger syndrome

- **Causes**
  - VSD (Eisenmenger's complex)
  - ASD
  - PDA
- **Complications of Eisenmenger syndrome**
  - Right ventricular failure
  - Massive haemoptysis
  - Cerebral embolism/abscess
  - Infective endocarditis (rare)

1.5.6 Tetralogy of Fallot

The most common cause of cyanotic congenital heart disease (10%), usually presenting after age 6

months (as the condition may worsen after birth).

Key features

- Pulmonary stenosis (causes the systolic murmur)
- Right ventricular hypertrophy
- VSD
- Overriding of the aorta
- Right-sided aortic knuckle (25%)

Clinical features

- Cyanotic attacks (pulmonary infundibular spasm)
- Clubbing
- Parasternal heave
- Systolic thrill
- Palpable A2
- Soft ejection systolic murmur (inversely related to pulmonary gradient)
- Single S2 (inaudible pulmonary closure)
- ECG features of right ventricular hypertrophy

Possible complications of Fallot's tetralogy

- Endocarditis
- Polycythaemia
- Coagulopathy
- Paradoxical embolism
- Cerebral abscess
- Ventricular arrhythmias

- Fallot's tetralogy is a spectrum disorder with clinical manifestations depending on the severity of the cardiac lesions. Typical presentation is with small for dates, difficulty feeding, failure to thrive and episodes of cyanosis when crying or feeding; clubbing is evident from 3–6 months
- Although classically considered to be only pulmonary stenosis, the principal lesion is right ventricular outflow tract obstruction, which can be valvular and/or infundibular. High-grade obstruction increases right-sided pressures, which may exceed LV pressure, promoting right-to-left shunting through the VSD, while simultaneously reducing pulmonary flow. Catecholamines and hypoxaemia trigger spasm of the infundibulum

- Cyanotic episodes occur in infants, triggered by exercise, anxiety, dehydration, fever, anaemia, sepsis or spontaneously. The infant becomes inconsolable and cyanosis and tachypnoea ensues
- Cyanotic attacks worsen with catecholamines, hypoxia and acidosis. The murmur lessens or disappears as the right ventricular outflow gradient increases
- During cyanotic episodes, ***emergency treatment is necessary to avoid death***. Parents should hold the infant against their shoulder, tucking the infant's knees up; this increases systemic vascular resistance and reduces venous return of acidotic blood from the lower extremities, which reduces right ventricular infundibular spasm and right ventricular pressure, so breaking the cycle. In older children, squatting achieves this.

Emergency treatment is necessary.

- The presence of a systolic thrill and an intense pulmonary murmur differentiates the condition from Eisenmenger's syndrome
- Traditionally, tetralogy of Fallot underwent a palliative procedure, such as the Blalock–Taussig shunt (the modern variant connects a graft between the subclavian artery and the pulmonary artery) with later complete resection. Modern practice favours total correction before 12 months. Infants may be stabilised on prostaglandins to maintain the patency of the ductus arteriosus and enable more elective surgery
- A Blalock-Taussigh shunt operation results in weaker pulses in the arm from which the subclavian artery is diverted to the pulmonary artery.

1.5.7 Important post-surgical circulations

Systemic right ventricle

Transposition of the great vessels and similar conditions in which the right ventricle supplies the aorta and the left ventricle supplies the pulmonary artery are now treated by arterial switch. Effectively this is a complete correction.

Before the development of the arterial switch procedure, treatment was by 'venous redirection' – the vena cavae redirected via the atria to the left ventricle and the pulmonary veins to the right ventricle via the atria, with the morphological right ventricle then pumping oxygenated blood into the aorta. However, there was a high risk of ventricular dysfunction, valve regurgitation and ventricular arrhythmias in these patients, and decompensation would be provoked by development of atrial arrhythmias.

Single ventricular circulation

Individuals born with only one functional ventricle are treated by redirecting the vena cavae directly into the pulmonary arteries (total cavopulmonary correction) and now do very well. Early versions of this operation (the classic Fontan) used the right atrium between the vena cavae, but this often led to atrial dilatation and then fibrillation with a risk of decompensation.

Common congenital circulations

Common congenital circulations are summarised in Table 1.5.

1.6 ARRHYTHMIAS AND PACING

Atrial fibrillation (AF) remains the most common cardiac arrhythmia, with incidence increasing with age (Framingham data indicate a prevalence of 76/1000 men and 63/1000 women aged 85–94 years). Atrial flutter frequently coexists with AF and, although it has a different immediate causal mechanism, it is a reflection of the same underlying disease. These arrhythmias assume particular significance because of the stroke risk associated with them.

'SVT' (supraventricular tachycardia) is the term usually used to indicate a presumed re-entry tachycardia involving the AV node or an accessory pathway.

Ventricular tachycardia and ventricular fibrillation are life-threatening conditions, but there is a clear evidence base for the use of implantable cardioverter defibrillators in both primary and secondary prevention (see Appendix II). Antiarrhythmic drugs or catheter ablation may be useful adjuncts to treatment or, in some cases, they can be used as alternatives to defibrillators.

1.6.1 Bradyarrhythmias

Any heart rate <60 beats/min is a bradycardia. A bradyarrhythmia is a pathological bradycardia. Bradyarrhythmias are considered according to their prognostic significance and symptomatic impact. High-grade AV block (Mobitz 2 or complete) is associated with sudden death and patients should be paced urgently even if asymptomatic. Permanent pacing is very effective in reducing symptoms in most bradyarrhythmias; the exception is neurocardiogenic syncope where the results are disappointing.

Table 1.5 Common congenital circulations

	Cardinal features	Pulmonary hypertension	Ventricular dysfunction	Ventricular arrhythmias	Endocarditis	Cyanosis	Atrial arrhythmias	Systemic embolism	Treatment of choice
VSD	Pansystolic murmur	May develop	Late feature	If ventricle dilates	High risk in restrictive defects	Only after shunt reverses			Percutaneous or surgical closure for significant shunt or endocarditis
ASD	Fixed-split-second sound	May develop			Low risk	Only after shunt reverses	Atrial fibrillation, typical and atypical flutter	Associated with paradoxical emboli	Percutaneous or surgical closure for significant shunt or emboli
PDA	Continuous murmur	May develop			High risk	Only after shunt reverses			Percutaneous closure
Transposition of the great vessels	Cyanosis		If right ventricle used for systemic circulation	If ventricle dilates		Early feature			Arterial switch
Single functioning ventricle	Cyanosis, heart failure	In some anatomical variants				Early feature			Total cavopulmonary connection
Systemic right ventricle	Post-surgical or congenital, corrected transposition		Late feature	After ventricular dilatation			Especially post-surgical types of anatomy		Medical management of heart failure and arrhythmias

Common bradyarrhythmias and associated conditions

Neurocardiogenic symptoms

An exaggerated vasodepressor (hypotension), cardioinhibitory (bradycardic) or mixed reflex may cause syncope or presyncope. Various drugs have been tried as treatment, with limited success. In patients with a predominant cardioinhibitory component, dual-chamber pacing may reduce the severity and frequency of syncopal episodes but results are often disappointing.

Sinus node disease

Sinus bradycardia and sinus pauses can cause syncope, presyncope or non-specific symptoms. Thyroid function and electrolytes should be checked on presentation and corrected before considering pacemaker therapy. Pacing is indicated only in significantly symptomatic cases (as there is no prognostic benefit of pacing in sinus node disease).

First-degree AV block

A PR interval >200 ms is abnormal but usually requires no treatment. The combination of first-degree AV block with (1) LBBB, (2) RBBB with axis deviation, or (3) alternating LBBB and RBBB is interpreted as trifascicular block (more accurately, block in two fascicles and delay in the third). If associated with syncope, trifascicular block represents an indication for pacing on both prognostic and symptomatic grounds.

Second-degree Mobitz I (Wenckebach's) AV block

Progressive prolongation and then block of the PR interval is categorised as Mobitz I. It may be

normal during sleep and in young, physically fit individuals (who have high vagal tone). If it occurs when the patient is awake and is associated with symptoms in older people, pacing may be indicated on symptomatic grounds.

High-grade AV block (second-degree Mobitz II block and third-degree complete heart block) Bradycardias with more than one P wave per QRS complex (second-degree Mobitz II) or with AV dissociation are grouped together as high-grade AV block. Untreated, they are associated with a mortality rate that may exceed 50% at 1 year, particularly in patients aged >80 years and in those with non-rheumatic structural heart disease. Pacing is indicated on prognostic grounds even in asymptomatic individuals.

- Complete heart block is the most common reason for permanent pacing
- When related to an infarction, high-grade AV block occurs mostly with right coronary artery occlusion, because the AV nodal branch is usually one of the distal branches of the right coronary artery
- In patients with an anterior infarct, high-grade AV block is a poor prognostic feature, indicating extensive ischaemia
- Congenital cases may be related to connective tissue diseases; however, in patients with normal exercise capacities, recent studies show that the prognosis is not as benign as was previously thought and pacing is therefore recommended in a wide range of circumstances (see European Society of Cardiology guidelines by Vardas *et al Eur Heart J* 2007;28:2256–95).

Tachyarrhythmias

Tachyarrhythmias are caused by re-entry, automaticity or triggered activity:

- Re-entry: the arrhythmia is anatomically dependent and usually the primary problem as opposed to sequelae of another reversible state
- Automaticity: arrhythmia is often secondary to a systemic cause (eg electrolyte imbalance, sepsis, adrenergic drive) and is multifocal
- Triggered activity: shares features of both mechanisms and is seen in both primary arrhythmias and drug toxicity.

1.6.2 Supraventricular tachycardias

There are two major groups of re-entrant tachycardias often described as SVT:

- **AV nodal re-entry tachycardia** (AVNRT; see Figure 1.6): involves a re-entry circuit in and around the AV node
- **AV re-entry tachycardia** (AVRT; see Figure 1.7): this involves an accessory pathway between the atria and ventricles some distance from the AV node (eg WPW syndrome and related conditions).

AV nodal re-entry tachycardia

Differential conduction in tissue around the AVN allows a micro re-entry circuit to be maintained (see

Figure 1.6), resulting in a regular tachycardia.

Accessory pathways

An accessory pathway that connects the atrium and ventricle mediates the tachycardia by enabling retrograde conduction from ventricle to atrium. More seriously, the accessory pathway may predispose to unrestricted conduction of AF from atria to ventricles as a result of anterograde conduction through the pathway. This may lead to ventricular fibrillation.

WPW is said to be present when a δ wave (partial pathway-mediated pre-excitation) is present on the resting ECG. Associations with WPW include: Ebstein's anomaly (may have multiple pathways), HCM, mitral valve prolapse and thyrotoxicosis; it is more common in men.

Some accessory pathways are not manifest by a δ wave on the resting ECG but are still able to participate in a tachycardia circuit.

Atrial tachycardias, including flutter, AF, sinus tachycardia and fascicular ventricular tachycardia, may all be mistaken for SVT.

Figure 1.6 Mechanism for atrioventricular nodal re-entry tachycardia

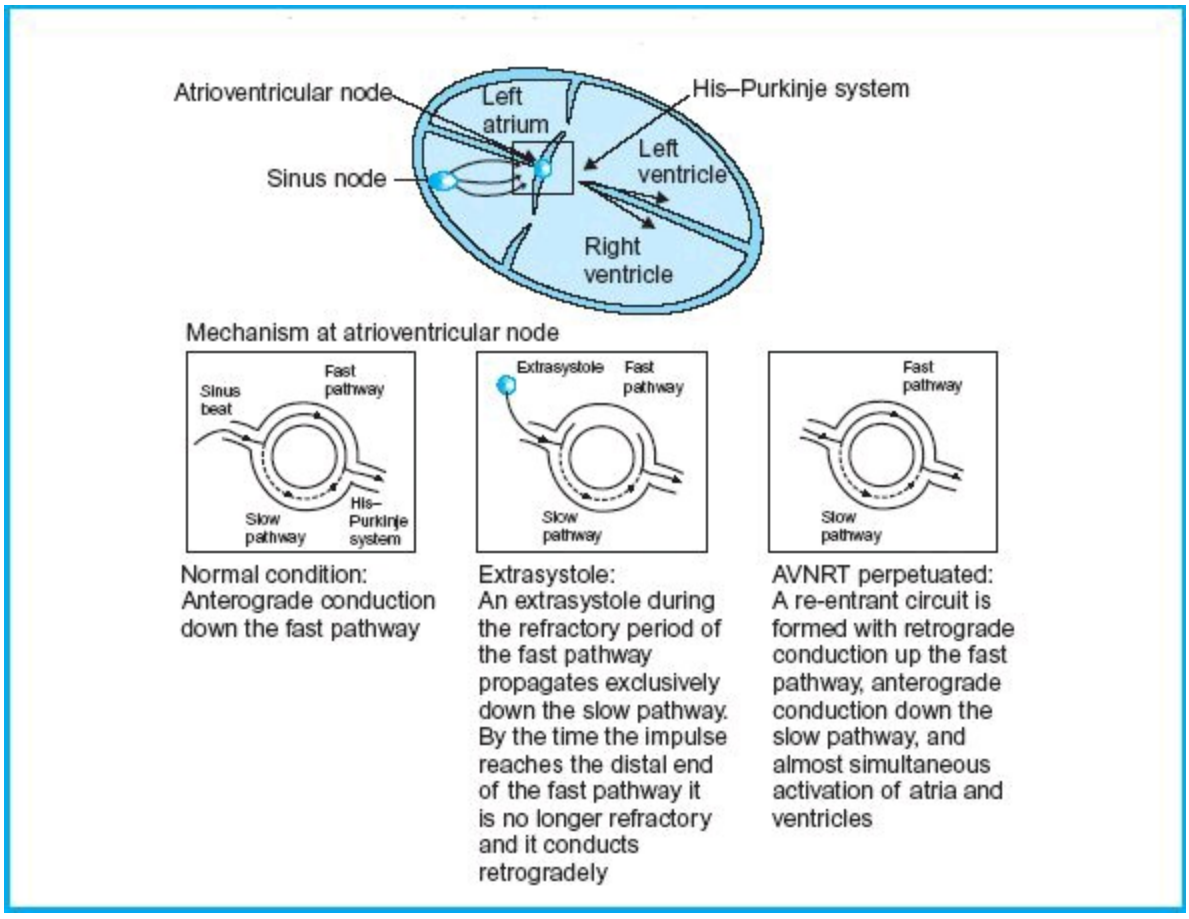
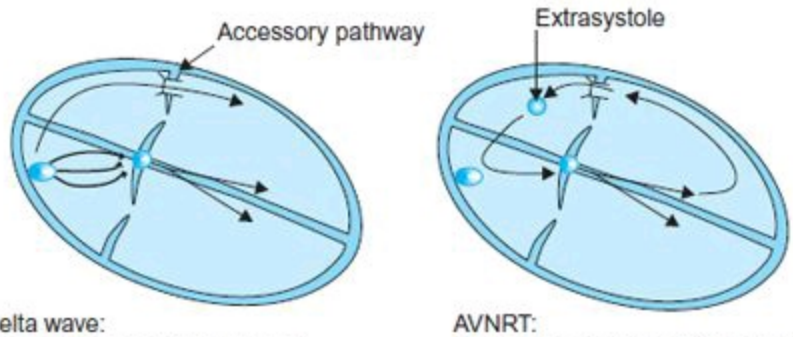
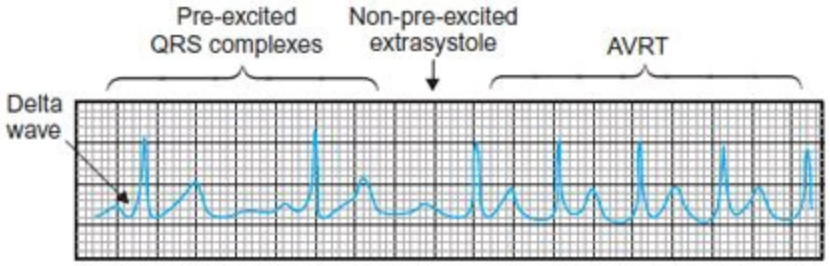


Figure 1.7 Mechanism for atrioventricular re-entry tachycardia



Delta wave:
Anterograde conduction via an accessory pathway usually produces pre-excitation of the ventricle, because the accessory pathway conducts more rapidly than the atrioventricular node. This early ventricular activation is manifest as a delta wave, which is a slurred upstroke at the start of the QRS complex. The terminal portion of the QRS complex is narrow, reflecting the rapid conduction via the His–Purkinje system once the atrioventricular node has been crossed

AVNRT:
Tachycardia is typically initiated by an extrasystole which occurs early and therefore cannot conduct via the accessory pathway but is able to conduct via the atrioventricular node (accessory pathway has a larger refractory period than the atrioventricular node). By the time the impulse reaches the accessory pathway from the ventricular side it is no longer refractory and can conduct retrogradely to the atrium



1.6.3 Atrial arrhythmias

Atrial flutter

Atrial flutter involves a macro re-entrant circuit where the electrical activation circles the right atrium. This generates characteristic sawtoothed flutter waves, which typically have a rate between 250 and 350 beats/min, with a ventricular response of 150 beats/min (2 : 1 block).

- The ventricular response may be slowed by increasing the vagal block of the AVN (eg carotid sinus massage) or by adenosine, which 'uncovers' the flutter waves on ECG
- This is the most likely arrhythmia to respond to DC cardioversion with low energies (eg 25 V)
- Amiodarone and sotalol may chemically cardiovert, slow the ventricular response or act as prophylactic agents
- Radiofrequency ablation is curative in up to 95% of cases
- Adenosine cannot terminate atrial flutter but can be useful in revealing it.

Atrial flutter is described as typical when associated with a sawtooth atrial pattern in the inferior leads and positive flutter waves in V1. Atypical flutters tend to occur in congenital heart disease or after surgery or prior ablation.

Atrial fibrillation

This arrhythmia is due to multiple wavelet propagation in different directions. The source of the arrhythmia may be myocardial tissue in the openings of the four pulmonary veins, which enter into the posterior aspect of the left atrium, and this is particularly the case in younger patients with paroxysmal AF. AF may be paroxysmal, persistent (but 'cardiovertable') or permanent, and in all three states it is a risk factor for strokes. Treatment is aimed at ventricular rate control, cardioversion, prevention of recurrence and anticoagulation. Catheter ablation is indicated in symptomatic individuals who are resistant to, or intolerant of, medical therapy.

With AF, a major decision is whether to control rate or alter the rhythm:

- Surprisingly, rhythm control does not reduce the risk of stroke (indeed paroxysmal AF carries the same stroke risk as chronic AF) and therefore does not affect the indications for anticoagulation
- Cardioversions, multiple drugs and ablations are all used to alter rhythm
- In asymptomatic individuals, rate control is recommended.

Associations with atrial fibrillation

- Ischaemic heart disease
- Pericarditis
- Mitral valve disease
- Pulmonary embolus
- Hypertension
- Atrial myxomas
- Thyroid disease
- LVH
- Acute alcohol excess/chronic alcoholic cardiomyopathy
- ASD
- Post-CABG
- Caffeine excess
- Dilated left atrium (>4.5 cm)
- Pneumonia
- WPW syndrome
- Bronchial malignancy

The overall risk of systemic emboli is 5–7% annually (higher with rheumatic valve disease); this falls to 1.6% with anticoagulation. TOE may exclude atrial appendage thrombus but cannot predict the development of a thrombus in the early stages post-cardioversion; anticoagulation is therefore always recommended post-cardioversion.

- **Risk factors for stroke with non-valvular AF**

- Previous history of cerebrovascular accident or transient ischaemic attack (risk × 22.5)
- Diabetes (×1.7)
- Hypertension (×1.6)
- Heart failure

- **Risk factors for recurrence of AF after cardioversion**
  - Long duration (>1–3 years)
  - Rheumatic mitral valve disease
  - Left atrium size >5.5 cm
  - Older age (>75 years)
  - Left ventricular impairment

The $CHADS_2$ risk score has been modified to CHA_2DS_2-VASc and includes further risk factors (Tables 1.6 & 1.7). Previously, aspirin was considered a suitable alternative to warfarin in low-risk groups, but new studies suggest that the protective effect is minimal with only deleterious side-effects encountered. Therefore, warfarin is the agent of choice in most cases.

Table 1.6 The CHA_2DS_2-VASc risk score

CHA_2DS_2- VASc score	**Annual stroke risk (%/year)**	**Suggested medication**
0	0	Nil
1	1.3	Aspirin or warfarin
2	2.2	Warfarin
3	3.2	
4	4.0	
5	6.7	
6	9.8	
7	9.6	
8	6.7	
9	15.2	

Table 1.7 The CHA_2DS_2-VASc risk factors

CHA_2DS_2-VASc risk factors	**Score**
Congestive heart failure	1
Hypertension	1
Age ≥75	2
Age 65–74	1
Diabetes mellitus	1

Stroke/TIA/thromboembolism	2
Vascular disease	1
Female gender	1

The HAS-BLED score (based on a *mnemonic*) helps consider a patient's bleeding risks on anticoagulation (Table 1.8). Online calculators can estimate the bleeding risk.

Table 1.8 The HAS-BLED score

Letter	Characteristics	Definition	Score
H	Hypertension	Systolic BP >160 mmHg	1
A	Abnormal renal and liver function	Dialysis, renal transplantation or Cr >200 βmol/L; cirrhosis or ALT/AST more than three times upper normal limit	1 point each (1 or 2)
S	Stroke		1
B	Bleeding	Previous bleeding or predisposition to bleeding	1
L	Labile INRs	INRs out of range >40% time	1
E	Elderly >65 years		1
D	Drugs or alcohol	Concomitant use of NSAIDs, antiplatelet agents or alcohol abuse	1 point each (1 or 2)

ALT, alanine transaminase; AST, aspartate transaminase; Cr, creatinine; INRs, international normalised ratios; NSAIDs, non-steroidal anti-inflammatory drugs.

1.6.4 Ventricular arrhythmias and channelopathies

Ventricular tachycardia (monomorphic) (Figure 1.8)

VT has a poor prognosis when left ventricular function is impaired. After the exclusion of reversible causes such patients may need implantable defibrillators and antiarrhythmic therapy.

- Ventricular rate is usually 120–260 beats/min
- Patients should be DC cardioverted when there is haemodynamic compromise; overdrive pacing may also terminate VT
- Amiodarone, sotalol, flecainide and lidocaine may be therapeutic adjuncts or prophylactic agents; magnesium may also be useful.

Associations of VT

- Myocardial ischaemia
- Hypokalaemia or severe hyperkalaemia

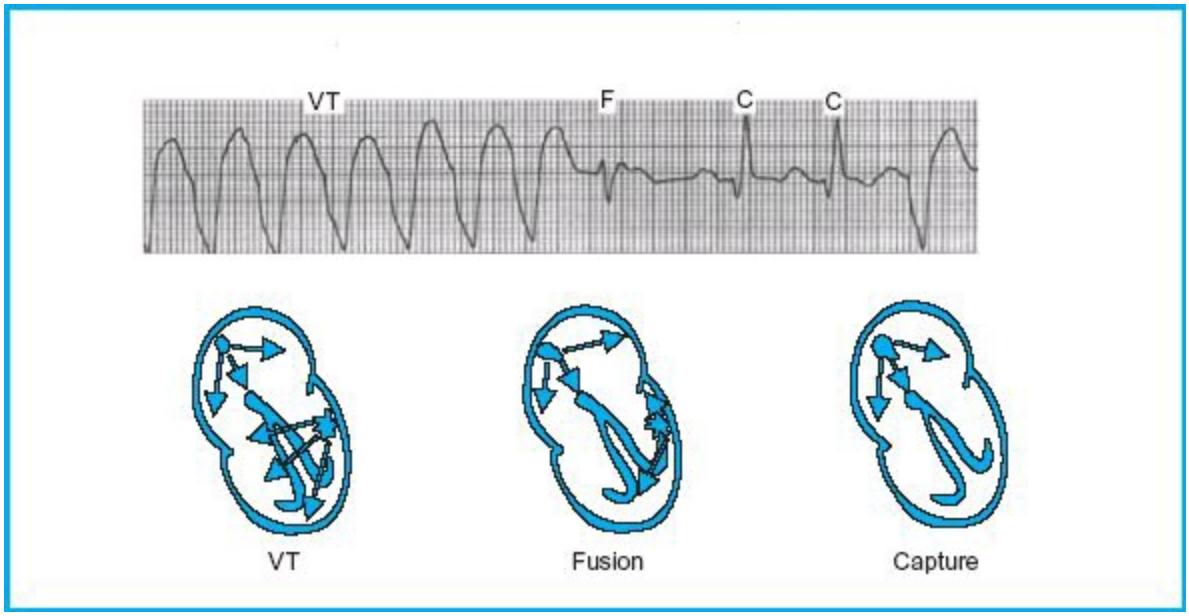
- Long QT syndrome (see below)
- Digoxin toxicity (VT may arise from either ventricle, especially with associated hypokalaemia)
- Cardiomyopathies
- Congenital abnormalities of the right ventricular outflow tract (VT with LBBB and right axis deviation pattern)

Features favouringVT in broad-complex tachycardia

It is often difficult to distinguish VT from SVT with aberration (disordered ventricular propagation of a supraventricular impulse); VT remains the most common cause of a broad-complex tachycardia, especially with a previous history of MI. The following ECG observations favour VT:

- **Capture beats**: intermittent sino-atrial (SA) node complexes transmitted to ventricle
- **Fusion beats**: combination QRS from SA node and VT focus meeting and fusing (causes cannon waves)
- RBBB with left axis deviation
- Very wide QRS >140 ms
- Altered QRS compared with sinus rhythm

Figure 1.8 Ventricular tachycardia can feature fusion and capture beats. Mechanisms and example ECG patterns are shown



- V lead concordance with all QRS vectors, positive or negative
- **Dissociated P waves**: marching through the VT
- **History of ischaemic heart disease**: very good predictor
- Variable S1
- Heart rate <170 beats/min with no effect of carotid sinus massage.

Note: none of the above has as high a positive predictive value for VT diagnosis as a history of structural heart disease (especially MI).

Ventricular tachycardia (polymorphic) – torsades de pointes

This is a particular type of VT in which the QRS complexes are of different amplitudes, appearing to 'twist' around the isoelectric line, with QT prolongation when the patient is in sinus rhythm. QT prolongation can be genetic (see below) or acquired – and can be of any cause to trigger torsades de pointes:

- Antiarrhythmic agents (particularly class III, such as sotalol) may predispose to torsades de pointes by induced bradycardia and QT prolongation. Premature ventricular contraction ('R-on-T' phenomenon) is more likely if the QT interval is very long, and can trigger torsades de pointes
- Intravenous magnesium and K^+ channel openers may control the arrhythmia, whereas isoprenaline and temporary pacing may prevent bradycardia and hence the predisposition to VT.

Pro-arrhythmic channelopathies

Abnormally prolonged QT intervals may be familial or acquired, and are associated with syncope and sudden death, due to VT (especially torsades de pointes). Mortality in the untreated symptomatic patient with a congenital abnormality is high but some patients may reach the age of 50–60 years despite repeated attacks. Causes and associations are shown below.

Pro-arrhythmic causes of abnormal repolarisation (ST – changes)

- **Familial**
  - Long QT syndromes 1–5
  - Brugada's syndrome
  - Short QT syndrome
  - Arrhythmogenic right ventricular dysplasia
- **Drugs**
  - Quinidine
  - Erythromycin
  - Amiodarone
  - Tricyclic antidepressants
  - Phenothiazines
  - Probucol
  - Non-sedating antihistamines (eg terfenadine)
- **Ischaemic heart disease**
- **Metabolic**
  - Hypocalcaemia
  - Hypothyroidism
  - Hypothermia
  - Hypokalaemia
- **Rheumatic carditis**

Long QT syndromes: the corrected QT is >540 ms (normal = 380–460 ms). Ninety per cent are familial, with chromosome 11 defects being common (Romano–Ward syndrome has autosomal dominant inheritance; Jervell–Lange–Nielsen syndrome is autosomal recessive and associated with congenital deafness). Arrhythmias may be reduced by a combination of β blockers and pacing.

Cardiac causes of electromechanical dissociation

When faced with a cardiac arrest situation it is important to appreciate the list of causes of electromechanical dissociation (EMD):

- Hypoxia
- Hypovolaemia
- Hypokalaemia/hyperkalaemia
- Hypothermia
- Tension pneumothorax
- Tamponade
- Toxic/therapeutic disturbance
- Thromboembolic/mechanical obstruction.

1.6.5 Pacing and ablation procedures

Temporary pacing

The pacing electrode is placed in the right ventricular apex causing activation from the right ventricle; as such the ECG will show LBBB morphology. If the pacing lead has perforated the septum, and entered the left ventricle, the morphology will show RBBB. Temporary pacing for emergencies such as heart block is typically ventricular only. Pacing post-cardiac surgery employs epicardial pacing wires, placed at the time of surgery, and this may be atrial or ventricular (atrial appendage and right ventricular apex) to optimise cardiac output.

Complications include:

- Crossing the tricuspid valve during insertion, which causes ventricular ectopics, as does irritating the outflow tract
- Atrial or right ventricular perforation and pericardial effusion
- **Pneumothorax**: internal jugular route is preferable to the subclavian one, because it minimises this risk and also allows control after inadvertent arterial punctures.

Permanent pacing

Permanent pacing can be ventricular only, or atrial and ventricular to preserve AV synchrony. The naming convention reflects the chamber paced, the chamber sensed and the pacemaker response to sensing, eg VVI means that the ventricle is paced and, when ventricular activity is sensed, the pacemaker inhibits itself. DDD is now increasingly used, with the device capable of ‘dual’ pacing, ‘dual’ sensing and ‘dual’ response to native cardiac beats (hence the term DDD). These capabilities

mean much more sophisticated pacing behaviour can be programmed, such that different actions are taken in response to cardiac rhythms. For example, if the pacemaker detects activity in both atria and ventricles, it is inhibited and does nothing; alternatively if atrial activity is present but ventricular activity is absent, it will pace only the ventricle in time with the natural atrial activity. This allows sophisticated programming to optimise the device for the patient. Most pacemakers are now also rate-responsive (denoted by 'R'); these use movement or physiological triggers (respiratory rate or QT interval) to increase heart rates. They reduce rates of pacemaker syndrome and act more physiologically for active patients. Pacemaker syndrome is a constellation of symptoms related to even subtle impairment of cardiac output or change in peripheral resistance caused by suboptimal pacemaker settings. Typically, it can be caused by subtle differences in atrioventricular synchrony which can cause loss of the atrial 'kick' (atrial contribution to cardiac output). Patients may be dizzy, hypotensive or develop signs of heart failure. Optimisation of pacemaker settings for the individual patient is now a routine clinical activity during pacemaker checks.

Pacing in heart failure

There are several synonymous terms for pacing in patients with cardiac failure. These include 'cardiac resynchronisation therapy', 'biventricular pacing' and 'multisite pacing'. In heart failure pacing is indicated when all of the following are present:

- NYHA III–IV heart failure
- QRS duration >130 ms
- Left ventricular ejection fraction >35% with dilated ventricle and patient on optimal medical therapy (diuretics, angiotensin-converting enzyme [ACE] inhibitors and β blockers).

The atria and right ventricle are paced in the usual fashion and in addition to this a pacing electrode is placed in a tributary of the coronary sinus on the lateral aspect of the left ventricle. The two ventricles are paced simultaneously or near simultaneously with a short AV delay. The aim is to optimise AV delay and reduce inter- and intraventricular asynchrony. This therapy is known to reduce mortality, to improve exercise capacity, to improve quality of life and to reduce hospital admissions.

Studies have not shown benefit in heart failure patients with narrow QRS duration, and echocardiographic markers of dyssynchrony are unreliable. A recent randomised study in which dyssynchrony markers were used to select patients for CRT instead of the traditional parameters showed no benefit and significant harm.

Implantable cardioverter defibrillators

Implantable cardioverter defibrillators (ICDs) are devices that are able to detect life-threatening tachyarrhythmias and terminate them by overdrive pacing or a counter-shock. They are implanted in a similar manner to permanent pacemakers. Current evidence supports their use in both secondary prevention of cardiac arrest and targeted primary prevention (eg for individuals with LV impairment and those with familial syndromes such as arrhythmogenic right ventricular dysplasia, Brugada's syndrome, long QT variants).

Radiofrequency ablation

Radiofrequency ablation is resistive, heat-mediated (65°C) protein membrane disruption causing cell

lysis. Using cardiac catheterisation (with electrodes in right- or left-sided chambers) it interrupts electrical pathways in cardiac structures. Excellent results are obtained in the treatment of accessory pathways and atrial flutter, and with complete AV nodal ablation or AV node modification. Ventricular tachycardia is technically more difficult to treat (ventricular myocardium is much thicker than atrial myocardium).

Isolation of the pulmonary veins by ablation therapy is now an established technique to treat AF. Current cure rates are around 85%, but more than one procedure is required in half the cases. Complete heart block and pericardial effusions are rare complications of radiofrequency ablation.

Indications to refer to an electrophysiologist

Indications for referral to an electrophysiologist are given in Table 1.9.

Table 1.9 Indications for referral to an electrophysiologist

Condition	When to refer	Potential treatment
SVT	More than one episode	Radiofrequency ablation
Atrial flutter	More than one episode	Radiofrequency ablation
Atrial fibrillation	Highly symptomatic, refractory to or intolerant of drug therapy	Radiofrequency ablation
Ventricular fibrillation	Unless there is an obvious reversible cause, eg ST-segment elevation MI (STEMI)	ICD
Ventricular tachycardia	Unless obvious reversible cause	Radiofrequency ablation or ICD
Ischaemic cardiomyopathy	Ejection fraction >30% on optimal medical therapy	Primary prevention ICD
NYHA class III–IV heart failure, QRS >130 ms, ejection fraction <35%	On optimal medical therapy	Heart failure pacing

1.7 ISCHAEMIC HEART DISEASE

Ischaemic heart disease has been the leading worldwide cause of death since 1990, claiming 7 million lives a year.

Risk factors for coronary artery disease

- **Primary**
  - Hypercholesterolaemia (LDL)
  - Hypertension

    - Smoking
- **Unclear**
    - Low fibre intake
    - Hard water
    - High plasma fibrinogen levels
    - Raised Lp(a) levels
    - Raised factor VII levels
- **Protective factors**
    - Exercise
    - Moderate amounts of alcohol
    - Low cholesterol diet
    - Increased HDL:LDL
- **Secondary**
    - Reduced HDL-cholesterol
    - Obesity
    - Type 1 diabetes mellitus
    - Type 2 diabetes
    - Family history of coronary artery disease
    - Physical inactivity
    - Stress and personality type
    - Gout and hyperuricaemia
    - Race (Asians)
    - Low weight at 1 year of age
    - Male sex
    - Chronic renal failure
    - Increasing age
    - Low social class
    - Increased homocystine levels and homocystinuria

HDL, high-density lipoprotein;
LDL, low-density lipoprotein.

Smoking and its relationship to cardiovascular disease

Smokers have an increased incidence of the following cardiovascular complications:

- Coronary artery disease
- Malignant hypertension
- Ischaemic stroke
- Morbidity from peripheral vascular disease

- Sudden death
- Subarachnoid haemorrhage
- Mortality due to aortic aneurysm
- Thromboembolism in patients taking oral contraceptives

Both active and passive smoking increase the risk of coronary atherosclerosis by a number of mechanisms, including:

- Increased platelet adhesion/aggregation and whole-blood viscosity
- Increased heart rate; increased catecholamine sensitivity/release
- Increased carboxyhaemoglobin level and, as a result, increased haematocrit
- Decreased HDL-cholesterol and vascular compliance
- Decreased threshold for ventricular fibrillation.

1.7.1 Angina

Other than the usual forms of stable and unstable angina, those worthy of specific mention include:

- **Decubitus**: usually on lying down – due to an increase in LVEDP or associated with dreaming, cold sheets, or coronary spasm during rapid eye movement (REM) sleep
- **Variant** (**Prinzmetal's**): unpredictable, at rest, with transient ST elevation on ECG. Due to coronary spasm, with or without underlying arteriosclerotic lesions
- **Syndrome X**: this refers to a heterogeneous group of patients who have ST-segment depression on exercise testing but angiographically normal coronary arteries. The patients may have very-small-vessel disease and/or abnormal ventricular function. It is commonly described in middle-aged women and oestrogen deficiency has been suggested to be an aetiological factor
- **Vincent's angina**: nothing to do with cardiology; infection of the pharyngeal and tonsillar space!

Causes of non-anginal chest pains

- **Pericardial pain**
- **Aortic dissection**
- **Mediastinitis**
  - Associated with trauma, pneumothorax or diving
- **Pleural**
  - Usually with breathlessness in pleurisy, pneumonia, pneumothorax or a large peripheral pulmonary embolus
- **Musculoskeletal**
- **Gastrointestinal**
  - Including oesophageal, gastric, gallbladder, pancreatic

- **Hyperventilation/anxiety**
  - Reproduction of sharp inframammary pains on forced hyperventilation is a reliable test
- **Mitral valve prolapse**
  - May be spontaneous, sharp, superficial, short-lived pain

Symptomatic assessment of angina

The Canadian cardiovascular assessment of chest pain is useful for grading the severity of angina:

- **Grade I**: angina only on strenuous or prolonged exertion
- **Grade II**: angina climbing two flights of stairs
- **Grade III**: angina walking one block on the level (indication for intervention)
- **Grade IV**: angina at rest (indication for urgent intervention).

1.7.2 Myocardial infarction

Conservative estimates suggest there are 103 000 MIs per year in the UK with significant prehospital mortality, and a 5–6% inhospital mortality rate and a 6–7% 30-day mortality rate for those surviving to hospital admission. Overall, 19% of UK deaths are directly attributable to coronary disease.

Acute coronary syndromes

MI is part of the diagnostic entity now commonly referred to as 'acute coronary syndrome' (ACS). This overlapping constellation of conditions helps identify patients at risk and needing further treatment. The chest pain is typically retrosternal or heaviness, with radiation to the arms, neck or jaw. It can be intermittent or persistent. It may be associated with sweating, nausea, dyspnoea or syncope. These accessory symptoms are rare in stable angina, and that pain typically settles upon resting or with nitrates and has a predictable onset. The chest pain characteristic of an ACS is:

- Prolonged (>20 min at rest)
- New-onset severe angina (Canadian Cardiovascular Society angina classification: Class III, angina symptoms with everyday activities with moderate limitation)
- Destabilisation

ACS includes three distinct conditions: ST-elevation myocardial infarctions (STEMI), non-ST-elevation MIs (NSTEMIs) and unstable angina. The diagnosis for all three requires ECG changes and an appropriate history with typical corresponding features.

An acute STEMI is when there is new ST-segment elevation (≥2 mm in two contiguous chest leads or ≥1 mm in two or more limbs). Posterior STEMI cause dominant R waves in V1 but will reveal ST elevation only if a posterior ECG is taken. New-onset LBBB with a typical history is also considered to be STEMI until proven otherwise. Patients are typically in pain, grey and sweaty. Most of those having STEMI have had prodrome symptoms in the previous weeks, with only a fifth having new-onset symptoms for the last 24 hours. In STEMI, the vessel is typically entirely occluded by plaque rupture and subsequent thrombus formation. STEMI has the highest risk of inhospital mortality.

NSTEMI includes ACS that features typical symptoms, ST depression, or new T-wave inversion and troponin rise. The spectrum of symptoms varies considerably. Patients' risk may be assessed using GRACE or TIMI scores; most will receive dual antiplatelet therapy, together with statins and β blockers if appropriate. The majority of NSTEMI patients are managed invasively, typically having inpatient angiography and PCI. Vessels are less likely to be entirely occluded in NSTEMI but the presentation is variable. Approximately 10% of patients may be referred for CABG. Although patients can appear well, NSTEMIs have a higher mortality than STEMI at 12 months.

Unstable angina refers to a sudden acceleration of anginal symptoms on minimal activity, either as new onset or on a background of stable angina. ECG changes may occur, but there is no troponin rise. Patients may be medically managed but those with higher risk characteristics may undergo invasive assessment.

Diagnosis of MI

Acute, evolving or recent MI Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

- Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
  - Ischaemic symptoms
  - Development of pathological Q waves on the ECG
  - ECG changes indicative of ischaemia (ST-segment elevation or depression)
- Pathological finding of an acute MI (eg postmortem).

Established MI

Any one of the following criteria satisfies the diagnosis of an established MI:

- Development of new pathological Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalised, depending on the length of time that has passed since the infarct developed
- Pathological finding of a healed or healing MI
- Previous MI is also suggested when coronary artery disease and a regional ventricular wall motion abnormality are seen, or characteristic myocardial scars are observed with MRI.

Cardiac enzymes

The widespread use of troponin assays has both simplified and lowered the bar for the diagnosis of MI. A number of markers of cardiac damage are now available. A number of markers of cardiac damage are available, the most popular being troponin which rises 3–12 hours after the event and falls over a week, and creatine kinase (with MB being the main isoenzyme), which rises and falls much more quickly. In general clinical practice, troponin is the mainstay for detecting myocardial damage. Consensus statements agree that troponin must rise over the 99th centile upper reference range, 12 hours after the episode of chest pain, together with symptoms and other features of ischaemia to diagnose myocardial infarction. Troponin is usually measured twice, on admission and at the 12-hour mark; it is this second troponin for which all study data is available. Troponin can be

raised in other conditions (see below), and as such, it adds most clinical value when the pretest probability of MI or coronary artery disease is highest. The level of troponin is directly related to the amount of cardiac damage and is associated with the likelihood of later adverse outcomes.

High-sensitivity troponin has recently been made available. These can measure low level troponin concentrations within the nanogram per litre range. These assays have revealed troponin is detectable in the plasma of healthy illness-free individuals. This means the specificity of the test has been reduced and leads to challenges in interpreting the results. The threshold for significance will depend upon the specific assay and manufacturer. Concerns include over-diagnosis of cardiac events with subsequent inappropriate investigation. The potential benefit is that high-sensitivity troponin assays can detect troponin rises more quickly after the index event, enabling the confirmed diagnosis to made on serial measurements performed within 2-3 hours of each other.

Troponin rise in other conditions

Troponin assays are now incredibly sensitive and can even detect fragments of the troponin molecule. Troponin is more closely linked to states of myocardial hypoperfusion rather than coronary occlusion as such, and it can leak from cardiomyocytes by any state that increases myocardial membrane permeability, even without true cell necrosis. There are a multitude of conditions that cause troponin leak (see box) and therefore high pretest probability, together with clear symptoms and new acute ECG changes, is mandatory to make a diagnosis of MI.

Conditions that cause troponin leak

- Critical illness – intensive care unit/sepsis
- Hypotension
- Hypertensive crisis/pre-eclampsia
- Pulmonary embolism
- Infective exacerbations of COPD
- Abdominal aortic aneurysm rupture
- Gastrointestinal bleeding
- Chemotherapy: some directly cardiotoxic
- Renal impairment
- Neurological conditions: stroke, subarachnoid haemorrhage and seizures

The advert of thrombolysis and then, primary percutaneous coronary intervention (PPCI) has greatly reduced complication rates. Late presentation (with completed infarctions) or failed PPCI in the STEMI setting is still associated with significant complications and the location of the infarct is related to the type seen.

Troponin assays in patients with renal failure

The troponin level may be elevated simply because a patient has renal failure. In patients with renal failure who present with chest pain, it is helpful to assess the troponin level at baseline as well as 12

h after the onset of symptoms, and sometimes at later time points. In these circumstances only a rising troponin level would be suggestive of ischaemic myocardial damage.

Complications of MI

Since the advent of thrombolysis, complication rates have been reduced (eg halved for pericarditis, conduction defects, ventricular thrombus, fever, Dressler's syndrome). All complications may be seen with any type of infarction, but the following are the most common associations:

- **Complications of anterior infarctions**
  - Late VT/VF
  - Left ventricular aneurysm
  - Left ventricular thrombus and systemic embolism (usually 1–3 weeks post-MI)[a]
  - Complete heart block (rare)
  - Ischaemic mitral regurgitation
  - Congestive cardiac failure
  - Cardiac rupture – usually at days 4–10 with EMD
  - VSD with septal rupture
  - Pericarditis and pericardial effusion (Dressler's syndrome with high erythrocyte sedimentation rate [ESR], fever, anaemia, pleural effusions and anti-cardiac muscle antibodies are seen occasionally)
- **Complications of inferior infarctions**
  - Higher re-infarction rate
  - Inferior aneurysm – with mitral regurgitation (rare)
  - Pulmonary embolism (rare)
  - Complete heart block and other degrees of heart block
  - Papillary muscle dysfunction and mitral regurgitation
  - Right ventricular infarcts need high filling pressures (particularly if posterior extension)

[a] Although warfarin provides no general benefit, it may reduce the overall cerebrovascular accident rate (1.5–3.6%) in those patients with ECG demonstrable mural LV thrombus after a large anterior MI, so recommended for up to 6 months after the infarction.

Heart block and pacing after MI

Temporary pacing is indicated in anterior MI complicated by complete heart block. This presentation is associated with high mortality due to the extensive myocardial damage affecting the AVN.

The right coronary artery is the dominant vessel (supplies the SA and AVN) in 85% of cases. Occlusion of the right coronary artery can cause complete heart block. The decision to temporarily pace a patient with inferior infarction is primarily dictated by the patient's haemodynamic status. Atropine and isoprenaline may be used but most often rapid PPCI with restoration of blood flow to the right coronary artery will resolve heart block. A temporary pacing wire may be placed in the acute situation to provide cover. An observational period post-MI is appropriate to allow the return

of sinus rhythm before considering permanent pacing.

1.7.3 PPCI for STEMI

PPCI has replaced thrombolysis for most patients with STEMI in the UK. Centres providing PPCI services aim to take patients presenting within 12 hours of the onset of symptoms directly from the ambulance to the catheter laboratory, which has extensive resuscitation facilities, to reduce 'door-to-balloon' times. An earlier invasive strategy is patients being assessed and, if meeting the diagnostic criteria of STEMI, will be consented for an immediate procedure. Urgent antiplatelets are given orally (aspirin 300 mg, and a second antiplatelet clopidogrel 600 mg, or prasugrel 60 mg or ticagrelor 180 mg), in addition to analgesia (Table 1.10). Arterial access is via the radial artery or femoral artery, and diagnostic angiographic images will typically reveal the occluded culprit vessel. Intraprocedure heparin or heparin-like drugs and/or bivalirudin (a direct thrombin inhibitor) may be used; adjunctive agents such as glycoprotein IIb/IIIa (GPIIb/IIIa) agents may be considered. If technically feasible, thrombus aspiration may be performed, but often flow is restored by the process of passing an intracoronary wire: this is accompanied by relief of pain and haemodynamic stabilisation. Culprit lesions are then stented, typically with the latest generation drug-eluting stents provided that there are no contraindications. Patients are cared for on a coronary care unit environment post-procedure.

PPCI has the greatest value if performed early and should be considered in all patients presenting within 12 hours of pain. Those who present after 12 hours should also be considered if there is ongoing pain or ECG evidence of ongoing ischaemia.

Thrombolysis

Thrombolysis is still used in many clinical settings worldwide where access to PPCI is limited. It is most effective if given within 6 hours of symptom onset, with the greatest benefit seen in the highest-risk patients (STEMI). Multiple agents are available, including streptokinase, alteplase (tissue plasminogen activator or tPA), reteplase (recombinant or rPA) and tenecteplase (TNK-tPA). Recanalisation occurs in 70% of patients (compared with 15% without thrombolysis). Reperfusion arrhythmias (VTs and ectopics) are common in the first 2 hours after thrombolysis.

Although now uncommon, examination questions may consider the contraindications to thrombolysis and these are given below.

Contraindications to thrombolysis

- **Absolute contraindications**
  - Active internal bleeding or uncontrollable external bleeding
  - Suspected aortic dissection
  - Recent head trauma (<2 weeks)
  - Intracranial neoplasms
  - History of proved haemorrhagic stroke or cerebral infarction <2 months earlier
  - Uncontrolled high BP (>200/120 mmHg)

- Pregnancy
- **Relative contraindications**
  - Traumatic prolonged cardiopulmonary resuscitation
  - Bleeding disorders
  - Recent surgery
  - Probable intracardiac thrombus (eg AF with mitral stenosis)
  - Active diabetic haemorrhagic retinopathy
  - Anticoagulation or international normalised ratio or INR >1.8

There is now a good evidence base for a range of pharmacological treatments in patients presenting with acute coronary syndromes (Table 1.10). These are aimed at dispersing clot (aspirin, clopidogrel, heparin), preventing arrhythmias (β blockers), stabilising plaque (statins) and preventing adverse remodelling.

1.7.4 Coronary artery interventional procedures

Percutaneous coronary intervention

PCI permits rapid and low-risk coronary revascularisation, which can be performed as an emergency (for STEMI), urgently (for NSTEMI or unstable angina) or electively (for stable angina, failed on medical therapy and with evidence of ischaemia). The principles are similar. Arterial access, either radial or femoral, permits catheter intubation of the coronary arteries and assessment of stenoses on fluoroscopy. Stenoses can be further assessed using imaging (to assess anatomical severity with IVUS or OCT) or functionally (to assess physiological significance of a stenosis using a pressure wire). Stenoses selected for intervention are then transversed using torquable intracoronary wires, before the stenosis is balloon-dilated and stented.

Plain balloon angioplasty (POBA) is successful in relieving stenoses, but vessel recoil can cause acute occlusion which causes endothelial injury and triggers hyperplasia; this in turn leads to 're-stenosis' – typically visible by 3 months. Bare-metal stents overcame these problems but can still undergo 'instent re-stenosis', where hyperplastic endothelium develops over the metal struts. This can be difficult to treat. Drug-eluting stents are coated in anti-mitotic agents to block smooth muscle and fibrous tissue proliferation and significantly reduce re-stenosis. However, this also means that metallic struts are exposed to blood for longer and dual antiplatelet therapy (typically aspirin and clopidogrel) is mandatory for 12 months.

- Lesions particularly amenable to PCI include those that are discrete, proximal, non-calcified, unoccluded, away from side branches and occur in patients with a short history of angina. Although there is a small acute occlusion rate, these can usually be managed successfully with intracoronary stenting, such that the need for emergency CABG has fallen to <1%
- More challenging lesions include those within grafts, at bifurcations, calcified or long lesions, and those within small vessels. People with diabetes have poorer outcomes compared with those who don't have diabetes

Almost any lesion can be stented, including left main stem disease, three-vessel disease and even

- chronic total occlusions, but careful evaluation and discussion with the patient are necessary, as in many situations bypass grafting may offer patients greater freedom from repeat procedures and may have better prognostic outcome.

Table 1.10 Summary of clinical trials in patients with acute myocardial infarction (MI)[a]

Type of therapy	Agents used for acute MI	Loading dose	Ongoing dose	Duration of use	Relevant studies	Notes
Supportive	Oxygen Nitrates Analgesia	-	-	-		Give oxygen, nitrates and analgesia to all. Give morphine analgesia when pain & anxiety is significant but it may delay gastric emptying and absorption of important antiplatelets.
Thrombolytics	Various Streptokinase, urokinase, tPA, rtPA	Varies according to weight	-	-	GISSI 1, ISIS 2, TIMI II, GUSTO	Significantly reduce mortality at 24 hours, 1 month and 1 year. Recanalise blocked vessel in 50-90% of cases depending on agent. Increase bleeding risk. Generally replaced by PPCI but valuable if cannot get patient to PPCI within 90 minutes of first medical contact. Failure to recanalise the infarct-related artery is ST-segment resolution <50% at 90 minutes.
Antiplatelet	Aspirin	300 mg	75 mg	Life long	ISIS 2	Standard for all; rare for patients to have true aspirin allergy, but if so, aspirin desensitisation can be performed.
	Clopidogrel	300–600 mg	75 mg	1 year	CURE CLARITY ARMYDA-6 OASIS-7	300 mg was standard loading protocol but 600 mg achieves antiplatelet effect more quickly and is likely appropriate for STEMI.
	Prasugrel	60 mg	10 mg	1 year	TRITON-TIMI 38 TRILOGY-ACS	More potent than clopidogrel with higher bleeding risk. Avoid if age ⩾75 years, weighing <60kg and previous history of stroke or TIA; appears only to show benefit in invasively managed patients.
	Ticagrelor	180 mg	90 mg bd	1 year	PLATO	More rapid onset and potent than clopidogrel. Twice a day preparation may impair compliance. Has an adenosine-like action with increased dyspnoea and some bradycardia.
	GPIIb/IIIa Antagonists: Abciximab, Eptifibatide, Tirofiban	Varies	-	-	ON-TIME 2 BRAVE-3	Intravenous antiplatelet medications typically used during PPCI in presence of high thrombus burden. Associated with significant thrombocytopenia and bleeding. Use together with heparin. Previously used to 'bridge' high-risk NSTEMI while awaiting invasive management.
Anticoagulants	Heparin/low-molecular-weight heparins (LMWH)	Depends on type	-	-	ESSENCE TIMI 11B ATOLL	STEMI: Unfractionated heparin is often given during PPCI: usually 70-100 IU per kg. LMWH are also used IV. Avoid fondaparinux in PPCI due to potential harm in OASIS-6. NSTEMI: LMWH are used prior to invasive management, for total of a week. Avoid on day of angiography and 24 hours prior to CABG.
	Bivalirudin	0.75 mg/kg bolus followed by continuous infusion at rate of 1.75 mg/kg/h for duration of procedure		Procedure	HORIZONS-AMI EUROMAX	Direct thrombin inhibitor. Given IV during PPCI. Alternative to heparins and GPIIb/IIIa. Principle benefit is reduced bleeding compared to other drugs but is associated with increased risk of stent thrombosis in the early phase.

Other therapeutics	Beta blockers	Metoprolol 25 mg tds Bisoprolol 1.25–10 mg od	Max tolerated	Life long	ISIS 1 COMMIT	Reduce rates of re-infarction and recurrent ischaemia. Ideally should be given to all unless contraindication. Consider starting within first 24 hours.
	ACE inhibitors/ angiotensin receptor blockers	Ramipril 2.5–10 mg Candesartan 2–32 mg	Max tolerated	Life long	SAVE, SOLVD, AIRE	Reduce mortality rates after MI; recommended as soon as patient has stable blood pressure. Greatest benefit seen in patients with impaired ventricular function. Angiotensin receptor antagonists are an alternative for those intolerant of ACE-I.
	Aldosterone receptor antagonists	Spironolactone 25 mg Epleronone 25 mg	25–50 mg	Life long	EPHESUS	The EPHESUS study showed a significant mortality reduction in patients with myocardial infarction found to have left ventricular dysfunction (EF <40%).
	Lipid-lowering therapy	Atorvastatin 20–80 mg Simvastatin 20–40 mg	10–80 mg	Life long	PROVE-IT TIMI 22 MIRACL	Statins should be started prior to discharge. Some data supports improved outcomes if started immediately. LDL levels will be artificially lower by 40-50% in first 2 months after ACS.

Coronary artery bypass grafting

CABG has benefits over coronary angioplasty in specific groups of patients with chronic coronary artery disease (when compared with medical therapy alone). Analysis has previously been limited because randomised trials included small numbers and were performed several decades ago; patients studied were usually men aged <65 years. The population now receiving CABG has changed, but so has medical therapy. The debate of CABG versus PCI is similarly complex. The recent FREEDOM trial compared CABG with PCI in people with diabetes with advanced coronary disease: they found that CABG had a superior reduction in a composite of mortality and myocardial infarction at 1 year compared with PCI.

- Prognostic benefits are shown for symptomatic, significant left main stem disease (Veterans' Study), symptomatic proximal three-vessel disease and two-vessel disease that includes the proximal left anterior descending artery (CASS data)
- Patients with moderately impaired LV function show greater benefit, but those with poor LV function have greater surgical mortality. Overall mortality rate is <2%, rising to between 5% and 10% for a second procedure. Eighty per cent of patients gain symptom relief
- Perioperative vein graft occlusion remains around 10%, with 1-2% per year for the next 6 years and then 5% per year thereafter. Intrathoracic arterial grafts (LIMA, RIMA) have much better patency, with some studies suggesting 98% patency at 10 years. However, occlusion rates vary considerably between studies and centres. On-pump and off-pump surgery and the use of adjuvant medications during the surgery contribute, as well as surgical technique
- A 'Dressler-like' syndrome may occur up to 6 months post-surgery
- Minimally invasive CABG involves the redirection of internal mammary arteries to coronary vessels without the need for cardiac bypass and full sternotomy incisions (often termed 'off-pump' coronary revascularisation). Recovery times after this procedure are shorter than for conventional surgery but the procedures are technically more challenging

Post-MI rehabilitation

After MI, patients are typically kept in hospital for 5 days, but this will depend upon the management approach taken. Patients should usually take 2 months off work and have 1 month's abstinence from sexual intercourse and driving (see following text). Cardiac rehabilitation is particularly important

for patient confidence. Depression occurs in 30% of patients. Patients who are fully revascularised or invasively investigated and found to have no ongoing ischaemic focus may be discharged after 3 days and be rehabilitated more rapidly.

Fitness to drive

The DVLA (Driver and Vehicle Licensing Agency) provides extensive guidelines for coronary disease and interventions. Their website (www.dvla.gov.uk) should be consulted, especially with regard to class 2 licences (for vehicles >3500 kg, minibuses and buses) but the essential points are given in Table 1.11.

1.8 HEART FAILURE AND MYOCARDIAL DISEASES

1.8.1 Cardiac failure

Cardiac failure can be defined as the pumping action of the heart being insufficient to meet the circulatory demands of the body (in the absence of mechanical obstructions). A broad echocardiographic definition is of an ejection fraction (EF) <40% (as in the SAVE trial, which enrolled patients for ACE inhibitors post-MI). Overall 5-year survival rate is 60% with EF <40%, compared with 95% in those with EF >50%.

The most common single cause of cardiac failure in the Western world is ischaemic heart disease (IHD).

- Hypertension is also a very frequent cause – either acting alone or in combination with IHD.

Table 1.11 Fitness to drive

Condition	Driving restriction	Notes
Solitary loss of consciousness likely to be of cardiovascular origin, but not confirmed, or likely vasovagal syncope	6 months from last episode or until effective treatment is given	Clear vasovagal events that occur only when the patient is erect do not preclude driving
Cardiac catheter procedure (including angiography, percutaneous coronary intervention, electrophysiological studies/ablation)	1 week	Should be able to perform emergency stop unhindered
Myocardial infarction	1 month	
Permanent pacemaker	1 month	Only 1 week if the patient has never been syncopal
Prophylactic ICD	1 month	No clinical arrhythmia or syncope
Secondary prevention ICD	6 months	DVLA must be informed

ICD shock therapy	6 months	Unless an inappropriate shock is preventable by reprogramming or intervention, eg a change in the detection or therapy programming to avoid shocks for sinus tachycardia or atrial arrhythmias

DVLA, Driver and Vehicle Licensing Agency; ICD, implantable cardioverter defibrillator.

EF is only a guide to cardiac function, which also depends on other factors including preload, afterload and tissue demand. However, EF is reduced in patients with systolic heart failure.

- Preload: will affect LVEDP
- Afterload: will affect LV systolic wall tension

Other echocardiographic features of LV dysfunction include reduced fractional shortening, LV enlargement and paradoxical septal motion.

The NYHA classification is a helpful indication of severity (Table 1.12).

Heart Failure with Normal or Preserved Ejection Fraction (HF-PEF)

Sometimes called 'Diastolic Heart Failure', this increasingly recognised condition should be considered in patients with breathlessness but no signs of fluid overload. It can overlap with systolic heart failure (being a concomitant problem) or be a distinct diagnosis. The principal problem is of impaired cardiac relaxation due to increased ventricular stiffness. This results in poor cardiac filling and elevated diastolic pressures in the heart and lungs causing dyspnoea. Patients will typically have elevated BNP levels, have no evidence of valve disease and have preserved systolic ejection fraction. Cardiac contractility may be reduced but since this is poorly reflected by the 'ejection fraction', then that itself may be within the normal range. The diagnosis is made using a number of echocardiographic volume and Tissue Doppler parameters that suggest it, but alone are not specific. A further difficulty is that some of these parameters change naturally with age and they are poorly reproducible over time, meaning there is no single parameter to confirm the diagnosis. Invasive tests and other imaging such as MRI have no role at present.

Table 1.12 New York Heart Association (NYHA) classification of heart failure

NYHA class	Symptoms	One-year mortality rate (%)
I	Asymptomatic with ordinary activity	5–10
II	Slight limitation of physical activities	15
III	Marked limitation of physical activities	30
IV	Dyspnoeic symptoms at rest	50–60

No treatment has been shown to reduce the morbidity or mortality in HF-PEF. Diuretics remain the mainstay, to reduce sodium and water retention and relieve dyspnoea. Controlling blood pressure and any ischaemia is important.

Drug therapy for cardiac failure

After diagnosis and during investigation for a cause of cardiac failure, drug therapy is commenced:

- If oedema is present a loop diuretic is used (eg Furosemide). If no peripheral oedema is present, care must be taken to avoid hypovolaemia; prolonged use of loop diuretics is associated with increased mortality and they should be stopped where possible.
- If oedema persists despite good doses, consider diuretic resistance or poor absorption of drug. Limited data suggests bumetanide has better bioavailability due to better absorption.
- Alternatively, changing the route of administration (oral to IV bolus or infusion) can overcome resistance, or adding a thiazide diuretic (bendroflumetazide or metolazone). Note this last combination may trigger a significant diuresis and renal function may temporarily suffer.
- Nitrates give symptomatic benefit and may be needed in the acute phase of decompensation; longer term, a nitrate-free period should be maintained. Hydralazine is another vasodilator that appeared to show benefit when combined with nitrates in African-American heart failure patients (A-HeFT). This combination is often considered when impaired renal function precludes ACE inhibitors.
- ACE inhibitors should be started early and titrated up rapidly to the maximum tolerated dose (CONSENSUS, SOLVD and ATLAS studies showed significant improvements in mortality and morbidity).
- Angiotensin receptor blockers should be considered in ACE-inhibitor intolerant patients (eg cough). Val-HeFT, VALIANT and CHARM-added studies support their use. Note that they should *not* be used in combination with ACE inhibitors, as there is little additional benefit and harm may occur from worsening renal function.
- Beta blockers should be started once the patient is diuresed. Newer agents such as metoprolol, bisoprolol and carvedilol should be used. The majority of stable patients tolerate these well if started at low dose and up-titrated to the maximum dose. They achieve significant mortality and morbidity improvements (COPERNICUS, MERIT-HF, CIBIS-II). Beta blockers can be safely started in hospital in even those with recent decompensation.
- Cessation of previously stable ACE inhibitor and β-blocker therapy (eg when the patient is admitted with intercurrent infection with hypotension and/or acute renal impairment) is associated with increased mortality. These drugs should be continued unless profoundly hypotensive, or at least restarted after clinical stability has been restored.
- Aldosterone receptor antagonists: Spironolactone and eplerenone should be added if patients continue to have symptoms despite ACE inhibitors and β blockers. RALES (spironolactone) and EMPHASIS-HF (eplerenone) both showed significant mortality and morbidity benefit in severe HF. Eplerenone is additionally indicated in patients who suffer heart failure after myocardial infarction (EPHESUS). Observe for hyperkalaemia and impaired renal function.
- Ivabradine is a rate-limiting drug with a novel mode of action, selectively inhibiting the I_f channel in the sinus node, to slow the sinus rhythm (but not arrhythmias). It has use-dependency meaning faster heart rates are most effected. The SHIFT study showed ivabradine added to HF patients with HR $\geq$70 bpm, despite other optimal medical therapy, reduced a composite of cardiovascular mortality and admission. It is recommended β blockers are at maximal doses before ivabradine is considered.

- Digoxin may help improve symptoms in patients with systolic heart failure and sinus rhythm. A single study, DIG, did not show a mortality benefit but showed reduction in hospitalisation. However this was before the β-blocker era and digoxin should only be considered once other therapies are maximal.
- Omega-3 polyunsaturated fatty acids (Omacor): these are purified fatty acids at high dose without the characteristic taste of fish oils. In the GISSI-HF PUFA study, patients randomised to these drugs had a just-significant reduction in cardiovascular mortality, felt to be due to reduction in arrhythmias.
- Heart failure patients should avoid glitazones (eg rosiglitazone and pioglitazone), calcium channel blockers (diltiazem, verapamil), NSAIDs and COX-2 inhibitors, since all cause worsening of fluid retention and heart failure.

Summary of therapeutic interventions in heart failure

A summary of therapeutic interventions in heart failure is given in Table 1.13.

Table 1.13 Summary of therapeutic interventions in heart failure

Intervention	Benefit	Comment
Diuretics	Symptom control	Loop diuretic or loop diuretic with thiazide
ACE inhibitors	Mortality and symptoms	Should be titrated to maximum tolerated dose
Angiotensin receptor blockers	Mortality and symptoms	In place of or in addition to ACE inhibitors
β blockers	Mortality and symptoms	Bisoprolol and carvedilol have the best evidence base
Aldosterone antagonists	Mortality and symptoms	NYHA III–IV
Ivabradine	Mortality and symptoms	NYHA II–IV
Digoxin	Symptom control	NYHA III–IV
Vasodilators	Symptom control	
Cardiac resynchronisation therapy	Mortality and symptoms	NYHA III–IV, see Section 1.6.5
Implantable cardioverter defibrillator	Mortality	See Section 1.6.5
Anticoagulation	Stroke morbidity	In AF or if there are prior thromboemboli

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; NYHA, New York Heart Association.

1.8.2 Hypertrophic cardiomyopathy

HCM is a spectrum disorder with a diverse range of gene mutations that lead to myocardial disarray

and hypertrophy. The hypertrophy can be apical, global or predominantly in the outflow tract. There is dynamic outflow tract obstruction, which causes an audible ESM and accounts for exertional symptoms and risk of sudden death.

Characteristic features of HCM

- Jerky pulse with large tidal wave as outflow obstruction is overcome
- Large a waves in the JVP
- Double apical impulse (palpable atrial systole, S4, in sinus rhythm)
- LSE systolic thrill (turbulence) with harsh ESM radiating to axilla
- Often accompanied by mitral regurgitation
- Often paradoxical splitting of second heart sound
- The ESM increases with Valsalva's manoeuvre and decreases with squatting.

Important points to remember

- Autosomal dominant in half the patients, associated with chromosomes 1, 11, 14 or 15. May also result from a gene mutation that leads to myocardial disarray and varying expression of hypertrophy. Prevalence <0.2% in the general population. Life expectancy is variable and the risk of sudden cardiac death (SCD) can be estimated from the presence of family history of SCD, severe symptoms including prior cardiac arrest or unexplained syncope, and key findings on investigation (including: non-sustained ventricular tachycardia on holter monitoring, severe LVH with wall thickness >30mm, BP fall during exercise)
- Associations with Friedreich's ataxia, WPW, phaeochromocytoma, familial lentiginosis
- ESM increases with: glyceryl trinitrate (GTN), digoxin and standing, due to volume reduction in diastole; ESM decreases with: squatting, βblockers, Valsalva's release, handgrip
- Cardiac catheterisation abnormalities include a 'banana' or 'spade-shaped' LV cavity in systole, MR and 'swordfish' narrowing of the left anterior descending artery
- Therapeutic options include β blockers, calcium antagonists, amiodarone, dual-chamber pacing, internal defibrillators, surgical myomectomy or therapeutic septal infarction
- Avoid digoxin (if in sinus rhythm), nitrates, atropine, inotropes, diuretics (unless in left ventricular failure)
- **Sudden death** may be due to catecholamine-driven extreme outflow obstruction, VF related to accessory pathway-transmitted AF, or massive MI. Sudden death may occur without hypertrophy. Annual mortality rate of 2.5% in adults and 6% in children
- Poor prognostic features include young age at diagnosis, family history of sudden death and syncopal symptoms, but there is no correlation with the LVOT gradient
- Pregnancy is possible, but haemorrhage, prolonged vaginal delivery effort and epidural analgesia are best avoided; antibiotic prophylaxis and counselling are advised.

1.8.3 Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a syndrome of global ventricular dysfunction and dilatation,

usually with macroscopically normal coronary arteries (if causes of ischaemic cardiomyopathy are excluded). The aetiology is often undetermined and the condition is more common in male and African-Caribbean patients (this association is possibly because of undiagnosed hypertensive cardiomyopathy). There is often LBBB or poor R-wave progression on ECG, and anticoagulation may be warranted as the incidence of AF and ventricular thrombus is high. DCM is treated as other forms of cardiac failure, with ACE inhibitors and βblockers, with escalating therapies, including *cardiac resynchronisation therapy*, as the NYHA class worsens.

Causes of DCM

- Alcohol
- Undiagnosed hypertension
- Autoimmune disease
- Nutritional deficiency (eg thiamine and selenium)
- Muscular dystrophies
- Viral infections (eg Coxsackie virus and HIV)
- Peripartum
- Drugs (eg doxorubicin)
- Infiltration (eg haemochromatosis, sarcoidosis)
- Tachycardia-mediated cardiomyopathy (uncontrolled fast heart rates, eg AF)
- Diabetes – combination of epicardial coronary disease, microvascular ischaemia, metabolic derangement of myocyte function

1.8.4 Restrictive cardiomyopathy

This produces identical symptoms to constrictive pericarditis (see Section 1.9.1) but surgery is of little use in restrictive cardiomyopathy. The ventricles are excessively rigid and impede diastolic filling. AF may supervene and stagnation of blood leads to thrombus formation.

- **Myocardial causes**
  - Idiopathic
  - Scleroderma
  - Amyloid (see below)
  - Sarcoid
  - Haemochromatosis
  - Glycogen storage disorders
  - Gaucher's disease
- **Endomyocardial causes**
  - Endomyocardial fibrosis

- Hypereosinophilic syndromes (including Löffler's)
- Carcinoid
- Malignancy or radiotherapy
- Toxin-related

Cardiac amyloidosis

Cardiac amyloidosis is caused by extracellular deposition of insoluble amyloid fibrils. The protein deposition can be due to a primary disorder (AL amyloidosis, a clonal plasma cell disorder with light chain production to form the fibrils) or a secondary disorder (any chronic inflammatory disorder). The deposition and resultant fibrosis cause the ventricles to become thickened and stiff, with poor systolic and diastolic function. The atria typically dilate in response and may develop AF. Infiltration of the conducting tissues leads to heart block. ECGs characteristically have low-voltage QRS complexes and the echocardiographic appearances of the myocardium are classically 'speckled'. Diagnosis can be confirmed by rectal biopsy with Congo red staining, which can demonstrate amyloid infiltration. Cardiac involvement is a marker of poor prognosis in amyloid disease, with congestive heart failure, syncope, pulmonary hypertension and conduction problems being causes of death. Treatment is palliative. Negative inotropic drugs (eg diltiazem) must be avoided and care taken with digoxin, which binds avidly to the fibrils and can reach toxic levels even within the therapeutic range.

1.8.5 Myocarditis

Myocarditis may be due to many different aetiological factors (eg viral, bacterial, fungal, protozoal, autoimmune, allergic and drugs). It may be difficult to differentiate from DCM, but the following features may help:

- Usually a young patient
- Acute history
- Prodrome of fever, arthralgia, respiratory tract infection, myalgia
- Neutrophilia
- Slight cardiomegaly on chest radiograph
- Episodes of VT, transient AV block and ST/T-wave changes
- Elevated viral titres
- Cardiac enzymes raised (with normal coronary arteries).

Myocarditis is associated with severe morbidity and mortality and needs careful support and management in the intensive care environment. Transplantation may be necessary if there is poor response to therapy. Those who recover may be left with significant cardiac impairment.

Rheumatic fever

This follows a group A streptococcal infection; pancarditis usually occurs and valvular defects are long-term sequelae. The cardiac histological marker is Aschoff's nodule. Patients are treated with

penicillin and salicylates or steroids.

Criteria for diagnosis include the need for evidence of preceding α-haemolytic streptococcal infection (raised antistreptolysin O titre [ASOT], positive throat swab or history of scarlet fever), together with two major (or one major and two minor) Duckett–Jones criteria (see below).

Rheumatic fever (Duckett–Jones diagnostic criteria)

- **Major criteria**
  - Carditis
  - Polyarthritis
  - Chorea
  - Erythema marginatum
  - Subcutaneous nodules
- **Minor criteria**
  - Fever
  - Arthralgia
  - Previous rheumatic heart disease
  - High ESR and C-reactive protein (CRP)
  - Prolonged PR interval on ECG

1.8.6 Cardiac tumours

Myxomas are the most common cardiac tumours, comprising 50% of most pathological series.

Atrial myxomas

- Post-mortem incidence of <0.3%; more common in females (2 : 1) and in the left atrium (75% of myxomas); usually benign and occasionally familial
- Signs: fever and weight loss occur in 25%, and this may be due to release of interleukin-6 (IL-6). There may be transient mitral stenosis, early diastolic 'plop', clubbing, Raynaud's phenomenon (rare) or pulmonary hypertension. Usually the rhythm is sinus. Atrial myxomas may present with the classic triad of systemic embolism, intracardiac obstruction and systemic symptoms
- Investigations: white cell count high, platelets low, haemolytic anaemia or polycythaemia, raised immunoglobulins, raised ESR in 60% (thought to be due to secretion of IL-6)
- Avoid left ventricular catheterisation; use TOE to diagnose. They occur most commonly on the interatrial septum
- Atrial myxomas grow rapidly with a risk of embolisation and sudden death, so they should be resected surgically without delay.

Other primary cardiac tumours

These include papillomas, fibromas, lipomas, angiosarcomas, rhabdomyosarcomas and mesotheliomas, which are all rare lesions.

1.8.7 Alcohol and the heart

Acute alcoholic intoxication is the most common cause of paroxysmal AF among younger individuals. Chronic excessive intake over 10 years is responsible for a third of the cases of DCM in Western populations; alcohol is also aetiologically related to hypertension, cerebrovascular accident (CVA), arrhythmias and sudden death. AF may be the first presenting feature (usually between the ages of 30 and 35 years).

Pathological mechanisms

- Direct myocardial toxic effect of alcohol and its metabolites
- Toxic effect of additives (eg cobalt)
- Secondary effect of associated nutritional deficiencies (eg thiamine)
- Effect of hypertension

Treatment includes nutritional correction and – most importantly – complete abstinence from alcohol, without which 50% will die within 5 years. Abstinence can lead to a marked recovery of resting cardiac function.

Beneficial mechanisms of modest amounts of alcohol

- Favourable effects on lipids (50% of this benefit is due to raised HDL levels)
- Antithrombotic effects (perhaps by raising natural levels of tissue plasminogen activator)
- Antiplatelet effects (changes in prostacyclin:thromboxane ratios)
- Increase in insulin sensitivity
- Antioxidant effects of red wine (flavonoids and polyphenols)

1.8.8 Cardiac transplantation

Six UK centres currently conduct heart transplantations with approximately 150 operations carried out per year, most often for intractable coronary disease and cardiomyopathy (44%); survival rates have been estimated at 80% at 1 year, 75% at 3 years and 40–50% at 10 years. Myocarditis is yet another indication; transplantation during the acute phase does not worsen prognosis, but myocarditis may recur in the donor heart.

The major complications encountered after transplantation include accelerated coronary atheroma, lymphoma, skin cancer (and other tumours) and chronic kidney disease (due to ciclosporin A or

tacrolimus toxicity).

1.9 PERICARDIAL DISEASE

1.9.1 Constrictive pericarditis

Rare in clinical practice, this presents in a similar way to restrictive cardiomyopathy, ie with signs of right-sided heart failure (cachexia, hepatomegaly, raised JVP, ascites and oedema) due to restriction of diastolic filling of both ventricles. It is treated by pericardial resection.

Other specific features include:

- A diastolic pericardial knock occurs after the third heart sound, at the time of the *y* descent of the JVP, and this reflects the sudden reduction of ventricular filling – 'the ventricle slaps against the rigid pericardium'
- Soft heart sounds and impalpable apex beat
- Severe pulsus paradoxus occurs rarely and indicates the presence of a coexistent tense effusion
- Thickened, bright pericardium on echocardiography.

Causes of constrictive pericarditis

- Tuberculosis (usually post-pericardial effusion)
- Mediastinal radiotherapy
- Pericardial malignancy
- Drugs (eg hydralazine, associated with a lupus-like syndrome)
- Post-viral (especially haemorrhagic) or bacterial pericarditis
- Following severe uraemic pericarditis
- Trauma/post-cardiac surgery
- Connective tissue disease
- Recurrent pericarditis

Signs common to constrictive pericarditis and restrictive cardiomyopathy

- Raised JVP with prominent $x + y$ descents
- AF
- Non-pulsatile hepatomegaly
- Normal systolic function

Some key features distinguish constrictive pericarditis from restrictive cardiomyopathy:

- Absence of LVH in constrictive pericarditis

- Absent calcification on chest radiograph, prominent apical impulse and conduction abnormalities on ECG, which are features of restrictive cardiomyopathy.

However, a combination of investigations, including cardiac CT, MRI and cardiac biopsy, may be necessary to differentiate between the two conditions.

1.9.2 Pericardial effusion

A slowly developing effusion of 2 L can be accommodated by pericardial stretching and without raising the intrapericardial pressure. The classic symptoms of chest discomfort, dysphagia, hoarseness or dyspnoea (due to compression) may be absent. A large effusion can lead to muffled heart sounds, loss of apical impulse, occasional pericardial rub, small ECG complexes and eventually EMD.

Other key features are:

- Pulsus alternans: variable left ventricular output and right ventricular filling
- Pulsus paradoxus: exaggerated inspiratory fall in systolic BP (mechanism described in section 1.2.2)
- Electrical alternans on ECG: 'swinging QRS axis'
- Globular cardiac enlargement on chest radiograph

Causes of pericardial effusion

- All causes as listed for constrictive pericarditis
- Aortic dissection
- Iatrogenic due to pacing or cardiac catheterisation
- Ischaemic heart disease with ventricular rupture
- Anticoagulation associated with acute pericarditis

1.9.3 Cardiac tamponade

In contrast, if a small amount of intrapericardial fluid (eg <200 mL) accumulates rapidly, it can significantly limit ventricular filling, reduce cardiac output and elevate intracardiac pressures (particularly right sided initially). Thus the *y* descent due to right ventricular filling with tricuspid valve opening is lost as right ventricular pressures are high, and the *x* descent of right atrium filling due to right ventricular contraction is prominent. The right atrium collapses in diastole as a result of impaired filling and high intrapericardial pressures. In early diastole even the right ventricle may collapse.

Occasionally the stretched pericardium may compress the lingular lobe of the left lung, causing bronchial breathing at the left base (Ewart's sign). The QRS axis of the ECG may also be altered (electrical alternans).

Common signs of cardiac tamponade

- Elevated jugular venous pressure
- Kussmaul's sign
- Tachypnoea
- Systolic hypotension
- Pulsus paradoxus
- Tachycardia
- Diminished heart sounds
- Impalpable apex beat

Treatment is by urgent drainage – usually under echocardiographic control. Surgical 'pericardial' windows may be necessary for chronic (eg malignant) effusions.

1.10 DISORDERS OF MAJOR VESSELS

1.10.1 Pulmonary hypertension

It is important to determine whether pulmonary hypertension is secondary to an underlying condition because this may be treatable. The most common cause of secondary pulmonary hypertension is COPD.

WHO Venice classification of pulmonary hypertension

WHO group 1: pulmonary arterial hypertension

- Idiopathic/Sporadic
- Familial
- Associated with pulmonary venous or capillary disease
- Associated with systemic diseases:
  - Collagen vascular disease (eg scleroderma)
  - HIV
- Drugs/Toxins (eg anorexigens)
- Portal hypertension
- Congenital heart disease with shunting left to right (ASD, VSD)
- Persistent pulmonary hypertension of newborn babies

WHO group 2: pulmonary hypertension associated with left heart disease

- Atrial or ventricular disease (DCM, IHD, HCM)

- Valvular disease (eg MS)
- Extrinsic compression of the central pulmonary veins

WHO group 3: pulmonary hypertension associated with lung diseases and/or hypoxemia

- COPD
- Interstitial lung disease
- Obstructive sleep apnoea
- Alveolar hypoventilation disorders
- Chronic high altitude
- Chronic hypoxia (polio, myasthenia)

WHO group 4: pulmonary hypertension due to chronic thrombotic and/or embolic disease

- Pulmonary emboli of proximal arteries
- Obstruction of distal pulmonary arteries
- Embolisation of thrombus, tumour, ova, parasites or foreign material
- In situ thrombosis
- Sickle cell disease

WHO group 5: pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature

- Inflammatory – schistosomiasis, sarcoidoisis
- Pulmonary capillary haemangiomatosis

Primary pulmonary hypertension

Primary pulmonary hypertension (PPH) is a rare disease with an incidence of 2/million per year; it is a disease of children and young adults, with a female:male ratio of 2 : 1. PPH constitutes <1% of all cases of pulmonary hypertension and is characterised by a mean pulmonary artery pressure >25 mmHg at rest, in the absence of another demonstrable cause. One in ten cases is familial. PPH is associated with connective tissue disease, vasculitis and HIV infection, and also the use of appetite suppressants (eg fenfluramine). The pulmonary arteries become dilated and abnormally thickened; there is dilatation of the proximal pulmonary vessels with thick-walled, obstructed, 'pruned' peripheral vessels. As a consequence of the high pulmonary pressure the right ventricle undergoes marked hypertrophy.

Patients present with gradually worsening exertional dyspnoea and, in the later stages, angina of effort and syncope occur. Fatigue is common and haemoptysis may occur.

- Signs include: cyanosis, right ventricular heave, loud P2, tricuspid regurgitation, peripheral oedema and ascites

  Diagnosis may be suggested on echocardiography with dilated right ventricle with impaired

- function; estimated pulmonary pressures will be elevated. Confirmation requires cardiac catheterisation and direct measure of mean pulmonary arterial pressure (>25 mmHg), in the presence of normal wedge pressure (≤15 mmHg)
- Untreated, the median survival is approximately 3 years.

Treatment of PPH

This would usually be undertaken at a specialist centre. The chief aspects involve:

- Advise avoidance of strenuous exercise and recommend contraception, because pregnancy is harmful
- Anticoagulation to avoid thrombus formation in situ in the pulmonary arteries and also pulmonary embolism
- Prostacyclin (PGI_2), a potent pulmonary and systemic vasodilator, is used, particularly to bridge patients to transplantation. The drug has an extremely short half-life and has to be given by continuous intravenous infusion, usually through a tunnelled central venous catheter. It is also very expensive
- Endothelin receptor blockade (eg bosentan)
- Calcium channel antagonists have been used to lower pulmonary (and systemic) pressure
- Diuretics are helpful in the management of right heart failure
- Continuous ambulatory inhaled nitric oxide is being developed, and this would provide good pulmonary vasodilatation, but without systemic effect.

The chief therapeutic option is transplantation, because other treatments are of limited benefit or are difficult to administer.

Summary of available treatments for pulmonary hypertension

- **General**
  - Address secondary causes where possible
  - Digoxin, even in patients with sinus rhythm
  - Diuretics for symptoms
  - Ambulatory supplemental oxygen for some
  - Anticoagulation
- **Vasodilator therapy (only helps some patients)**
  - Endothelin receptor blockers (eg bosentan)
  - PGI_2 or PGE (chronic infusion)
  - Adenosine infusions or boluses
  - Nitric oxide inhalation, nitrates (chronic infusion)
  - Calcium channel blockers
- **Surgical options (in selected cases)**
  - Heart–lung or single/double lung transplantation

- Atrial septostomy (only if no resting hypoxia)

1.10.2 Venous thrombosis and pulmonary embolism

The true incidence of pulmonary embolism (PE) is unknown but PE probably accounts for 1% of all admissions. Predisposing factors are discussed in Chapter 9, Haematology.

One or more predisposing risk factors are found in 80–90% of cases. The oral contraceptive increases the risk of deep vein thrombosis (DVT)/PE two to four times. However, thromboembolism is rare in women taking oestrogens without other risk factors.

Clinical features

Nearly all patients have one or more of the following symptoms: dyspnoea, tachypnoea or pleuritic chest pain. With a large PE patients may present with collapse. Hypoxaemia may be present with moderate or large pulmonary emboli.

Investigations

- **Chest radiograph**: may be normal; pleurally based, wedge-shaped defects described classically are rare and areas of oligaemia may be difficult to detect
- **D-Dimer**: will be raised in PE but the test is non-specific
- **Helical CT scanning**: will demonstrate pulmonary emboli in the large pulmonary arteries but may not show small peripheral emboli
- **CTPA**: the test of choice but really is to exclude major PE and subsegmental PE. True small peripheral PEs can be missed – and first generation scanners were only 70% sensitive compared to invasive pulmonary angiography
- **ECG**: may show sinus tachycardia and, in massive PE, features of acute right heart strain; non-specific ST-segment and T-wave changes occur
- **Arterial blood gases**: show a low or normal *P*CO2 and may show a degree of hypoxaemia
- **Ventilation/perfusion ($\dot{V}/\dot{Q}$) scanning**: shows one or more areas of *V*/*Q* mismatching
- **Pulmonary angiography**: remains the 'gold standard', but this is underused

In each case a clinical assessment of the probability of PE should be made. As demonstrated in the PIOPED study:

- Cases of high clinical probability combined with a high-probability $\dot{V}/\dot{Q}$ scan are virtually diagnostic of PE
- Similarly, cases of low clinical suspicion combined with low-probability or normal *V*/*Q* scans make the diagnosis of PE very unlikely
- All other combinations of clinical probability and *V*/*Q* scan result should be investigated further

- Patients who present with collapse need urgent echocardiography, helical CT scan or pulmonary angiogram to demonstrate PE.

Management

In all cases of moderate or high clinical probability of PE, anticoagulation with heparin or low-molecular heparin should be started immediately after baseline coagulation studies have been taken. If unfractionated heparin is used, the dose should be adjusted to maintain the activated partial thromboplastin time (APTT) to 1.5–2.5 times the control). Low-molecular-weight heparin has the advantage of once-daily subcutaneous injections that do not need monitoring. Warfarin should be started concurrently and heparin can be discontinued once the INR is 2–3.

- Warfarin is continued for 3–6 months in most cases; for PE occurring postoperatively, 6 weeks' anticoagulation is adequate. In recurrent PE, anticoagulation should be for longer periods (eg 1 year) and consideration should be given to lifelong treatment
- In cases of collapse due to massive PE, thrombolysis with streptokinase or recombinant tPA given by peripheral vein should be considered. This should be avoided when the embolic material is an infected vegetation (eg intravenous drug abusers)
- Occasionally, pulmonary embolectomy is used for those with massive PE where thrombolysis is unsuccessful or contraindicated
- Inferior vena caval filters should be considered in patients in whom anticoagulation is contraindicated or in those who continue to embolise despite anticoagulation.

1.10.3 Systemic hypertension

Overall, 30% of the UK adult population have hypertension, with the prevalence increasing with age to 70% in the eighth decade. Guidelines for treatment continually adapt to new clinical evidence, but the British Hypertension Society (BHS) has issued guidelines (Table 1.14) to identify those in need of treatment.

Suggested treatment targets are <140/85 mmHg in general, and <130/80 mmHg for high-risk patients, such as patients with diabetes.

A suggested treatment algorithm is given in Table 1.15.

Other considerations in hypertension management

- Investigation of **phaeochromocytomas**: recommend three 24-h urinary catecholamine derivatives of all drugs on a vanilla-free diet (and off all drugs). Urinary metadrenalines may also be measured
- Hypertension **increases the risk** (Framingham data) of: stroke (37); cardiac failure (34); coronary artery disease (33); peripheral vascular disease (32)
- Potassium salt should be substituted for sodium salt where possible
- **Drugs to avoid in pregnancy**: diuretics, ACE inhibitors, angiotensin II receptor blockers. **Drugs with well-identified risks preferred in pregnancy**: β blockers (especially labetalol), methyldopa and hydralazine

- Young Black men have a poor response to ACE inhibitors and β blockers because they are salt conservers by background, and so are resistant to renin manipulation and particularly likely to develop the side-effect of impotence.

Table 1.14 British Hypertension Society Guidelines

Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Observation	Cofactor	Recommendation
180	110	Single reading		Treat
160–179	100–109	Multiple readings		Treat
140–159	90–99	Multiple readings	DM, TOD, 10-year risk >20%	Treat
140–159	90–99	Multiple readings	None of the above	Reassess annually
<140	<90	Multiple readings		Reassess annually
130–139	80–85	Single reading		Reassess annually
>130	>0		Reassess in 5 years	

DM, diabetes mellitus; TOD, target organ damage (eg any cardiovascular disease, left ventricular hypertrophy by echocardiography or ECG, proteinuria).

Table 1.15 Treatment algorithm for hypertension

First line for those aged >55 years or Black patients	Calcium blocker or thiazide
First-line treatment for others	ACE inhibitor or ARB
Second-line treatment	ACE inhibitor or ARB + calcium blocker or thiazide
Third-line treatment	ACE Inhibitor or ARB + calcium blocker + thiazide
Additional possibilities	Other diuretic, α/β blockers

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

1.10.4 Aortic dissection

Two-thirds of tears occur in the ascending aorta with about a fifth occurring in the descending aorta. Mortality is highest in the first few hours if the dissection is untreated. The differential diagnosis for ascending dissection includes MI if the vulnerable right coronary ostium is involved (giving rise to an inferior infarct pattern). This is particularly important when considering thrombolysis; aortic regurgitation provides supportive evidence of the diagnosis.

Associations with aortic dissection

- Systemic hypertension (present in 80%)
- Marfan's syndrome
- Cystic medial degeneration (rare in the absence of Marfan's syndrome)
- Noonan's and Turner's syndromes
- Trauma
- Aortic coarctation
- Congenital bicuspid aortic valve (present in 10–15% and dissection is therefore associated with aortic stenosis)
- Giant-cell arteritis
- Pregnancy (particularly in patients with Marfan's syndrome)
- Cocaine abuse

Involvement of ascending aorta may cause

- Aortic regurgitation
- Inferior MI
- Pericardial effusion (including cardiac tamponade)
- Carotid dissection
- Absent or decreased subclavian pulse

Medical therapy to be considered for

- Old, stable dissections (>2 weeks)
- Uncomplicated dissection of descending aorta
- Isolated arch dissections

Investigations for aortic dissection

- TOE, aortic MRI and contrast-enhanced spiral CT all have a high diagnostic sensitivity, but CT rarely identifies the site of the tear or the presence of aortic regurgitation or coronary involvement
- MRI is of the highest quality but is contraindicated in patients with pacemakers and certain vascular clips
- TOE is probably the most widely used investigation because it is available in the acute situation and has high sensitivity and specificity
- Aortography is no longer the gold standard and coronary angiography is applicable only when deciding on the need for concomitant CABG.

Management of aortic dissection

- Suspected aortic dissection is a medical and surgical emergency and requires prompt response, with mortality increasing by 1% for every hour. Long delays for diagnosis should be minimised.
- Untreated proximal dissection are almost always fatal. Descending aortic dissections have a better prognosis with 85% surviving their hospital stay but can still cause significant mortality if shock, organ ischaemia and renal failure occurs.
- Medical therapy with intravenous agents to reduce the blood pressure may help prevent extension of the dissection flap. Medical therapy remains the first-line therapy for Type B dissections (descending aorta only), with subsequent treatment based upon the clinical course.
- The mainstay of treatment of proximal dissections (Type A) is urgent surgery and even if successful, mortality can be as high as 20% at 2 weeks from complications of the dissection, including aortic rupture, stroke, visceral ischaemia, cardiac tamponade and circulatory failure.
- The aim of the surgery is to resect the region of intimal tear to prevent aortic rupture and cardiac tamponade. If the tear is extensive, partial or total aortic arch replacement may be required. The aortic valve may be suitable to be resuspended or may require replacement. Medical hypothermia is used but has not significantly improved post-operative mortality.
- Endovascular stent-graft placement has no role in Type A dissections but may help in Type B dissections when key aortic branches are compromised.

APPENDIX I

Normal cardiac physiological values

ECG

- PR interval 0.12–0.20 s
- QRS duration >0.10 s
- QTc (males) 380 ms, (females) 420 ms
- QRS axis −308 to +908.

Indices of cardiac function

- Cardiac index = Cardiac output/body surface area (BSA) = 2.5–4.0 L/min per m^2
- Stroke volume index = stroke volume/BSA = 40–70 mL/m^2
- Systemic vascular resistance (SVR) = 80 × (Ao − RA)/cardiac output = 770–1500 dyn s/cm^5, where Ao is the mean aortic pressure and RA the mean right atrial pressure
- Ejection fraction = Proportion of blood ejected from left ventricle = 50–70%.

Cardiac catheterisation pressures	mmHg	Criteria for significant oxygen saturation set-up	
Mean right atrial	0–8	SVC/IVC to RA	>7% (eg ASD)
Right ventricular systolic	15–30	RA to RV	>5% (eg VSD)

End-diastolic	0–8	RV to PA	>5% (eg PDA)
		Any level:	
Pulmonary artery systolic	15–30	SVC to PA	>7%
End-diastolic	3–12	Usual saturations (*Sa*O2)	
Mean	9–16	Venous	65–75%
Pulmonary artery wedge		Arterial	96–98%
A	3–15		
V	3–12		
Left atrial mean	1–10		
Left ventricular systolic	100–140		
End-diastolic	3–12		
Aortic systolic	100–140		
End-diastolic	60–90		
Mean	70–105		

APPENDIX II

Summary of further trials in cardiology

Major trials

Condition	Intervention	Trials	Main finding	References
Heart failure	β blockers	MERIT-HF, CIBIS II, COPERNICUS	β blockers reduce mortality and morbidity	*Lancet* 1999;**353**:2001–7, *Lancet* 1999;**353**:9–13, *N Engl J Med* 2001;**344**:1659–67
Heart failure	ACE inhibitors	SOLVD, ATLAS, CONCENSUS	ACE inhibitors reduce mortality and morbidity	*N Engl J Med* 1991;**325**:293–302, *Circulation* 1999;**100**: 2312–18
Heart failure	Cardiac resynchronisation therapy (CRT)	MUSTIC, MIRACL, COMPANION, CARE-HF	CRT reduces mortality and morbidity	*N Engl J Med* 2001;**344**:873–80, *N Engl J Med* 2002;**346**:1845–53, *N Engl J Med* 2004;**350**:2140–50, *N Engl J Med* 2005;**352**:1539–49

Ventricular arrhythmia	Implantable defibrillators (ICD)	AVID, MADIT II, COMPANION	ICD reduce mortality in primary and secondary prevention	*N Engl J Med* 1997;337:1576–83, *N Engl J Med* 2002;**346**:877–83, *N Engl J Med* 2004;**350**:2140–50
Acute MI	Aspirin	ISIS 2	Aspirin reduces mortality	*Lancet* 1988;**ii**:349–60
Acute MI	Thrombolysis	ISIS 2, ISIS 3, GUSTO, GISSI 1	Thrombolysis reduces mortality	*Lancet* 1988;**ii**:349–60, *Lancet* 1992;**339**:753–70, *New Engl J Med* 1993;**329**:673–82, *Lancet* 1986;**i**:397–401
Ischaemic heart disease	β blockers	ISIS, BHAT, CAPRICORN	β blockers reduce mortality	*Lancet* 1986;**ii**:57–66, *JAMA* 1982;**247**:1707–14, *Lancet* 2001;**357**:1385–90
Ischaemic heart disease	ACE inhibitors	AIRE, SAVE, GISSI 3, TRACE	ACE inhibitors reduce mortality	*Lancet* 1993;**342**:821–8, *N Engl J Med* 1992;**327**:669–77, *Lancet* 1994;**343**:1115–22, *N Engl J Med* 1995;**333**:1670–6
Ischaemic heart disease	Statins	SSSS, WOSCOPS, HPS	Statins are effective in primary and secondary prevention	*Lancet* 1994;**344**:1383–89, *N Engl J Med* 1995;**333**:1301–7, *Lancet* 2002;**360**:7–22

Chapter 2
Clinical Pharmacology, Toxicology and Poisoning

CONTENTS

Clinical Pharmacology, Toxicology and Poisoning

2.1 CLINICAL PHARMACOLOGY TERMS

2.1.1 Pharmacokinetic terms

Half-life ($t_{\frac{1}{2}}$) is the time taken for plasma drug concentrations to fall by half, ie after $1 \times t_{\frac{1}{2}} = 50\%$, $2 \times t_{\frac{1}{2}} = 25\%$, $3 \times t_{\frac{1}{2}} = 12.5\%$, etc.

Volume of distribution (V_d) is a theoretical volume that describes the extent to which a drug is retained within the circulation or distributed elsewhere, eg a drug with a V_d of 5 L is mostly confined to the circulating compartment, a drug with V_d of 30 L is distributed within the extracellular compartment, and a drug with a V_d of 3000 L is highly distributed to extravascular tissues.

2.1.2 Pharmacodynamic terms

Efficacy (E) is a measure of drug effects on a particular system, including maximal effect (E_{max}). A partial agonist (eg buprenorphine) has a lower E_{max} than a full agonist (eg morphine) and cannot elicit a full response even if the dose is increased.

Potency expresses drug efficacy with respect to drug concentrations or dose, and is less clinically relevant than efficacy, eg if atorvastatin 10 mg may lower cholesterol to the same extent as simvastatin 40 mg, then the former has a fourfold higher potency.

2.2 DRUG METABOLISM AND INTERACTIONS

2.2.1 Genetic variations in drug metabolism

Genetic variation may alter response to drug therapy, eg angiotensin-converting enzyme (ACE) inhibitors prevent the occurrence of diabetes in homozygous carriers of the *1166A* variant of the angiotensin type 1 receptor gene, but not in heterozygotes and non-carriers. Polymorphisms affecting tumour necrosis factor promoter regions may predict the response to infliximab in patients with rheumatoid arthritis.

Drug acetylation occurs within the liver and to a lesser extent within the bowel, kidney and other tissues. It is subject to genetic variation, and about 50% of all White individuals are rapid or slow

acetylators. Rapid acetylator phenotype is associated with lower drug concentrations and diminished therapeutic effects, whereas metabolite concentrations are higher, eg rapid acetylator phenotype may make isoniazid less effective against tuberculosis and confer a higher risk of hepatitis from its metabolite. Conversely, slow acetylator phenotype may be associated with a higher risk of peripheral neuropathy as a direct toxic effect of isoniazid.

Other genetic variations in drug metabolism include:

- **Nateglinide** is metabolised more slowly by patients with the *CYP2C9*3/*3* genotype than by carriers of *CYP2C9*1*, so that the former patients may be at increased risk of hypoglycaemia
- **s-Mephenytoin**: 3–5% of the UK population are poor metabolisers of this antiepileptic agent.

Drug-induced lupus is associated with slow acetylation and possession of HLA-DR4. In contrast to autoimmune systemic lupus erythematosus (SLE), the incidence is equal in men and women, and laboratory findings include antibodies to histones and single-stranded DNA. Clinical features of drug-induced lupus include:

- arthralgia
- butterfly rash
- pleurisy.

Renal involvement is uncommon (apart from hydralazine), and neuropsychiatric manifestations are unusual.

Drugs causing a lupus erythematosus-like syndrome

- β Blockers
- Hydralazine
- Phenytoin
- Chlorpromazine
- Isoniazid
- Procainamide
- Clonidine
- Lithium
- Sulfasalazine
- Flecainide
- Methyldopa
- Sulfonamides
- Haloperidol
- Penicillin
- Tetracyclines

2.2.2 Liver enzyme induction

Many drugs are capable of inducing liver enzyme systems, thereby increasing the metabolism (and decreasing the effectiveness) of other drugs. Enzyme induction normally takes several days to occur due to the time required to synthesise new enzyme. Enzyme induction may decrease the effectiveness of:

- hydrocortisone
- oral contraceptive pill
- phenytoin
- warfarin.

Some drugs that cause this effect can be remembered by the mnemonic PC BRAS:

Phenytoin
Carbamazepine
Barbiturates
Rifampicin
Alcohol (chronic excess)
St John's wort

2.2.3 Liver enzyme inhibition

A number of drugs are capable of inhibiting hepatic enzyme systems, and the effect may be immediate. Enzyme inhibition can slow the metabolism of other drugs, thereby increasing their plasma concentrations and the risk of adverse effects. Enzyme inhibition can increase the effects of:

- carbamazepine
- ciclosporin
- phenytoin
- statins
- theophylline
- warfarin.

Drugs capable of inhibiting liver cytochrome P450 enzymes often exert their therapeutic effects via enzyme inhibition too. Some examples may be recalled by the mnemonic AODEVICCES:

Allopurinol (xanthine oxidase inhibitor)
Omeprazole (proton pump inhibitor)
Disulfiram (aldehyde dehydrogenase inhibitor)
Erythromycin
Valproate (GABA [γ-aminobutyric acid] transaminase inhibitor)
Isoniazid (nucleic acid synthetase inhibitor) and Itiaconazole/fluconazole (inhibit enzymes in ergosterol synthesis)
Ciprofloxacin
Cimetidine

Ethanol: acute intoxication
Sulfonamide (dihydropteroate synthase inhibitor)

2.2.4 Failure of the combined oral contraceptive pill

Any condition that leads to impaired absorption of the components of the contraceptive pill (eg travellers' diarrhoea) can result in its failure as a contraceptive agent. In addition:

- The oestrogen component may be metabolised more rapidly in the presence of liver enzyme induction (see Section 2.2.2), leading to pill failure
- Pill failure may also result from concomitant broad-spectrum antibiotic usage, eg penicillins, cephalosporins, quinolones or tetracyclines may eradicate gut flora that deconjugate bile salts, thereby interrupting enterohepatic cycling and reducing oestrogen reabsorption

2.3 PRESCRIBING IN SPECIAL SITUATIONS

2.3.1 Pregnancy and drug therapies

During the first 16 weeks of pregnancy, drugs may exert teratogenic effects resulting in fetal malformations and drug treatment is generally avoided if possible. Particular associations are as follows:

- ACE inhibitors and angiotensin receptor blockers: oligohydramnios
- Lithium: cardiac abnormalities
- Phenytoin: facial fusion abnormalities such as cleft lip and palate
- Sodium valproate and retinoids: neural tube defects and spina bifida
- Warfarin: abnormalities of long bones and cartilage.

Later in pregnancy, certain drugs may cross the placenta and cause harm to the fetus:

- Carbimazole: neonatal goitre (which may even be large enough to obstruct labour)
- Gentamicin: cranial nerve VIII deafness in the newborn.

2.3.2 Drugs and breastfeeding

Infants under 1 month of age are highly susceptible to the effects of drugs in breast milk due to immature mechanisms of metabolism and excretion. Drugs that may be excreted in breast milk and are recognised as causing toxicity include the following:

- Amiodarone: thyroid anomalies
- Cytotoxics and chloramphenicol: blood dyscrasia
- Gold: haematological reactions and kidney injury
- Indometacin: neonatal seizures
- Iodides: thyroid disturbance
- Lithium: involuntary movements

- Oestrogens: feminisation of male infants.

2.3.3 Liver disease

Patients with liver impairment are more susceptible to sedative effects of drugs, and certain drugs may provoke hepatic encephalopathy, eg opioids and benzodiazepines. Thiazides and loop diuretics may worsen hypokalaemia and cause acute encephalopathy. The presence of liver disease may have important effects on drug pharmacokinetics and alter their clinical effects:

- Drugs excreted via the bile, such as rifampicin, may accumulate in patients with obstructive jaundice
- Hypoalbuminaemia reduces the extent of drug protein binding so that there is an increased proportion of 'free' unbound drug, and increased risk of drug toxicity, eg phenytoin
- Reduced clotting factor synthesis may enhance the risk of bleeding associated with warfarin
- Salt and water retention and ascites may be worsened by non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.

2.3.4 Renal failure

In patients with established renal impairment, nephrotoxic agents may exacerbate renal damage (especially in acute renal failure). Patients with low glomerular filtration rate (GFR) will be prone to accumulation of drugs normally eliminated by the kidney, eg water-soluble drugs.

The following drugs that may cause toxicity due to accumulation in patients with severe renal failure (GFR < 10 mL/min) include:

- Atenolol: bradycardia, heart block
- Digoxin: cardiac arrhythmias, heart block
- Enoxaparin: bleeding risk
- Erythromycin: encephalopathy
- Lithium: cardiac arrhythmias and seizures
- Penicillins (high dose): lead to encephalopathy
- Cephalosporins (high dose): encephalopathy
- Trimethoprim: hyperkalaemia.

Nephrotoxic drugs capable of precipitating or worsening acute renal impairment should be avoided where possible. Therapeutic drug monitoring may be required in some cases, eg intravenous gentamicin and vancomycin. The following are examples of nephrotoxic drugs:

- ACE inhibitors and angiotensin receptor antagonists
- Aminoglycosides
- Amphotericin
- Cytotoxics eg cisplatin
- Diuretics (especially high doses of loop diuretics)

- NSAIDs including high-dose aspirin
- Calcineurin inhibitors (ciclosporin and tacrolimus).

Other drugs may have specific nephrotoxic effects, such as gold-induced proteinuria or nephrotic syndrome, which is usually due to membranous glomerulonephritis. (See also Chapter 15, Nephrology.)

2.4 SELECTED DRUGS USED IN SPECIFIC CLINICAL CONDITIONS

2.4.1 Cardiology

Abciximab (ReoPro)

This chimaeric monoclonal antibody irreversibly binds GPIIb/IIIa glycoprotein receptors, preventing the final common pathway of platelet activation and aggregation. It is capable of preventing acute thrombosis and restenosis in patients with unstable angina who are undergoing coronary artery stent insertion. Risks of thrombocytopenic haemorrhage may be reversed by platelet administration. Abciximab should be used only once, due to concerns about efficacy and adverse effects, although emerging data suggest that repeated administration might be safe and efficacious.

Adenosine

Adenosine is a purine nucleoside with a half-life of 8–10 seconds. It acts via adenosine receptors that activate K^+ channels in sino-atrial and atrioventricular nodes. It is capable of terminating supraventricular tachycardia (SVT), and is used as a diagnostic aid to distinguish SVT from ventricular tachycardia. Its duration of action may be significantly increased by dipyridamole.

Side-effects of adenosine

- Anxiety
- Chest tightening
- Bronchospasm (avoid in asthmatic patients)
- Facial flushing

Aliskiren

Aliskiren is a direct renin inhibitor (inhibits conversion of angiotensinogen to angiotensin I). It is licensed for treatment of essential hypertension, and is effective alone or in combination with other antihypertensives (including optimal doses of ACE inhibitor or angiotensin receptor antagonist). Adverse effects include renal impairment and hyperkalaemia, especially in patients receiving other medications capable of increasing serum potassium (eg spironolactone, ACE inhibitor, angiotensin receptor antagonists).

Amiodarone

Amiodarone may be used to control supraventricular and ventricular arrhythmias. Its main action is to prolong the refractory period, with corresponding QT prolongation on the ECG. It reduces mortality in patients with recurrent ventricular tachycardia (VT) or hypertrophic cardiomyopathy.

- It is iodine-containing and has a very long half-life (26–127 days), hence its effects may persist for a long time after discontinuation
- Protein-binding interaction causes increased effects of digoxin and warfarin
- Given intravenously, the antiarrhythmic action occurs within a few hours; given orally this may take 1–3 weeks, usually a loading dose being given
- Amiodarone is the least negatively inotropic antiarrhythmic, with the exception of digoxin, however, a rapid bolus of amiodarone can still reduce blood pressure significantly
- Hypothyroidism may arise from increased production of reverse triiodothyronine (T3) in the liver
- Hyperthyroidism may result from enhanced peripheral deiodination of thyroxine (T4) to T3

Side-effects of amiodarone

- Arrhythmias (torsades de pointes)
- Ataxia
- Alveolitis
- Hepatitis
- Hyperthyroidism
- Hypothyroidism
- Metallic taste
- Peripheral neuropathy
- Photosensitivity
- Pulmonary fibrosis
- Reversible corneal microdeposits
- Slate-grey discoloration of skin

Angiotensin-converting enzyme inhibitors

ACE inhibitors reduce mortality in heart failure, prolong survival after myocardial infarction and slow progression of diabetic nephropathy. They are contraindicated in bilateral functional renal artery stenosis and should be used with caution in severe renal impairment.

- Dry cough occurs in 10–20%, thought to be due to increased alveolar and bronchiolar concentrations of kinins
- Hypersensitivity reactions can occur, including angio-oedema
- Potassium may increase due to inhibition of aldosterone effects.

Angiotensin-receptor blockers

Angiotensin II receptor (type AT1) antagonists do not inhibit bradykinin breakdown (unlike ACE inhibitors). Cough is a recognised adverse effect but it is less common than after ACE inhibitors. There is improved survival in hypertension, cardiac failure and myocardial infarction. Angiotensin receptor blockers (ARBs) also delay progression of diabetic nephropathy (see Nephrology, Chapter 15). They may precipitate acute renal failure in patients with reduced renal blood flow (eg bilateral renal artery stenosis, severe cardiac failure, hypovolaemia) in an identical manner to that seen with ACE inhibitors. Angio-oedema is a recognised complication.

Clopidogrel

Clopidogrel is a prodrug that exerts antiplatelet effects via irreversible binding to the P2Y12 receptor on the platelet surface, thereby blocking ADP binding and preventing glycoprotein GPIIb/IIIa activation. The duration of the antiplatelet effects is longer than with aspirin, and the bleeding risk may remain increased for up to 7 days after drug cessation. Clopidogrel may be used as monotherapy in patients who cannot tolerate aspirin, or in combination with aspirin to treat acute coronary syndrome, for up to 12 months, then reverting to aspirin alone. Neutropenia is a rare but recognised adverse effect.

Digoxin

Digoxin delays atrioventricular node conduction, and may slow ventricular rate in atrial fibrillation and flutter. It has a limited role as a positive inotrope but may be effective in patients with coexistent heart failure and atrial fibrillation.

- Eight-five per cent is eliminated unchanged in the urine; digoxin may accumulate in renal impairment
- The steroid-like structure of digoxin has occasionally caused gynaecomastia with chronic use
- Digoxin has a narrow therapeutic index, and small increases in dose may cause toxicity.

Digoxin toxicity

Any arrhythmia may occur with digoxin toxicity, including heart block and atrial arrhythmias. Toxicity often causes severe bradycardia and hypotension, and may be accompanied by hyperkalaemia.

- The ‘reversed tick’ (ST-segment depression in the inferior and lateral leads on the ECG) may occur with digoxin therapy and does not necessarily indicate toxicity
- Electrolyte imbalance may predispose to digoxin toxicity: hypokalaemia, hypomagnesaemia and hypercalcaemia
- Amiodarone may displace digoxin from tissue-binding sites, leading to toxicity. Quinine and calcium antagonists may impair renal tubular clearance of digoxin and cause toxicity.

Toxic effects of digoxin

- Anorexia

- Nausea/vomiting
- Arrhythmias (eg ventricular tachycardia, heart block)
- Severe hypotension
- Yellow vision (xanthopsia)
- Diarrhoea

Flecainide

This is a class 1c agent used for treatment of ventricular arrhythmias and pre-excitation syndromes, and for chemical cardioversion of acute atrial arrhythmias. The CAST trial suggests that flecainide is pro-arrhythmic after a myocardial infarction and it is normally avoided in patients with ischaemic heart disease or left ventricular impairment. Its half-life is about 16 hours; other adverse effects are vertigo and visual disturbance.

HMG-CoA reductase inhibitors

Statins inhibit the rate-limiting enzyme in cholesterol synthesis (3-hydroxy-3-methyl-glutaryl coenzyme A [HMG-CoA] reductase), which is normally most active during sleep (due to fasting and increased hepatic blood flow). Statins cause upregulation of low-density lipoprotein (LDL) receptors, thereby reducing LDL by 30%, and increase high-density lipoprotein (HDL). Some statins may cause a modest decrease in triglyceride concentrations; Atrovastatin has been associated with reduction in triglyceride levels, there is only limited data to suggest this alters cardiovascular events.

- Statins reduce mortality in patients with ischemic heart disease, diabetes mellitus, hypertension or other major cardiovascular risk factors.
- Statins may cause rhabdomyolysis and 10–20% of patients discontinue treatment annually due to myopathy. This is more likely in patients with renal impairment, after high doses or if combined with a fibrate; drug-induced hepatitis may also occur. Drug concentrations and the risk of adverse effects are increased for most statins when patients concomitantly receive an enzyme-inhibiting drug, eg clarithromycin (see 2.2.3)
- In patients with established coronary heart disease, the Joint British Societies recommend a target total serum cholesterol of ≤4 mmol/L and LDL cholesterol of ≤2 mmol/L.

Ivabradine

Ivabradine acts on the If channel (an inward sodium-potassium channel) found predominantly in the sino-atrial node, resulting in reduced resting and exercising heart rate. It is indicated for the treatment of angina, and may be less negatively inotropic than β blockers and may cause fewer symptoms attributed to reduced peripheral blood flow (muscle cramps, cold peripheries). Although patients may report less angina and have improved exercise times in smaller studies, major trials have not shown improved outcomes for patients with angina. A signal of harm was noted in a subset of the SHIFT study which may require reassessment of the use of this drug for angina. It is contraindicated in patients with resting bradycardia and sick sinus syndrome, or if patients are taking a β blocker or rate-limiting calcium channel blocker (diltiazem, verapamil). Ivabradine is also licenced for the treatment of heart failure patients in whom the heart rate is not adequately controlled on beta-

blockers. The SHIFT study suggested an improvement in heart failure related readmissions and death.

Nicorandil

A potassium channel opener that induces arterial vasodilatation, this also possesses a nitrate component that promotes venous relaxation. It is used as an antianginal agent. The side-effects are transient headache, flushing and dizziness. In large doses it may cause hypotension with a reflex tachycardia.

Prasugrel and Ticagrelor

Both drugs are new generation antiplatelets with greater antiplatelet potency than clopidogrel and a faster time to onset. Both are P2y12 receptor inhibitors and are used for acute coronary syndrome patients, particularly those undergoing coronary stenting. Both are associated with greater rates of bleeding complications. Tricagrelor is commonly associated with bradycardia on monitoring and the sensation of breathlessness which may lead to discontinuation.

Thiazide diuretics

Thiazides are capable of lowering blood pressure. The mechanism is uncertain, but is independent of the modest diuretic effect provided by these agents. Maximum blood pressure reduction is achieved using low doses (eg bendroflumethiazide 2.5 mg daily) with little additional BP lowering beyond this dose range. They are associated with a number of dose-dependent metabolic effects:

- Hyponatraemia, hypokalaemia and hypomagnesaemia: a hypochloraemic alkalosis
- Raised plasma urate due to reduced tubular clearance; gout may be precipitated
- Diabetic glycaemic control may worsen on thiazides due to impaired insulin release and increased insulin resistance
- Postural hypotension, photosensitivity and impotence (mechanism unclear).

Rare dose-independent side-effects of thiazide diuretics

- Agranulocytosis
- Pancreatitis
- Thrombocytopenia

Novel anticoagulant agents

Dabigatran is a direct inhibitor of free and fibrin-bound thrombin, and of thrombin-induced platelet aggregation. Apixaban and rivaroxaban are direct inhibitors of activated factor X. These novel oral anticoagulants are licensed for prevention of venous thromboembolism after elective hip or knee replacement, and stroke prevention in non-valvular atrial fibrillation. Rivaroxaban is also licensed for treatment and prevention of deep vein thrombosis and pulmonary embolus. There is no specific antidote available for these anticoagulants, and they are contraindicated in patients at high risk of haemorrhage, including gastrointestinal ulcer or malignancy, recent surgery, recent intracranial

haemorrhage, or suspected oesophageal varices or vascular abnormalities. They should not be administered at the same time as other anticoagulation therapy, including low-molecular-weight heparin.

2.4.2 Endocrinology

Carbimazole

Carbimazole inhibits a peroxidase enzyme that catalyses several steps in the conversion of tyrosine to thyroid hormone. It takes at least 6 weeks to reduce blood levels of thyroid hormones. Therefore, somatic symptoms of hyperthyroidism, such as tachycardia and anxiety, require control by β blockers (eg propranolol).

- Agranulocytosis may occur within the first 16 weeks of therapy and in the event of sore throat, patients should be advised to seek medical help
- The drug crosses the placenta, and may cause neonatal goitre and hypothyroidism.

Exenatide

This is a synthetic form of exendin-4 that potentiates the release of insulin in response to hyperglycaemia. It is licensed for use in patients with type 2 diabetes in combination with metformin or sulfonylurea or both, and in patients with inadequate glycaemic control. It requires subcutaneous administration, and its adverse effects include dyspepsia and altered bowel habit.

Hormone replacement therapy

On average, over a third of a woman's life is in the postmenopausal phase, yet only 12% of women receive hormone replacement therapy (HRT); 60–75% experience vasomotor symptoms that may be reduced by HRT.

- Without HRT, women aged 70 years have a 50% reduction in bone mass and one in two will have an osteoporosis-related fracture
- HRT may reduce the occurrence of fractures. There is uncertainty over the possible impact of HRT on heart disease and stroke risk, and HRT may be associated with an increased risk of breast cancer. (See also Chapter 4, Endocrinology, Section 4.3.6).

Nateglinide and repaglinide

These agents have a short duration of action and may be used to stimulate insulin release in patients with type 2 diabetes before meals. Similar mechanism of action to sulphonylureas but much shorter duration of action and so can be taken before meals to control postprandial hyperglycaemia. They may also be given alongside metformin. Side-effects include gastrointestinal upset and hypersensitivity reactions.

Acarbose

Acarbose inhibits intestinal α-glucosidase and thereby delays absorption of starch and sucrose. It

reduces postprandial hyperglycaemia in type 1 diabetes and is used as an adjunct to metformin or sulfonylurea therapy in type 2 diabetes. Excess flatus is a common adverse effect.

Sitagliptin

Sitagliptin is a dipeptidylpeptidase-4 (DPP-4) inhibitor that increases insulin secretion and inhibits glucagon secretion. Sitagliptin may be added to metformin or a thiazolidinedione (see below) if glycaemic control is inadequate. DPP-4 inhibitors depend on intrinsic insulin secretion and therefore are not expected to cause hypoglycaemia.

2.4.3 Gastroenterology

Sulfasalazine

Sulfasalazine consists of a sulfonamide molecule plus 5-ASA. It is used in the treatment of ulcerative colitis, and also as a disease-modifying anti-rheumatic in rheumatoid arthritis. The sulfonamide moiety frequently leads to gastrointestinal upset. Other key features are as follows:

- Oligospermia, leading to male infertility, may occur, but this is usually reversible on stopping sulfasalazine
- Patients may note orange discoloration of body fluids
- Slow acetylators may experience more toxicity with sulfasalazine due to exposure to higher levels of the sulfonamide constituent
- Rare adverse effects include Stevens–Johnson syndrome, blood dyscrasias (especially agranulocytosis and aplasia) and the nephrotic syndrome.

Mesalazine and olsalazine

Mesalazine and olsalazine differ from sulfasalazine in being purely 5-aminosalicylic acid (5-ASA) molecules that are split for local action in the colon. They suppress local inflammation in ulcerative colitis.

- They have some systemic side-effects, including nausea, abdominal pain, headache and sometimes worsening of colitis
- Rare side-effects of mesalazine and olsalazine include reversible pancreatitis, blood dyscrasias and interstitial nephritis (with mesalazine).

Orlistat

Orlistat inhibits the action of pancreatic lipase and may be used in obesity where the body mass index is >30 kg/m2 and a prerequisite of treatment is that the patient has been able to lose 2.5 kg in weight over a 4-week period. It causes liquid, oily stools and may reduce the absorption of fat-soluble vitamins.

Probiotic therapy

Probiotics have been proposed as a means of reducing the occurrence of antimicrobial-associated

diarrhoea; however, a large recent study (PLACIDE) found that daily administration of a mixed preparation of lactobacilli and bifidobacteria for 21 days had no effect on the occurrence of antibiotic-associated diarrhoea or *Clostridium difficile* gastroenteritis in patients aged ≥65 years.

2.4.4 Neurology

Treatment of Parkinson's disease

Enhanced dopaminergic transmission is central to the medical management of Parkinson's disease:

- Selegiline is a type B monoamine oxidase inhibitor (MAO-B); inhibition of monoamine oxidase potentiates dopamine and reduces end-dose akinesia. It was thought that selegiline might also retard progression of Parkinson's disease by preserving dopaminergic neurons. This is now known to be untrue
- Amantadine potentiates dopamine by preventing its reuptake into presynaptic terminals
- Levodopa (L-dopa) is absorbed in the proximal small bowel by active transport, but the presence of amino acids (and thus meals) may reduce absorption. It is a prodrug that must be converted to dopamine within the nigrostriatal pathway. The drug is largely metabolised by catechol-*O*-methyltransferase. After 8 years of therapy with L-dopa, 50% of patients will have choreoathetoid dyskinesia and end-dose akinesia. By this time many patients will have deteriorated to pretreatment levels of disability due to progression of Parkinson's disease
- Dopamine receptor agonists include apomorphine, bromocriptine, cabergoline, pergolide, pramipexole and ropinirole. These agents cause less dyskinesia than L-dopa but they are associated with more neuropsychiatric adverse effects. Certain of these agents have been associated with pulmonary and retroperitoneal fibrosis (bromocriptine, cabergoline and pergolide). Apomorphine is a powerful dopamine agonist which needs to be given by parenteral administration under specialist supervision. It is highly emetogenic and domperidone must therefore be given 2 days before the start of therapy.

Side-effects of L-dopa

- Cardiac arrhythmias
- Involuntary movements (dyskinesia) occur commonly; seizures are rare
- Nausea and vomiting
- Postural hypotension
- Psychosis (depression or mania)
- Somnolescence (including sudden onset)

Treatment of epilepsy

Recent developments in the therapeutics of epilepsy have concentrated on agents that interact with neurotransmitters:

Lamotrigine inhibits the excitatory effects of glutamate within the central nervous system (CNS).

- Used to treat partial or generalized seizures, absence seizures, Lennox-Gastaut syndrome and bipolar disorder. Adverse effects include mood changes, maculopapular rashes, influenza-like symptoms and Stevens–Johnson syndrome. It has no significant effect on hepatic cytochrome P450 enzyme activity

- **Gabapentin** is a pentameric isomer of γ-aminobutyric acid (GABA), an inhibitory CNS neurotransmitter. It is used to treat partial seizures with or without secondary generalization, and neuropathic pain.
- **Leviracetam** binds to SV2A, a synaptic vesicle protein, and modulates the release of various CNS neurotransmitters, including increased GABA release. It is used in combination with other antiepileptic drugs for the treatment of partial or generalised seizures and myoclonic jerks
- **Vigabatrin** irreversibly inhibits GABA transaminase, so that GABA activity is enhanced. Used to treat partial complex seizures or secondary generalization, infantile spasms and other resistant seizure types. Adverse effects include mood disturbance and psychosis in 5%. Severe visual field defects may occur from 1 month to several years after initiation, so regular visual field assessment is advised
- **Benzodiazepines** (eg clonazepam, lorazepam) act at a specific receptor site linked to the GABA receptor to cause increased binding affinity between GABA and its receptor
- **Carbamazepine** is a derivative of the tricyclic antidepressants and is useful for epilepsy and also neural pain (eg trigeminal or postherpetic neuralgia). Patients commonly experience headaches and diplopia soon after initiation of carbamazepine, and 5–15% of patients develop a generalised morbilliform rash. More serious dermal complications have been reported, including toxic epidermal necrolysis
- **Sodium valproate** may be used in generalised epilepsy, absence attacks and temporal lobe epilepsy. It inhibits liver enzymes and thereby increases drug concentrations and toxicity of other antiepileptics such as phenytoin. It may cause alopecia, with curly regrowth after stopping the drug, and causes hyperammonaemia; ammonia concentrations can be used to monitor valproate toxicity.

Adverse effects of valproate

- Alopecia
- Hepatitis (sometimes fatal)
- Amenorrhoea
- Liver enzyme inhibition
- Ataxia
- Thrombocytopenia
- Gynaecomastia
- Weight gain

5-Hydroxytryptamine agonists (sumatriptan and rizatriptan)

5-Hydroxytryptamine (5HT) agonists are used during the acute phase of migraine. They maintain vascular tone and prevent headache associated with the vasodilator phase of migraine. They must not be given in hemiplegic migraine, or within 24 hours of ergotamine, because intense vasospasm may lead to permanent neurological damage. Sumatriptan may lead to permanent neurological damage. It may also cause angina due to coronary vasospasm. For this reason it is now rarely used.

Side-effects of sumatriptan

- Chest pain
- Flushing
- Drowsiness
- Vasospasm
- Fatigue

2.4.5 Psychiatry

Chlorpromazine

Chlorpromazine blocks many different receptors, it acts as a dopamine blocker, an α blocker, an anti-cholinergic and an antihistamine. It may cause QT prolongation on the ECG, particularly when used in high doses.

Adverse effects of chlorpromazine

- Agranulocytosis
- Contact dermatitis and purple pigmentation of the skin
- Dystonias (including oculogyric crisis)
- Neuroleptic malignant syndrome
- Photosensitivity
- Tardive dyskinesia (chronic use)
- Ventricular tachycardia (prolonged QT)

Other antipsychotics

Newer, so-called 'atypical' antipsychotic agents have a different adverse effect profile, and generally cause less sedation. Olanzapine and risperidone are associated with an increased risk of stroke in elderly patients, and should be used only with caution in this group.

Lithium

Lithium carbonate is used for prophylaxis in bipolar affective disorder, acute mania/hypomania and

aggressive behaviour in patients with learning disabilities. It has a narrow therapeutic range (0.5–1.0 mmol/L). Toxic effects occur at levels >2.0 mmol/L.

- Toxicity is more likely in renal impairment or when there are imbalances of electrolytes, or if lithium excretion is impaired by diuretics, ACE inhibitors or NSAIDs
- Lithium may cause histological changes in the kidney, and it has been recommended that long-term treatment is reviewed every 2–3 years
- Polyuria arises due to nephrogenic diabetes insipidus; lithium prevents antidiuretic hormone (ADH) from interacting with the collecting duct receptor, so leading to water loss. There is a compensatory increase in ADH release. Lithium is thought to downregulate expression of Aquaporin2, thereby decreasing sensitivity to ADH in the collecting ducts.
- Antacids, theophylline and acetazolamide lead to decreased plasma lithium carbonate
- CNS toxicity has been described with selective serotonin reuptake inhibitors (SSRIs), carbamazepine and phenytoin, methyldopa, antipsychotics (especially haloperidol), calcium channel blockers and sumatriptan.

Toxic effects of lithium

- At 1–2 mmol/L
  - Anorexia and vomiting
  - Ataxia and dysarthria
  - Blurred vision
  - Coarse tremor
  - Diarrhoea
  - Drowsiness
  - Muscle weakness
- Severe toxicity >2 mmol/L
  - Circulatory failure
  - Coma
  - Convulsions
  - Death
  - Hyperreflexia
  - Oliguria
  - Toxic psychoses

Side-effects of lithium[a]

- Common
  - Fine tremor (in about 15% of patients)
  - Leukocytosis

    - Loose motions
    - Nausea
    - Oedema
    - Polydipsia
    - Polyuria
    - Weight gain
- Rare
    - Goitre
    - Hypothyroidism
    - Interstitial nephritis
    - Worsening of psoriasis and acne

[a]May arise despite therapeutic range dosing.

Citalopram and escitalopram

Recent data have shown that citalopram and its *S*-enantiomer escitalopram may cause dose-dependent prolongation of the QT interval on the ECG, raising concerns about the possibility of potentially fatal arrhythmias, including torsades de pointes. Citalopram and escitalopram should not be used in patients with congenital long QT syndrome or preexisting QT interval prolongation, or combined with other medicines that prolong the QT interval. An ECG should be performed before starting treatment in patients with cardiac disease or electrolyte disturbances. The maximum citalopram daily dose is 40 mg in adults and 20 mg for those aged >65 years or with liver disease. The maximum dose of escitalopram is 20 mg and 10 mg in those aged >65 years.

2.4.6 Rheumatology

Methotrexate

Methotrexate is a folate antagonist (blocking dihydrofolate reductase) that is widely used as an immunosuppressant in autoimmune rheumatic diseases. It is the first line Disease Modifying Anti-Rheumatic Agent (DMARD) in rheumatoid arthritis, but it's use is common in many of the other rheumatic diseases (eg vasculitis, lupus). Methotrexate is administered once weekly, either as an oral tablet or as a subcutaneous injection. Awareness of weekly dosing is important, as inadvertent prescribing daily may result in severe toxicity, including mucositis, bone marrow suppression and pancytopenia. Treatment is to provide the active metabolite of folic acid: IV folinic acid.

Methotrexate toxicity may occur when a patient is inadvertently prescribed a second folate antagonist, for example trimethoprim (this combination is hazardous and must be avoided.

In standard doses of methotrexate, there are several common side effects that are encountered:

- Nausea
- Hepatitis
- Pneumonitis

- Bone marrow suppression

Therefore all patients on methotrexate should have regular monitoring, including monthly blood tests. Methotrexate is also an abortive agent and a 3-month washout is needed prior to conception; patients prescribed the drug must have appropriate pregnancy counselling.

Agents used in the treatment of gout

Allopurinol inhibits xanthine oxidase, the enzyme that converts purines into uric acid, and so prevents gout. However, commencement of therapy will occasionally provoke an acute attack of gout. Established gouty tophi may regress with chronic use of allopurinol.

- Azathioprine, a prodrug, is converted to 6-mercaptopurine in the body and may accumulate, causing bone marrow toxicity in patients receiving allopurinol
- The renal clearance of cyclophosphamide may also be impeded in patients receiving allopurinol, and this again leads to marrow toxicity.

Colchicine inhibits macrophage migration into a gouty joint but its use is limited by the frequent occurrence of diarrhoea. It has therefore been said that with colchicine 'you run before you can walk!'.

Urate oxidase enzymatically degrades urate to allantoin. Intravenous administration causes a significant reduction in serum urate concentrations (by up to 95%) and is used to prevent renal impairment in tumour lysis syndrome.

Febuxostat

Febuxostat is a novel xanthine oxidase inhibitor. It inhibits the formation of urate and over a sufficient period will lower total body urate and minimize the risk of gout. It is generally reserved for patients intolerant of allopurinol.

2.4.7 Respiratory

Leukotriene antagonists

Agents such as montelukast block the effects of leukotriene in the airways. They are used as adjunctive therapy in mild-to-moderate asthma, particularly with an allergic component, but they are ineffective in the setting of acute asthma. Churg–Strauss-like eosinophilic vasculitis and peripheral neuropathy have been reported with these agents.

Omalizumab

Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE), and is licensed for use in the prophylaxis of severe allergic asthma confirmed by allergy testing. It requires subcutaneous administration, and adverse effects include hypersensitivity reactions and the Churg–Strauss syndrome.

Tiotropium

Tiotropium is an M_3-selective muscarinic receptor antagonist that alleviates bronchospasm and minimises respiratory secretions. It has high receptor affinity, and its dissociation half-life is 27 hours, so that it is administered once daily. Adverse effects include dry mouth, tachycardia, dizziness, blurred vision, constipation and acute urinary retention. It should be used with caution in patients with narrow-angle glaucoma and bladder neck obstruction, or benign prostatic hyperplasia.

2.4.8 Miscellaneous

A detailed description of the mechanism of action, important pharmacokinetics and characteristic or serious side-effects of commonly used antibacterial, antiviral and anthelmintic agents is provided in Chapter 11, Infectious Diseases and Tropical Medicine.

Ciprofloxacin

This 4-quinolone inhibits DNA bacterial gyrase, an enzyme that prevents supercoiling of bacterial DNA. It is active against both Gram-positive and Gram-negative organisms. It is a liver enzyme inhibitor and may increase the effect of theophylline in particular. Ciprofloxacin is not recommended for children aged <12 years (except in cystic fibrosis) because of the potential for causing bony anomalies.

Adverse effects of ciprofloxacin

- Anaphylaxis
- Impaired motor function
- Arthralgia
- Photosensitivity
- Crystalluria
- Sedation (which may affect driving)
- Diarrhoea
- Seizures – occur because ciprofloxacin can compete with the inhibitory neurotransmitter, GABA, within the brain

Ciclosporin A

Ciclosporin A may be used to treat psoriasis and is used to reduce transplant rejection and it has significantly improved graft survival. After initiation of therapy (when doses are usually highest) it causes dose-dependent nephrotoxicity and has a narrow therapeutic range; therapeutic drug monitoring is indicated. Unfortunately, late nephrotoxic effects do occur and are often unrelated to plasma levels. (See also Chapter 15, Nephrology.)

Gum hyperplasia is common; it is increased in individuals with poor oral hygiene, and also those concomitantly taking dihydropyridine calcium channel blockers. As with most immunosuppressants, there is an increased risk of skin and lymphoproliferative malignancy with long-term therapy.

Adverse effects of ciclosporin

- Burning hands and feet (especially during first week of therapy)
- Hypertension
- Hypertrichosis
- Fluid retention
- Liver dysfunction
- Gum hyperplasia
- Nephrotoxicity
- Hyperkalaemia
- Algodystrophy (complex regional pain syndrome)

Cytotoxics

Most cytotoxic agents have the potential to cause marrow suppression.

Specific-side effects of cytotoxic agents

- **Bleomycin**
  - Causes dose-dependent lung fibrosis; it is one of the least myelotoxic chemotherapeutic agents
- **Capecitabine**
  - Desquamation (hand-foot syndrome)
- **Cisplatin**
  - May cause ototoxicity, nephrotoxicity (interstitial nephritis), hypomagnesaemia and peripheral neuropathy
- **Doxorubicin**
  - May cause skin irritation and cardiomyopathy; risk of dilated cardiomyopathy is reduced by dexrazoxane (an iron-chelating agent)
- **Methotrexate**
  - May cause severe mucositis and myelosuppression, which is prevented by the use of folinic acid rescue. During chronic administration, pneumonitis and liver fibrosis may occur
- **Vincristine and vinblastine**
  - Cause a reversible peripheral neuropathy

Retinoids

Oral retinoids are indicated for the treatment of severe psoriasis and acne that is resistant to other therapies. They are teratogenic, leading to neural tube defects. Similar to other vitamin A derivatives they may cause benign intracranial hypertension. Dryness of mucous membranes, leading to

intolerance of contact lenses, has been noted during treatment with retinoids.

High-dose retinoids can rarely cause diffuse interstitial skeletal hyperostosis, similar to Foriestier's disease.

Adverse effects of retinoids

- Alopecia
- Photosensitivity
- Benign intracranial hypertension
- Reduced night vision
- Dry mucous membranes
- Skeletal abnormalities (with high doses)
- Hepatitis
- Hypertriglyceridaemia
- Teratogenicity
- Mood changes
- Thrombocytopenia

Strontium

Strontium ranelate is licensed for postmenopausal osteoporosis. It increases new bone formation and suppresses bone resorption. Recognised adverse effects include severe allergy and **d**rug **r**ash with **e**osinophilia and **s**ystemic **s**ymptoms (DRESS).

2.5 SPECIFIC ADVERSE EFFECTS

2.5.1 Secondary amenorrhoea

Dopamine inhibits prolactin release, so dopamine-blocking drugs, such as chlorpromazine and cimetidine (but not ranitidine), may provoke hyperprolactinaemia and hence amenorrhoea. Sodium valproate may also cause amenorrhoea.

2.5.2 Bronchospasm

Bronchospasm may be induced by aspirin and NSAIDs, particularly in patients with late-onset asthma. Sensitivity to these agents relates to pharmacological effects on prostaglandin metabolism; the effect is a non-IgE anaphylactic mechanism.

- Adenosine causes bronchoconstriction via adenosine receptors within the bronchial smooth muscle, and it should be avoided in patients with asthma
- β Blockers (even cardioselective ones such as nebivolol) may provoke bronchospasm

- Sodium cromoglicate is a mast-cell stabiliser; it is an inhaled, preventive agent in asthma. However, bronchospasm has occasionally been reported, because cromoglicate is administered as a dry powder
- Acetylcysteine may cause bronchospasm and non-IgE-mediated anaphylaxis.

2.5.3 Dyskinesia and dystonia

Both dopamine agonists and antagonists can lead to movement disorders:

- Drugs with dopamine-like effects that are used to treat Parkinson's disease may cause dyskinesia (L-dopa, bromocriptine and pergolide)
- Dopamine-blocking agents such as phenothiazines (chlorpromazine) or butyrophenones (haloperidol) may also cause dyskinesias. This is a recognised complication of treatment with dopamine antagonists such as metoclopramide. It is less common with domperidone due to poorer uptake of this agent across the blood–brain barrier
- SSRIs may cause dystonias and rarely are associated with serotoninergic syndromes which are a group of clinical disorders characterized by excess serotonergic effects, often occurring when SSRI combined with another drug capable of exerting effects on serotonergic pathways eg tramadol, tricyclics, antipsychotics.

2.5.4 Gynaecomastia

Gynaecomastia can complicate treatment with drugs that are oestrogen-like in action or anti-androgens.

Oestrogen-like action
Digoxin spironolactone diethylstilbestrol Anti-androgen action Cimetidine Cyproterone acetate Luteinising hormone-releasing hormone (LHRH) analogues (eg goserelin)

2.5.5 Hypothyroidism

Impaired thyroid hormone production may result from the following:

- amiodarone
- carbimazole
- lithium
- propylthiouracil

- radioiodine.

Others: sulfonamides, sulfonylureas and ketoconazole inhibit iodination and iodotyrosine coupling within the thyroid gland.

Lithium inhibits iodide transport into the thyroid gland and inhibits thyroid function.

2.5.6 Drug-induced liver injury

Drug-induced liver injury may represent either dose-dependent or dose-independent effects.

- Dose-dependent liver injury includes paracetamol poisoning, fatty change due to tetracycline or alcoholic hepatitis
- Dose-independent liver injury usually involves either hepatitis or cholestasis; it generally has an allergic basis and may on occasion be associated with liver failure
- Liver tumours may be associated with use of androgens and oestrogens (which can also cause Budd–Chiari malformations); liver fibrosis may accompany methotrexate treatment.

Drug-induced hepatitis occurs with

- Amiodarone
- Exanetide
- HMG-CoA reductase inhibitors
- Isoniazid metabolite
- Methyldopa
- Paracetamol
- Phenytoin
- Pyrazinamide
- Valproate (especially in patients receiving other antiepileptics and those aged <2 years)

Causes of drug-induced cholestasis

- Carbamazepine
- Chlorpromazine
- Co-amoxiclav (combination of amoxicillin and clavulanic acid)
- Erythromycin
- Flucloxacillin
- Sulfonylureas

2.5.7 Drugs provoking myasthenia

- Aminoglycosides, certain β blockers (propranolol, oxprenolol), phenytoin, lidocaine, quinidine and procainamide may all impair acetylcholine release, leading to worsening or unmasking of myasthenia
- Penicillamine may cause formation of antibodies against the acetylcholine receptor, and a syndrome indistinguishable from myasthenia results. This resolves in two-thirds of cases after penicillamine withdrawal
- Lithium may also cause myasthenia-like weakness by impairing synaptic transmission.

2.5.8 Photosensitivity

Drugs causing photosensitivity

- Amiodarone
- Piroxicam
- Ciprofloxacin
- Psoralens
- Griseofulvin
- Retinoids
- Loop and thiazide diuretics
- Sulfonylureas
- Oral contraceptives
- Tetracyclines

2.5.9 Drug-induced vasculitis

Drug-induced vasculitis can affect the skin or internal organs.

Recognised drug causes of vasculitis

- Allopurinol
- Captopril
- Cimetidine
- Hydralazine
- Leukotriene antagonists
- Penicillin
- Quinidine

- Sulfonamides
- Thiazides

2.5.10 Acute pancreatitis

Acute pancreatitis is a recognised adverse effect of a number of drugs.

Drugs causing acute pancreatitis

- Antiretrovirals (ritonavir, didanosine, zalcitabine, stavudine, lamivudine)
- Azathioprine
- Corticosteroids
- Fibrates
- HMG-CoA reductase inhibitors
- Omega-3 fish oils
- Thiazide diuretics

2.5.11 Syndrome of inappropriate ADH secretion

SIADH is characterised by hyponatraemia, concentrated urine and low plasma osmolality, all occurring in the absence of oedema, diuretic use or hypovolaemia. Treatment involves cessation of the responsible drug and, in persistent cases, demeclocycline may be considered.

Drugs causing SIADH

- Carbamazepine
- Chlorpropamide
- Cytotoxic agents
- Opiates
- Oxytocin
- Psychotropic agents
- Rifampicin

In addition, there are a number of non-pharmacological causes, which include malignancy, CNS disorders, suppurative pulmonary disease and porphyria. (See Chapter 4, Endocrinology, Section 4.4.)

2.5.12 Drug-induced diabetes insipidus

Drug-induced diabetes insipidus is generally nephrogenic, namely diminished responsiveness of the kidneys to ADH and an impaired ability to concentrate urine. Lithium is the most common cause, affecting around 10% of patients treated for >15 years; the risk is minimised by limiting treatment to a maximum of 5 years, and maintaining 12-hour trough serum concentrations between 0.4 and 0.6 mmol/L. Other recognised drugs include foscarnet, clozapine, amphotericin B, orlistat, ifosfomide and cidofovir. Management involves stopping the offending drug, and some patients may respond to treatment with thiazide diuretics, amiloride or NSAIDs.

2.6 POISONING

2.6.1 Paracetamol overdose

Paracetamol overdose is one of the most common means of self-poisoning. Early features are minor (nausea and vomiting). Acute liver injury may occur later, typically with peak transaminases at 2–3 days after ingestion, but fulminant liver may occur in severe poisoning. Toxicity is thought to be due to excess reactive oxygen species and a paracetamol metabolite that binds to liver cell macromolecules causing necrosis.

- The international normalised ratio (INR), or prothrombin ratio, is the most sensitive indicator of impaired liver function. Hypoglycaemia is a feature of advanced liver damage
- Poor prognosis is indicated by an INR >3.0, raised serum creatinine and plasma pH <7.3 more than 24 hours after overdose
- Acute kidney injury may occur, onset is typically 2–3 days after ingestion and may occur in the absence of liver injury
- Acetylcysteine improves prognosis in paracetamol poisoning even after hepatic encephalopathy has developed
- Paracetamol concentrations determined at 4 to 15 hours after an acute single time-point overdose may be used to estimate the extent of drug exposure by comparison to a standardised nomogram: acetylcysteine antidote is indicated in all patients with paracetamol concentration higher than the treatment nomogram
- The nomogram approach cannot be applied if patients present to hospital >15 hours after acute overdose, or if patients have taken multiple paracetamol ingestions, or have taken a prolonged overdose >1 hour, so-called staggered ingestion: in these cases, the need for antidote is based upon clinical judgement and the stated dose ingested
- A small number of patients will develop fulminant hepatic failure despite paracetamol concentrations lower than the treatment nomogram, so that in some countries all patients that present to hospital after paracetamol overdose receive antidote treament.

2.6.2 Tricyclic antidepressant and venlafaxine overdose

Tricyclic antidepressants and venlafaxine exert a number of toxic effects:

- **Anticholinergic effects**: pupillary dilatation, acute confusion, tachycardia, dry mouth
- **α-Blocking effects**: systemic hypotension and reduced conscious level
- **Sodium channel blockade**: arrhythmia and seizures
- Prolongation of the QRS complex >100 ms may be associated with increased risk of arrhythmia
- Seizure threshold is reduced and status epilepticus may occur; abnormalities of thermoregulation can also occur
- Treatment is supportive, and activated charcoal should be considered if <1 hour after ingestion and airway protected. Seizures should be treated with benzodiazepines. Intravenous sodium bicarbonate reduces the risk of arrhythmias and seizures and should be considered for patients at high risk (reduced conscious level, acidosis, QRS duration >100 ms)
- Duration of venlafaxine toxicity may be prolonged for up to 48 hours after ingestion of standard-release preparations and up to 72 hours after overdose involving modified-release formulations.

2.6.3 Theophylline toxicity

This may cause tachyarrhythmia due to phosphodiesterase inhibition. Electrolyte abnormalities include severe acidosis and hypokalaemia (the latter partly due to intractable vomiting). Reduced conscious level, seizures and confusion may also occur.

- Treatment is with repeated doses of oral activated charcoal (which significantly enhances theophylline clearance), and correction of fluid and electrolyte depletion
- Haemodialysis is indicated for patients with severe toxicity (plasma theophylline >60 mg/L).

2.6.4 Carbon monoxide poisoning

Carbon monoxide binds to haemoglobin with high affinity (200 times that of oxygen), and decreases oxygen-carrying capacity, resulting in tissue hypoxia. Normal carboxyhaemoglobin levels are <3% in non-smokers and 5–6% in smokers. Mild exposure (10–30% carboxyhaemoglobin) may be associated with headache and mild exertional dyspnoea.

Signs of marked toxicity (carboxyhaemoglobin 30–60%)

- Acute renal failure
- Agitation and confusion
- Bullous lesions
- ECG changes and arrhythmias
- Hyperpyrexia
- Hypertonia and hyperreflexia
- Muscle necrosis
- Pink mucosae

- Vomiting

- Severe toxicity may be associated with coma, convulsions and cardiorespiratory arrest
- Treatment is with 100% oxygen by mask; hyperbaric oxygen (2.5 atmospheres pressure) will increase the elimination (half-life reduced from 4 hours to 0.5 hour)
- Neuropsychiatric changes may develop over several weeks after recovery from poisoning and these include intellectual deterioration, personality change, cerebral and cerebellar damage, and extrapyramidal damage.

2.6.5 Quinine toxicity

Quinine poisoning may result in visual disturbance due to anticholinergic effects and direct neurotoxicity. **Blindness** may occur at between 6 and 24 hours after ingestion, and may be irreversible.

- **Arrhythmias**: increased risk of QT prolongation and torsades de pointes
- **Hypotension**: may occur due to α-adrenoceptor blockade
- **Tinnitus**
- **Severe metabolic acidosis**
- **Abdominal pain**.

2.6.6 Iron poisoning

The key features of iron poisoning are shown in the box below. Gastric lavage should be contemplated if the patient presents within 1 hour of life-threatening ingestion. Desferrioxamine chelates iron and may improve clinical outcome when given by intravenous infusion. The decision to administer desferrioxamine is based on the serum iron concentration, although in severe symptomatic cases it may be started before this is available.

Clinical features

- Abdominal pain
- Diarrhoea
- Haematemesis
- Lower gastrointestinal blood loss
- Nausea and vomiting

Severe poisoning

- Coma

- Death
- Delayed hepatocellular necrosis
- Metabolic acidosis
- Hypotension

2.6.7 Salicylate overdose

In early salicylate poisoning there is direct stimulation of the CNS respiratory centre causing a tachypnoea, 'air hunger' and respiratory alkalosis. As systemic aspirin absorption progresses, patients may develop a metabolic acidosis that can be severe or fatal.

Early features of poisoning

- Hypokalaemia
- Respiratory centre stimulation in the CNS, and hence alkalosis
- Sweating
- Tinnitus

Later features of poisoning

- Acute renal failure
- Hypoglycaemia
- Hypoprothrombinaemia
- Metabolic acidosis
- Pulmonary oedema

Key aspects of management of salicylate poisoning involve the following:

- Activated charcoal
- Correction of electrolyte and metabolic abnormalities
- Intravenous fluids to ensure adequate hydration (forced alkaline diuresis is unsafe and not recommended)
- Intravenous sodium bicarbonate to correct acidosis (this will reduce the quantity of salicylate taken up into tissues, and may enhance renal clearance of aspirin)
- Haemodialysis: for very severe salicylism (eg blood salicylate >750 mg/L).

2.6.8 Ethylene glycol poisoning

Poisoning with ethylene glycol may have a similar clinical appearance to ethanol intoxication, within

the first 12 hours. Initially there is a raised plasma osmolar gap due to the presence of ethylene glycol. This is then broken down, the degradation products, including oxalate, giving rise to a metabolic acidosis with a wide anion gap. Toxic effects include severe metabolic acidosis, hypocalcaemia, acute tubular necrosis, crystalluria, and cardiac failure and pulmonary oedema.

Treatment for ethylene glycol poisoning

- **Sodium bicarbonate**
  - To correct acidosis and enhance clearance of active metabolites
- **Intravenous ethanol**
  - Can inhibit ethylene glycol metabolism
- **Fomepizole**
  - This blocks the conversion of ethylene glycol to toxic metabolites, so that ethylene glycol may be excreted unchanged
- **Calcium**
  - To correct hypocalcaemia
- **Haemodialysis**
  - Active elimination of ethylene glycol is by haemodialysis

2.6.9 Haemodialysis for overdose or poisoning

Certain drugs and poisons may be effectively removed by haemodialysis, particularly those with a low volume of distribution that are largely confined to the circulating compartment. Conversely, haemodialysis is ineffective for drugs with a wide volume of distribution (eg amiodarone and paraquat), or those that are highly protein bound (eg digoxin and phenytoin). Repeated or continuous dialysis treatment for >16 hours may be required for drugs that are distributed throughout the extracellular fluid compartment (eg lithium), and a rebound increase in plasma concentrations may occur after shorter periods of dialysis. There are limited data concerning the impact of haemodialysis on patient outcomes, and it is normally only undertaken in patients with severe poisoning by selected agents.

Removal of drugs or toxins by haemodialysis/haemoperfusion

- Barbiturates
- Ethanol
- Ethylene glycol
- Lithium

- Methanol
- Salicylate

Chapter 3
Dermatology

CONTENTS

Dermatology

3.1 STRUCTURE AND FUNCTION OF SKIN AND TERMINOLOGY OF SKIN LESIONS

3.1.1 Structure

The skin consists of three distinctive layers: the epidermis, dermis and the subcutis.

- **Epidermis**: this forms the outermost layer and is the largest organ in the body. The principal cell is the keratinocyte. The epidermis has four layers, which are the basal cell layer, stratum spinosum, stratum granulosum and the stratum corneum
- **Dermis**: this lies beneath the epidermis and is a support structurally and nutritionally, and contributes 15–20% of total body weight. The principal cell is the fibroblast, which makes collagen (giving the skin its strength), elastin (providing elasticity) and proteoglycans. It also contains adnexal structures, including hair follicles, sebaceous glands, apocrine glands and eccrine glands
- **Dermoepidermal junction**: separates the epidermis from the dermis. Anomalies of this can give rise to some of the blistering disorders
- **Subcutis**: contains adipose tissue, loose connective tissue, blood vessels and nerves.

3.1.2 Function

The skin has numerous functions, all of which are designed to protect the rest of the body.

- **Barrier properties**: the skin acts as a two-way barrier, preventing the inward or outward passage of fluid and electrolytes
- **Mechanical properties**: the skin is highly elastic and so can be stretched or compressed
- **Immunological function**: the skin provides defence against foreign agents. In the epidermis, antigen presentation is carried out by Langerhans' cells
- **Sensory function**: the skin perceives the sensations of touch, pressure, cold, warmth and pain
- **Endocrine properties**: as a result of exposure to ultraviolet B radiation, vitamin D_3 is synthesised from previtamin D_3
- **Temperature regulation**: the rich blood supply of the dermis plays an important role in thermoregulation
- **Respiration**: the skin plays a minor role in gaseous exchange with the environment.

3.1.3 Terminology of skin lesions

- **Macule**: a flat lesion due to a localised colour change; when >1 cm in diameter, this is termed a 'patch'
- **Papule**: a small solid elevation of skin <1 cm diameter
- **Plaque**: a raised flat-topped lesion >1 cm diameter
- **Nodule**: a raised lesion with a rounded surface >1 cm diameter
- **Bulla**: a fluid-filled lesion (blister) >1 cm diameter
- **Vesicle**: a fluid-filled skin lesion <1 cm diameter
- **Pustule**: a pus-filled lesion
- **Weal**: a raised compressible area of dermal oedema
- **Scale**: flakes arising from abnormal stratum corneum
- **Crust**: dried serum, pus or blood.

3.2 SPECIFIC DERMATOSES AND INFECTIONS OF THE SKIN

3.2.1 Psoriasis

This is an immune-mediated, chronic, multisystem inflammatory disease occurring in 1–2% of the UK population. It affects both genders equally and occurs at any age, with two peak age ranges (16–22 and 57–60 years).

Its aetiology is unknown but multiple genetic factors in combination with environmental factors are thought to be important. Of individuals with psoriasis, 30% have an affected first-degree relative, and the risk of a child developing psoriasis if both parents are affected is 75%.

A number of psoriasis-susceptibility gene loci (eg *PSOR1*) and genes involved in interleukin (IL)-23 signalling, modulation of T-helper (Th)-2 immune responses (IL-4, IL-13) and activated B-cell (NF-κB) signalling have been identified.

The understanding of psoriasis has moved from one of a hyperkeratotic disorder of keratinocytes to a dysregulation of the immune system mediated by cytokines.

It is now understood that Th-1, Th-17 and Th-22 cell populations are expanded and stimulated to release inflammatory cytokines, including IL-17, IL-22 and tumour necrosis factor α (TNF-α).

Clinical presentation

- **Chronic plaque** (90% of cases): well-defined, red, disc-like plaques covered by white scale, which classically affect elbows, knees and scalp
- **Pustular (generalised pustular):** sheets of small, sterile yellow pustules on a red background. This presentation may be accompanied by systemic symptoms and progression to erythroderma
- **Erythrodermic**: confluent areas affecting most of the skin surface
- **Nail psoriasis**: onycholysis, pitting and subungal hyperkeratosis

  Pustular (palmoplantar pustulosis): yellow/brown sterile pustules and erythema on palms or

- soles. Strongly associated with smoking. This is most often seen in middle-aged women
- **Guttate**: an acute eruption of drop-like lesions, often following a streptococcal sore throat
- **Flexural**: affects axillae, submammary areas and the natal cleft. Lesions are often smooth, red and glazed in appearance.

Associations with psoriasis

Psoriasis is now known to be a systemic disease mediated via T cells; the inflammatory processes involved are associated with the development of a number of co-morbidities as well as reduced life expectancy.

- **Major cardiac adverse events (MACE):** studies show that patients with psoriasis have a 53% increased incidence of MACE (MI, stroke, cardiac death) compared with the general population. There is known to be an increased risk of cardiovascular disease independent of other risk factors, however. Psoriasis is also strongly associated with the metabolic syndrome (hypertension, obesity, diabetes and dyslipidaemia). Obesity has been shown to be a risk factor for the development of psoriasis and an increasing body mass index (BMI) is associated with greater degrees of severity. Psoriasis of any type, especially if severe, is a risk factor for venous thromboembolism.
- **Arthropathy**: psoriatic arthritis occurs in about 20% of patients with psoriasis. There are several different forms (see Chapter 20) – distal interphalangeal joint disease, large single-joint oligoarthritis, arthritis mutilans, sacroiliitis and psoriatic spondylitis have all been described
- **Gout**: this is due to deposits of urate crystals
- **Malabsorption**: Crohn's disease and ulcerative colitis are associated with psoriasis
- **Lymphoma**: there is a reported threefold increase in the rates of lymphoma in psoriasis patients.

Factors that can exacerbate psoriasis

- **Trauma**: the Köbner phenomenon (the development of the disease in areas of trauma)
- **Infection**: eg streptococci (guttate psoriasis, as above)
- **HIV**: psoriasis is more common in patients with HIV; the severity may dwindle in the late stages of the disease
- **Endocrine**: psoriasis generally tends to improve during pregnancy and deteriorate in the post-partum period
- **Drugs**: β blockers, lithium, antimalarials, interferon and the withdrawal of oral steroids can exacerbate psoriasis
- **Alcohol**
- **Stress**: most patients report a flare of disease with physical or psychological stress
- **Smoking**: smokers have an increased risk of psoriasis and heavy smokers have more severe disease
- **UV light**: although most patients find UV light beneficial, a small proportion find it flares their skin condition.

Causes of the Köbner phenomenon

- Psoriasis
- Lichen planus
- Vitiligo
- Viral warts
- Molluscum contagiosum

Causes of erythroderma

- Psoriasis
- Eczema
- Mycosis fungoides
- Adverse drug reactions
- Underlying malignancy
- Pityriasis rubra pilaris

Management of psoriasis

Offer people with any type of psoriasis support and information tailored to suit their individual needs and circumstances, in a range of different formats, so that they can confidently understand the following:

- Their diagnosis and treatment options
- Relevant lifestyle risk factors
- When and how to use prescribed treatments safely and effectively
- When and how to seek further general or specialist review
- Strategies to deal with the impact of psoriasis on physical, psychological and social wellbeing

Assess the following:

- Disease severity
- The impact of disease on physical, psychological and social wellbeing
- Whether they have psoriatic arthritis
- The presence of co-morbidities.

First-line treatment: topical therapy

- **Coal tar preparations**: available over the counter in weak forms; crude coal tar can be useful in thick plaque psoriasis
- **Dithranol**: a synthetic derivative of anthracene. It is an effective therapy but needs to be applied accurately because it can stain clothing and burn surrounding skin

- **Vitamin D analogues**, eg calcipotriol cream or ointment or calcipotriol with betamethasone
- **Tarazotene**: a topical retinoid for plaque psoriasis
- **Topical steroids**: may be used solely or in combination with other topicals for face, genitalia, flexures, hands and feet, and scalp. The strength of steroid varies according to the body site and severity.

Second-line treatment

Offer phototherapy or non-biological systemic agents when topical therapy alone is unlikely to control disease (eg extensive disease <10% body surface area [BSA], or nail disease **and** the disease has a significant impact on physical, psychological or social wellbeing), psoriasis is extensive (eg >10% BSA affected or a psoriasis area severity index [PASI] score >10) psoriasis is localised and associated with significant functional impairment and/or high levels of distress (eg severe nail disease or involvement at high-impact sites) or phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as >50% of baseline disease severity within 3 months).

Phototherapy (ultraviolet radiation)

- **UVB narrowband** (311–313 nm) is a well-established and effective treatment
- **PUVA** (oral/topical psoralen and UVA): oral psoralen use necessitates the need for protective eyewear and is associated with an increase risk of skin cancers.

Non-biological systemic treatment

The benefits must be weighed against the side-effects of the drugs.

Methotrexate is used as a first-line non-biological systemic treatment; it blocks DNA synthesis by inhibiting dihydrofolate reductase. It is administered once weekly, orally or subcutaneously. The risks of nausea, anaemia and pancytopenia are reduced with folic acid supplementation. There is a risk of liver fibrosis with long-term use. A serological marker for fibrosis, amino-terminal peptide procollagen III (P3NP), is measured 3-monthly and a liver biopsy is performed if consistently high, further evaluation of liver fibrosis may be indicated.

Ciclosporin: is used as a first-line non-biological systemic treatment particularly where rapid or short-term disease control is required, there is palmoplantar pustulosis or conception is being considered (in men and women in whom systemic treatment cannot be avoided); it inhibits T-lymphocyte transcription of IL-2. Major side-effects are renal toxicity and hypertension.

Retinoids: acitretin is the retinoid of choice and is used alone or in combination with UVB or PUVA. Teratogenicity is a problem and treatment should be avoided in women of childbearing potential. Mucocutaneous side-effects are common and elevated triglyceride levels are often observed.

Treatments used less commonly include: azathioprine, hydroxyurea, mycophenolate mofetil (MMF) and fumaric acid esters.

Third-line treatment: biologic agents

Biologics are considered for patients with severe disease. Strict eligibility criteria are in place and patients may have been unresponsive/intolerant to standard systemic and phototherapy, systemic therapy may be contraindicated or they may have severe life-threatening disease.

A PASI score is a tool used to measure the extent and the severity of the psoriasis and a DLQI (dermatology life quality index) assesses the impact of the disease on quality of life. For biological treatment these scores must be at least 10.

The current National Institute for Health and Care Excellence (NICE)-approved biologics target TNF-α or the interleukin pathway is as follows:

- **Etanercept**: human fusion protein of the TNF receptor that acts as a TNF-α inhibitor. Delivered subcutaneously
- **Adalimumab**: a human monoclonal antibody that binds to TNF-α. Delivered subcutaneously
- **Infliximab**: a chimeric monoclonal antibody that binds to TNF-α. Delivered by infusion
- **Ustekinumab**: a human monoclonal antibody that targets IL-12 and IL-23. Delivered subcutaneously.

Other biologic agents are in development, but at this stage are not NICE approved.

3.2.2 Eczema (dermatitis)

Eczema is an inflammatory skin disorder with characteristic histology and clinical features, which include itching, redness, scaling and a papulovesicular rash. Eczema can be divided into two broad groups, exogenous or endogenous:

- **Exogenous eczema**: irritant dermatitis, allergic contact dermatitis
- **Endogenous eczema**: atopic dermatitis, seborrhoeic dermatitis, pompholyx.

Seborrhoeic dermatitis is a red, scaly rash caused by *Pityrosporum ovale*. The eruption occurs on the scalp, face and upper trunk, and is more common in young adults and patients with HIV.

Pompholyx is characterised by itchy vesicles occurring on the palms and soles.

Atopic dermatitis affects 20–30% of the UK population. It is a characteristic dermatitic eruption associated with a personal or family history of atopy. Both genetic and environmental factors interact to contribute to pathogenesis, with convincing evidence of both a barrier defect (caused by a compromise in epidermal permeability through null mutations in the filaggrin gene) and a Th-2-driven cutaneous inflammatory response.

Management of atopic eczema

Initial treatment consists of avoidance of irritants and exacerbating factors. Thereafter:

- **Topical therapy**: regular emollients, topical steroids, tar bandages, wet wraps and antibiotic ointment (for minor infections). Topical calcineurin inhibitors are considered when treatment has failed with the appropriate strength of topical steroid or there is a risk of skin atrophy. Tacrolimus is used for moderate-to-severe eczema in children age >2 and adults. Pimecrolimus is used for the face and neck of children aged >2

- **Ultraviolet radiation**: UVB or PUVA (see Psoriasis, section 3.2.1)
- **Systemic treatment**: this can be with ciclosporin, azathioprine and antihistamines, as well as antibiotics for any infective episodes. Occasionally oral prednisolone is used for severe flares. Alitretinoin is an oral retinoid licensed for hand dermatitis; unresponsive to topical steroids.

3.2.3 Acne

Acne is the most common of the dermatological disorders and affects most people at some time during their life. Although not life-threatening, acne can have severe psychosocial consequences and may lead to poor self-esteem, social isolation and depression.

Pathogenesis

Acne has a multifactorial pathogenesis and results from the interplay of the following four factors:

1. Plugging of the follicle due to epidermal proliferation
2. Excess sebum production
3. Colonisation with *Propionibacterium acnes*
4. Inflammation.

Clinical features

Acne is characterised by comedones, papules, pustules, nodules, cysts and scars. It affects the areas of skin where the sebaceous follicles are most dense: the face, back and chest.

Treatment

Choice of treatment should be based on the severity of the disease and the type of acne, eg comedonal, non-inflammatory acne may require only a keratolytic agent. Most moderate-grade acne needs a combined approach to treat both the comedones and the inflammatory lesions.

Topical treatments

- **Topical antibiotics**: these are not comedolytic and are best used in combination with benzoyl peroxide or another keratolytic agent
- **Topical retinoids**: comedolytic and anti-inflammatory. They may be used in combination with other acne medications. They often cause skin irritation
- **Benzoyl peroxide**: a keratolytic that comes in many formulations
- **Azelaic acid**: keratolytic and anti-inflammatory.

Systemic treatments

- **Antibiotics**: tetracyclines or erythromycin should be considered with moderate acne, especially if there is a risk of scarring
- **Combined oral contraceptive**: a standard combined oral contraceptive should be considered in

- all women with acne who require contraception or in whom there is a suspected hormonal basis for the acne. Co-cyprindiol (Dianette), a combination of ethinylestradiol and the anti-androgen cyproterone, may be considered

Isotretinoin: a systemic retinoid that is highly effective. It is indicated if there is scarring, if the acne is resistant to multiple treatments (including long-term systemic antibiotics) or if the disease is causing severe psychological distress. Isotretinoin is a teratogen and strict guidelines for its
- use and prescription are now in place. Women of childbearing age are advised to use two methods of contraception and to have monthly pregnancy testing. The most common side-effects are mucocutaneous, with severe drying of lips and skin. Mood changes and severe depression have been reported.

3.2.4 Rosacea

Rosacea is an inflammatory skin disease that causes erythema, telangiectasia, inflammatory papules and pustules. The skin tends to be dry and sensitive. It may cause flushing and in severe cases rhinophyma (usually in men). Ocular rosacea may occur and cause blepharitis, conjunctivitis or keratitis. Trigger factors include alcohol, sunlight, exercise, high and low temperatures, and spicy foods.

Treatment

Topical

Topical metronidazole or azelaic acid may help to control inflammation in mild-to-moderate rosacea.

Mirvaso is a new treatment for the erythema of rosacea. The active ingredient brimonidine (α_2 agonist) causes vasoconstriction.

Systemic

Most commonly, tetracyclines or erythromycin are used. A third of patients respond to 2 months of treatment. Many patients need long-term treatment. A β blocker or clonidine may help flushing. In severe, resistant cases isotretinoin may be used.

3.2.5 Lichen planus

This presents as an itchy, shiny, violaceous, flattopped, polygonal, papular rash with white lines on the surface known as Wickham's striae. Other affected sites include mucous membranes, genitalia, palms, soles, scalp and nails. Lichen planus causes a white lace-like pattern on the buccal mucosa.

Causes of white lesions in the oral mucosa

- Lichen planus
- Leukoplakia
- Chronic candidiasis
- Chemical burns.

3.2.6 Erythema multiforme

This is usually a maculopapular, targetoid rash, which can occur anywhere, including the palms, soles and oral mucosa. The cause is unknown but it is thought to be associated with infections, mainly viral. Stevens–Johnson syndrome, on the other hand, is more likely to affect mucosal surfaces and is believed to be associated with drug reactions.

Causes of erythema multiforme

- **Infections**
  - Herpes simplex virus
  - *Mycoplasma* spp.
  - Psittacosis
  - *Rickettsia* spp.
  - HIV
  - Hepatitis B virus
  - Orf
  - Infectious mononucleosis
  - Mumps
- **Drug reactions**
  - Barbiturates
  - Penicillin
  - Sulfonamides
- **Others**
  - Lupus erythematosus
  - Polyarteritis nodosa
  - Wegener's granulomatosis
  - Underlying malignancy
  - Sarcoidosis

3.2.7 Erythema nodosum

This is a hot, tender, nodular, erythematous eruption lasting 3–6 weeks, which is more common in the third decade and in females.

Causes of erythema nodosum

- **Bacterial infection**
  - Streptococcal throat infection (commonly)

- Salmonellae
- Campylobacters
- Tuberculosis
- *Mycoplasma pneumoniae*
- *Yersinia enterocolitica*

- **Mycoses**
  - Coccidioidomycosis
  - Histoplasmosis
  - Blastomycosis
- **Inflammatory bowel disease**
- **Sarcoidosis**
  - Behçet's syndrome
- **Drugs**
  - Penicillin
  - Tetracyclines
  - Oral contraceptive pill
  - Sulfonamides
  - Sulfonylureas
- **Malignancy**
  - Hodgkin's lymphoma
  - Acute myelocytic leukaemia
- **Pregnancy**
  - Viral infection

3.2.8 Specific skin infections

These can be subdivided into bacterial, fungal and viral infections as well as infestations.

Specific infections of the skin

- **Bacterial infections**
  - Streptococcal: cellulitis, erysipelas, impetigo, necrotising fasciitis, rheumatic fever (erythema marginatum), scarlet fever
  - Staphylococcal: folliculitis, impetigo, staphylococcal scalded-skin syndrome, toxic shock syndrome
  - Mycobacterial: TB (lupus vulgaris, scrofuloderma), fish-tank granuloma, Buruli's ulcer, leprosy

- Spirochaetal: syphilis, Lyme disease (erythema chronicum migrans)

- **Fungal**
  - Dermatophytes: *Trichophyton rubrum*, *T. interdigitale*, *Epidermophyton floccosum* (tinea pedis, tinea corporis, tinea cruris, tinea unguium)
  - Yeasts: *Candida* spp. (intertrigo, oral, genital or systemic); *Pityrosporum orbiculare*; pityriasis versicolor
- **Viral**
  - Human papillomavirus: warts
  - Herpes virus: varicella (chickenpox), zoster (shingles), simplex 1 (face and lips), simplex 2 (genital)
  - Pox virus: molluscum contagiosum, parapox virus (orf)
  - Parvovirus B19: erythema infectiosum (fifth disease)
  - RNA virus: measles, rubella
  - Coxsackie A16 virus: hand, foot and mouth disease
  - HIV/AIDS: skin disease is common, affecting 75% of patients, who can be at any stage of HIV disease (see Chapter 8)
- **Infestations**
  - *Sarcoptes scabiei*: scabies mite infestation
  - Lice infestation (pediculosis): head lice, pubic lice

3.3 BULLOUS ERUPTIONS

This is a rare group of disorders characterised by the formation of bullae. The development of blisters can be due to congenital, immunological or other causes. The level of split within the epidermis or within the dermoepidermal junction determines the type of bullous disorder.

Causes of bullous eruptions

- **Congenital**
  - Epidermolysis bullosa
- **Others**
  - Streptococcal infection
  - Staphylococcal scalded-skin syndrome
  - Toxic epidermal necrolysis
  - Diabetic bullae
  - Chronic renal failure
  - Haemodialysis
- **Immunological**

- Pemphigus
- Bullous pemphigoid
- Cicatricial pemphigoid
- Herpes gestationis
- Dermatitis herpetiformis

- **Drug overdose**
  - Barbiturates

Epidermolysis bullosa (EB) is the term used for a clinically and genetically heterogeneous group of rare inherited disorders characterised by fragility and blistering of skin and mucosae. It is caused by mutations involving at least 18 genes encoding structural proteins in the skin and mucosae.

There are three main types:

1. **EB simplex**: 70% of cases and tends to be the mildest form
2. **Junctional EB**: 5% of cases and considered the most severe form
3. **Dystrophic EB**: symptoms vary widely but severe cases can result in loss of vision, scarring, disfigurement, skin cancer and gastrointestinal tract blistering.

Pemphigus is a rare group of disorders characterised by blistering of the skin and mucous membranes. The bullae are superficial and confined to the epidermal layer. Pathogenic IgG autoantibodies bind to transmembrane desmosomal proteins of keratinocytes called desmogleins. The binding process results in loss of cell-to-cell adhesion and the production of superficial bullae in the epidermal layer. These superficial bullae rupture easily.

Three major variants have been described:

1. **Pemphigus vulgaris** is the most common variant and accounts for 70% of cases; there are autoantibodies to desmoglein 1 and desmoglein 3. It most commonly presents with painful erosions or blisters on the oral mucosa; skin lesions may present months later
2. **Pemphigus foliaceus** is generally a benign variant and is characterised by lesions that occur only in the skin and is associated with antibodies to desmoglein 1
3. **Paraneoplastic pemphigus** presents in association with a tumour which may be occult.

Untreated, the mortality rate associated with pemphigus vulgaris was 75%. The use of corticosteroids and adjuvant drugs has reduced the mortality rate significantly. It has been reported as 12% in the UK, with a three times higher risk of death than age-matched controls.

Bullous pemphigoid is more common than pemphigus. It is a disorder characterised by large, tense blisters found on the limbs, trunk and flexures in elderly people. Oral mucosal involvement is rare. Autoantibodies are present to two hemidesmosomal proteins: BP antigen II (BP180) and BP antigen I (BP230).

Cicatricial pemphigoid is a rare, chronic blistering disease of the mucous membranes and skin, which results in permanent scarring, particularly of the conjunctivae.

Dermatitis herpetiformis is an itchy, vesiculobullous eruption mainly occurring on the extensor

areas. The majority of patients have asymptomatic gluten-sensitive enteropathy.

3.4 THE SKIN IN CONNECTIVE TISSUE DISORDERS

3.4.1 Systemic sclerosis

This is a rare, multisystem, connective tissue disease of unknown aetiology, characterised by fibrosis of the skin and visceral organs, and accompanied by the presence of relatively specific antinuclear antibodies. The incidence peaks in the fifth and sixth decades and women are more affected than men (see also Chapter 20, Rheumatology).

Morphoea (localised scleroderma) consists of indurated plaques of sclerosis in the skin; systemic features are not found.

Skin changes in systemic sclerosis

- Facial telangiectasia
- Restricted mouth opening
- Perioral puckering
- Smooth, shiny, pigmented indurated skin
- Raynaud's phenomenon with gangrene
- Sclerodactyly
- Pulp atrophy
- Dilated nail-fold capillaries
- Ragged cuticles
- Calcinosis cutis
- Livedo reticularis
- Leg ulcers

3.4.2 Rheumatoid arthritis

Specific skin changes in rheumatoid arthritis

- Rheumatoid nodules
- Nail-fold infarcts
- Vasculitis with gangrene
- Pyoderma gangrenosum.

3.4.3 Dermatomyositis

Specific skin changes in dermatomyositis

- Heliotrope rash around eyes

- Gottron's papules: red plaques on extensor surfaces of finger joints
- Gottron's sign: erythema over knees and elbows
- Dilated nail-fold capillaries and prominent, ragged cuticles
- Nail-fold infarct.

3.4.4 Lupus erythematosus

Cutaneous discoid lupus erythematosus is associated with scaly erythematous plaques with follicular plugging on sun-exposed sites. These tend to heal with scarring.

Systemic lupus erythematosus (SLE) is commonly associated with dermatological manifestations. These include malar rash, photosensitivity, vasculitis, Raynaud's phenomenon, alopecia and oropharyngeal ulceration.

3.5 THE SKIN IN OTHER SYSTEMIC DISEASES

3.5.1 Sarcoidosis

Skin lesions are found in approximately 25% of patients with systemic sarcoid and can occur in the absence of systemic disease:

- Erythema nodosum
- Scar sarcoid
- Lupus pernio
- Scarring alopecia.

3.5.2 The porphyrias

- **Porphyria cutanea tarda**: the most common of the porphyrias. Skin signs develop in sun-exposed areas. Patients have decreased levels of uroporphyrinogen decarboxylase. Eighty per cent of cases are acquired, in which case the condition is provoked by a hepatotoxic factor such as alcohol, oestrogens, hepatitis C, iron, lead and certain aromatic hydrocarbon hepatotoxins
- **Acute intermittent porphyria**: skin signs are not seen
- **Congenital erythropoietic porphyria**: patients have brown teeth which fluoresce red under Wood's light, giving the 'werewolf' appearance

The typical skin signs of the porphyrias are:

- Photosensitivity
- Blister formation
- Scarring with milia
- Hypertrichosis.

3.5.3 Pyoderma gangrenosum

This is a painful ulcerating disease of unknown aetiology. It typically affects the legs; it may occur peristomally in inflammatory bowel disease or superficially on the hands. Fifty per cent of cases are associated with underlying medical disorders.

Conditions associated with pyoderma gangrenosum

- **Gastrointestinal**
  - Ulcerative colitis
  - Crohn's colitis
- **Rheumatological**
  - Rheumatoid arthritis
  - Ankylosing spondylitis
- **Liver**
  - Chronic active hepatitis
  - Primary biliary cirrhosis
  - Sclerosing cholangitis
- **Haematological**
  - Leukaemia
  - Lymphoma
  - Myeloproliferative disorders
- **Others**
  - Diabetes mellitus
  - Thyroid disease
  - Sarcoidosis
  - Wegener's granulomatosis
- **Other malignancies**

3.5.4 Diabetes

Skin signs in diabetes mellitus

- Necrobiosis lipoidica
- Disseminated granuloma annulare
- Diabetic rubeosis
- Candidiasis and other infections
- Vitiligo
- Neuropathic foot ulcers.

Diabetic rubeosis is an odd redness of the face, hands and feet thought to be due to diabetic microangiopathy.

3.6 GENERALISED PRURITUS

Pruritus is an important skin symptom and occurs in dermatological diseases such as atopic eczema. In the absence of localised skin disease or skin signs, patients should be fully investigated to exclude an underlying cause.

Causes of generalised pruritus

- **Obstructive liver disease**
- **Haematological**
  - Iron-deficiency anaemia
  - Polycythaemia
- **Endocrine**
  - Hyperthyroidism
  - Hypothyroidism
  - Diabetes mellitus
- **Chronic renal failure**
- **Malignancy**
  - Internal malignancies
  - Lymphoma
- **Drugs**
  - Morphine
- **Other**
  - Pregnancy
  - Senility

3.7 CUTANEOUS MARKERS OF INTERNAL MALIGNANCY

There are numerous skin changes associated with internal malignancy. These can be either genetically determined syndromes with cutaneous manifestations, where there is a recognised predisposition to internal malignancy, or paraneoplastic syndromes, where the cutaneous signs are significantly associated with malignancy of various organs.

3.7.1 Genetically determined syndromes with skin manifestations

Most of these diseases have an autosomal dominant inheritance.

- **Gardner syndrome**: epidermal cysts, lipomas and fibromas are associated with colonic carcinoma
- **Peutz–Jeghers syndrome**: mucocutaneous pigmentation is associated with mainly gastrointestinal malignancy
- **Howel–Evans syndrome**: tylosis (palmoplantar keratoderma) has been reported with oesophageal carcinoma
- **Torre–Muir syndrome**: sebaceous tumours are associated with gastrointestinal malignancy
- **Cowden disease**: tricholemmomas (facial nodules) and warty hyperplasia of the mucosal surface is associated with breast and thyroid carcinoma
- **Neurofibromatosis**: the presence of six or more café-au-lait macules, axillary freckling and neurofibromas is associated with malignant schwannomas and astrocytomas
- **Tuberous sclerosis**: angiofibromas, together with periungual fibromas, shagreen patches and ash-leaf macules are associated with sarcomas and rhabdomyomas
- **Multiple endocrine neoplasia type 2B**: mucosal neuromas are associated with medullary thyroid carcinoma and phaeochromocytoma
- **Gorlin syndrome (basal cell naevus syndrome)**: multiple basal cell carcinomas associated with medulloblastoma, meningioma, astrocytoma and ovarian tumours
- **Von Hippel–Lindau syndrome**: café-au-lait macules and haemangiomas are associated with vascular tumours of the central nervous system, phaeochromocytoma, and renal and pancreatic carcinoma
- **Sturge–Weber syndrome**: port-wine stain associated with ipsilateral vascular meningeal malformation and epilepsy
- **Wiskott–Aldrich syndrome**: a sex-linked recessive disease characterised by eczema, immunodeficiency and an increased risk of lymphoma and leukaemia
- **Chédiak–Higashi syndrome**: a fatal autosomal recessive disease with recurrent bacterial infections and widespread infiltration with lymphocytes suggesting a lymphoma
- **Ataxia telangiectasia**: an autosomal recessive disease characterised by mucocutaneous telangiectasia and an increased risk of lymphoma and leukaemia
- **Xeroderma pigmentosum**: an autosomal recessive group of conditions characterised by multiple melanomas and non-melanoma skin malignancies which start developing from childhood in sun-exposed skin.

3.7.2 Skin signs as paraneoplastic features

Dermatological features can be seen in all types of malignant disease but some are more common in certain types of neoplasia.

Specific dermatological features and the common types of malignancy with which they are associated

- **Acanthosis nigricans**: gastrointestinal adenocarcinoma
- **Acanthosis palmaris (tripe palms)**: bronchial carcinoma
- **Acanthosis palmaris with nigricans**: gastrointestinal adenocarcinoma
- **Generalised pruritus**: lymphoma
- **Dermatomyositis (in adults)**: bronchial, breast and ovarian tumours
- **Erythema gyratum repens**: bronchial carcinoma
- **Acquired hypertrichosis lanuginosa**: gastrointestinal and bronchial tumours
- **Necrolytic migratory erythema**: glucagonoma
- **Migratory thrombophlebitis**: pancreatic carcinoma
- **Acquired ichthyosis**: lymphoma
- **Pyoderma gangrenosum**: myeloproliferative tumours
- **Erythroderma**: lymphoma and leukaemia
- **Clubbing**: bronchial carcinoma
- **Herpes zoster**: myeloproliferative tumours.

Causes of acanthosis nigricans

- Internal malignancy
- Acromegaly
- Cushing syndrome
- Obesity
- Insulin-resistant diabetes mellitus
- Oral contraceptive pill
- Familial
- Nicotinic acid
- Hypothyroidism

3.8 DISORDERS OF PIGMENTATION

The major colour determinant of the skin is melanin. This is produced by melanocytes, which are found in the basal layer of the epidermis. Pigmentary disorders usually present with either hypo- or hyperpigmentation.

Causes of hypopigmentation

- **Genetic**
  - Albinism

- Phenylketonuria
- Tuberous sclerosis

- **Chemical**
  - Chloroquine
- **Infections**
  - Pityriasis versicolor
- **Endocrine**
  - Hypopituitarism
- **Autoimmune**
  - Vitiligo
- **Post-inflammatory**
  - Eczema
  - Psoriasis
  - Lupus erythematosus

Causes of hyperpigmentation

- **Genetic**
  - Peutz–Jeghers syndrome
  - Xeroderma pigmentosum
  - Albright syndrome
- **Metabolic**
  - Cirrhosis
  - Haemochromatosis
  - Porphyria
  - Renal failure
- **Drugs**
  - Oral contraceptive pill
  - Minocycline
  - Amiodarone
- **Endocrine**
  - Addison’s disease
  - Cushing syndrome
  - Nelson syndrome
  - Pregnancy
- **Nutritional**
  - Malabsorption

- Carcinomatosis
- Kwashiorkor
- Pellagra

- **Post-inflammatory**
  - Lichen planus
  - Eczema
  - Secondary syphilis
  - Cutaneous amyloid

3.9 DRUG ERUPTIONS

The incidence of drug eruptions is approximately 2%.

The most common drug eruptions are:

- **Toxic erythema**: the most common type of eruption. It is usually characterised by a morbilliform or maculopapular eruption, which may become confluent. Causes include antibiotics (including sulfonamides), carbamazepine, allopurinol, gold, thiazides and anti-tuberculous drugs
- **Fixed drug eruption**: this occurs in a localised site each time the drug is administered (see below)
- **Toxic epidermal necrolysis**: a life-threatening eruption due to extensive skin loss. This can be associated with allopurinol, sulfonamides, penicillin, carbamazepine, phenytoin, nonsteroidal anti-inflammatory drugs (NSAIDs), gold, salicylates and barbiturates
- **Urticaria**: see below
- **Photosensitivity** (see Chapter 2, Clinical pharmacology, toxicology and poisoning)
- **Lupus erythematosus-like syndrome**: a number of drugs have been implicated as causes of this relatively rare disorder (see Chapter 2, Clinical pharmacology, toxicology and poisoning)
- **Vasculitis**: (see Chapter 2, Clinical pharmacology, toxicology and poisoning)
- **Erythema multiforme**: this is associated with penicillins, sulfonamides, phenytoin, carbamazepine, angiotensin-converting enzyme (ACE) inhibitors, NSAIDs, gold, barbiturates, thiazides
- **Contact dermatitis**
- **Hyperpigmentation** (see above): associated with amiodarone, minocycline, bleomycin, chlorpromazine, antimalarials.

Drugs that cause a fixed drug eruption

- Tetracyclines
- Barbiturates

- Dapsone
- Chlordiazepoxide
- Sulfonamides
- Benzodiazepines
- NSAIDs
- Quinine
- Paracetamol

Diseases aggravated by sunlight

- Lupus erythematosus
- Dermatomyositis
- Xeroderma pigmentosum
- Herpes simplex infection
- Rosacea
- Porphyrias (except acute intermittent)
- Pellagra
- Carcinoid syndrome

3.10 URTICARIA

Urticaria is the term for a group of conditions that involve the onset of itchy weals and may be accompanied by angio-oedema.

Acute urticaria is common and usually lasts 24–48 hours.

Chronic urticaria lasts for more than 6 weeks, it has a prevalence of 1%. It occurs as chronic spontaneous urticaria (CSU) or is inducible. This group contains physical, cholinergic, contact and aquagenic types.

Drugs that cause urticaria

- Penicillin
- Salicylates
- Quinidine
- Cephalosporin
- ACE inhibitors
- Hydralazine
- Opiates

Management of urticaria

Acute: a history may identify a trigger; diagnostic tests are not usually necessary because there is spontaneous remission.

CSU: stop any potential triggering drugs, eg NSAIDs; screen for underlying inflammatory disease (ESR/CRP and FBC).

Treatment of CSU starts with non-sedating antihistamines, which may be increased to up to four times standard dosing, patients not responding may be treated with montelukast or ciclosporin. Omalizumab (anti-IgE) has recently been shown to be effective in CSU.

3.11 SKIN TUMOURS

3.11.1 Malignant melanoma

This has an incidence of around 10/100 000 per year but the rate is doubling every decade. The prognosis is related to tumour thickness. Early lesions are often curable by surgical excision. Melanoma causes the majority (75%) of deaths relating to skin cancer. Any changing mole (bleeding, increase in size, itching, etc) should be viewed suspiciously.

The different types of melanoma are:

- **Superficial spreading**: this is the most common. An irregularly pigmented macule or plaque which may have an irregular edge and colour variation
- **Nodular**: a pigmented nodule, often rapidly growing and aggressive
- **Lentigo maligna melanoma**: occurs in elderly people in a long-standing lentigo maligna (a slowly expanding, irregularly pigmented macule)
- **Acral lentiginous melanoma**: occurs on the palms, soles and nail beds. This is the most common type of melanoma in Chinese and Japanese people.

Management

- Initially lesions suspicious for melanoma are excised with a 2-mm margin
- A wide local excision is performed, the margin dependent on the Breslow thickness
- Sentinel lymph node biopsy is used for staging in many centres
- If lymph node involvement is confirmed, a block dissection may be performed
- Various chemotherapy agents for metastatic, unresectable disease are used. Vemurafenib (used for patients with a *BRAF* gene mutation) shows a survival benefit over dacarbazine. Ipilimumab, a monoclonal antibody that targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), shows the best survival response, with 22% patients alive at 3 years and 17% at 7 years.

3.11.2 Basal cell carcinoma

These are the most common skin cancers and are seen most commonly on the face of elderly or middle-aged patients. They only very rarely metastasise. Predisposing factors for basal cell carcinoma (BCC) are:

- Prolonged sun exposure (most common)
- Radiation treatment
- Chronic scarring
- Ingestion of arsenic (tonics)
- Basal cell naevus syndrome (Gorlin syndrome).

Recently, there have been advances in the understanding of the molecular genetics of sporadic BCC. Malfunctioning of the hedgehog-signalling pathway and gene mutations increase the risk of BCC development (the hedgehog pathway influences differentiation of various tissues during fetal development and continues to play a role in cell growth and differentiation in adults).

Basal cell carcinomas are classified as:

- Nodular/cystic
- Morphoeic
- Pigmented
- Superficial.

Management

- Surgical excision is the mainstay of treatment
- Mohs' micrographic surgery obtains complete margin control and has a high cure rate
- Topical immunotherapy with imiquimod may be used for small, low-risk BCCs.

Other treatments include radiotherapy, photodynamic therapy and cryotherapy.

Vismodegib is a new systemic agent that targets hedgehog-pathway signalling and is indicated for advanced or metastatic BCC.

3.11.3 Squamous cell carcinoma

There are several predisposing factors for squamous cell carcinoma (SCC):

- **Actinic damage**: squamous carcinomas can also develop in just sun-damaged skin (in the absence of actinic keratosis)
- **X-irradiation**
- **Chronic scarring or inflammation**
- **Smoking (particularly lesions of the lip)**
- **Arsenic ingestion**
- **Organic hydrocarbons**
- **Immunosuppression**

- **Human papillomavirus**.

Management of SCC

Surgical management is the treatment of choice. Other treatments include radiotherapy, Mohs' surgery and cryosurgery.

Keratoacanthoma

Keratoacanthoma is a rapidly growing tumour that arises in sun-damaged skin. It is now considered to be a low-grade SCC and often cannot be reliably distinguished from SCC. Treatment is usually surgical

3.11.4 Other skin tumours

CutaneousT-cell lymphoma

Cutaneous lymphoma may be T-cell type or B-cell type. Approximately two-thirds of primary cutaneous lymphoma are of T-cell origin. Mycosis fungoides is the most common form (72%). It has several clinical variants and tends to have an indolent course. It may progress over years, from patch stage to plaque stage, and then to tumour stage.

Sézary syndrome occurs in 5% of cases and patients have advanced disease with erythroderma, and nodal and blood involvement. Patients have a median survival of <5 years.

3.12 HAIR AND NAILS

3.12.1 Disorders of hair

The first signs of hair follicles appear in the region of the eyebrows, upper lip and chin at around 9 weeks' gestation. By 22 weeks the full complement of follicles is established. Hair abnormalities comprise either excessive hair growth or hair loss.

Excessive hair growth can be androgen-independent 'hypertrichosis' or androgen-dependent 'hirsutism'.

Causes of hypertrichosis

- **Congenital/hereditary**
  - Congenital hypertrichosis lanuginosa
  - Porphyrias
  - Epidermolysis bullosa
  - Hurler syndrome
- **Acquired**
  - Acquired hypertrichosis lanuginosa

- **Endocrine**
  - Hypothyroidism
  - Hyperthyroidism
- **Drugs**
  - Diazoxide
  - Minoxidil
  - Ciclosporin
  - Streptomycin
- **Other**
  - Malnutrition
  - Anorexia nervosa

Causes of hirsutism

- **Ovarian**
  - Polycystic ovary syndrome
  - Ovarian tumours
- **Androgen therapy**
- **Adrenal**
  - Congenital adrenal hyperplasia
  - Cushing syndrome
  - Prolactinoma

Loss of hair is called alopecia and can be scarring or non-scarring. Scarring alopecia is loss of hair with destruction of the hair follicles. Non-scarring alopecia is when the hair follicles are preserved. A good example of this is the 'exclamation mark' hair seen in alopecia areata.

Causes of scarring alopecia

- **Hereditary**
  - Ichthyosis
- **Bacterial**
  - Tuberculosis
  - Syphilis
- **Physical injury**
  - Burns
  - Radiotherapy
- **Fungal**

    - Kerion
- **Others**
    - Lichen planus
    - Lupus erythematosus
    - Morphoea
    - Sarcoidosis
    - Cicatricial pemphigoid

Causes of non-scarring alopecia

- **Male pattern/androgenic alopecia** (the most common in men and women)
- **Alopecia areata**
- **Endocrine**
    - Hypopituitary state
    - Hypothyroidism
    - Hyperthyroidism
    - Hypoparathyroidism
    - Pregnancy
- **Drugs**
    - Retinoids
    - Anticoagulants
    - Anti-mitotic agents
    - Oral contraceptive pill
    - Carbimazole
    - Thiouracil
    - Lithium
- **Iron deficiency**
- **Chronic illness**

Alopecia areata is associated with nail dystrophy, cataracts, vitiligo, autoimmune thyroid disease, pernicious anaemia and Addison's disease.

3.12.2 Disorders of nails

Nails are derived from keratin. This is a protein complex and gives the nail its hard property. The nail can be affected in a variety of skin and systemic disorders.

Causes of nail changes associated with skin disorders

- **Psoriasis**: nail changes include onycholysis, nail pitting, hyperkeratosis, pustule and occasional loss of nail
- **Fungal**: signs include discoloration, onycholysis and thickening of the nail
- **Bacterial**: usually due to staphylococcal infections. Pseudomonas infections give a green discoloration to the nail
- **Lichen planus**: nail changes occur in 10% of cases, with thinning of the nail plate and longitudinal linear depressions. Occasionally there is destruction of the nail (pterygium)
- **Alopecia areata**: pitting, thickening and ridging of the nail (sandpaper nail) are seen
- **Dermatitis**: coarse pits, cross-ridging and onycholysis may be seen.

Causes of nail changes associated with systemic disease

- **Koilonychia**: the nails are thin, brittle and concave. There is an association with iron-deficiency anaemia
- **Yellow nail syndrome**: the nails are yellow and excessively curved. Associations include recurrent pleural effusions, chronic bronchitis, bronchiectasis, nephrotic syndrome and hypothyroidism
- **Nail–patella syndrome**: loss of ulnar half of the nails, usually the thumbnail, is seen. Associations include small patellae, bony spines over posterior iliac crests, renal abnormalities, over extension of joints and laxity of the skin
- **Beau's lines**: these are transverse depressions in the nail due to temporary arrest in growth. They usually occur after a period of illness or infection
- **Half-and-half nails**: the proximal nail bed is white and distal, pink or brown. They are associated with chronic renal failure and rheumatoid arthritis.

Causes of onycholysis (lifting of the nail plate from the nail bed)

- **Idiopathic**: excessive manicuring or wetting
- **Dermatological disease**: psoriasis, fungal infection, dermatitis
- **Systemic disease**: impaired peripheral circulation, hypothyroidism, hyperthyroidism
- **Trauma**.

Chapter 4
Endocrinology

CONTENTS

Endocrinology

4.1 HORMONE ACTION

There are three main types of hormone:

- amine
- steroid
- peptide.

Knowing which category a particular hormone fits into makes it possible to guess much of its physiology. Thyroxine is an exception to this, as shown below.

4.1.1 Types of hormone

- Amine: catecholamines, serotonin, thyroxine
- Steroid: cortisol, aldosterone, androgens, oestrogens, progestogens and vitamin D
- Peptide: everything else! (made up of a series of amino acids).

Thyroxine is chemically an amine but it acts like a steroid. Vitamin D has the structure of a steroid hormone and it acts like one.

Amines/peptides

- Short half-life (minutes)
- Secretion may be pulsatile
- Act on a cell surface receptor
- Often act via a second messenger

Steroids

- Longer biological half-life (hours)
- Act on an intracellular receptor
- Act on DNA to alter gene expression

This information can be used to predict hormone action, eg aldosterone is a steroid hormone so it must have a biological half-life of several hours, bind to an intracellular receptor and affect gene transcription. Glucagon is not a steroid or an amine so it must be a polypeptide hormone, which has a short circulation half-life, acts via a cell surface receptor and probably utilises a second messenger (adenosine cyclic monophosphate, or cAMP, in fact).

4.1.2 Hormones that act at the cell surface

Peptide and amine hormones act at the cell surface via specific membrane receptors. The signal is transmitted intracellularly by one of three mechanisms:

- Via cAMP
- Via a rise in intracellular calcium
- Via receptor tyrosine kinases.

If in doubt, assume the action of a peptide or amine hormone (excluding thyroxine) is via cAMP, unless it is insulin or has the word 'growth' in its name, in which case it is likely to act via a receptor tyrosine kinase (Table 4.1).

Cyclic AMP and G-proteins

Hormone receptors linked to cAMP (eg thyroid-stimulating hormone [TSH] receptor) typically have seven transmembrane domains. The receptor does not directly generate cAMP but acts via separate 'G-proteins' on the cell surface which, in turn, interact with the cAMP-generating enzyme, adenylyl cyclase, on the cell surface. (See Figure 14.4 in Chapter 14, Molecular Medicine.)

Hormones that raise the level of cAMP intracellularly (all hormones in this category except somatostatin) act via a stimulatory G-protein, 'Gs'. Hormones that lower the level of cAMP (somatostatin) act via an inhibitory G-protein, 'G_i'.

Table 4.1 Mechanisms of hormone action

Via cAMP	Via Ca^{2+}	Via receptor tyrosine kinases
Adrenaline (β receptors)	GnRH	Insulin
All pituitary hormones except GH, PRL	TRH	GH, PRL
Glucagon	Adrenaline (α receptors)	'Growth factors': IGF-1, EGF
Somatostatin		

cAMP, adenosine cyclic monophosphate; EGF, epidermal growth factor; GH, growth hormone; GnRH, gonadotrophin-releasing hormone; IGF-1, insulin-like growth factor 1; PRL, prolactin; TRH, thyrotrophin-releasing hormone.

G-proteins are important in endocrinology because mutations in Gs have been found to be associated with certain diseases:

Acromegaly: 40% of patients with acromegaly have an activating somatic mutation of Gs in their

- pituitary tumour. As a result, the cells are always 'switched on' and continuously make growth hormone (GH), resulting in acromegaly

McCune–Albright syndrome: an activating mutation of Gs early in embryonic development causes hyperfunction of one or more endocrine glands with the following sequelae: precocious puberty (gonad hyperfunction), acromegaly (GH hypersecretion), Cushing syndrome (adrenal
- gland hyperfunction), thyrotoxicosis or hyperparathyroidism. The syndrome is associated with café-au-lait spots and polyostotic fibrous dysplasia. As the mutation occurs after the zygote stage, affected individuals are a mosaic and different patterns of tissue involvement may be seen between individuals

Pseudohypoparathyroidism: inactivating germline mutations in Gs result in pseudohypoparathyroidism type 1A if maternally inherited, with dysmorphic features (including short fourth or fifth metacarpal) and resistance to a variety of hormones that act via cAMP
- (including parathyroid hormone, TSH and gonadotrophins). Spontaneously occurring or paternally inherited mutations cause the dysmorphic features alone (pseudopseudohypoparathyroidism). The dysmorphic bone features are sometimes referred to as 'Albright's hereditary osteodystrophy' and can be present in either the maternally or the paternally inherited form.

Intracellular Ca^{2+}

Some hormones release intracellular Ca^{2+} as a second messenger (see Table 4.1 for examples). The receptors for these hormones activate different G-proteins (eg Gq), which in turn activate the cytoplasmic enzyme phospholipase C (PLC). PLC releases the small molecule inositol-1,4,5-triphosphate (IP3) from membrane phospholipids. IP3 in turn binds to the IP3-sensitive receptor on the endoplasmic reticulum within the cell, causing Ca^{2+} to be released from stores in the endoplasmic reticulum into the cytoplasm. The Ca^{2+} subsequently affects cell metabolism by binding to the protein calmodulin.

Receptor tyrosine kinases

The insulin, GH, prolactin and growth factor receptors do not use second messengers. The receptors themselves can act as enzymes that phosphorylate ('kinase activity') other proteins when hormone is bound at the cell surface. This is followed by a cascade of proteins phosphorylating other proteins until gene transcription in the nucleus is modulated.

4.1.3 Hormones that act intracellularly

Steroids, vitamin D and thyroxine are sufficiently lipid-soluble that they do not need cell surface receptors but can diffuse directly through the cell membrane. They then bind to receptors in the cytoplasm, which results in shedding of heat shock proteins that protect the empty receptor. The hormone–receptor complex migrates into the nucleus where it alters the transcription of a large number of genes (see Figure 14.6 in Chapter 14, Molecular Medicine).

4.1.4 Hormone resistance syndromes

The following are conditions of hormone resistance with the site of the defect shown.

- **Receptor defect (hormone involved)**
  - Laron's dwarfism (GH)
  - Leprechaunism (Donahue's syndrome, Rabson–Mendenhall syndrome [insulin])
  - Nephrogenic diabetes insipidus (antidiuretic hormone [ADH])
  - Androgen resistance (testicular feminisation syndrome (testosterone))
  - Vitamin-D-dependent rickets type 2 – hereditary vitamin D resistance rickets (vitamin D)[a]
- **Second messenger defect**
  - Pseudohypoparathyroidism
- **Defect unknown**
  - Type 2 diabetes

[a]Vitamin D-dependent rickets type 1 is due to a failure of 1-hydroxylation of vitamin D.

4.2 SPECIFIC HORMONE PHYSIOLOGY

4.2.1 Hormones in illness

During illness/stress, the body closes all unnecessary systems down 'from the top', eg the thyroid axis closes down by a fall in thyrotrophin-releasing hormone (TRH), TSH and L-thyroxine/L-triiodothyronine (T4/T3). It is orchestrated by the hypothalamus, not by the end-organs. Hormones involved in the stress response may rise.

Hormones that fall

- TSH, T4/T3[a]
- LH, FSH
- Testosterone, oestrogen
- Insulin (starvation)

May rise (stress hormones)

- GH (though IGF-1 falls)
- ACTH, glucocorticoids
- Adrenaline
- Glucagon (starvation)

- Prolactin

[a]In this case conversion of T4 to T3 is inhibited so T3 falls more than T4
ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinising hormone; T3, L-triiodothyronine; T4, L-thyroxine; TSH, thyroid-stimulating hormone.

In starvation alone, without illness, all hormones fall except glucagon. In anorexia nervosa there is also stress: all hormones fall except glucagon, GH and glucocorticoids.

4.2.2 Hormone changes in obesity

In the absence of other diseases (eg type 2 diabetes), which might develop in obese patients, the following changes are seen in obesity:

- Hyperinsulinaemia
- Increased cortisol turnover but not hypercortisolism
- Increased androgen levels in women
- Reduced GH
- Conversion of androgens to oestrogens
- A proatherogenic lipid profile develops (low high-density lipoprotein [HDL], high low-density lipoprotein [LDL] and triglyceride).

Leptin, adipokines and other hormones involved with appetite and weight

Leptin was identified as a product of the '*ob*' gene in 1994. *Ob/ob* mice make no leptin, owing to a homozygous *ob* gene mutation, and are grossly obese.

- Leptin is a polypeptide hormone, released from fat cells, that acts on specific receptors in the hypothalamus to reduce appetite
- Circulating leptin levels are directly proportional to fat mass, and so they tell the brain how fat an individual is
- Leptin appears to have stimulatory effects on metabolic rate and levels fall in starvation (appropriate change for weight homeostasis)
- Adequate leptin levels are required for the onset of puberty
- Persistently obese individuals appear relatively resistant to leptin
- Congenital leptin deficiency presents in childhood with gross obesity and hyperphagia. This changes dramatically with treatment of exogenous leptin.

Several other hormones have recently been shown to affect appetite and weight:

- **Ghrelin**: this was first identified as a GH-releasing hormone. It is released from the stomach when subjects are fasting or in conditions of negative energy balance and triggers hunger. It stimulates gastric contraction and hence gastric emptying. Ghrelin levels fall after gastric bypass surgery, which may help weight loss by reducing appetite

  Peptide YY (a member of the neuropeptide Y family): released from L cells in the small and

- large bowel. Levels rise after meals and reduce appetite. This may be the main regulator of dayto-day appetite
- **Glucagon-like peptide-1** (GLP-1): also released from L cells of the intestine after meals and powerfully promotes insulin secretion in response to raised glucose ('incretin effect'), as well as possibly reducing appetite. Inactivated by the enzyme dipeptidylpeptidase-4 (DPP-4). Derived from tissue-specific cleavage of proglucagon
- **Oxyntomodulin**: also released from L cells and derived from proglucagon; appears to act on the same receptor as GLP-1, but with less incretin, and has more of an appetite-suppressing effect
- **Neuropeptide Y** (NPY), from the hypothalamus itself, and Agouti-related protein (AgRP) increase appetite, whereasα-melanocyte-stimulating hormone (α-MSH, a melanocortin) reduces appetite.

In addition to leptin, a number of other hormones have recently been identified as being released from fat cells. These 'adipokines' include adiponectin, which reduces insulin resistance, and resistin and acylation-stimulating protein (ASP), which both increase insulin resistance. Visfatin (also known as nicotinamide phosphoribosyltransferase [NAMPT] and pre-B-cell colony-enhancing factor) is released predominantly from visceral fat and has insulin-like actions. The role of these adipokines in the association between obesity and insulin resistance remains uncertain.

4.2.3 Hormones in pregnancy

As a general rule, most hormone levels rise in pregnancy. Insulin resistance develops, causing a rise in circulating insulin levels. Insulin requirements are highest in the last trimester but fall slightly in the last 4 weeks of pregnancy.

Other key features of hormone metabolism in pregnancy are as follows:

- **Prolactin** levels rise steadily throughout pregnancy and, in combination with oestrogen, prepare the breast for lactation. Post-partum surges of prolactin and oxytocin are generated by the nipple stimulation of breastfeeding. However, after several weeks, prolactin levels fall almost to normal, even if breastfeeding continues
- **LH/FSH** from the pituitary are no longer necessary after conception for continued pregnancy (although the pituitary may double in size) and the placenta takes over
- **Thyroid axis**: thyroid-binding globulin (TBG) levels rise in the first trimester, causing a rise in total T4 and total T3. However, human chorionic gonadotrophin (hCG) from the placenta shares its α subunit with TSH, and very high levels in the first trimester can cause true mild thyrotoxicosis (not just a binding protein rise), especially associated with hyperemesis gravidarum. Note that T4 and T3 do not cross the placenta very efficiently, but sufficient T4 does cross to prevent a fetus with congenital hypothyroidism becoming hypothyroid until after birth.

4.2.4 Investigations in endocrinology

The plasma level of almost all hormones varies through the day (because of pulsatile secretion, environmental stress or circadian rhythms) and is influenced by the prevailing values of the substrates that they control. This makes it hard to define a 'normal range', eg insulin values depend on the

glucose level, and GH levels depend on whether a pulse of GH has just been released or the blood sample is taken in the trough between pulses.

Dynamic testing is therefore frequently used, ie suppression or stimulation tests. The principle is, 'If you think a hormone level may be high, suppress it; if you think it may be low, stimulate it'.

- **Suppression tests** are used to test for hormone EXCESS, eg dexamethasone suppression for Cushing syndrome, glucose tolerance for GH in acromegaly
- **Stimulation tests** are used to test for hormone DEFICIENCY, eg Synacthen tests for hypoadrenalism, insulin-induced hypoglycaemia for GH deficiency and/or hypoadrenalism.

4.2.5 Growth hormone

This is secreted in pulses lasting 30–45 minutes separated by periods when secretion is undetectable. The majority of GH pulses occur at night ('children grow at night'). In response to GH pulses, the liver makes insulin-like growth factor 1 (IGF-1, previously called somatomedin C), the plasma level of which is constant and which mediates almost all the actions of GH, ie GH does not act directly. The effective levels of IGF-1 are influenced by changes in the level of its six binding proteins (IGF-BP 1–6).

4.2.6 Prolactin

Prolactin causes galactorrhoea but not gynaecomastia (oestrogen does this). Raised prolactin levels are essentially the only cause of galactorrhoea, although occasionally prolactin levels in the normal range can cause milk production in a sensitised breast. Raised prolactin levels also 'shut down' the gonadal axis 'from the top' (hypothalamic level), resulting in low GnRH, LH and oestrogen/testosterone levels. Surprisingly, prolactin is a stress hormone and can rise in various levels of stress, from anxiety about venepuncture to an epileptic fit.

Prolactin release from the pituitary is under negative control by dopamine from the hypothalamus. Oestrogens (the pill, pregnancy) and nipple stimulation raise prolactin.

Prolactin is raised by

- Phenothiazines, haloperidol (not tricyclics)
- Antiemetics (eg metoclopramide)
- Damage to hypothalamus (eg radiation)
- Pregnancy
- Nipple stimulation
- Damage to pituitary stalk (eg pressure from a pituitary tumour)
- Oestrogens
- Polycystic ovary syndrome

Prolactin is suppressed by

- Dopamine agonist drugs (eg bromocriptine, cabergoline)

Gynaecomastia

This is due to a decreased androgen:oestrogen ratio in men. Gynaecomastia is unrelated to galactorrhoea (which is always due to prolactin). Breast enlargement is not necessary to make milk.

Causes of gynaecomastia:

- Pubertal (normal)
- Obesity – not true gynaecomastia
- Hypogonadism (eg Klinefelter's syndrome, testicular failure)
- Cirrhosis, alcohol
- Hyperthyroidism
- Drugs: including spironolactone, digoxin, oestrogens, cimetidine, anabolic steroids, marijuana
- Tumours, including adrenal or testicular, making oestrogen; lung, pancreatic, gastric, making hCG; hepatomas converting androgens to oestrogens.

4.2.7 Adrenal steroids

These act intracellularly to alter the transcription of DNA to mRNA (see Section 4.1, Hormone action). Surprisingly, the mineralocorticoid (aldosterone) and glucocorticoid receptors have an equal affinity for cortisol. However, the cellular enzyme 11-β-hydroxysteroid dehydrogenase 'protects' the mineralocorticoid receptor by chemically modifying any cortisol that comes near the receptor to an inactive form, while having no effect on aldosterone itself. Inactivating mutations of this enzyme, or inhibition of it by liquorice, causes 'apparent mineralocorticoid excess', because cortisol (which circulates at much higher concentrations than aldosterone) is able to stimulate the mineralocorticoid receptor. The effects of adrenal steroids and their duration of action are given in Table 4.2.

Table 4.2 Adrenal steroids

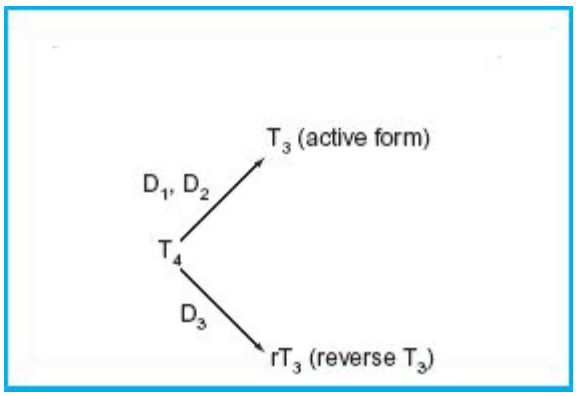
	Relative glucocorticoid effect	Relative mineralocorticoid effect	Duration of action
Cortisol = hydrocortisone	1	+	Short
Prednisolone	4	±	Medium
Dexamethasone	30	−	Long
Fludrocortisone	10	+++	

4.2.8 Thyroid hormone metabolism

More than 95% of thyroid hormones are bound to plasma proteins in the circulation, predominantly TBG and thyroid-binding prealbumin (TBPA). T4 (four iodine atoms per molecule) has a half-life of 7 days (so, if a patient is in a confused state, it is possible to administer his or her total weekly dose of thyroxine once a week). It is converted partly in the thyroid and partly in the circulation to T3 (three iodine atoms per molecule), which is the active form and has a half-life of 1 day.

There are three deiodinase enzymes that act on thyroid hormones (D1–D3). D1 and D2 promote the generation of active hormone (T3) by converting T4 to T3 (Figure 4.1). D3 opposes this by promoting conversion of T4 to reverse T3 (rT3) and destroying T3 by conversion to T2 (inactive). The D1 and D2 enzymes are inhibited by illness, propranolol, propylthiouracil, amiodarone and ipodate (formerly used as X-ray contrast medium for study of gallbladder disease). This reduces the level of active hormone, T3, with little change or a rise in T4. Reverse T3 levels rise (T4 spontaneously converts to rT3 if the monodeiodinase is not available), but rT3 is not detected in laboratory tests of T3 levels.

Figure 4.1 Metabolism of thyroid hormones, D1–D3, different deiodinase enzymes that act on thyroid hormone.



It is said that you should ‘never measure thyroid function tests on the intensive care unit because you will not be able to interpret them’. In illness, TSH and free T3 levels fall (‘sick euthyroidism’). The only interpretable finding in sick patients is a raised free T3 – this would almost definitely indicate thyrotoxicosis.

4.2.9 Renin–angiotensin–aldosterone

Aldosterone secretion is controlled almost completely by the renin–angiotensin system, not by ACTH. The initial letters of the zones of the adrenal cortex from outside inwards spell ‘GFR’, similar to glomerular filtration rate: glomerularis, fasciculata, reticularis. Aldosterone is the ‘outsider hormone’ and is made on the ‘outside’ (zona glomerulosa).

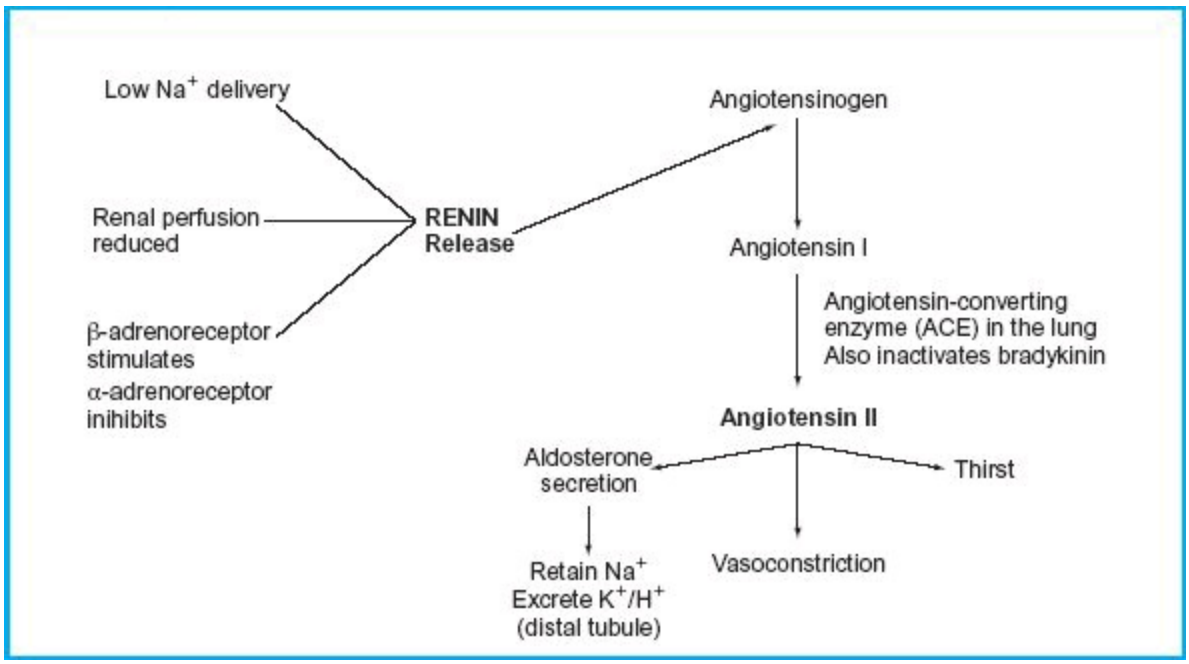
Renin is released from the JGA (juxtaglomerular apparatus) of the kidney in response to low Na^+ delivery or reduced renal perfusion. Renin is an enzyme that converts angiotensinogen to angiotensin I (10 amino acids). ACE (angiotensin-converting enzyme) in the lung converts angiotensin I to angiotensin II, which is the active form. ACE also breaks down bradykinin: ACE inhibitors (eg captopril) are believed to cause cough as a result of a build-up of bradykinin in the lung. The renin–angiotensin system is designed to restore circulating volume. It is therefore activated by hypovolaemia (Figure 4.2) and its end product, angiotensin II, has three actions that restore volume:

- Releasing aldosterone from the adrenal (retains Na^+, excretes K^+ in the distal tubule)
- Vasoconstriction (powerful)
- Induction of thirst (powerful).

4.2.10 Calcium, PTH and vitamin D

(See also Chapter 13, Metabolic Diseases.)

Figure 4.2 The renin–angiotensin system.



Plasma calcium is tightly regulated by parathyroid hormone (PTH) and vitamin D, acting on the kidney (PTH), bone (PTH) and gut (vitamin D).

PTH controls Ca^{2+} levels minute to minute by mobilising Ca^{2+} from bone and inhibiting Ca^{2+} excretion from the kidney. Vitamin D has a more long-term role, predominantly by promoting Ca^{2+} absorption from the gut. Its actions on the kidney and bone are of lesser importance. Ca^{2+} levels are sensed by a specific calcium-sensing receptor on the parathyroid glands. Mutations that reduce the activity of this receptor result in a resetting of calcium and PTH to higher levels (familial hypocalciuric hypercalcaemia, FHH). Activating mutations can also occur, which result in a picture almost indistinguishable from hypoparathyroidism, with a low Ca^{2+} (autosomal dominant hypocalcaemia with hypercalciuria). It is important to identify these conditions because they run a benign course and only attempted treatment causes problems (eg raising the serum Ca^{2+} in autosomal dominant hypocalcaemia will predispose to renal stone formation).

Precursor vitamin D, obtained from the diet or synthesised by the action of sunlight on the skin, requires activation by two steps:

- 25-hydroxylation in the liver
- 1-hydroxylation in the kidney.

PTH can promote 1-hydroxylation of vitamin D in the kidney, ie it can activate vitamin D, thereby

indirectly stimulating Ca^{2+} absorption from the gut.

Calcitonin (from the C cells of the thyroid) behaves almost exactly as a counter-hormone to PTH (secreted by high Ca^{2+}, acts to lower serum Ca^{2+} by inhibiting Ca^{2+} release from bone), but its physiological importance is in doubt (thyroidectomy does not affect Ca^{2+} levels if the parathyroid glands are undisturbed).

4.2.11 Atrial natriuretic peptide

Atrial natriuretic peptide (ANP) physiology can be predicted from its name:

- **Atrial**: it is synthesised by the myocytes of the right atrium and ventricle
- **Natriuretic**: it causes a natriuresis (urinary excretion of sodium). It thereby reduces circulating volume (opposite of renin–angiotensin). As you would predict, therefore, it is secreted in conditions of hypervolaemia – via stretch of the right atrial and ventricular walls. It also antagonises the other actions of angiotensin II by causing vasodilatation and reduced thirst/salt craving
- **Peptide**: it is a peptide hormone (which acts via cAMP).

There are two other natriuretic peptides, B-type and C-type natriuretic peptides (BNP and CNP). BNP is similar to ANP, and is produced from the heart, especially in heart failure. Serum levels are more stable than those of ANP, and BNP is proving to be a useful test of heart failure. CNP is produced by the vascular endothelium rather than cardiac myocytes.

4.3 THE PITUITARY GLAND

4.3.1 Anatomy

The anatomical relations of the pituitary (Figure 4.3) are important because enlarging pituitary tumours may press on surrounding structures.

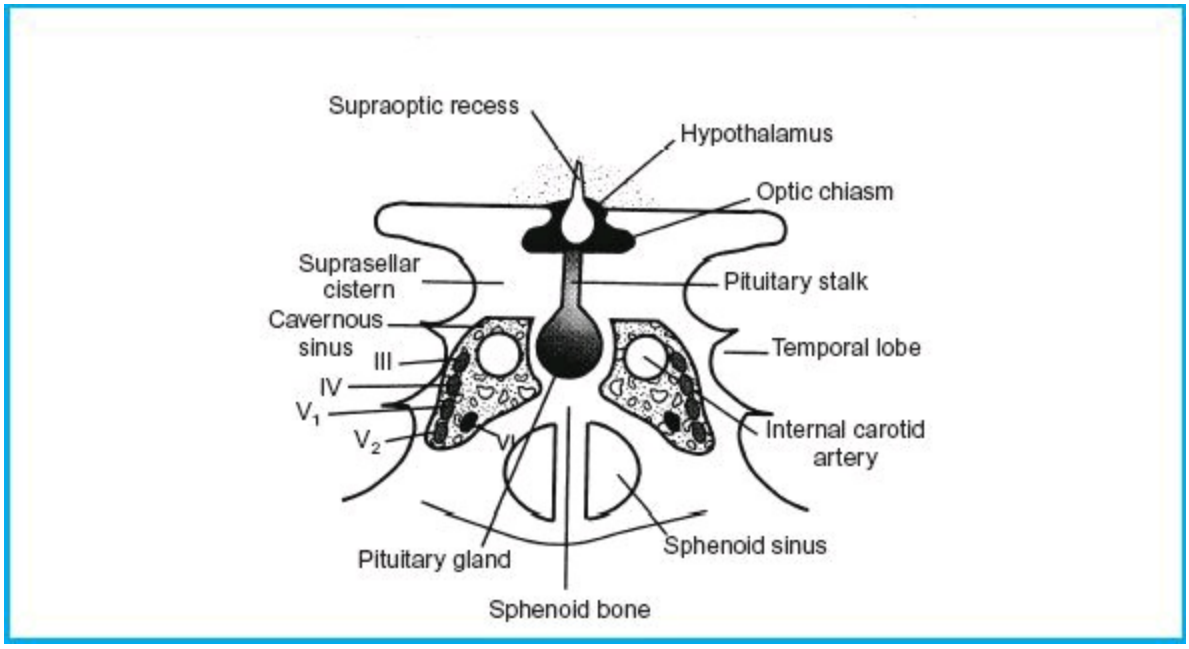
- Above: optic chiasma (classically causing bitemporal hemianopia if compressed, but any visual field defect may occur), pituitary stalk, hypothalamus, temporal lobes
- Below: sphenoid sinus (in front and below to allow trans-sphenoidal surgery), nasopharynx
- Lateral: cavernous sinus, internal carotid arteries, III, IV, V, and V and VI cranial nerves.

Expanding pituitary tumours may also compromise remaining anterior pituitary function, but rarely affect posterior pituitary hormones.

4.3.2 Pituitary tumours

A microadenoma is a pituitary tumour <**10 mm** in size. The size and frequency of pituitary tumours are related.

Figure 4.3 Schematic sagittal section through the pituitary to show its relation to surrounding structures.



Pituitary tumours

- Large – non-secreting (typically chromophobe): 50% of all tumours
- Large – prolactinomas in men: 25% of all tumours
- Medium – acromegaly (typically 'acidophil', 70% are about 1 cm): 12% of all tumours
- Small – Cushing's disease (often undetectable on CT/MRI, typically basophil): 5–10% of all tumours
- Small – TSH secreting: 1% (very rare)

The most common tumours are small, nonfunctioning microadenomas, which have been reported to occur in up to 20% of people *post mortem*.

Prolactinomas are the most common functioning pituitary tumours. Microprolactinomas are more frequent than macroprolactinomas.

True Cushing's disease is used to describe pituitary-dependent Cushing syndrome. This is caused by excessive ACTH production from the pituitary gland (usually by a microadenoma). They are in themselves rare.

For further discussion about Cushing syndrome diagnosis and management, please see Section 4.6.1.

Excessive secretion of GH from the pituitary gland in adults is termed 'acromegaly'. There is a preponderance to macroadenomas with blunting of the normal pulsatile GH secretion.

Pituitary apoplexy is sudden enlargement of the pituitary by haemorrhage into a tumour, typically causing the combination of headache, neck stiffness and sudden blindness associated with cardiovascular collapse due to hypopituitarism. Treatment is with steroid replacement and urgent surgery for visual loss (to decompress optic chiasma). In pituitary failure the only two hormones that must be replaced for survival are T4 and hydrocortisone. It is important to ensure that the patient is adequately replaced with glucocorticoids before starting replacement of T4, because levothyroxine increases glucocorticoid clearance.

Craniopharyngiomas are benign tumours that arise from remnants of Rathke's pouch. Two-thirds arise in the hypothalamus itself (suprasellar) and a third in the sella. They are usually cystic, frequently calcify, often recur after aspiration and, although they represent an embryonic remnant, they not infrequently present in adulthood.

4.3.3 Diabetes insipidus

ADH (also called vasopressin or arginine–vasopressin, AVP) is synthesised in the hypothalamus and transported to the posterior pituitary, along with oxytocin, for storage and release. Diabetes insipidus (DI) is caused either by a failure to secrete vasopressin from the posterior pituitary (central or cranial DI) or resistance to the action of vasopressin in the kidney (nephrogenic DI). To cause cranial DI, the hypothalamic nuclei (supraoptic and paraventricular) need to be damaged – it is not sufficient simply to compress the posterior pituitary, because vasopressin can be secreted directly from the hypothalamus itself. Pituitary tumours therefore rarely cause Dl.

Major causes of cranial diabetes insipidus

- Idiopathic
- Craniopharyngiomas
- Infiltrative processes of the hypothalamus (eg sarcoid, histiocytosis X)
- Trauma
- Pituitary surgery
- Lymphocytic hypophysitis
- Dysgerminomas

Causes of nephrogenic DI

Reduced action of ADH on the kidney can have several causes:

- **Primary**
  - Childhood onset: X-linked/dominant abnormality in tubular ADH receptor
- **Secondary (common)**
  - Hypercalcaemia
  - Hypokalaemia
  - Renal disease (particularly if it involves the medullary interstitium)
  - Lithium
  - Demeclocycline

Water deprivation test

A water deprivation test (Table 4.3) is used to identify the cause of polydipsia and/or polyuria. It is

worth confirming polyuria (urine output >3000 mL/24 h) before proceeding to a water deprivation test. Major metabolic causes should first be excluded (eg hyperglycaemia, hypercalcaemia, hypokalaemia, chronic renal failure). The patient is then deprived of water (from the night before if polyuria is not excessive) and hourly urine and plasma osmolality are measured until 3% of the body weight is lost. The patient is then given an injection of DDAVP (a synthetic analogue of ADH).

Interpretation of the water deprivation test

- **Primary polydipsia** (compulsive water drinking): in this condition the patient is not dehydrated but water overloaded in the resting state (Na+ <140 mmol/l). Chronic polydipsia in this condition can result in washout of the renal medullary-concentrating gradient so that, even if the patient does become dehydrated, with a rise in ADH, urine cannot be concentrated

Table 4.3 Interpretation of the water deprivation test

	Initial plasma osmolality	Final urine osmolality (mosmol/kg)	Urine osmolality post-DDAVP (mosmol/kg)	Final plasma ADH
Normal	Normal	>600	>600	High
Cranial Dl	High	<300	>600	Low
Nephrogenic Dl	High	<300	<300	High
Primary polydipsia	Low	300–400 (approx.)	400 (approx.)	Moderate
Partial cranial Dl	High	300–400	400–600	Relatively low

ADH, antidiuretic hormone; Dl, diabetes insipidus.

- **Cranial Dl**: in this condition there is failure to concentrate urine due to lack of ADH. This is observed with a high plasma osmolality and a relatively low urine osmolality throughout the test. Administration of DDAVP allows the kidneys to concentrate urine, thus raising the osmolality. If the thirst mechanism is intact, patients attempt to compensate by increasing their fluid intake orally. If, however, this mechanism is disrupted (patient is unconscious or has intracerebral lesion rendering the patient adipsic), there is a significant risk of becoming dehydrated very quickly
- **Partial cranial Dl**: in this condition there is weak ADH production. There is a similar effect on the renal medullary-concentrating gradient to that seen in primary polydipsia, and so the two conditions cannot be differentiated unless a post-hydration serum ADH level is obtained
- **Nephrogenic diabetes inspidus**: despite adequate circulating ADH, there is renal resistance to the action of ADH, resulting in an inability to concentrate urine. Therefore urine osmolality does not improve on administration of DDVAP during the water deprivation test. Treatment is by correcting the underlying cause and ensuring adequate hydration. Sometimes high doses of DDAVP can be used.

4.3.4 Acromegaly

The common features of acromegaly are well known (hand and foot enlargement, coarse facial features, overbite of the lower jaw, splaying of the teeth) but the following also occur (see box).

Features of acromegaly

- Diabetes
- Arthropathy – often pseudogout
- Sleep apnoea
- Carpal tunnel syndrome
- Multinodular goitre
- Increase in malignancies, especially colonic polyps
- Hypertension
- Twofold increase in death from cardiovascular disease
- Cardiomyopathy
- Left ventricular hypertrophy
- Enlarged testes
- Renal stones (hypercalciuria)
- Raised phosphate
- Raised prolactin, galactorrhoea, menstrual change
- Raised triglycerides

Acromegaly is almost always due to a GH-secreting pituitary tumour. Rarely, the condition is due to ectopic GH-releasing hormone (GHRH) secretion from a tumour (typically carcinoid) which stimulates the normal pituitary (no discrete tumour seen on MRI). Biochemical tests usually reveal a raised serum IGF-1 level (above the age- and gender-specific normal range). The diagnosis is confirmed by failure to suppress GH to a nadir of 0.4 ng/mL on an oral glucose tolerance test.

First-line treatment is trans-sphenoidal surgery to resect the pituitary tumour (or transcranial surgery if there is a large suprasellar extension of the tumour). The cure rate is very variable (40–80%), and is dependent on the extent of lateral and superior extension and the skill of the surgeon. Alternative therapies are dopamine agonists (bromocriptine, cabergoline, quinagolide, pergolide, which reduce GH secretion in approximately 20% of cases), somatostatin analogues (octreotide, which inhibit GH secretion), GH antagonists (pegvisamant, which blocks GH) and pituitary radiotherapy (may take years to take effect and may result in hypopituitarism). After successful treatment of acromegaly most physical features do not regress, although some soft-tissue effects do. Features of active disease are increased sweating and oedema, together with evidence of metabolic effects such as poor glycaemic and hypertensive control.

4.3.5 Prolactinomas

Prolactinomas are the most common functioning pituitary tumours. They present with galactorrhoea,

gonadal dysfunction (amenorrhea, oligomenorrhoea, poor libido, erectile dysfunction, subfertility) and symptoms of mass effect (headache and deterioration in visual fields). Diagnosis is based on raised serum prolactin concentrations and demonstration of a pituitary lesion on MRI. Microadenomas can be hard to detect on imaging and may appear as gland asymmetry, but generally speaking the size of the lesion is proportional to the prolactin level.

Treatment is aimed at normalising the prolactin level, restoring gonadal function and reducing the size of the lesion. The first-line treatment of prolactinomas is medical management. Dopamine agonists such as cabergoline and bromocriptine suppress prolactin levels to normal in approximately 95% of cases, with shrinkage of the tumour in about 85%. Surgery is usually reserved for patients who are intolerant or resistant to dopamine agonists.

4.3.6 Hypopituitarism and growth hormone deficiency in adults

Panhypopituitarism can be caused by enlarging pituitary tumours, cranial irradiation (including specific pituitary radiotherapy), pituitary apoplexy, Sheehan's syndrome (infarction after post-partum haemorrhage), and then by any of the conditions that can cause cranial diabetes insipidus (see box on p. 118).

Patients present with a soft, smooth 'baby' skin, 'crows' feet' lines around the eyes and features related to their specific hormonal deficiencies – hypotension in relation to ACTH deficiency, weight gain in relation to TSH deficiency, etc.

Typically, hormone loss follows a common pattern, with GH deficiency being most common, followed in order by LH, FSH, ACTH and TSH deficiency. Secondary hypothyroidism is suggested by a low free T4 (fT4) in the context of a low or inappropriately normal TSH. ACTH deficiency is diagnosed by an insulin stress test or glucagon test or, if longstanding, may be suggested by a failed short Synacthen test with low or inappropriately normal ACTH levels, although this test depends on the presence of adrenal atrophy subsequent to ACTH deficiency. The following points should be noted:

- Only replacement therapy with corticosteroids and T4 is essential for life
- In suspected hypopituitarism, the steroids should be given first and certainly before thyroid replacement therapy. This is because correction of hypothyroidism will accelerate cortisol metabolism and would precipitate a hypoadrenal crisis (if T4 is given before exogenous steroids)
- If the pituitary is damaged, GH production is lost early, so that most patients are GH-deficient (see below)
- Despite conventional hormone replacement therapy (T4, glucocorticoid and sex steroids), mortality rates are increased in hypopituitarism due to cardiovascular events or malignancy. The potential for GH therapy to reverse this trend is currently undergoing research.

GH deficiency

The main role for GH in children is growth; however, in adults GH is required for musculoskeletal, metabolic and possibly psychological wellbeing.

Adult GHD is associated with the following:

- Reduced muscle tone and power, increased fat mass, easy fatigability, poor exercise tolerance
- Low mood, poor concentration and memory
- Osteoporosis
- Increased cardiovascular risk (impaired endothelial function, proatherogenic lipid profile, impaired left ventricular function).

Based on guidance of the National Institute for Health and Care Excellence (NICE), GH replacement in adults is indicated for impaired quality of life in patients with severe GH deficiency (defined as a peak GH response <9 mU/L [3 ng/mL] during a stimulation test). These symptoms are reassessed after a 9-month period of treatment.

Treatment is with recombinant GH given nightly by subcutaneous injection. Longer-acting preparations are currently under review

4.4 HYPONATRAEMIA AND SIADH

ADH (or vasopressin) is synthesised in magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary. ADH is released in response to rising plasma osmolality and acts on the distal tubule and renal collecting ducts to increase water permeability. Water is reabsorbed and the urine becomes more concentrated. When the ADH system is working normally, 'the urine should reflect the blood', ie concentrated urine should occur when the plasma osmolality is high, and vice versa.

However, hypovolaemia is also a strong signal for ADH release, and in the presence of hypovolaemia, ADH will be secreted even if the osmolality is low. This explains the hyponatraemia seen in renal, cardiac and liver failure, as well as after excessive sodium loss (eg diarrhoea). Other stimuli can also commonly override control of ADH secretion by osmolarity (see Syndrome of inappropriate ADH secretion [SIADH] below).

Syndrome of inappropriate ADH secretion

Many common stimuli override the control of osmolality and cause inappropriate amounts of ADH to be secreted, causing hyponatraemia. Sodium concentration should be high in the urine (excluding hypovolaemia), renal, adrenal and thyroid function should be normal, and diuretic therapy needs to be excluded before SIADH is diagnosed. Treatment is by fluid restriction or, if necessary, oral demeclocycline.

Causes of inappropriate secretion of ADH include

- Nausea
- Pain
- Fits
- Pneumonia

- Other central nervous system/lung insults
- Smoking
- Chlorpropamide
- Carbamazepine
- Head injury
- Cerebrovascular accidents (CVAs)
- Tumours making ectopic ADH (eg bronchus)

If a tumour is the cause, it is usually obvious: a search for malignancy beyond a chest radiograph is not required in SIADH. Smoking makes you pass less urine (releases ADH); drinking (alcohol) makes you pass more (inhibits ADH secretion).

Causes of hyponatraemia

Hyponatraemia can be divided into three categories:

- 'Real' (low serum osmolality)
- Pseudohyponatraemia: high triglycerides, high protein (eg myeloma) (normal serum osmolality)
- Dilutional: high glucose, ethanol, mannitol (serum osmolality may be raised).

If hyponatraemia is confirmed to be 'real' (low plasma osmolality, glucose not raised, and no suggestion of ethanol or mannitol in blood), then the following clinical and laboratory pointers must be considered:

- Careful history for drug use (especially diuretics) and of fluid loss (eg diarrhoea)
- Examination for circulatory volume status (oedema, postural hypotension and skin turgor)
- Measurement of urinary sodium concentration (Table 4.4).

Hypoadrenalism is the most important diagnosis not to be missed, because untreated, it can result in death.

4.5 THE THYROID GLAND

4.5.1 Hyperthyroidism and hypothyroidism

The common features of hyperthyroidism (eg weight loss, tremor, palpitations) and hypothyroidism (eg weight gain, lethargy, dry skin) are well known but questions are often asked on the more unusual features. 'Recognised' features of the two major thyroid syndromes are summarised in Table 4.5.

Table 4.4 Causes of hyponatraemia

Urine sodium (mmol/L)	Hypovolaemia present	Features of hyper- and hypothyroidism
>20	Diuretics	SIADH

	Hypoadrenalism	Hypothyroidism
	Salt-losing nephropathy	Renal failure
<10	Vomiting, diarrhoea	Congestive cardiac failure, cirrhosis, nephrotic syndrome
	Loss of other fluid	

SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Features of hyper- and hypothyroidism

Amenorrhoea may be associated with hyperthyroidism because of associated weight loss. In hypothyroidism, everything slows down except the periods! The menorrhagia can cause a microcytic anaemia in contrast to the more usual macrocytosis. In both conditions there may be subfertility. In the gastrointestinal tract, the symptoms of hyperthyroidism are almost indistinguishable from those of anxiety. The diarrhoea is actually more like the increased bowel frequency before an examination.

- Both hyperthyroidism (if Graves' disease) and hypothyroidism can cause periorbital oedema (see note in Section 4.5.5 on eye signs in thyrotoxicosis)
- The leukopenia of thyrotoxicosis can be misdiagnosed: thionamide drugs (eg carbimazole) used as treatment also commonly cause a lymphopenia. Both of these are separate from the agranulocytosis that rarely occurs with thionamide drugs
- In hyperthyroidism the urticaria due to the disease itself can cause confusion with the maculopapular rash, which develops in 10% of patients treated with thionamide drugs.

Table 4.5 Features of hyper- and hypothyroidism

Features	Hyperthyroidism	Hypothyroidism
General	Weight gain (rarely) Gynaecomastia Occult in elderly people Hair loss	Weight gain Serous effusions (pleural, pericardial, ascites, joint) Hair loss
Gynaecological	Raised sex hormone-binding globulin (SHBG)	Amenorrhoea, menorrhagia Infertility
Gastrointestinal	Raised alkaline phosphatase (derived from liver and bone) Vomiting	Diarrhoea Constipation
Muscle	Proximal myopathy Periodic paralysis (especially Chinese)	Raised creatine kinase Chest pain (muscular) Muscle cramps
		Dyspnoea

Cardiovascular system	Atrial fibrillation with high stroke rate High-output cardiac	Hypercholesterolaemia Ischaemic heart disease failure
Bone	Osteoporosis Hypercalcaemia	
Neurological	'Apathetic thyrotoxicosis'	Deafness Ataxia, confusion, coma
Eyes	Eye signs (see Section 4.5.5)	Periorbital oedema
Blood	Leukopenia Microcytic anaemia	Macrocytic anaemia Microcytic, if menorrhagia
Skin	Urticaria	Dry, orange (carotenaemia)

Side-effects of anti-thyroid drugs (carbimazole, propylthiouracil)

- **Common**
  - Rash
  - Leukopenia
- **Rare**
  - Agranulocytosis
  - Aplastic anaemia
  - Hepatitis
  - Fever
  - Arthralgia
  - Vasculitis (propylthiouracil)

(See also Chapter 2, Clinical Pharmacology, Toxicology and Poisoning)

4.5.2 Causes of thyrotoxicosis

The three common causes of thyrotoxicosis are:

- Graves' disease
- toxic multinodular goitre
- toxic (hot) nodule.

In all these conditions all or part of the gland is overactive and the gland takes up a normal or increased amount of radioiodine.

In the following conditions, there is thyrotoxicosis without increased production of new hormone by the thyroid gland itself, ie radioiodine uptake is suppressed:

- Excess thyroxine ingestion
- Thyroiditis: post-viral (de Quervain's), post-partum or silent thyroiditis
- Ectopic thyroid tissue, eg lingual thyroid or ovary (struma ovarii)
- Iodine administration: gland is actually still active, but cold iodine competes with radioiodine during scanning.

4.5.3 Thyroid cancer and nodules

Only 5–10% of thyroid nodules are malignant (the rest are adenomas). Thyroid cancer virtually never causes hyperthyroidism, so 'hot nodules' can usually be presumed to be benign. In order of increasing malignancy and decreasing frequency, the thyroid epithelial cancers are:

- papillary
- follicular
- anaplastic.

Lymphomas occur in Hashimoto's disease. Medullary thyroid cancer is from the C cells (calcitonin), not from the thyroid epithelium. Serum calcitonin is a tumour marker for this cancer, which often occurs in families, sometimes as part of the multiple endocrine neoplasia type 2 syndrome (see Section 4.7).

4.5.4 Drugs and the thyroid

- **Lithium**
  - Inhibits T4 release from the gland, causing hypothyroidism
- **Oestrogens**
  - Raised TBG and hence 'total' T4 /T3
- **Amiodarone**
  - Inhibits T4 to T3 conversion, increasing reverse T3
  - High iodine content can cause hyper- or hypothyroidism[a]
- **Iron** – if taken at the same time as thyroxine, can reduce its absorption
- **Interferon**
  - Induces anti-thyroid autoantibodies and hypothyroidism (usually transient)

[a]Note on amiodarone-induced hyperthyroidism. This may be due to drug-induced damage (thyroiditis) or to the excess iodine in amiodarone, and can be very resistant to treatment.

4.5.5 Autoimmunity and eye signs in thyroid disease

In areas such as the UK, where there is relatively little iodine deficiency, more than 90% of

spontaneous hypothyroidism is due to autoimmunity. Anti-thyroglobulin autoantibodies are present in 60% of cases and anti-microsomal antibodies (now identified as anti-thyroid peroxidase antibodies) are present in up to 90%. Antibodies that block the TSH receptor may also be present. Similar antibodies are present in Graves' disease, but the anti-TSH receptor antibodies are stimulatory, causing the thyrotoxicosis.

The eye signs in thyroid disease are shown in the box (see also Chapter 17, Ophthalmology). Retro-orbital inflammation and swelling of the extraocular muscles are only seen in Graves' disease.

Note that each of the features listed can occur separately in thyroid eye disease (eg diplopia without exophthalmos) and, surprisingly, disease of the two eyes is usually asymmetrical. The target of the antibody or T-cell reaction causing this inflammation is not known for certain, and eye disease activity can occur in the absence of thyrotoxicosis and even with hypothyroidism.

Thyrotoxicosis from any cause

- Lid retraction
- Lid lag

Graves' disease only

- Soft-tissue signs: periorbital oedema, conjunctival injection, chemosis
- Proptosis/exophthalmos
- Diplopia/ophthalmoplegia
- Optic nerve compression causing visual failure

4.5.6 Thyroid function tests

TSH is the most sensitive measure of thyroid status in patients with an intact pituitary. T4 and T3 are over 95% protein-bound, predominantly to TBG. The conditions in the box alter TBG levels and hence total, but not free, hormone levels.

Conditions that alter thyroid-binding globulin (TBG)

Raised TBG	Low TBG
Pregnancy	Nephrotic syndrome
Oestrogen	Congenital TBG abnormality
Hepatitis	
Congenital TBG abnormality	

Interpretation of thyroid function tests

This is generally straightforward in ambulant out-patients if the causes of different patterns of thyroid function tests (TFTs) are known (Table 4.6). Special care in interpretation should be taken in the following circumstances:

- Known or suspected pituitary disease (TSH is misleading and should NOT be used as a test)
- Acutely ill patients (eg in intensive care) – TSH often low with low free T3 (fT3)
- Patients taking T3 supplements alone.

4.6 ADRENAL DISEASE AND HIRSUTISM

4.6.1 Cushing syndrome

Cushing syndrome refers to the sustained over-production of cortisol (hypercortisolism), which causes the following:

- centripetal obesity with moon face
- 'buffalo hump'
- hirsutism
- recurrent infections
- osteoporosis
- oligomenorrhoea
- hypokalaemia
- striae

Table 4.6 Thyroid function tests

	TSH		
	Low	**Normal**	**Raised**
Raised fT4/fT3	**Thyrotoxicosis**	Rare: (applies to both normal and raised) • TSH-secreting pituitary tumour (TSHoma) • Thyroid hormone resistance (receptor defect) • Hypoadrenalism • Acute psychiatric illness • Intermittent T4 therapy (poor compliance) • T4 acute overdose (TSH normal) • Interfering anti-T4/T3 antibody (TSH normal) • Familial dysalbuminaemic hyperthyroxinaemia (TSH normal)	
Normal fT4/fT3	Subclinical thyrotoxicosis: • Excess thyroxine • Steroid therapy • Non-thyroidal illness • Dopamine infusion	**Normal**	Subclinical hypothyroidism: • Poor compliance with T4 therapy • Interfering (heterophile) antibody • Recovery from non-thyroidal illness • Hypoadrenalism
Low fT4/fT3	Non-thyroidal illness: (applies to both low and normal) • Pituitary failure • Recent (excessive) treatment for hyperthyroidism		**Hypothyroidism**

- acne
- proximal muscle weakness
- hyperglycaemia
- psychiatric disturbances
- hypertension.

If untreated, the mortality rate is high (59% within 5 years), and death is usually due to cardiovascular disease or infection. Fortunately, apart from iatrogenic Cushing syndrome secondary to steroid use, Cushing syndrome is rare. Other endocrine causes of obesity should be excluded:

- hypothyroidism
- leptin deficiency
- hypothalamic tumours (hyperphagia)
- Prader–Willi syndrome
- GH deficiency.

Possible causes of Cushing syndrome are:

- Adrenal tumour
- Pituitary tumour (Cushing's disease)

- Ectopic production of ACTH – either from cancer (eg small-cell cancer of lung) or from a bronchial adenoma (often very small)
- Ectopic production of corticotrophin-releasing hormone (CRH) (very rare).

The diagnosis of Cushing's is made in three phases.

Screening tests

- Loss of diurnal variation (midnight cortisol similar to morning cortisol)
- Overnight dexamethasone suppression test (1 mg at midnight then 9am cortisol). Cortisol should suppress to <50 nmol/L
- Raised urinary free cortisol (24-hour collection).

Diagnostic tests

- Low-dose dexamethasone suppression test (0.5 mg four times daily for 48 hours). Cortisol should suppress to <50nmol/l
- ACTH will be inappropriately normal/raised in pituitary (Cushing's disease) or ectopic ACTH secretion, both of which are referred to as 'ACTH-dependent Cushing syndrome'
- ACTH will be suppressed in adrenal disease (Cushing syndrome or 'non-ACTH-dependent Cushing syndrome').

If one or more of these are positive then one can proceed to localisation. Note that depression or alcoholism can cause cortisol overproduction ('pseudo-Cushing syndrome'). If these conditions are present, further investigation is very difficult.

Localisation studies

- High-dose/low-dose dexamethasone suppression test (2 mg four times daily for 48 hours). ACTH levels suppress by 50% in 50% of people with pituitary disease, but not with ectopic production. Many have now abandoned this test due to lack of sensitivity
- MRI of the adrenal or pituitary alone cannot be relied on to localise the cause. First, the tumours of the pituitary causing Cushing's disease are often too small to see and, second, incidental tumours of both the pituitary and adrenal are common and may not be functional. Tests used to identify the causes of Cushing syndrome are shown in Table 4.7
- Inferior petrosal sinus sampling (IPSS) is an invasive radiological technique in which blood samples are drawn from the sinuses, draining the left and right sides of the adrenal gland, and also from the periphery. By looking at the ACTH gradients between samples, localisation may be determined. However, due to cross-drainage and difficulties in cannulating the sinuses, results may be difficult to interpret.

Treatment of Cushing syndrome

The aim of treatment is to normalise cortisol levels. Primary treatment is therefore surgical resection of the tumour with either pituitary or adrenal surgery.

Surgery

Pituitary

Cushing's disease is primarily treated with transsphenoidal surgery (successful in approximately 60% of cases). 'Biochemical cure' is achieved if post-operative cortisol levels are undetectable, as non-tumorous pituitary tissue will have been dormant in the presence of the ACTH-producing tumour and may remain dormant for up to 2 years post-operatively. During this time, the patient will require cortisol replacement therapy. Sometimes recovery never occurs and the patient remains permanently ACTH-deficient.

If surgical cure has not been achieved, due to incomplete resection of the tumour, then pituitary radiotherapy or medical treatment may be offered.

Adrenal

Adrenal cortisol-secreting tumours are usually treated with laparoscopic resection, although occasionally this is not possible due to the large size. The whole adrenal is resected and cortisol levels should be undetectable post-operatively, as the contralateral adrenal gland will be dormant due to lack of ACTH stimulation. Recovery of this adrenal gland may take up to 2 years, although, as with the pituitary gland, this may never occur and the patient will remain cortisol-dependent. Failure to cure because of incomplete resection may be treated medically.

Table 4.7 Tests used to identify causes of Cushing syndrome

	Adrenal	**Pituitary**	**Ectopic**
ACTH	Suppressed	Mid-range	High
High-dose dexamethasone suppression	No change in cortisol	Suppression of cortisol[a]	No change
CRH stimulation test	No change	Rise in ACTH and cortisol[a]	No change
Metyrapone	Rise in 11-deoxycortisol <220-fold	Rise in 11-deoxycortisol >220-fold[a]	Rise in 11-deoxycortisol <220-fold
Petrosal sinus sampling ACTH[b]	Equals peripheral level	Higher than peripheral level	Equals peripheral level

[a]'Under pressure' (ie at high doses), pituitary adenomas behave like a normal pituitary in dynamic endocrine testing, whereas adrenal or ectopic sources do not. A positive response to high-dose suppression (2 mg four times daily for 48 h) is >10% suppression of plasma cortisol or 24-hour urinary free cortisol.

[b]In a petrosal sinus sampling, a catheter is placed in the draining sinus of the pituitary gland, via a femoral or jugular venous approach. The ACTH level is compared with that in the peripheral blood before and after CRH injection.

Occasionally, bilateral adrenalectomy is performed when it is not possible to normalise ACTH secretion (source unknown, or pituitary surgery/radiotherapy has been ineffective). This causes cortisol deficiency but may result in Nelson's syndrome: loss of suppression (provided by the

previously high cortisol levels) may allow a pre-existing pituitary adenoma to grow very rapidly, years later, causing local damage and generalised pigmentation.

Radiotherapy
Pituitary irradiation may reduce ACTH production and reduce tumour growth. It is insidious in onset but can be effective for up to 15 years.

Medical therapy
Where surgery is not possible, normalisation of cortisol levels can be sought with metyrapone (although long-term complications include hirsuitism and hypertension) and more recently SOM230, which also inhibits cortisol production. Ketoconazole, previously used with a similar intent, has recently been withdrawn because of concerns of hepatotoxicity. Mitotane can be used in patients with adrenal cortical carcinoma as adjunct chemotherapy. However, medical therapies rarely normalise cortisol levels long term.

4.6.2 Primary hyperaldosteronism

Primary hyperaldosteronism comprises hypertension, hypokalaemia (80% of cases), hypomagnesaemia and metabolic alkalosis. Patients can, however, have a serum potassium within the normal range. Primary hyperaldosteronism is now thought to account for 1–3% of all cases of hypertension.

- **Symptoms (if present) relate to hypokalaemia**: weakness, muscle cramps, paraesthesiae, polyuria and polydipsia. Patients rarely develop peripheral oedema ('sodium escape' mechanism)
- **Causes**: aldosterone-secreting adenoma (Conn's syndrome is almost never caused by a malignancy), idiopathic bilateral adrenal hyperplasia, unilateral hyperplasia (rare)
- **Investigations (not standardised)**: the **aldosterone:renin ratio** (ARR) should be assessed to confirm high aldosterone levels in the presence of low renin. Ideally, the ratio should be assessed after the patient has ceased antihypertensive drugs (β blockers reduce renin levels and therefore increase the ARR, giving a false-positive result. Spironolactone, calcium channel blockers, ACE inhibitors and angiotensin antagonists increase renin levels causing a lowering of ARR and therefore a false-negative result. Alpha blockers (eg doxazosin) have the least effect. Ideally, where possible, these agents should be stopped to allow a washout period of between 4 and 6 weeks. If hyperaldosteronism is confirmed, a CT or MR scan of the abdomen may identify a unilateral adrenal adenoma. However, the tumours are usually <2 cm in diameter and so, if imaging is negative, adrenal vein sampling may be required in order to distinguish unilateral hypoplasia or a tiny adenoma from idiopathic bilateral hyperplasia
- **Treatment**: spironolactone and amiloride are often successful treatments when the cause is bilateral hyperplasia. Eplerenone is a selective aldosterone antagonist that can be used in patients who develop gynaecomastia or breast soreness with spironolactone. An adenoma or unilateral adrenal hyperplasia may be surgically removed; hypertension may persist if this was previously long-standing.

(See Chapter 1, Cardiology, Section 1.9.3 Systemic hypertension. See also Chapter 15, Nephrology,

Section 15.3.4 for differential diagnoses of hypokalaemia.)

4.6.3 Congenital adrenal hyperplasia

Two enzyme defects account for 95% of all CAH:

- 21-hydroxylase (90%)
- 11-hydroxylase (5%).

The block caused by these enzyme defects leads to reduced production of cortisol, but increased production of other intermediates in steroid metabolism, including androgenic steroids. 17-hydroxylase, 3-β-hydroxysteroid dehydrogenase and cholesterol side-chain cleavage enzyme defects are very rare causes of congenital adrenal hyperplasia (CAH) and have different effects (see the box).

Features of congenital adrenal hyperplasia

- Autosomal recessive
- Both gene deletions and point mutations can occur
- Plasma ACTH is high (renin is high if salt-losing)
- Can cause male precocious puberty (not 17-hydroxylase or side-chain enzyme); can cause ambiguous genitalia in females (not 17-hydroxylase or side-chain enzyme)
- Treat with glucocorticoids mineralocorticoids at night
- Can have a minor, late-onset form resembling polycystic ovary syndrome
- Surgery may be required to correct ambiguous genitalia/cliteromegaly
- Antenatal steroid therapy to the mother has been used

It is possible to distinguish between the different enzyme defects in CAH (Table 4.8).

Table 4.8 Differentiating features in congenital adrenal hyperplasia

	21-hydroxylase	11-hydroxylase	17-hydroxylase/side-chain enzyme
Frequency	90% cases	5% cases	Very rare
Presentation in females	Virilising, intersex 70% salt-losing[a]	Virilising, hypertension, low K^+	Non-virilising (intersex in boys)
Biochemistry	Raised 17-hydroxylase, progesterone	Raised 11-dehydroxycortisol	

[a]Salt-losing individuals can have Addisonian crises soon after birth.

4.6.4 Hypoadrenalism

In the UK, spontaneous hypoadrenalism is most commonly due to autoimmune destruction of the adrenal glands (Addison's disease – adrenal autoantibodies present in 70% of cases). Vitiligo is present in 10–20% of cases and can be associated with other autoimmune diseases. Other causes of primary adrenal insufficiency include tuberculosis (TB), HIV or haemorrhage into the adrenal glands.

Secondary hypoadrenalism is due to ACTH deficiency, most commonly caused by a pituitary lesion. Hypoadrenalism after withdrawal of longstanding steroid therapy is similar to secondary hypoadrenalism.

The following are 'recognised' features of hypoadrenalism:

- **Biochemical**: raised urea, hypoglycaemia, hyponatraemia, hyperkalaemia, raised TSH, hypercalcaemia
- **Haematological**: eosinophilia, lymphocytosis, normocytic anaemia
- **Clinical features**: weight loss, abdominal pain, psychosis, loss of pubic hair in women, hypotension, auricular cartilage calcification, increased pigmentation.

Hyperkalaemia and increased pigmentation are absent in secondary hypoadrenalism, because there are low levels of circulating ACTH and mineralocorticoids continue to be secreted via the renin–angiotensin–aldosterone system.

The gold standard in diagnosing hypoadrenalism is by failure of plasma cortisol to rise above 550 nmol/L at 30 or 60 min after intramuscular or intravenous injection of 250 g synthetic ACTH (short Synacthen 1 test).

Treatment is with steroid replacement, and this is most commonly done with oral hydrocortisone. Patients are told to double their steroid doses in times of stress or intercurrent illness. It is imperative that steroid replacement is not stopped, and therefore if patients are unable to take their tablets for any reason (ie vomiting), they are told to seek medical attention.

Acute adrenal failure (Addisonian crisis)

Acute adrenal failure is one of the few endocrine emergencies. Addisonian crisis presents with hypovolaemia, hyponatraemia, hyperkalaemia (if primary adrenal failure), hypoglycaemia and cardiovascular collapse, which can be fatal. A mildly raised TSH may also be seen even in the absence of thyroid disease. Urgent treatment is necessary, and this includes intravenous fluid and electrolyte replacement as well as, most importantly, steroid replacement. All patients with hypoadrenalism are advised to wear/carry a MedicAlert bracelet with them at all times.

4.6.5 Polycystic ovary syndrome and hirsutism

Hirsutism (Table 4.9) is the increased growth of terminal (dark) hairs in androgen-dependent areas. Virilisation is temporal hair recession (male pattern), breast atrophy, voice change, male physique and (most important) cliteromegaly. Hirsutism and acne are invariably also present.

A serum testosterone 4.5 nmol/L (normal <1.8 nmol/L), recent onset of hirsutism and signs of

virilisation in women should prompt a search for other causes (eg a tumour). Dehydroepiandrostenedione (DHEA) is a weak androgen produced in the adrenal only.

- Measure the 17-hydroxyprogesterone level after stimulation with ACTH to check for late-onset 21-hydroxylase deficiency (partial enzyme deficiency)
- Other than androgens, the drugs listed strictly cause hypertrichosis, an increase in vellus hair, rather than an increase in androgen-sensitive terminal hairs (see Chapter 3, Dermatology).

Polycystic ovary syndrome

There is no widely recognised definition, and up to 20% of women have a degree of hirsutism. In practice, the three main presenting complaints in polycystic ovarian syndrome (PCOS) are hirsutism/acne, oligo-/amenorrhoea and subfertility. The following are recognised associations of PCOS:

Table 4.9 Causes of hirsutism

Ovarian	Adrenal	Drugs
PCOS (<90% of cases)	CAH (may be late onset)	Minoxidil
Virilising tumour	Cushing syndrome/adrenal carcinoma	Phenytoin
		Diazoxide
		Ciclosporin
		Androgens

CAH, congenital adrenal hyperplasia; PCOS, polycystic ovarian syndrome.

- **Clinical features**: obesity, acanthosis nigricans, oligomenorrhoea, polycystic ovaries, subfertility, hypertension, premature balding in male relatives, hirsutism
- **Biochemical**: insulin resistance and hyperinsulinaemia, raised testosterone, raised LH/FSH ratio, raised prolactin, low HDL.

Treatment: metformin will lower insulin resistance and it has been shown to promote ovulation, improve conception rates and reduce hirsutism. Weight loss may also be beneficial. Separate specific treatments are available for hirsutism (eg flutamide, cyproterone, finasteride, topical creams) and infertility (ovulation induction).

4.7 PHAEOCHROMOCYTOMA AND MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

Phaeochromocytomas are rare tumours of the adrenal medulla or ganglia of the sympathetic nervous system. They are the ‘tumour of 10%’:

- 10% are outside the adrenal glands – paragangliomas (including organ of Zuckerkandl)
- 10% are multiple (eg bilateral)

- 10% are malignant
- 10% are familial.

The most sensitive and specific test for the diagnosis of phaeochromocytoma is the measurement of plasma or urinary fractionated metanephrines. This is not available in all centres and measurement of urinary catecholamines is an alternative (measurement of urinary catecholamine metabolites – 3-methoxy-4-hydroxymandelic acid or vanillylmandelic acid [VMA] – has now been superseded). As is the case with most endocrine tumours, the histology is not a reliable guide to the malignant potential in phaeochromocytomas. The diagnosis of malignancy is made by the presence of metastases.

Familial phaeochromocytomas occur in

- Multiple endocrine neoplasia type 2 (see below)
- Spontaneously in some families (not associated with a syndrome)
- Von Hippel–Lindau syndrome (retinal and cerebral haemangioblastomas and renal cystic carcinomas)
- Von Recklinghausen's disease (neurofibromatosis) – 1–2%
- Carney's triad: gastric leiomyosarcoma, pulmonary chondroma, Leydig's testicular tumour
- Paraganglioma syndromes (PGL types 1–4): associated with head and neck paragangliomas and phaeochromocytomas. Mutations in one of the four succinate dehydrogenase subunits (SDH), especially SDHD (PGL1) and SDHB (PGL 4)

Important features of phaeochromocytomas

- 70% have persistent rather than episodic hypertension
- The triad of headache, sweating and palpitations is said to be >90% predictive
- Extra-adrenal tumours do not make adrenaline (they secrete noradrenaline/dopamine)
- Hypotension or postural hypotension may occur, particularly if adrenaline is produced
- They give characteristically a 'bright' (white) signal on T2-weighted MRI
- MIBG (*m*-iodobenzylguanidine) scanning may help localisation
- Phaeochromocytomas may produce chromogranin A
- Preoperative preparation is with α-adrenergic blockade (eg phenoxybenzamine) before β blockade

Causes of episodic sweating and/or flushing

- Oestrogen/testosterone deficiency (eg menopause, castration)
- Carcinoid syndrome (flushing, diarrhoea, wheeze)
- Phaeochromocytoma (sweat but do not flush)
- Hypoglycaemia (in diabetes)

- Thyrotoxicosis (not usually episodic)
- Systemic mastocytosis (histamine release)
- Allergy.

Multiple endocrine neoplasia (MEN) syndromes are syndromes with multiple benign or malignant endocrine neoplasms (Table 4.10). They should not be confused with polyglandular autoimmune syndromes which relate to autoimmune endocrine diseases.

Table 4.10 Classification of multiple endocrine neoplasia (MEN)

	MEN-1	**MEN-2A**	**MEN-2B**
Genetics	The *menin* gene Chromosome 11	The *ret* gene Chromosome 10	The *ret* gene Chromosome 10
Tumours	Parathyroid Pituitary Pancreas (carcinoid) (Adrenal adenomas)	Parathyroid Phaeochromocytoma Medullary thyroid cancer	Parathyroid Phaeochromocytoma Medullary thyroid cancer Marfanoid Mucosal neuromas

- MEN-1 was formerly known as Werner's syndrome. MEN-2A was known as Sipple's syndrome. All MEN syndromes are autosomal dominant. Genetic (DNA-based) screening is available for both MEN-1 and MEN-2. The MEN-2 mutation in *ret* activates the protein. Inactivating mutations of *ret* are seen in Hirschsprung's disease
- All MEN syndromes can be associated with hypercalcaemia. This is usually due to hyperplasia of all four parathyroids, not a single parathyroid adenoma as with sporadic hyperparathyroidism. Hypercalcaemia is often the first manifestation in MEN-1
- Gastrinomas and insulinomas are the most common pancreatic tumours in MEN-1. Of the pituitary tumours, prolactinomas are the most common, followed by acromegaly and Cushing's disease.

Medullary thyroid cancer (MTC) is always malignant, secretes calcitonin and is preceded by C-cell hyperplasia. Prophylactic thyroidectomy in patients with genetically confirmed MEN-2 should be performed to prevent this most serious manifestation. The exact site of the *ret* gene determines the age at which thyroidectomy should be performed, in many cases under the age of 2 years.

4.8 PUBERTY/GROWTH/INTERSEX

4.8.1 Normal puberty

In 95% of children, puberty begins between the ages of 8 and 13 years in females and 9 and 14 years in males. The mean age of menarche is 12.8 years. The events of puberty occur in a particular order, although the later stages overlap with the earlier ones.

Order of events in normal puberty (earliest events listed first)

- **Male**
  - Scrotal thickening (age 9–14)
  - Testicular enlargement (>2 mL)
  - Pubic hair
  - Phallus growth
  - Growth spurt (age 10–16) + increasing bone age
- **Female**
  - Breast development (age 8–13)
  - Growth spurt
  - Pubic hair
  - Menstruation (age 10–16) + increasing bone age

4.8.2 Precocious puberty

True precocious puberty is rare. It is diagnosed if multiple signs of puberty develop before age 8 in females and age 9 in males, accompanied by increased growth rate, accelerated bone age and raised sex steroid levels. Isolated premature breast development (thelarche) or the appearance of pubic hair alone (from adrenal androgens – adrenarche) are both benign conditions if no other stages of puberty are entered.

Causes of precocious puberty

- True 'central' gonadotrophin-dependent precocious puberty
  - Idiopathic
  - Other CNS disease (eg hydrocephalus, encephalitis, trauma)
  - CNS hamartoma (eg pineal)
- Other causes (gonadotrophin-independent)
  - Adrenal, ovarian tumour
  - CAH (males)
  - Testotoxicosis (males)
  - Exogenous oestrogen (females)
  - McCune–Albright syndrome
  - Follicular cysts (females)
  - Profound hypothyroidism

McCune–Albright syndrome is more common in girls (see Section 4.1.2 on activating G-protein

mutations).

4.8.3 Delayed puberty/short stature

Short stature in children is often due to delayed puberty and hence the two problems are usually grouped together. Three per cent of children are 'statistically delayed', ie for girls no breast development by age 13 or menses by age 15, and for boys no testicular enlargement by age 14. The majority will have 'constitutional delay' and will later enter puberty spontaneously. However, there is no endocrine test that can reliably distinguish constitutional delay from other organic causes of delayed puberty.

In investigation, systemic diseases or syndromes that can cause delayed puberty should be excluded before considering pituitary testing. A karyotype (for Turner's syndrome) should always be requested in girls (see following text).

Causes of delayed puberty/short stature

- **General causes**
  - Overt systemic disease
  - Social deprivation
  - Anorexia, excess exercise
  - Chemotherapy/gonadal irradiation
  - Cranial irradiation
- **Syndromes causing delayed puberty/short stature**
  - Turner's syndrome (XO)
  - Noonan's syndrome ('male Turner's syndrome')
  - Prader-Willi syndrome
- **Occult systemic disease**
  - Renal failure/renal tubular acidosis
  - Crohn's/coeliac disease
  - Hypothyroidism
  - Asthma
  - Anterior pituitary disease
  - Hyperprolactinaemia
  - Isolated GH deficiency
- **Syndromes causing delayed puberty but normal stature**
  - Androgen insensitivity (testicular feminisation – XY female)
  - Polycystic ovary syndrome (delayed menarche only)
  - Kallman's syndrome (XY), anosmia
  - Klinefelter's syndrome (XXY) – males

In Turner's syndrome, Noonan's syndrome, androgen insensitivity and Klinefelter's syndrome, raised LH and FSH are present. Kallman's syndrome is due to failure of GnRH-secreting neurons migrating to the hypothalamus. LH and FSH levels, as well as sex steroids, are low and patients typically have associated anosmia. Mutations in at least five genes can cause the syndrome, the best recognised being the classic X-linked locus (KAL-1 also known as anosmin-1 – the syndrome associated with anosmia) and the autosomal loci fibroblast growth factor receptor 1 (FGFR1, a syndrome associated with orofacial clefting and hypodontia).

However, gene mutations account for only around 40% of cases of idiopathic hypogonadotrophic hypogonadism. There is no biochemical test that can currently distinguish Kallman's syndrome from constitutional delay of puberty, and therefore a clinical diagnosis is made when delayed puberty is associated with anosmia.

Turner's syndrome (XO) (see Chapter 7, Genetics) occurs in 1 in 2500 live births. The typical features (abnormal nails, neonatal lymphoedema, web neck, widely spaced nipples, wide carrying angle) may be absent. A karyotype should always be requested in girls with short stature/delayed puberty because the final height can be increased by early treatment with high doses of growth hormone. Other important complications which may occur in Turner's syndrome include aortic root dilatation (often the cause of death) or coarctation, renal abnormalities, abnormal liver function tests and deafness. Women with Turner's syndrome are generally infertile, but in some cases will have relatively minor X deletions and/or chimaerism with cells of a normal karyotype, so both menstruation and pregnancy can occur.

Klinefelter's syndrome (XXY) (see Chapter 7, Genetics) occurs in 1 in 1000 live births (by meiotic non-disjunction), but is usually undiagnosed until adulthood. Testosterone production is around 50% of normal, but is sufficient to allow secondary sexual characteristics and normal height to develop. Patients usually come to attention because of small testes, gynaecomastia or infertility.

4.8.4 Intersex

(See also Chapter 7, Genetics.) Ambiguous genitalia at birth require urgent diagnosis with steroid profile and karyotype to assign the appropriate sex of rearing and identify the risk of a salt-losing crisis (CAH). Causes can be grouped as shown in the box.

Causes of intersex

- **Virilised female (XX)**
  - CAH (21-OH or 11-OH)
  - Maternal androgen ingestion
- **Non-masculinised male (XY)**
  - Unusual CAH (17-OH/side-chain/3-β-OH)
  - Androgen resistance:
    - Receptor defect ('testicular feminisation')
    - 5α-reductase deficiency

Mothers who have a virilised daughter with CAH can be treated antenatally with steroids in subsequent pregnancies in order to suppress androgen production by the fetus. Steroids are continued until the sex of the baby can be established by chorionic villous sampling.

4.9 DIABETES MELLITUS

Diabetes may be defined as chronic hyperglycaemia at levels sufficient to cause microvascular complications:

- 10% of cases are due to type 1 diabetes where there is autoimmune destruction of the pancreatic islets of Langerhans
- Around 85% are due to type 2 diabetes characterised by insulin resistance and relative deficiency of insulin secretion
- The remaining 5% of cases are due to a collection of secondary causes

4.9.1 Risk factors and clinical features of types 1 and 2 diabetes mellitus

Table 4.11 summarises the differences between type 1 and type 2 diabetes mellitus. Note that type 2 diabetes is more common in non-Caucasian races and is actually more strongly inherited than type 1 diabetes, despite being 'adult-onset'.

Table 4.11 Comparison between type 1 and type 2 diabetes mellitus

	Type 1	**Type 2**
Genetics	Both parents affected: up to 30% risk for child Identical twins: 64% concordance by 60 years Caucasians Increased risk conferred by over 15 gene loci identified so far, the more of these present, the greater the risk	Both parents affected: 75% risk for child Identical twins: up to 90% concordance Asian, Black, Hispanic, Native Americans Over 20 genes have been identified that increase susceptibility
Autoantibodies	In new type 1 diabetics: 60–75% have insulin antibodies 70–80% have GAD (glutamic acid decarboxylase) antibodies 65–75% have IA-2 (islet antigen-2) antibodies 70–80% have ZnT8 (zinc transporter-8) antibodies	No antibody association

Incidence	Approximately 1/10 000 per year and rising	Approximately 1/200 per year
Prevalence	Approximately 1/1000	Approximately 5/100
Clinical features	Age <40 Weight loss Ketosis prone Insulin deficient Autoimmune aetiology (other autoimmune disorders may be present)	Age usually >20 but increasing numbers of paediatric patients Insidious onset Overweight Usually ketone negative Insulin resistant Acanthosis nigricans Associated with metabolic syndrome (with obesity, hypertension, dyslipidaemia)

Maturity onset diabetes of the young (MODY) is a term used to describe a group of disorders describing autosomal dominantly inherited monogenic diabetes. It causes 1–2% of diabetes and there is usually a family history. Age of onset of diabetes is usually less than 25 years and the condition is caused by beta cell dysfunction. Treatment depends on the underlying gene defect (Table 4.12).

4.9.2 Diagnostic criteria for diabetes

This remains an area of ongoing debate. There have been recent changes to the diagnostic criteria for diabetes with the official addition of the use of HbA1c for diagnosis rather than to solely look at glycaemic control. The current practical use of the OGTT (oral glucose tolerance test) is for those patients with a fasting glucose level between 6.0 and 7.0 mmol/L, or in the diagnosis of gestational diabetes.

Diagnoses of diabetes and pre-diabetes*

- With symptoms: fasting glucose >7.0 mmol/L or random glucose over 11.1 mmol/L or glucose over 11.1 mmol/L 2 hours into an OGTT
- HbA1c ≥48 mmol/mol or 6.5%
- Without symptoms: fasting glucose >7.0 mmol/L or random glucose 11.1 mmol/L on 2 occasions
- Impaired glucose tolerance is defined by a 2 hour OGTT value of 7.8–11.1 mmol/L
- Impaired fasting glucose is a value > 5.6 but <7.0 mmol/L.

*Values are based on venous rather than capillary blood values.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are two conditions of 'pre-diabetes'. IGT confers increased cardiovascular risk. Twenty percent of patients with IGT will progress to type 2 diabetes within 5 years. A number of interventions have been identified that can reduce the risk of this occurring or slow the progression. A programme of diet and exercise, weight

loss (any cause including bariatric surgery), and drugs including metformin, acarbose, thiazolindenediones and orlistat have all been shown to be effective.

Table 4.12 Classification of MODY (maturity-onset diabetes of young people) disorders

Gene	Percentage of MODY cases	Classification
Glucokinase	20	MODY 2 – mild, complications are rare
HNF-1α	60	MODY 3 – progressive beta cell failure but very sensitive to sulphonylureas
HNF-4α	1	1 MODY 1 – neonatal hyperinsulinism
HNF 1β	1	MODY 5 – associated renal anomalies or cysts
IPF-1	1	MODY 4 – very rare
	<1	MODY 6–11
Unknown	15	MODY X
SUR1, Kir6.2	<1	Hyperinsulinism in infancy and βcell failure in adulthood

Classification of diabetes

- Type 1 diabetes
- Type 2 diabetes
- Genetic disorders
  - MODY
  - Mitochondrial disorders eg MELAS, MIDD
- Exocrine pancreas disease eg
  - Pancreatitis
  - Pancreatectomy
  - Haemochromatosis
  - Cystic fibrosis
  - Neoplasm
- Drugs eg corticosteroids, antipsychotics
- Endocrine disorders eg
  - Cushings
  - Acromegaly
  - Thyrotoxicosis

- Phaeochromocytoma
- Other genetic syndromes eg
  - Down's syndrome
  - Klinefelter's syndrome
  - Turner's syndrome
  - Wolfram syndrome (also known as DIDMOAD – diabetes insipidus, diabetes Mellitus, optic atrophy and deafness)
- Gestational diabetes mellitus

4.9.3 Treatment of type 1 diabetes

Insulin replacement is essential in type 1 diabetes. There is ample evidence to show that improved glycaemic control reduces the risk of complications. Subcutaneous insulin administration can vary from two to five injections per day. Multiple dose regimes with a combination of basal insulin (intermediate or usually long acting) and varying doses of rapid-acting insulin meals according to capillary glucose levels, carbohydrate intake and exercise, allow greater flexibility and improve control. In the UK, NICE has licensed continuous subcutaneous insulin infusions (CSII, insulin pumps) for type 1 diabetics in whom multiple dose regimes of insulin have not improved control sufficiently (HbA1c over 8.5%, 69mmol/mol) or led to disabling hypoglycaemic episodes. Additional treatments include islet cell transplantation and whole pancreas transplantation, which may be indicated in patients with recurrent severe hypoglycaemia despite best medical treatment. In addition, cardiovascular risk factor management is also indicated in all patients. Types of insulin are shown in Table 4.13.

Table 4.13 Types of insulin

	Examples	Peak (hours)	Duration (hours)
Rapid	Aspart, Lispro	1	3–4
Short	Regular	2–4	6–8
Intermediate	NPH	4–8	12–16
Long	Detemir	–	18–24
	Glargine	–	20–24
Mixed	Insuman Comb 25 Humulin M3	Varies depending on type – combined intermediate and rapid acting insulin	

4.9.4 Treatment of type 2 diabetes

There are a number of drug categories available to treat patients with type 2 diabetes (Table 4.14), and drug choice needs to be based on a number of factors including glycaemic control, patient preference, side effects and associated comorbidities. A gradual decline in insulin reserves leads to

an increasing requirement for medication and around 30% of type 2 diabetics ultimately need insulin therapy to achieve glycaemic targets. Weight loss (whether by diet and exercise, medication or bariatric surgery) is an important adjunct to medication to improve glycaemic control, and in some cases can cause the remission of diabetes. In addition, cardiovascular risk reduction with control of hypertension, lipids and the use of aspirin are important for management.

Table 4.14 Drugs used in the glucose control of type 2 diabetes

Drug	Action/comments
Sulphonylureas	Increase insulin secretion; risk of hypoglycaemia, weight gain
Biguanides (eg metformin)	Reduced insulin resistance (lower hepatic glucose production). GI side effects. Rare risk of lactic acidosis (usually in the context of concurrent illness and reduced GFR)
α-Glucosidase inhibitors (eg acarbose)	Slows carbohydrate absorption. Unacceptable flatus production for most patients
Thiazolindenediones (eg pioglitazone)	Activate intracellular PPAR-γ thereby reducing insulin resistance. Can cause fluid retention, osteoporosis and link with bladder cancer
Insulin	Used frequently in combination with other drugs; causes weight gain
Glucagon-like peptide agonists (eg exenatide)	Increase secretion of endogenous insulin, suppress glucagon, reduce appetite and promote weight loss. Injected
Dipeptidyl peptidase IV inhibitors (eg sitagliptin)	Increase secretion of endogenous insulin. No weight gain
SGLT-2 inhibitors (eg dapagliflozin)	Allow glycosuria by blocking glucose reabsorption in the kidneys. Some weight loss. Increased risk of urinary tract infections

4.9.5 Glycated HbA1c

Red cell haemoglobin is non-enzymatically glycated at a low rate according to the prevailing level of glucose. The percentage of glycated haemoglobin provides an accurate estimate of mean glucose levels over the preceding 2–3 months and correlates with the risk of microvascular complications. Modern assays for HbA1c are rarely misleading but a few considerations should be made if home glucose monitoring results don't correlate well:

Abnormally low HbA1c

- Haemolysis
- Increased red cell turnover
- Blood loss

- HbS or HbC

Abnormally high HbA1c

- Persistent HbF
- Thalassaemia
- Uraemia (carbamylated haemoglobin)

One thing this does highlight is the potential pitfall of using HbA1c in the diagnosis of diabetes – care must be taken if there is a high red cell turnover or if symptoms are of a rapid onset.

4.9.6 Microvascular and macrovascular complications of diabetes

Long-term diabetic complications are due to vascular damage. Damage to the microvasculature and its consequences correlate well with levels of glycaemic control and can be delayed or prevented by maintaining near-normal glucose levels. Microvascular complications usually take a minimum of 5 years to develop, even with poor glycaemic control. In paediatric cases, the changes in hormones during puberty lead to acceleration of risk as compared to pre-puberty. Complications may be apparent at diagnosis in type 2 diabetes due to delayed diagnosis. Neuropathy (70–90%) and retinopathy (90%) occur in virtually all patients with suboptimal control and longer duration of diabetes. Thirty to forty per cent of patients will develop diabetic nephropathy, usually within 20 years of onset of diabetes.

The incidence of microvascular complications was reduced in type 1 diabetics by around 50% in the Diabetes Control and Complications Trial (DCCT) by tight glycaemic control.

In contrast, macrovascular disease, which is responsible for most of the increased mortality in diabetes, does not appear to be as closely related to the level of glycaemic control. The increased risk of macrovascular disease is partly explained by a combination of hypertension, lower HDL and higher triglyceride levels. Treatment of hypertension reduces not only cardiovascular risk but also the risk of neuropathy and retinopathy (especially the use of ACE inhibitors).

- Note that chest pain due to ischaemic heart disease is often absent or atypical in diabetes and easily missed
- Proteinuria is a strong risk factor for ischaemic heart disease in diabetes, presumably as a marker of endothelial dysfunction. Individuals with microalbuminuria or proteinuria should have more aggressive blood pressure control.
- Peripheral neuropathy predisposes to foot ulceration (occurs in 10% of patients) and, particularly in combination with peripheral vascular disease, increases the risk of amputation (0.5–1%). Some patients with neuropathy develop Charcot's osteoarthropathy with collapse of the bony architecture of the foot and development of deformity.

Micro- and macrovascular complications of diabetes

- **Microvascular**
  - Retinopathy (90%)*
  - Neuropathy (70–90%)*
  - Nephropathy (30–40%)*
  - HbA1c dependent
- **Macrovascular**
  - Ischaemic heart disease (accounts for up to 70% of deaths in diabetes)
  - Peripheral Vascular disease
  - Cerebrovascular disease
  - Less HbAC1c-dependent

*Approximate percentages of diabetics who will have this complication to some degree during their lifetime (data from retrospective studies).

4.9.7 Autonomic neuropathy

Autonomic complications of diabetes may occur in long-standing diabetes, especially in the context of poor control. Complications can be very difficult to treat and there is high morbidity, reduced quality of life and increased mortality.

Manifestations of diabetic autonomic neuropathy

- Postural hypotension
- Gastroparesis
- Gustatory sweating
- Generalised sweating
- Cardiac arrhythmia (‘dead in bed’)
- Diarrhoea, constipation
- Reduced appreciation of cardiac pain

4.10 HYPOGLYCAEMIA

4.10.1 Hypoglycaemia in diabetes mellitus

Autonomic symptoms of hypoglycaemia (sweating, tremor) appear when the blood glucose is <3.5 mmol/L, but can also occur at higher levels when diabetics have poorer glycaemic control, or when there is a rapid drop in glucose levels. Neurogycopaenic symptoms (impaired cerebral function, coma, seizures) occur when glucose levels drop <2.5 mmol/L. In patients on insulin, failure of the

normal counter-regulatory responses (sympathetic nervous system activation, adrenaline and glucagon release) may develop in long-standing diabetes, particularly in the context of frequent hypoglycaemic episodes. This results in hypoglycaemic unawareness. With no warning of impending neurological impairment, the patient cannot take appropriate action. More frequent hypoglycaemic episodes result, exacerbating the problem – 'hypos beget hypos'. Hypoglycaemic awareness can be restored by relaxing control to allow a prolonged hypoglycaemia-free period.

4.10.2 Hypoglycaemia unrelated to diabetes

True hypoglycaemia unrelated to diabetes is relatively rare. Whipple's triad consists of symptoms consistent with hypoglycaemia, measured hypoglycaemia and resolution of symptoms with correction of the low glucose. A supervised 72-hour fast can be used to precipitate and document an episode, particularly to diagnose an insulinoma (where there will be inappropriately elevated insulin and C-peptide levels in conjunction with a low glucose level).

Causes of hypoglycaemia

- Fasting
  - Insulinoma
  - Tumour (IGF-2 mediated)
  - Hypoadrenalism
  - Alcohol
  - Severe liver failure
  - Factitious (insulin or sulphonylurea)
  - Drugs
  - Anti-insulin antibodies (delayed postprandial release of insulin)
- Post prandial
  - Post-gastrectomy/bariatric surgery
  - Reactive
  - Idiopathic (rare)

Chapter 5
Epidemiology

Contents

Epidemiology

5.1 INTRODUCTION

Epidemiology is the study of patterns, associations and effects of diseases that affect a specific population. In modern research this definition is often expanded to consider endemic conditions, ie diseases pre-existing within defined populations, and the effects of health states not classically considered to be a disease, eg body mass index. Epidemiological studies can therefore do the following:

- Suggest which **variables** may cause a disease
- Describe **associations** between variables and **end-points**
- Identify possible interventions and their expected **clinical effect**.

5.1.1 Variables

A variable is a characteristic that is not entirely fixed. Differences in a variable can exist between patients, eg male or female, or within patients, eg change in blood pressure over time.

When designing a study, it is vital to consider how variables interact. Typically, a study will aim to consider the relationship between an exposure variable and an outcome variable in a specific population, eg does treatment with a statin (*exposure variable*) alter risk for death (*outcome variable*) in patients with chronic kidney disease (*population*)? However, in **non-randomised** studies, other variables can directly and indirectly impact on exposure and outcome variables. These relationships must be accounted for to provide accurate results. A drawing of the interactions between variables (termed a 'directed acyclic graph') is helpful in this situation (Figure 5.1).

Confounding

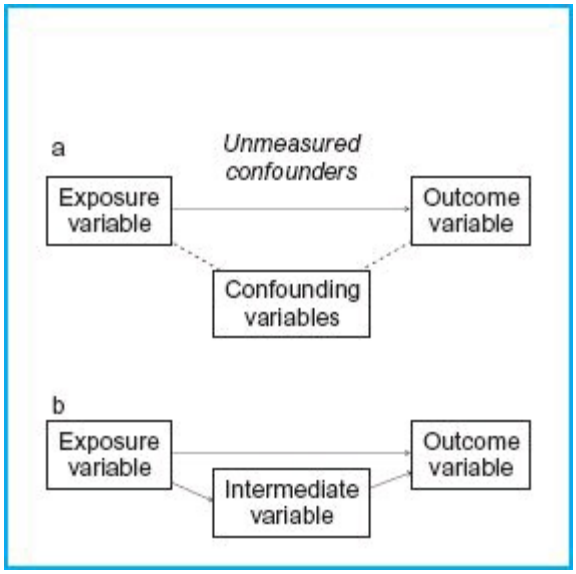
A variable that is directly related to both the exposure variable and the outcome variable, but does not link the two, is referred to as a confounder or confounding variable (Figure 5.1a). An example often used to illustrate this is the significant association between ice-cream sales and open water drowning. Here, hot weather is a confounding variable. When it is warm more people buy ice-cream, but also people will be more inclined to swim, thus increasing drowning risk. The relationship between ice-cream sales and drowning is therefore spurious. This highlights the importance of clinical plausibility when **interpreting results**.

Intermediate variables

Intermediate variables lie on a direct causal pathway between exposure and outcome variables

(Figure 5.1b). An example here is obesity, blood pressure and coronary artery disease. It is known that obesity can increase blood pressure and that increased blood pressure can lead to coronary artery disease. Therefore, when considering if obesity is associated with coronary artery disease, blood pressure is an intermediate variable.

Figure 5.1 Two directed acyclic graphs showing possible relationships between variables in an epidemiological study.



Effect-modifying variables

Where an association exists between exposure and outcome, the strength of association may differ between levels of a given variable, eg increased cholesterol levels are associated with the development of coronary artery disease. However, the **relative risk** associated with higher cholesterol levels is greatest in younger patients. Age is therefore termed an 'effect modifier'. This can alternatively be described as a statistical interaction between age and outcome, or as heterogeneity between strata of patient ages. Where effect modifiers exist, it can be helpful to present overall results and results for subgroups, eg all patients, young patients and older patients.

5.1.2 End-points

Outcome variables can also be referred to as study end-points. These can be measured in different ways:

- *Number of events*: the absolute number of participants in the event who did or did not reach the outcome under investigation. Typically proportions of patients are described as a percentage. This is termed the 'incidence proportion', or 'average risk'

  Rate of events: this describes the number of end-points that occur over a specific time period and is often presented as number of events per 100 patient-years. This is the incidence rate and is calculated by:

- Event rate per 100 patient-years =

$$\frac{\text{Total number of observed events}}{\text{Total number of observed patient-years}} \times 100$$

  Prevalence: this is the proportion of patients in a given population with a disease at any given

- time point. As prevalence is affected by duration of disease, rate of new cases, rate of cure and rate of death, it has greater use in public health studies than in estimating the effect of an exposure variable
- *Survival time*: the length of time each patient is in the study before reaching the end-point or leaving the study.

Study end-points should be clearly defined before the study begins. However, some end-points are difficult to study, because they are rare. In these cases other outcome variables thought to be correlated with the end-point of interest are often substituted, eg doubling of creatinine used instead of starting dialysis. This is referred to as a surrogate end-point. It is important to remember that these cannot be directly substituted for the primary endpoint when considering the results.

5.1.3 Associations

If, after accounting for confounding, the outcome variable occurs with greater frequency in one exposure group than the other, then the exposure is said to be associated with the outcome. When reading results, it is important to remember that evidence of association is not necessarily evidence of **causation**, and that the clinical significance (ie real-world utility) of the association must be considered alongside the statistical significance. Associations should therefore be thought of in terms of absolute risk and relative risk.

Absolute risk

Absolute risk describes what occurs within each exposure group without consideration of confounding effects. This is often presented as the incidence proportion and incidence rate within each exposure group. Absolute risk can be useful when assessing clinical significance and estimating disease burdens at a population level.

Relative risk

The simplest measures of relative risk are the ratio of incidence rate between exposure groups (the incidence rate ratio), and the ratio of incidence proportion between groups (the risk ratio). These measures begin to provide an estimate of treatment effect, but, as they are based on measures of absolute risk, they do not account for confounding caused by differences between groups. These differences can be accounted for using regression equations that adjust for confounding effects – this is referred to as a multivariate analysis.

- *Odds ratio*: this statistic represents the probability of an outcome event in one exposure group relative to the other over a specific time frame. An odds ratio (OR) >1 suggests an increased risk, and an OR <1 a reduced risk. These can be interpreted as percentages, ie an OR of 1.2 represents a 20% increase in risk, and an OR of 0.7 represents a 30% reduction in risk
- *Hazard ratio*: these values are interpreted in the same manner as an OR but can be more useful because information on survival time for each patient is considered. This allows patients with greatly different times in a study (eg 1 year and 10 years) to be accurately compared with each other in the same analysis
- *Time-varying risk:* as variables can change over a study period, eg blood pressure, using a

- single measurement taken at the start of the study, can lead to inaccurate results. Several approaches can be used to account for these changes, with the simplest being to use an average of all values. As a hazard ratio incorporates information on survival time; this methodology can be used to calculate risk for each patient between each measurement. Use of time-varying variables allows a greater amount of data to be analysed and therefore provides a more accurate estimate of risk.

Examples of absolute and relative risk

- If in a study of a drug, the relative risk associated with treatment was 0.5 but the population event rate (absolute risk) was only 1 event per 1000 patient-years, then the clinical benefit that a patient would receive from treatment would be smaller than suggested by looking at the relative risk in isolation
- If in a western European population the annual incidence rate of coronary heart disease was 100 per 10 000 people in obese patients and 50 per 10 000 people in non-obese patients, whereas in an eastern Asian population it was 10 and 5 per 10 000 people in these two groups, then although the relative risk would still be 2 in both populations, the annual absolute risk would be 50 per 10 000 people in the European population, but only 5 per 10 000 people in the Asian population. Thus, although obesity would be as strong a cause of coronary heart disease in the two populations (as indicated by the relative risks), the importance of the association with population health would be much greater in the European population (as indicated by the absolute risks). This is also an example of ethnicity acting as an effect modifier.

5.1.4 Causation

The existence of a statistically significant association between an exposure and an outcome variable cannot be taken to mean that a causal relationship exists. To suggest a causal link, the Bradford–Hill criteria should be satisfied:

- *Temporality*: the outcome must follow the exposure
- *Strength*: larger associations are more likely to have a causal relationship
- *Consistency*: associations should be replicated in separate studies
- *Biological gradient*: a higher level of exposure is associated with a higher incidence of the outcome
- *Plausibility*: the link between cause and effect should be plausible given what is already known. The inverse of this statement can also be considered; the effect is probably causal if no other exposure variable is plausibly linked to the outcome
- *Coherence and experimental evidence*: the observed association can be placed in a context of other laboratory and epidemiological studies (this links to consistency and plausibility)
- *Analogy*: if a similar association can be demonstrated in another setting it is more likely to be causal
- *Specificity*: the more specific the population, exposure and outcome being considered, the more likely any association is to be causal.

An example is given in Table 5.1.

Even when all the Bradford–Hill criteria are addressed, other possibilities should be considered. Chance findings can occur, no matter how statistically significant the results are. More likely are problems related to study design (leading to confounding or **selection bias**), measurement error or incorrect statistical analysis.

5.2 RANDOMISED CONTROLLED TRIALS

Randomised trials randomly allocate patients between exposure variables with the aim of reducing confounding and bias in exposure. These studies are considered ethical where genuine uncertainty exists as to which treatment is the most appropriate. Different methods of **randomisation** exist. As such they are ideal tools for investigating the effect of a treatment, eg a new drug, but cannot be used to investigate exposures where direct allocation to an exposure group cannot be made, eg diabetes. Randomised trials can be open, where the participants and investigators are aware of exposure assignment, single-blinded where either the participants or the investigators are unaware of exposure assignment, or double-blinded, where both the participants and investigators are unaware of treatment assignment. The benefit of blind studies is that it removes any incentive for patients and investigators to introduce bias to data based on preconceived ideas. Well-designed, run and analysed randomised trials provide the strongest standard of evidence.

All randomised trials are required to be registered in the public domain (eg www.clinicaltrials.gov). Such registries provide details of the study design and population of interest, outcome measures, number of participants and intended follow-up period.

5.2.1 Methods and benefits of randomisation

Study powering

Before starting a randomised trial a power calculation is required. The power of the study is the probability of correctly rejecting the null hypothesis (avoiding a type II error). By defining the power required, the difference expected between exposure groups, and the level of statistical significance required between exposure groups (protection from a type I error), it is possible to estimate the minimum number of participants needed in the study. Increasing the power of the study and the final level of statistical significance required will make the final result more likely to be genuine, but can greatly increase the number of patients needed, especially if the expected effect size (the difference in the outcome variable between exposure groups) is small. Table 5.2 shows the number of patients needed.

Table 5.1 Bradford–Hill criteria applied to smoking and lung cancer

Bradford–Hill criteria	Study results
Temporality	In almost all cases, smoking preceded development of lung cancer
Strength of association	Over a 10-fold increased risk for lung cancer associated with smoking

Consistency	Findings replicated in many different studies and patient groups
Biological gradient	Greatest risk for lung cancer seen in the heaviest smokers
Plausibility	Laboratory data had shown that smoking could cause tissue damage
Coherence and experimental evidence	Exposure of animals to cigarette tar had led to development of cancer
Analogy	A causal link between lung cancer and smoking was shown in rats
Specificity	In prospective studies, smoking was the best predictor of developing lung cancer

Randomisation techniques

Properly conducted randomisation avoids any form of systematic allocation of patients to the exposure group. Assigning patients to an exposure group based on factors such as day of visit, hospital record number or date of birth is not truly random.

The simplest form of truly random allocation can be compared with a flip of a coin. Although simple to implement, this approach often results in unequal groups and/or an imbalance in variables between groups. Therefore forms of restricted randomisation are commonly used, including:

- *Block randomisation*: recruited patients are allocated to randomisation blocks of a certain number, eg 10. Within each block, half of the patients are randomised to one exposure and half to another
- *Random allocation*: here the entire study population is treated as a single block. A commonly used example is, for a study of 100 patients, 50 white and 50 black balls placed in a bag. As each patient is recruited, a ball is drawn to define their exposure allocation.

Restricted randomisation prevents imbalance in group sizes but cannot protect against uneven distribution of variables between groups. Although in sufficiently large studies this rarely occurs, some small trials use stratified restricted randomisation. Here subsets of patient are identified based on certain characteristics, eg diabetes. These subsets then undergo restricted randomisation separately from the other recruited patients. This aims to create numerically equal groups with evenly distributed variables.

5.2.2 Trial monitoring

In addition to outcome data, a range of information, primarily about patient safety, is collected during randomised trials.

- *Treatment compliance*: adherence to study medications is regularly assessed, normally by means of a pill count. This is an important measure because poor compliance with medications can alter study results, usually reducing the estimated treatment effect. High levels of non-compliance should be considered when considering the clinical utility of results
- *Adverse events*: all unexpected events that occur during a randomised trial are recorded and a possible relationship to the study drug considered. This information is important when considering the number needed to treat and number needed to harm.

Table 5.2 Number of patients required in each exposure group as required power and statistical significance vary

	Effect size		
	10	**5**	**2**
	Statistical significance set at 0.05		
Power 0.80	42	162	1010
Power 0.90	55	217	1350
Power 0.95	68	268	1670
	Power set at 0.80		
Significance 0.1	33	128	795
Significance 0.05	42	162	1010
Significance 0.01	62	242	1503

A data monitoring committee regularly reviews all available study information. In addition to ensuring that sufficient patients are recruited to the trial, they may terminate the study ahead of schedule for several reasons:

- *Safety concerns*: protection of patient safety is the most important consideration. The number and severity of adverse events is compared between treatment groups. If an imbalance exists, the trial may be stopped
- *Overwhelming benefit*: if an early analysis suggests that a new treatment is unequivocally superior, then it would no longer be ethical to continue the trial
- *Futility:* if there is absolutely no benefit of a new treatment seen at a stage when it would have been expected to be observable, a trial may be stopped in the interests of financial prudence.

5.2.3 Classifications of randomised trials

Randomised trials can be classified by their design. The most common form of randomised trial is a parallel group study, where patients are allocated to a single exposure group for the duration of the study. Other study designs include:

- *Crossover*: participants switch exposures at a defined point in the study
- *Factorial*: this design is used when more than two exposures can be defined. Patients are randomised to a combination of possible exposures
- *Cluster*: participants are not randomised individually, but instead are randomised by preexisting groups, eg dialysis unit.

Another means of classifying randomised trials is by their outcome measure. For a trial to be ethical, new treatments must be compared with the current, accepted, best treatment. A study that aims to prove the new treatment results in better patient outcomes is termed a ‘superiority trial’. Other

designs include non-inferiority and equivalence studies, which aim to demonstrate that a new treatment is no worse than the current standard. These trials are typically performed where a new treatment is cheaper or is thought to have fewer side-effects.

5.3 OBSERVATIONAL STUDIES

5.3.1 Cohort studies

Cohort studies are longitudinal and typically observe a specific patient subgroup, eg those with chronic kidney disease. Although many studies are performed over a relatively short time period, some cohort studies, eg the Framingham heart study, have a period of observation in excess of 50 years. As with randomised controlled trials, patient groups are defined by exposures; however, these are not randomly allocated and can be defined in a prospective or retrospective manner. Cohort studies are most commonly used to identify risk factors for the development of disease:

- *Prospective*: here patient groups are defined before the period of observation starts, reducing the risk of introducing selection bias. Follow-up occurs at regular intervals and multiple endpoints can be considered
- *Retrospective*: here, data about exposure are collated after the event of interest has occurred. Although this can allow research questions to be answered in a much shorter time, there is a risk of recall bias affecting results. This is due to difficulties that patients can have in remembering details from a number of years previously. An alternative form of this is response bias, where an apparent difference between groups may be due to only one group being more prepared to discuss a specific health issue.

Cohort studies, especially those performed over a period of years, can be heavily influenced by loss of patients to follow-up, whether this is due to choosing to leave the study or death. This can result in only the healthiest patients remaining in the study, introducing bias into the results. Recently, **joint models** have been developed and are partly able to address this issue. Here, a change in a measured characteristic over time, eg renal function, is analysed in relation to patient survival.

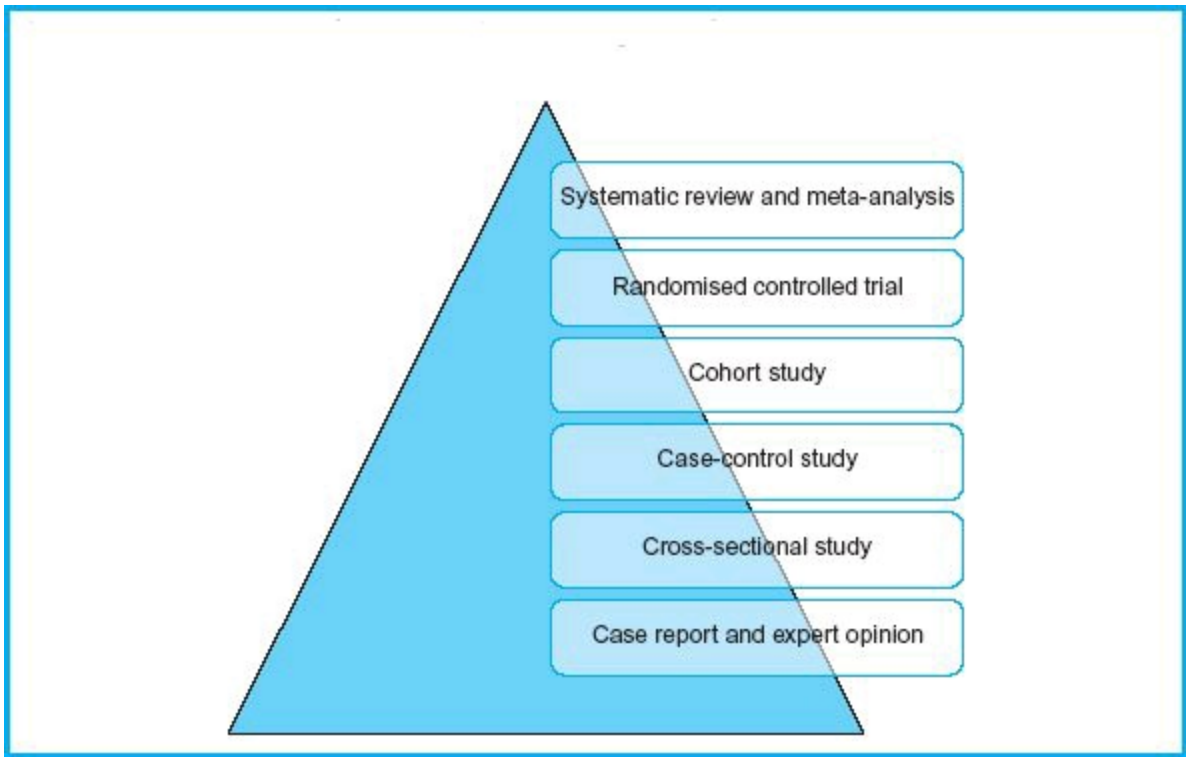
5.3.2 Case-control studies

In a case-control study two patient groups, one with a specific outcome/exposure and one without, are identified and compared. Case-control studies are most commonly used to identify variables associated with a disease where little information already exists. To consider the role of smoking in causing lung cancer, the case group would be formed from people with lung cancer and the control group from people without lung cancer. As with retrospective cohort studies, recall bias is a recognised problem. Equally important is the selection of the control group. To allow an accurate comparison to be made, these patients should be drawn from the same population as the cases, have a similar range of other disease risk factors, and have been selected independently of the outcome/exposure in question. Where this is not the case, selection bias will influence results. Due to these potential problems, case-control studies are placed below cohort studies on the hierarchy of evidence (Figure 5.2).

5.3.3 Cross-sectional studies

Cross-sectional studies consider relationships between exposure and outcome at a single time point, and are therefore commonly used to describe disease prevalence. By using odds ratios, cross-sectional studies can also be used to generate hypotheses about risk factors for disease. This can be made challenging where reverse causality exists, eg in a study considering a possible association between increased body weight and cancer, the tendency for cancer to lead to weight loss may affect results.

Figure 5.2 The hierarchy of evidence with the strongest evidence at the top and the weakest at the bottom.



An important limitation of cross-sectional data (and other forms of observational study) is that assumptions about individuals are made based on conclusions drawn from a population level. This can lead to a phenomenon termed 'Simpson's paradox', where an association exists in one direction at a population level, but is entirely reversed when subgroups of patients are considered. The most famous example of this is based on data from admissions to the University of California, Berkley in 1973. Overall, 44% of male applicants were admitted, compared with 35% of female applicants, suggesting a gender bias. However, when admissions to the university were broken down by individual department, most actually admitted a greater proportion of female applicants than male. In the final analysis it was noted that male students had applied to less competitive departments, leading to the apparent imbalance.

5.3.4 Case reports

Case reports are anecdotal evidence, typically describing events related to a single patient. As such they are placed at the bottom of the hierarchy of evidence. Typically they describe rare events – either details surrounding a rare diagnosis or uncommon features of a common disease. Case reports are

prone to **publication bias**, where only results deemed highly important or statistically significant are submitted, and negative findings are not published. Despite this, case reports are an important means of communicating novel findings.

5.3.5 Ecological studies

In ecological studies average values for one or more groups of people are collected. Data of this kind sometimes permit the average incidence rate or prevalence of a given disease to be compared between different populations (eg comparing bowel cancer mortality rates between countries), or within a given population over time (eg bowel cancer mortality rates in a country over a period of decades). Although potentially providing clues about causes of disease, ecological studies are not themselves adequate for testing aetiological hypotheses, primarily because the absence of data on confounders in individuals greatly hampers the ability to control for confounding.

The shared and distinguishing characteristics of different study designs are shown in Figure 5.3.

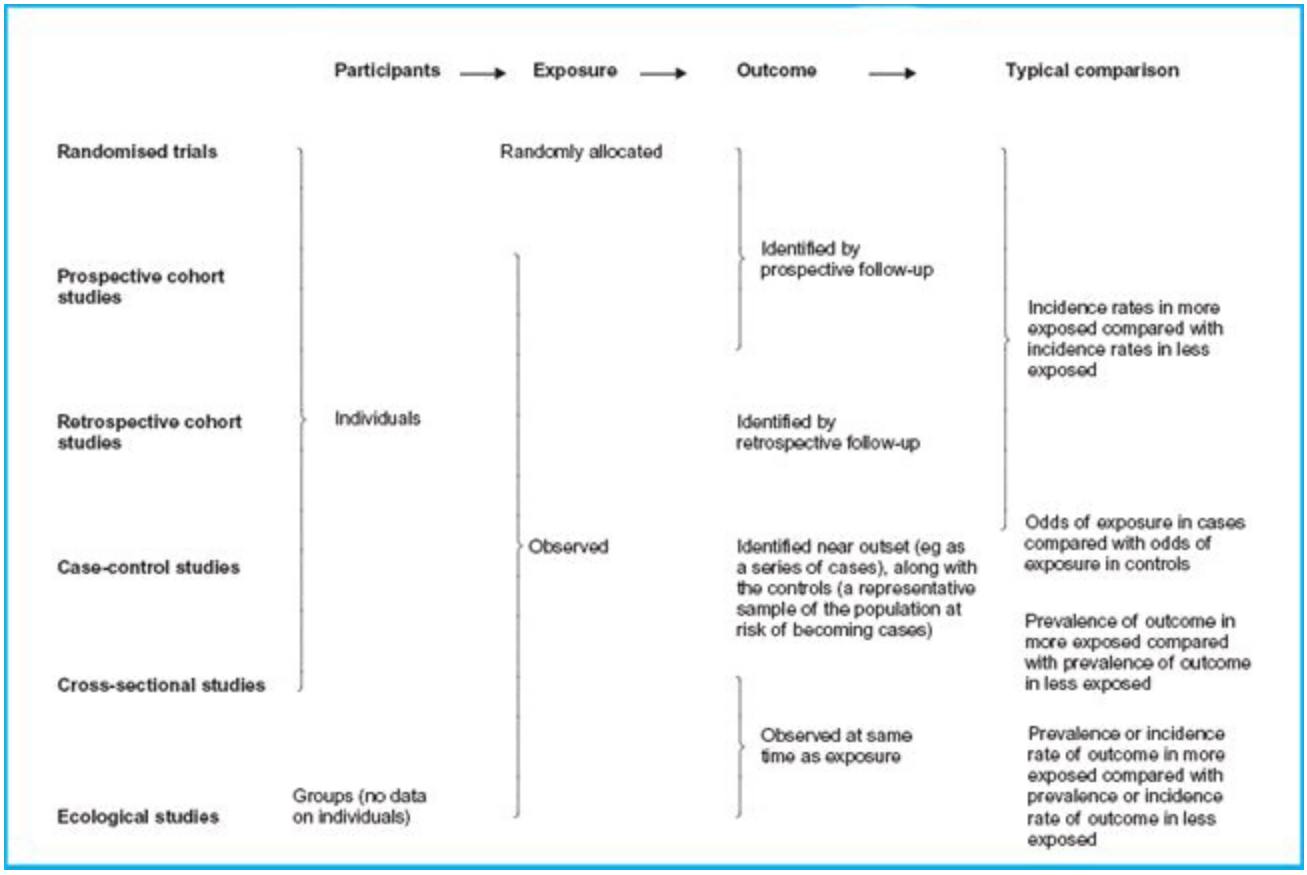
5.4 INTERPRETING RESULTS

Results of all studies, whether randomised or observational, should be interpreted in the light of what is already known on the subject and what the latest study can add. Then the clinical and statistical significance of the presented results should be considered. It is rare that a single study can provide a definitive answer, so evidence from many sources must be considered. When doing this, the quality of the evidence must also be considered to allow greater weight to be placed on more credible studies. In the UK, evidence is labelled from A to D, in line with the hierarchy of evidence (Table 5.3). More detailed approaches have been proposed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group.

Table 5.3 Grading of evidence in the UK

Grade of evidence	Description
A	Consistent randomised controlled trial and/or cohort study results. Clinical decision rule validated in different populations
B	Consistent retrospective cohort, exploratory cohort, ecological study or case-control study and/or results extrapolated from level A studies
C	Case study or case series and/or extrapolated results from level B studies
D	Expert opinion

Figure 5.3 Some shared and distinguishing characteristics of common epidemiological study designs.



5.4.1 Randomised studies

Randomised trials must pre-specify outcomes of interest to allow a power calculation to be performed. If a different outcome is assessed at the end of the study, there is no certainty that the study was sufficiently powered to assess this and the validity of the result is less. Equally if a pre-specified outcome is assessed but insufficient patients were recruited to meet the power calculation, then the finding must be considered less reliable. Other issues to consider include the following:

- *Treatment compliance*: when patients in a trial do not adhere to the study medication, results may be affected. If equal proportions of patients in each exposure group have poor compliance, then an estimated treatment effect will be harder to detect. If non-compliance is uneven between groups, then this may over- or understate the treatment effect. Poor compliance may also suggest a high side-effect profile in one group, raising questions about tolerance of a medication, and therefore its real-life use
- *Loss of blinding*: a blinded trial protects against bias. Occasionally specific patients need to be unblinded. Should this occur in a substantial number, then there is a risk of bias having been introduced
- *Intention-to-treat analysis*: when patients drop out of a study, cease taking a study drug or move into a different exposure group, results could be altered. In an intention-to-treat analysis, outcomes for all patients are compared based on their randomly assigned exposure group at the start of the trial. This minimises any confounding that may occur due to deviations from randomisation
- *Subgroup analysis:* as subgroups, by definition, comprise a smaller number of patients than the overall study, analyses on these groups have a greater risk for type II error. Subgroup analyses

- specified before the study began are more likely to be adequately powered. Analyses designed after the study finished (post hoc analyses) should be interpreted with more caution.

5.4.2 Observational studies

The following are key questions when assessing an observational study:

- *Control of confounding*: differences in variables between exposure groups should be considered and (if relevant to the exposure or outcome) adjusted for in the statistical analysis. Where this does not occur the chance of an incorrect result is greater
- *Verification of events*: in randomised trials it is common to have an event adjudication committee to review case records and apply a consistent definition for events, eg myocardial infarction. In cohort studies this is less common, and in retrospective cohort studies almost impossible. This may introduce variability into reported events and hence the results
- *Selection bias*: as for case-control studies it is important to consider if it is appropriate to directly compare all patients in cohort studies with each other. If exposure groups are drawn from two distinct populations, they may systematically differ. Alternatively, if the study is based on a non-random sample of the population, it may not be appropriate to extrapolate the results beyond this patient group (this is the external validity of the study).

Due to the potential for error or disagreement to exist in even the best-designed studies, formal approaches for aggregating and comparing the results of studies have been devised.

5.5 SYSTEMATIC REVIEW AND META-ANALYSIS

A systematic review of a topic provides a complete summary of all the available literature. First, detailed searches of research databases are performed to locate all potentially relevant papers. These are then reviewed in relation to predetermined selection criteria for inclusion in the review. Published results from all papers selected for inclusion in the review are compared, often by meta-analysis, with the quality of each paper also considered.

A meta-analysis typically examines the relationship between a single exploratory and a single outcome variable. Data from two or more studies are pooled to increase patient numbers and therefore the validity of findings. To provide accurate results, all published data must be considered and unpublished data sought. This aims to limit the problem of publication bias and is demonstrated using funnel plots. In these, sample size is plotted against effect size, with a symmetrical funnel shape becoming visible where there is no publication bias. Meta-analysis has the greatest statistical power where individual patient data are used, but can also be performed where only overall study results are available.

The Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) groups publish guidelines for the undertaking and reporting of a systematic review or meta-analysis.

Although a properly performed systematic review and meta-analysis of multiple randomised studies

can be considered the highest level of evidence available, important limitations may exist:

- *Quality of available data*: the quality of a meta-analysis depends upon the quality of available data to pool for analysis. Meta-analysis does not improve or mitigate poor design of original studies: garbage in leads to garbage out!
- *Inappropriate generalisation*: although a benefit of meta-analysis is to generalise results over a wider population than is represented in a single study, over generalisation can occur
- *Impact of unpublished data*: as discussed above, efforts should be spent to identify all available results to limit publication bias
- *Publication delay*: with vast amounts of research being published each month, there is potential for systematic reviews and meta-analyses to be 'out of date' by the time of publication.

Chapter 6
Gastroenterology

CONTENTS

6.11.1 Investigations of acute abdomen

Gastroenterology

6.1 ANATOMY AND PHYSIOLOGY OF THE GI TRACT

6.1.1 Oesophagus

The oesophagus is 25 cm long, and is composed of outer longitudinal and inner circular muscle layers. In the upper part these are both striated muscle and in the lower part both are smooth muscle, with the myenteric plexus lying between the two layers. The mucosa is lined with squamous epithelium.

The oesophagus is protected from acid damage by a number of defences, including the lower oesophageal sphincter pressure (10–30 mmHg), salivary bicarbonate, oesophageal *bicarbonate* secretion, gravity and the 'pinchcock' effect of the diaphragmatic crura.

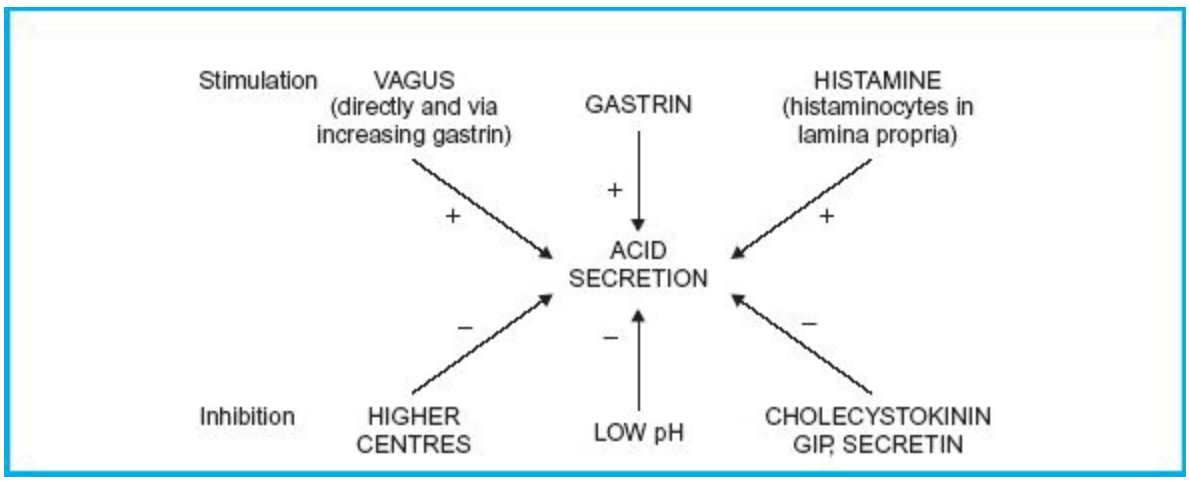
6.1.2 Stomach

At the gastro-oesophageal junction, the squamous epithelium of the oesophagus changes to columnar epithelium. Secretions total approximately 3 litres per day. In gastric pits, there are chief cells producing pepsin, and parietal cells (fuelled by H+ K+ ATPase) producing hydrochloric acid and intrinsic factor. Mucus and bicarbonate are secreted by surface cells.

Innervation is both parasympathetic via the vagus (motor and secretory supply) and sympathetic via Meissner's and Auerbach's plexuses. Blood supply is derived from the coeliac trunk.

The control of gastric acid secretion is summarised in Figure 6.1 (GIP = gastric inhibitory peptide).

Figure 6.1 Control of gastric secretion.



6.1.3 Pancreas

Between 1200 ml and 1500 ml of alkaline fluid, containing proteins and electrolytes, is secreted daily. Ninety-eight per cent of the pancreatic mass consists of exocrine acini of epithelial cells; the islets of Langerhans from which endocrine secretion occurs make up the remaining 2%. Innervation is via the coeliac plexus.

Pancreatic secretions

- **Exocrine** (from acini of epithelial cells)
  - Trypsinogen
  - Chymotrypsinogen
  - Pancreatic amylase
  - Lipase
- **Endocrine** (from islets of Langerhans)
  - Glucagon from α cells
  - Insulin from cells
  - Somatostatin from cells
  - Pancreatic polypeptide

6.1.4 Liver

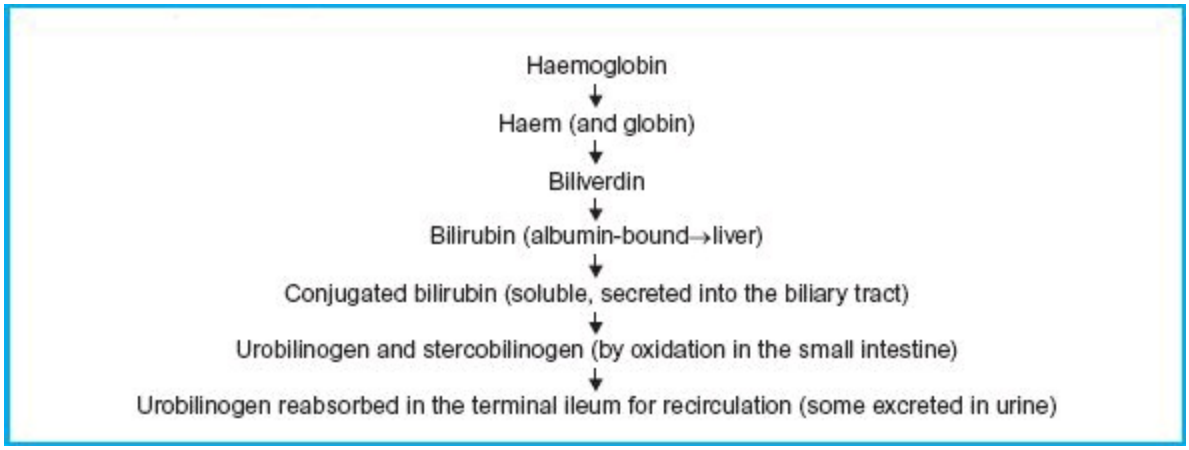
Blood supply is from the hepatic artery and portal vein (bringing blood from the gut and spleen); drainage is via the hepatic vein into the inferior vena cava. Between 250 ml and 1000 ml of bile is produced daily; stimulation of release from the gall bladder is by cholecystokinin. A schema of biliary metabolism is shown in Figure 6.2.

6.1.5 Small intestine

This is 2–3 metres in length, with the villi and enterocytes providing a huge surface area that allows the absorption of up to 6 litres daily. The main function of the small intestine is absorption, with most taking place in the duodenum and jejunum. However, it also has an important immune role, with lymphoid aggregates throughout, especially in the form of Peyer's patches in the ileum.

There is secretion of approximately 2 litres of alkaline fluid with mucus and digestive enzymes daily from the enterocytes of the villi, Paneth cells at the bases of the crypts of Lieberkühn and Brunner's glands.

Figure 6.2 Biliary metabolism.



Blood supply from the mid-duodenum onwards is derived from the superior mesenteric artery.

6.1.6 Colon

This is 90–125 cm in length and its main function is the absorption of water, sodium and chloride. Typically 1–1.5 litres is absorbed daily but in some circumstances this can rise to 5 litres per day. Secretion of mucus, potassium and bicarbonate also takes place.

The blood supply is derived from the superior mesenteric artery up to the distal transverse colon; the inferior mesenteric artery supplies the remainder.

6.1.7 Gut hormones

The response to a meal is regulated by complex hormonal and neural mechanisms (Table 6.1). Secretion of most hormones is determined by the composition of the intestinal contents.

Table 6.1 Major gut hormones

Hormone	Source	Stimulus	Action
Gastrin	G cells in antrum	Gastric distension Amino acids in antrum	Secretion of pepsin, gastric acid and intrinsic factor
Cholecystokinin-pancreozymin (CCK-PZ)	Duodenum and jejunum	Fat, amino acids and peptides in small bowel	Pancreatic secretion Gallbladder contraction Delays gastric emptying
Secretin	Duodenum and jejunum	Acid in small bowel	Pancreatic bicarbonate secretion Delays gastric emptying
Motilin	Duodenum and jejunum	Acid in small bowel	Increases motility
Vasoactive intestinal	Small intestine	Neural stimulation	Inhibits gastric acid and pepsin secretion

peptide (VIP)			Stimulates secretion by intestine and pancreas
Gastric inhibitory peptide (GIP)	Duodenum and jejunum	Glucose, fats and amino acids	Inhibits gastric acid secretion Stimulates insulin secretion Reduces motility
Somatostatin	D cells in pancreas	Vagal and adrenergic stimulation	Inhibits gastric and pancreatic secretion
Pancreatic polypeptide	PP cells in pancreas	Protein-rich meal	Inhibition of pancreatic and biliary secretion

6.1.8 Metabolism of haematinics

Iron

Total body iron is between 4 g and 5 g, with iron content being maintained by control of absorption in the upper small intestine. Most iron intake is in the Fe^{3+} form, and approximately 5–10% of that consumed is absorbed, which amounts to only 1–2 mg/day. This intake is balanced by identical daily losses through the GI tract, largely resulting from red cell breakdown. Iron is better absorbed from foods of animal than of plant origin.

Factors which affect iron absorption

- **Increased absorption**
  - Increased erythropoiesis (eg pregnancy)
  - Decreased body iron (eg GI blood loss)
  - Vitamin C*
  - Gastric acid*
- **Decreased absorption**
  - Partial/total gastrectomy
  - Achlorhydria
  - Disease of the small intestine (eg Crohn's disease, coeliac disease)
  - Drugs (eg desferrioxamine)

*Gastric acid and vitamin C promote reduction of Fe^{3+} to Fe^{2+} which is more easily absorbed.

For a more detailed account of iron metabolism see Chapter 9, Haematology.

Folate

The usual requirement for this nutrient is approximately 50–200 g/day. It is present in green

vegetables. Absorption takes place in the duodenum and jejunum, so deficiency may occur with coeliac disease, Crohn's disease or any other small-bowel pathology. Dietary folate is converted into 5-methyltetrahydrofolate, which enters the portal blood. Deficiency may also develop if the demands of the body increase, for example in haemolysis, pregnancy and in patients being treated with antimetabolites such as methotrexate. Clinical deficiency results in a macrocytic anaemia, and in pregnancy this can be associated with neural tube defects in the fetus.

Vitamin B_{12}

Adults require 1–2 g of dietary vitamin B_{12} daily. This is predominantly obtained from foods of animal origin. It is tightly protein-bound and is released by peptic digestion. Oral B_{12} binds to intrinsic factor in the stomach and is then absorbed in the terminal ileum. Deficiency can therefore occur for several reasons:

- Dietary deficiency in vegetarians or vegans
- Post-gastrectomy (lack of intrinsic factor)
- Atrophic gastritis (pernicious anaemia)
- Terminal ileal disease
- Blind loops

Investigations for pernicious anaemia

Until 2003, the Schilling test was used to differentiate between deficiency due to terminal ileal malabsorption and lack of intrinsic factor (eg post-gastrectomy, pernicious anaemia), however, this test is no longer available. Gastric parietal cell antibodies, whilst present in the majority of patients, are non-diagnostic. Diagnosis can be confirmed in 50% of cases with serum intrinsic factor antibodies and hypergastrinaemia. In patients with low B_{12} without intrinsic factor antibodies, intrinsic factor secretion can be measured via nasogastric tube following pentagastrin stimulation (*N* > 2000 U/h).

6.2 DISORDERS OF THE MOUTH, TONGUE AND SALIVARY GLANDS

6.2.1 Mouth ulcers (aphthous ulcers)

Aphthous ulcers can be minor aphthae, major aphthae or herpetiform ulcerations. Minor aphthae are small, cause minimal symptoms, heal within 7–10 days and leave no scar. Major aphthae are larger, heal slowly over a month, occur more frequently and can leave a scar. Herpetiform ulceration is common in elderly females, can be very painful, recurrent, and begins with vesicles and progresses to ulceration.

Causes of mouth ulcers

- Inflammatory bowel disease
- HIV
- Drugs
- Malignancy
- Nutritional deficiency (B_{12}, folate, iron)
- Behçet's disease
- Coeliac disease
- Sweet syndrome

6.2.2 Oral manifestations of systemic and dermatological disorders

The following can cause oral lesions:

- systemic lupus erythematosus
- sjögren syndrome
- inflammatory bowel disease
- gastro-oesophageal reflux disease
- sarcoidosis
- amyloidosis
- HIV
- drugs
- infections
- Stevens–Johnson syndrome
- pemphigus vulgaris
- pemphigoid
- epidermolysis bullosa
- acanthosis nigricans
- lichen planus.

6.3 DISORDERS OF THE OESOPHAGUS

6.3.1 Achalasia

Achalasia is a condition of unknown aetiology resulting in abnormal peristalsis and lack of relaxation of the lower oesophageal sphincter. There is a concentric thickening of the muscularis propria layer of the oesophagus. The incidence is approximately 1/100 000 per year, occurring at any age (usually 3rd to 5th decade) but rarely in children.

It is demonstrable on manometry, endoscopy or barium studies, where it is characterised by oesophageal dilatation with a smooth distal 'bird's beak' stricture. Chest X-ray may show an air/fluid

level behind the heart. Presentation is usually with dysphagia which, unlike other types of stricture, may affect solids and liquids from the outset.

Regurgitation, pain and weight loss may occur. There is a risk of recurrent aspiration. Squamous carcinoma is a late and rare complication.

Treatment is with endoscopic dilation or surgical myotomy. In some cases, injection of botulinum toxin to the lower oesophageal sphincter may be effective.

6.3.2 Reflux oesophagitis

Reflux oesophagitis is an endoscopic diagnosis. Symptoms of acid reflux are extremely common – *approximately 40% of Western populations experience 'heartburn' at least once per month*. The development of reflux oesophagitis depends on a number of factors.

Factors predisposing to reflux oesophagitis

- **GI factors**
  - Acid/bile content of refluxate
  - Mucosal defences in oesophagus
  - Gastric/oesophageal motility
  - Hiatus hernia
- **Other factors**
  - Obesity
  - Smoking
  - Alcohol and coffee intake
  - Large meals (especially late at night)
  - Drugs (most commonly theophyllines, nitrates, calcium antagonists and anticholinergics)

The correlation between symptoms and endoscopic appearances is poor; severe symptoms are compatible with a normal gastroscopy. The gold standard for diagnosis is 24-hour oesophageal pH monitoring. The advent of impedance pH monitoring also enables the detection of non-acidic reflux events (pH >4), which may be of diagnostic importance, particularly if there is correlation between these episodes and symptoms, enabling differentiation from functional heartburn.

- The main symptom is heartburn but other symptoms include chest pain, odynophagia (painful swallowing) and dysphagia due to oesophageal dysmotility
- Complications include strictures, haemorrhage, Barrett's oesophagus and carcinoma of the oesophagus (independent of Barrett's).

Treatment of reflux oesophagitis

Treatment is with lifestyle modifications (not evidence-based), antacids, H_2 antagonists or proton pump inhibitors. There is currently no evidence for addition of a pro-motility agent (metoclopramide or domperidone) for refractory symptoms. Baclofen has been shown to be effective in reducing reflux events and controlling refractory symptoms, but its use is limited by poor tolerability. Surgery is indicated for patients failing medical therapy, those with large-volume reflux, bile reflux and those preferring to avoid long-term medical therapy. Most fundoplication procedures are now performed laparoscopically, and endoscopic anti-reflux procedures are under evaluation.

Patients with functional heartburn (after negative pH impedance studies) may benefit from pain modulator therapies (eg selective serotonin reuptake inhibitors and tricyclic antidepressants).

Complications of gastro-oesophageal reflux:

- Barrett's oesophagus
- benign oesophageal stricture
- dental erosions
- nocturnal asthma
- laryngitis.

6.3.3 Other causes of oesophagitis

Candidal oesophagitis may occur in patients who are immunosuppressed, on antibiotics or steroids (especially inhaled corticosteroids), or suffering from diabetes mellitus. Barium swallow shows irregular filling defects in the oesophagus and white patches can be seen on endoscopy – biopsy will confirm the diagnosis.

Chemical oesophagitis may be caused by drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), tetracycline and potassium chloride tablets.

Eosinophilic oesophagitis is now an increasingly recognised entity, presenting as dysphagia or with food bolus obstruction.

Recognised endoscopic oesophageal abnormalities include:

- rings (trachealisation)
- longitudinal furrows
- narrowed calibre
- felinisation (transient rings)
- oedema and crêpe paper oesophagus.

Diagnosis requires histological finding of the eosinophilic-predominant infiltration of the oesophageal mucosa. The mainstay of treatment is with topical swallowed corticosteroids (eg fluticasone and budesonide, via metered-dose inhalers). Data supporting the use of specific dietary approaches for management of eosinophilic oesophagitis are currently lacking.

Herpes simplex virus (HSV) may cause oesophagitis in the immunocompromised.

6.3.4 Barrett's oesophagus

This is found in 10–20% of patients with longstanding acid reflux. It consists of extension of the columnar gastric epithelium into the oesophagus to replace the normal squamous epithelium. It is usually caused by chronic acid exposure, and it is premalignant, although estimates of the rate of transformation to adenocarcinoma vary widely from 30 to 100 times greater than in the normal population. Treatment is of the underlying reflux disease; the benefits of regular endoscopic surveillance and biopsy to detect dysplastic change are controversial, although most centres undertake periodic endoscopy with multiple biopsies to detect evidence of dysplastic change. Photodynamic therapy, argon-beam ablation and endoscopic mucosal resection are being assessed as potential cures. Patients need to receive long-term acid suppression therapy.

Hiatus hernia occurs when part of the upper stomach herniates through the diaphragm into the chest and is extremely common, especially with increasing age and obesity. The majority are asymptomatic and found incidentally during investigations. There are two types:

- Sliding, 80% – may cause aspiration and acid reflux
- Rolling, 20% – may obstruct or strangulate.

Hiatus hernia can be diagnosed at endoscopy, by CT scan or with barium studies, and may be seen on a plain chest X-ray. Treatment is symptomatic with acid suppression where necessary. Surgical correction may sometimes be warranted.

6.3.5 Oesophageal carcinoma

Oesophageal carcinomas can be squamous or adenocarcinoma. The incidence of the latter is rising rapidly, and adenocarcinomas might soon be the most common oesophageal malignancies. It also increases with advancing age. The squamous tumours arise in the mid-thoracic portion of the oesophagus, while adenocarcinomas arise in the lower oesophagus or on a background of Barrett's mucosal changes.

Risk factors for and clinical features of oesophageal carcinoma

- **Risk factors**
  - Smoking
  - High alcohol intake
  - Plummer–Vinson syndrome
  - Achalasia
  - Barrett's oesophagus
  - Chronic reflux (independent of Barrett's oesophagus)
  - Chinese or Russian ethnicity
  - Obesity (for adenocarcinoma)
  - Tylosis (autosomal dominant palmar and plantar keratosis – very high risk)
- **Clinical features**

- Pain and dyspepsia
- Progressive dysphagia for liquids then solids
- Weight loss
- Vomiting

Oesophageal carcinoma is often asymptomatic until a late stage, resulting in poor survival figures. Diagnosis is usually by endoscopy, allowing biopsy and histological confirmation. Barium swallow typically shows a stricture with irregular shouldering, unlike the smooth outline of a benign peptic stricture. CT scanning is used for staging, particularly for detection of distant metastases, although the accuracy is very poor, especially for lymph node spread; laparoscopy may be useful. Endoscopic ultrasound is especially useful for assessing the locoregional (T and N) staging and is becoming increasingly available.

Treatment of oesophageal carcinoma

- **Surgery**
  - Radical, high operative mortality (up to 10%)
  - Only a third of lesions are suitable for resection at presentation
  - Improves 5-year survival to approximately 10%
- **Oesophageal stenting**
- **Radical radiotherapy***
- **Chemotherapy*** (eg epirubicin, cisplatin, 5-fluorouracil)

*Used alone or in combination with surgery.

Over 50% of patients have local or distant spread such that palliation is the only option. The overall 5-year survival is less than 10%, but survival is age-related. Those diagnosed at an early stage may be cured by surgery.

6.4. DISORDERS OF THE STOMACH

6.4.1 Peptic ulcer disease

Most epidemiological data are from studies predating the rediscovery and treatment of *Helicobacter pylori*. The incidence rates of peptic ulcer are 0.1–0.3%; the ratio of duodenal to gastric ulceration is 4:1, and males are more susceptible than females. Incidence increases with age and peaks at approximately 60 years of age. Most patients are treated medically with acid suppression and *H. pylori* eradication, and surgery is limited to those with complications unresponsive to medical or endoscopic therapy.

Current NICE guidelines recommend a ‘test and treat’ strategy for the management of dyspepsia. This will heal underlying lesions and avoid the necessity for endoscopy in many cases. Patients with ‘sinister’ symptoms (weight loss, iron deficiency, dysphagia, haematemesis/melaena or an abdominal

mass) require urgent endoscopy to exclude gastric and oesophageal malignancy.

Peptic ulcer disease

- **Risk factors**
  - *H. pylori* colonisation
  - High alcohol intake
  - NSAID use
  - Severe stress
  - High-dose steroids*
  - Male sex
  - Smoking (increases acid, decreases protective prostaglandins)
  - Zollinger–Ellison syndrome

*When combined with NSAIDs.

- **Clinical symptoms**
  - Epigastric pain (sometimes radiating to the back if a posterior duodenal ulcer)
  - Vomiting
  - Symptoms often relapsing/remitting
  - Weight loss
  - Iron-deficiency anaemia
  - Acute haemorrhage**

**Duodenal ulcers are the most common cause of upper GI haemorrhage.

Causes of upper gastrointestinal haemorrhage

- **Common**
  - Duodenal ulcer – 35%
  - Gastric ulcer – 20%
  - Gastric erosions – 18%
  - Mallory–Weiss tear – 10%
- **5% or less**
  - Duodenitis
  - Oesophageal varices
  - Oesophagitis
  - Upper GI neoplasia
- **Rare (1% or less)**
  - Angiodysplasia

- Hereditary haemorrhagic telangiectasia
- Portal hypertensive gastropathy
- Aortoduodenal fistula

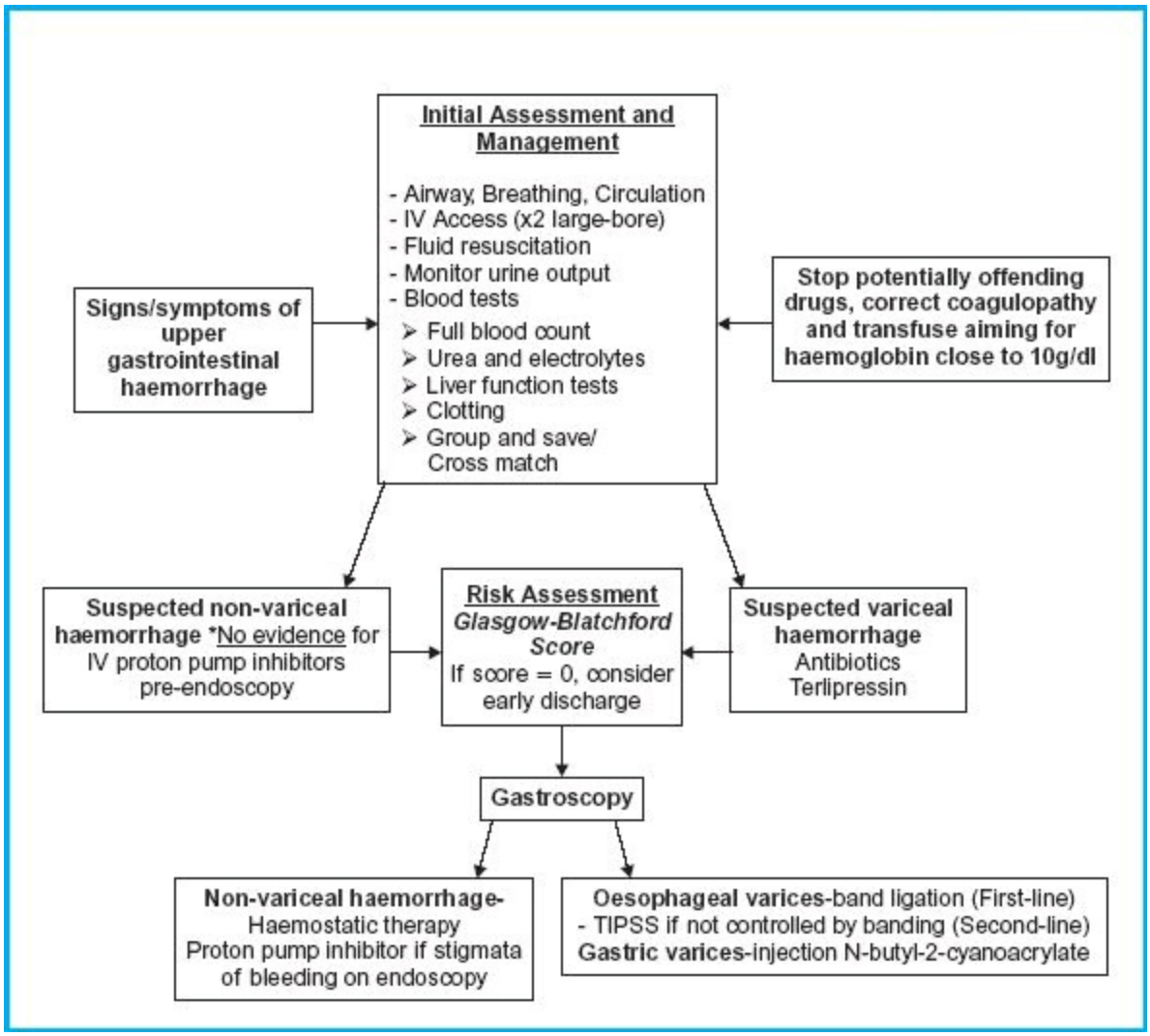
Risk assessment in the management of upper gastrointestinal bleeding

The Glasgow–Blatchford score is a useful calculation of risk to identify the urgency of treatment to manage upper gastrointestinal haemorrhage (see Figure 6.3). This score takes into account factors such as blood tests (haemoglobin and urea), physiological parameters (systolic blood pressure and heart rate), presenting symptoms (melaena and syncope) and co-morbidities (hepatic disease and cardiac failure).

Helicobacter pylori

This Gram-negative spiral bacillus is the primary cause of most peptic ulcer disease. Infection rates increase with age – more than half of those over 50 years of age are colonised by *H. pylori* in the gastric antral mucosa. *H. pylori* has been detected in 70% of patients with gastric ulcer and over 90% of patients with duodenal ulcer, compared with 50% of control subjects.

Figure 6.3 Management algorithm for upper gastrointestinal hemorrhage (adapted from NICE guidelines: Acute upper gastrointestinal bleeding: management, 2012).



Detection of *Helicobacter pylori*

- In patients <55 years of age, without alarm symptoms, non-invasive investigations such as urea breath tests (sensitivity 88–95% and specificity 95%–100%) and stool antigen tests (sensitivity 94% and a specificity of 92%) are recommended. (Malfertheiner *et al*. *Gut* 2012;61:646-664
- Urea breath test – the patient ingests urea labelled with ^{14}C; CO_2, produced by urease, is detected in the exhaled breath
- Stool antigen testing – detection of Helicobacter antigen by enzyme immunoassay
- Serology (stays positive after treatment and NOT useful for confirming eradication)

In patients requiring endoscopy:

- Antral biopsy at endoscopy with haematoxylin/eosin or Giemsa stain
- Urease testing – the bacillus secretes a urease enzyme which splits urea to release ammonia. A biopsy sample is put into a jelly containing urea and a pH indicator; this will change colour if *H. pylori* is present
- In cases of recurrent *H. pylori*, culture from antral biopsies may be used to detect antibiotic sensitivities

Proton pump inhibitors should be stopped for 2 weeks before testing by culture, histology, urease test, Urea breath test or stool antigen test.

H. pylori causes chronic gastritis and is associated with gastric carcinoma. All symptomatic patients found to be positive should undergo eradication therapy. Effective eradication should be assessed by stool testing (least invasive, cost-effective, highly specific and sensitive), repeat biopsies or breath testing in patients with complications (perforation or haemorrhage) and those with persistent symptoms. Tests to confirm eradication, when indicated, should be performed at least 4 weeks after treatment.

Relapse of peptic ulcer disease after *H. pylori* eradication is less than 5% per year, compared with more than 60% in patients without eradication therapy. Evidence to support eradication of *H. pylori* in patients with non-ulcer dyspeptic symptoms is mixed, although meta-analysis data suggests that the number needed to be treated to cure one patient is 20. Eradication regimes vary but usually involve triple therapy of a proton pump inhibitor and two antibiotics (eg amoxicillin and clarithromycin); metronidazole resistance is a problem in some areas.

6.4.2 Zollinger–Ellison syndrome

This is a rare condition with an incidence of one per million population. Gastrin-secreting adenomas cause severe gastric and/or duodenal ulceration – the tumour is usually pancreatic in origin, although it may arise in the stomach, duodenum or adjacent tissues. Fifty to sixty per cent are malignant; 10% are multiple neoplasms. It may occur as part of the syndrome of multiple endocrine neoplasia type 1, in which case malignancy is more likely.

Clinical signs of Zollinger–Ellison syndrome

- **Pain and dyspepsia**
  From multiple ulcers
- **Steatorrhoea**
  From acid-related inactivation of digestive enzymes and mucosal damage in the upper small bowel
- **Diarrhoea**
  Due to copious acid secretion

Diagnosis is suggested by very high serum fasting gastrin levels, with little further increase with pentagastrin, and elevated basal gastric acid output. There is a rise in gastrin with secretin (unlike raised gastrin secondary to achlorhydria or proton pump inhibitor (PPI) therapy). Tumour location investigations should include upper GI endoscopy with careful duodenal examination, followed by CT or MR scanning to locate the adenoma and assess for hepatic metastases, although 40% of adenomata are smaller than 1 cm and thus difficult to detect on CT and somatostatin receptor scintigraphy, the best initial test to stage the disease (ENETS consensus guidelines, 2012). If these studies are negative, endoscopic ultrasonography may help in the detection of small lesions (particularly pancreatic gastrinomas).

Treatment of Zollinger–Ellison syndrome

- **High-dose acid suppression**
  (eg omeprazole 80–120 mg od)
- **Surgical resection of adenoma**
  (May be possible)
- **Chemotherapy**
  (Although poor response) and embolisation may be used for hepatic metastases
- **Somatostatin analogues**
  To reduce gastric secretion and diarrhoea

The 5-year survival rate is 80% for a single resectable lesion, but falls to 20% if hepatic metastases are present.

6.4.3 Gastric carcinoma

The incidence of gastric carcinoma is decreasing in the Western world but it remains one of the commonest causes of cancer deaths. It usually takes the form of an adenocarcinoma, most commonly in the pyloric region; however, the incidence of carcinoma occurring in the cardia is rising. There is very little early detection in the UK, unlike Japan where the extremely high incidence of the disease merits an intensive screening programme. Most patients have local spread at the time of diagnosis,

making curative resection unusual.

Gastric carcinoma

- **Risk factors**
  - Japanese
  - Hypo/achlorhydria (pernicious anaemia, chronic atrophic gastritis, partial gastrectomy)
  - Male sex
  - Dietary factors (high salt, nitrites)
  - Gastric polyps (rare)
- **Clinical presentation**
  - Dyspepsia (often only symptom)
  - Epigastric pain
  - Anorexia and weight loss
  - Early satiety
  - Iron-deficiency anaemia
  - Haematemesis/melaena

Very few tumours are confined to the mucosa at diagnosis, when cure rates are above 90%. Overall survival is below 10%. Diagnosis is by endoscopy and biopsy; endoscopic ultrasound and CT scan of the abdomen and thorax are used to determine resectability. Adjuvant chemotherapy before and after surgery may improve prognosis, although patients are often too unwell post-operatively to receive the second course.

Other gastric tumours include lymphoma (about 5%), which has a good prognosis, and leiomyosarcoma (<1%), which has a 50% 5-year survival.

Gastrointestinal stromal tumours (GIST) are being increasingly identified as incidental lesions as a result of widespread use of imaging and endoscopic investigations. They are submucosal tumours with malignant potential, initially thought to be benign leiomyomas. GIST have a characteristic histological appearance and typical staining with CD117 (CKIT). Treatment is by resection and, if advanced, with chemotherapy.

6.4.4 Other gastric pathology

Gastroparesis

Reduced gastric motility results in vomiting, bloating and weight loss. Some cases are idiopathic, and others are due to diabetes or autonomic neuropathy, or follow vagotomy. Gastric distension and delayed emptying can be demonstrated using a barium meal (which, along with gastroscopy, is useful to exclude obstructing lesions) or isotope scintigraphy (which is more useful for quantifying the amount of delay). Treatment is with dietary modification and pro-motility agents such as metoclopromide, domperidone or erythromycin, but, if symptoms are severe or if aspiration

pneumonia occurs, a feeding jejunostomy may be required. Recent MHRA guidance suggest that domperidone use should be at the lowest effective dose for the shortest possible duration, and avoided in patients with cardiac co-morbidity. Injection of botulinum toxin into the pyloric sphincter may produce temporary symptom improvement in selected patients; however, there is a lack of clear evidence supporting any benefit. Electrical stimulation with gastric pacemakers is currently being evaluated.

Ménétrier's disease

This is a very rare condition associated with mucus cell hypertrophy and parietal cell atrophy, mediated by epidermal growth factor. This results in gross thickening of the gastric mucosa, hypochlorhydria and protein-losing enteropathy.

Gastric polyps

Unlike colonic polyps, gastric polyps are rare and usually benign, occurring in about 2% of the population.

- Multiple hamartomatous polyps are occasionally found in Peutz–Jeghers syndrome and adenomata in polyposis coli, but over 90% are hyperplastic (usually arising from Brunner's glands)
- Adenomatous polyps should be removed in view of their premalignant potential.

6.4.5 Complications of gastric surgery – dumping syndrome

Gastric surgery is much less common since the advent of H_2 antagonists and PPIs, but long-term complications of previous gastric surgery are frequently encountered. **Dumping syndrome** results from an inappropriate metabolic response to eating and can occur within half an hour of eating (early dumping) or between 1 and 3 hours (late dumping). It occurs in about 20% of patients following gastrectomy/vagotomy.

- Symptoms include palpitations, sweating, hypotension and light-headedness
- Early dumping is a vagally mediated response to rapid gastric emptying
- Late dumping is due to hypoglycaemia – a rebound insulin-mediated phenomenon following transient hyperglycaemia due to a heavy carbohydrate load to the duodenum
- Diagnosis is usually clinical, but may be confirmed by glucose, electrolyte or blood pressure monitoring during an attack
- Treatment is conservative, with small frequent meals with high protein and fat for early dumping and high carbohydrate for late dumping
- Anecdotal reports suggest a benefit from somatostatin analogues (eg Octerotide).

6.5 DISORDERS OF THE PANCREAS

6.5.1 Acute pancreatitis

Acute pancreatitis is a common and potentially fatal disease. Mortality in hospital remains at 7–10%, usually due to multi-organ failure or peripancreatic sepsis. Scoring systems, such as the APACHE II, Ranson's criteria or the Glasgow criteria, aim to identify those patients at high risk by assessing factors such as age, urea, hypoxia and white cell count (WCC), but are unreliable within the first 48 hours. Obstruction of the pancreatic duct by gallstones accounts for over 50% of cases, most of the rest being alcohol-related. Four per cent are thought to have a viral aetiology; all other causes are rare. Oxygen-free radicals are thought to mediate tissue injury.

Acute pancreatitis

- **Causes**
  - Gallstones
  - Alcohol
  - Viral (eg mumps, Coxsackie B)
  - Trauma
  - Drugs (eg azathioprine, oral contraceptive pill, furosemide, steroids)
  - Hypercalcaemia
  - Hypertriglyceridaemia
  - Ascariasis in tropics
  - Post-surgery to bile duct/endoscopic retrograde cholangiopancreatography (ERCP)
- **Early complications**
  - Adult respiratory distress syndrome
  - Acute renal failure
  - Disseminated intravascular coagulation
  - Pleural effusions
- **Poor prognostic indicators (Glasgow criteria)**
  - Age 55 >years
  - WCC >15 × 10^9 /l
  - Urea >16 mmol/l
  - pO_2 <8 kPa
  - Calcium <2 mmol/l
  - Albumin <32 g/l
  - Glucose >10 mmol/l
  - Lactate dehydrogenase (LDH) >600 IU/l
  - Aspartate aminotransferase (AST) >200 IU/l
  - (Severe attack if more than three factors are present within 48 hours)
- **Late complications**
  - Splenic or portal vein thrombosis
  - Pseudocyst

- Abscess

Clinical presentation is usually with severe epigastric pain, radiating to the back and vomiting, with tachycardia and hypotension in more severe cases. Amylase (in blood, urine or peritoneal fluid) is raised, usually to at least four times normal values. A plain abdominal X-ray may show a sentinel loop of adynamic small bowel adjacent to the pancreas.

Treatment is supportive, with fluids and analgesia; the presence of three or more poor prognostic indicators suggests that referral to ITU should be considered. Routine use of prophylactic antibiotics in severe pancreatitis are not recommended and should only be used to treat extra pancreatic infection or infected necrosis (American College of Gastroenterology guidelines, 2013). In severe pancreatitis due to gallstones (where jaundice and cholangitis are present), early ERCP to achieve duct decompression is of proven value. Any patient with a biliary cause should have cholecystectomy during the same admission once the acute symptoms have settled.

6.5.2 Chronic pancreatitis

Chronic pancreatitis is an inflammatory condition characterised by irreversible damage to the exocrine and later to the endocrine tissue of the pancreas. Most cases are secondary to alcohol, but it is occasionally due to cystic fibrosis. There is a male predominance, often with a long history of alcohol abuse.

Chronic pancreatitis

- **Clinical signs**
  - Malabsorption and steatorrhoea
  - Abdominal pain radiating to the back, often severe and relapsing
  - Diabetes mellitus
- **Diagnosis**
  - X-ray may show speckled calcification, present in 50–60% of advanced cases
  - CT is the most sensitive for detection of pancreatic calcification
  - ERCP shows irregular dilatation and stricturing of the pancreatic ducts, although magnetic resonance cholangiopancreatography (MRCP) is now the modality of choice for diagnostic pancreatography
  - Endoscopic ultrasonography has emerged as being sensitive and accurate for diagnosing early and late changes of chronic pancreatitis
  - Pancreolauryl and PABA (*p*-aminobenzoic acid) testing are of use to assess exocrine function – both these involve ingestion of an oral substrate which is cleaved by pancreatic enzymes and can then be assayed in the urine
  - The faecal elastase test is increasingly used for detecting exocrine insufficiency and is more acceptable to patients
  - An oral glucose tolerance test can be used to diagnose early glucose intolerance

Treatment is with abstention from alcohol, pancreatic enzyme supplementation, analgesia and insulin to treat diabetes. Antioxidants (vitamins A, C and E) are of unproved value, and coeliac axis block for pain relief is now rarely performed because of poor results and surgical complications. Sixty per cent survive for 20 years – death is usually from complications of diabetes or alcohol.

6.5.3 Pancreatic carcinoma

Carcinoma of the exocrine pancreas is responsible for more than 6000 deaths per year in the UK, with an incidence of 110–120 per million, rising to 800–1000 per million over the age of 75 years. Seventy to eighty per cent arise in the head of the pancreas where there is maximal pancreatic tissue; those in the tail are often silent in the early stages and present at an advanced stage. Pancreatic carcinoma may invade the common bile duct causing obstructive jaundice and the typical 'double duct sign' at ERCP. It can also invade the duodenum, leading to small-bowel obstruction.

- The risk is increased 2–3-fold in smokers, and also possibly in those with diabetes, although it has been suggested this is an early symptom of carcinoma rather than a risk factor. Alcohol does not increase the risk
- Clinical signs include abdominal pain radiating through to the back, weight loss and obstructive jaundice in 80–90%. The exocrine and endocrine functions are usually maintained
- Ultrasound and pancreatic protocol CT is used to detect any distant metastases
- Endoscopic ultrasound is useful for locoregional staging and allows histological diagnosis via fine-needle aspiration
- ERCP with a view to bile duct stenting is probably of most use in relieving jaundice and pruritus
- CA-19.9 is released from exocrine pancreatic cancer cells, and baseline levels may guide treatment and follow-up and have prognostic significance.

Between 10% and 20% of patients are suitable for surgery but perioperative mortality is high. The only curative treatment of pancreatic cancer is radical surgical treatment, so accurate staging to determine resectability is critical. If unresectable, the goals of treatment are to optimise local control, control metastatic growth, prolong survival and palliate symptoms.

Novel techniques such as intraoperative radiotherapy and irreversible electroporation (soft tissue ablation using ultra short, strong electrical fields) are experimental and not currently recommended in routine clinical practice for unresectable disease. For metastatic disease, gemcitabine or combination chemotherapy (5-FU, irinotecan and oxaliplatin) are considered first-line options, and median survival can be improved from 2–3 months from diagnosis, to 6 and 11 months, respectively, using these regimens. However, the overall 1- and 5-year survival rates remain poor.

6.5.4 Endocrine tumours

These are very rare, with an annual incidence of 4 per million, but they are incidentally detected at post-mortem. They can occur independently, or as part of multiple endocrine neoplasia (MEN-1) syndrome.

The more important lesions include:

- **insulinoma**
- **gastrinoma (Zollinger–Ellison syndrome**, see Section 6.4.2)
- **glucagonoma**
- **VIPoma**
- **somatostatinoma**.

Insulinoma

These arise from the islets of Langerhans and often present with unusual symptoms (visual disturbances, irritability, abnormal behaviour, confusion, amnesia, paraesthesiae and drowsiness) after an overnight fast or before meals as a result of hypoglycaemia. Patients often discover that glucose is helpful and may go for years without diagnosis.

Glucagonoma

These tumours arise from α cells of the pancreas and present clinically with a characteristic rash (migratory necrolytic erythema), weight loss, glucose intolerance or frank diabetes, and anaemia. Tumours are often very large at diagnosis and are usually malignant.

VIPoma

Excessive VIP (vasoactive intestinal polypeptide) produces an extreme secretory diarrhoea (usually >3 litres per day) resulting in hypochlorhydria and hypokalaemia.

Somatostatinoma

This rare tumour produces a syndrome of diabetes mellitus, diarrhoea, gallbladder disease, weight loss, steatorrhoea and hypochlorhydria due to inhibition of insulin and pancreatic enzymes.

6.6 SMALL-BOWEL DISORDERS

The small bowel is the main site of absorption of nutrients for the body, so small-bowel diseases such as coeliac disease or Crohn's disease often result in malabsorption and malnutrition.

Small-bowel pathology can be difficult to diagnose because of the inaccessibility of this part of the GI tract. Small-bowel enteroscopy may be of use in addition to tests such as gastroduodenoscopy or barium studies. CT/MR enterography and wireless capsule endoscopy are increasingly being used.

6.6.1 Coeliac disease

Also known as gluten-sensitive enteropathy, this common and under diagnosed condition is caused by an immunological reaction to the gliadin fraction of wheat and other cereals. Some 0.1–0.2% of the population are affected and the onset may be at any age, although peaks occur in babies and in the third decade. The incidence is greatly increased in western Ireland, and it has been postulated that this is due to increased reliance on potatoes rather than wheat products as a source of carbohydrate. Thus those affected with gluten intolerance continued to thrive and reproduce.

HLA-B8, DRw3 is present in 90%. Pathologically, gliadin provokes an inflammatory response which results in partial or total villous atrophy in the proximal small bowel; this reverses on a gluten-free diet but recurs on rechallenge.

Coeliac disease

- **Clinical picture**
  - Diarrhoea
  - Oral aphthous ulcers
  - Weight loss
  - Growth retardation
  - General malaise
  - Neurological symptoms – ataxia, weakness and paraesthesiae
  - Abdominal pain
  - Amenorrhoea
- **Complications**
  - Anaemia–folate, B_{12} or iron deficiency
  - Increased malignancy*
  - Hyposplenism
  - Dermatitis herpetiformis – itchy rash, improves with dapsone
  - Osteomalacia
  - Abnormal liver function tests
- **Diagnosis**
  - Anti-endomysial/Anti-tissue transglutaminase antibodies

*There is an increased risk of all GI malignancies but especially small-bowel lymphoma, occurring in approximately 6% of cases. This risk returns to almost normal with treatment of the disease.

Treatment is by strict avoidance of wheat, rye and barley. The role of oats is debatable, and many patients can eat oats without significant pathological or clinical effects. Patients require folate, iron and calcium supplements in the early stages of treatment. Failure to respond to treatment is usually due to non-compliance with diet (often unwittingly), but the possibility of supervening pathology, such as lymphoma, should always be excluded. A small number of patients with refractory coeliac disease may require steroids to control their symptoms.

Although 10% of first-degree relatives will develop coeliac disease, routine screening is not advocated unless they have symptoms to suggest the diagnosis.

Other causes of villous atrophy:

- Whipple's disease
- Hypogammaglobulinaemia
- Lymphoma

- Giardiasis
- Cow's milk protein intolerance
- Tropical sprue: aetiology unknown, but likely to be infective as it responds to long-term tetracycline therapy
- Collagenous sprue: rare small-bowel disorder with villous atrophy and subepthelial collagen deposition histologically. Often non-responsive to gluten-free diet.

6.6.2 Carcinoid tumours

These are relatively common; it is estimated that carcinoid tumours are an incidental finding in up to 1% of post-mortems. **Carcinoid syndrome**, however, is extremely rare. Carcinoid tumours arise from the enterochromaffin cells of intestinal mucosa (neuroendocrine cells found in the lamina propria) throughout the gut. The most common GI sites are the appendix (from which site metastasis is rare) and the ileum.

- The tumours secrete serotonin and therefore can be detected by assay of the metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the urine
- Serotonin causes bronchoconstriction and increased gut motility, resulting in the symptoms documented below
- Histamine and adrenocorticotrophin may also be synthesised
- Carcinoid syndrome occurs only when secondaries in the liver release serotonin into the systemic circulation; any hormone from non-metastatic gut carcinoids will be metabolised in the liver.

Clinical features of carcinoid syndrome

- Diarrhoea
- Bronchospasm
- Local effect of the primary (eg obstruction, intussusception)
- Flushing
- Right heart valvular stenosis (left heart may be affected in bronchial carcinoid or if an atrial septal defect (ASD) is present)
- **Treatment** depends on the site of the primary and presence of metastases. Many carcinoids are very slow growing, with patient survival of more than 20 years. With widespread metastases 5-year survival varies from zero to 25%, the better figures reflecting the less aggressive nature of appendiceal primaries

Treatment of carcinoid tumours and syndromes

- **Surgical resection**
  - Good prognosis if no metastases

- **Octreotide, methysergide and cyproheptadine**
  - For diarrhoea
- **Resection or embolisation**
  - Of hepatic metastases
- **Phenoxybenzamine**
  - For flushing

Carcinoid tumours may occasionally cause pellagra due to tumour uptake of tryptophan (the precursor of nicotinic acid).

6.6.3 Whipple's disease

This is an uncommon condition usually affecting middle-aged men (occasionally women and children) caused by infection with the Gram-positive actinobacteria, *Tropheryma whippelei*. Jejunal biopsy shows deposition of macrophages containing PAS-positive granules within villi. Clinical features include abdominal pain, weight loss, diarrhoea, and arthropathy. The central nervous system can be involved in later stages, characterised by cognitive function abnormalities, as well as oculomasticatory and oculofacioskeletal myorhythmia (rhythmic movements of masticatory and other skeletal muscles synchronised with ocular movements). Whipple's endocarditis can also occur. Whipple's disease remains poorly understood but symptoms respond to extended courses of tetracycline or penicillin.

6.6.4 Angiodysplasia

Although most commonly occurring in the caecum and ascending colon, angiodysplasia is included here because of the diagnostic challenge it may present when present in the small intestine. Angiodysplasia can be found throughout the GI tract and its frequency in the population is unknown. It is an uncommon but significant cause of acute gastrointestinal haemorrhage, but presents more frequently as occult iron-deficiency anaemia.

Diagnosis of angiodysplasia

This can be difficult, but useful investigations include:

- **Gastroscopy/colonoscopy**: may detect gastric and large-bowel lesions
- **Mesenteric angiography**: only of use if currently bleeding; if so, will locate source in approximately 40%
- **Small-bowel enteroscopy**: intubation of the upper small bowel is possible using an elongated endoscope with an overtube to provide rigidity
- **Capsule enteroscopy**: this is the most effective method of detecting small-bowel angiodysplasia and other sources of small-bowel bleeding. A small (11 × 27 mm) capsule is swallowed which transmits thousands of images from the gut as it transits. Images are analysed manually and with

computer assistance. Typical capsule transit times are: oesophagus 1–4 seconds, stomach 22–48 minutes and small bowel around 4 hours.

The main risk that patients should be informed about before consenting to capsule enteroscopy is capsule retention (capsule remaining in the digestive tract for at least 2 weeks, sometimes requiring medical, endoscopic or surgical removal). In the general population the risk of capsule retention is quoted as 1.4-2.5%. For this reason, capsule enteroscopy should not be performed in patients with obstructive symptoms and/or radiological evidence of intestinal obstruction. Patients with small-bowel Crohn's disease, those taking high doses of nonsteroidal anti-inflammatory drugs and those with abdominal radiation injury are at higher risk of capsule retention. Such patients may benefit from an examination using an M2A (lactose-filled) patency capsule, which is designed to dissolve when impacted in stenosed bowel.

Treatment of angiodysplasia

Treatment is by argon plasma photocoagulation at endoscopy, or by embolisation of the bleeding point during angiography. Second-line treatment with Thalidomide and/or Octreotide has been shown to achieve clinically meaningful responses in patients that are refractory or unsuitable for other interventions. Surgery may be indicated if the lesions are very numerous or if there is severe bleeding. Patients need to receive long-term iron supplementation. Hormonal treatment with oestrogen (± progesterone) has been tried with poor results.

6.7 NUTRITION

6.7.1 Assessment of nutritional status

In practice, nutritional assessment should be based on a pragmatic approach using a combination of history, examination and blood tests to identify specific nutrient deficiencies. The following assessments help evaluate nutritional status and risk:

- Reported recent weight loss
- Dietary assessment: food diary
- Behavioural patterns to food intake
- Body mass index (BMI): weight in kilograms/(height in metres)^2
- Biochemical markers: renal profile, electrolytes (magnesium, phosphate and potassium), albumin (unreliable – often normal in severe malnutrition and affected by inflammation and synthetic liver function), C-reactive protein (CRP), glucose and HbA1c (glycated haemoglobin)

Given that around a third of hospitalised patients are at risk of malnutrition, and provision of good nutritional status improves clinical outcomes, NICE recommends that all patients admitted to hospital should be screened for risk of malnutrition using a validated screening tool. The British Association of Parenteral and Enteral Nutrition (BAPEN) has developed the Malnutrition Universal Screening Tool (MUST) which is widely used for this purpose. Using this tool, the overall risk of malnutrition is calculated based on the BMI, the percentage of unintentional weight loss over a 3- to 6-month period and whether the patient has had, or is likely to have had, no nutritional intake for more than 5

days.

The maintenance of adequate nutrition requires three main criteria to be fulfilled:

1. **Intact GI tract**
   This may be compromised by resections resulting in a short-bowel syndrome, or by fistulae such that segments of bowel are bypassed. As different nutrients are absorbed from different parts of the gut, a variety of clinical sequelae may occur depending on the segment of bowel affected (eg vitamin B_{12} deficiency after terminal ileal resection, iron deficiency after partial gastrectomy)
2. **Ability to absorb nutrients**
   Impairment of absorptive function may be caused by mucosal damage as occurs in Crohn's or coeliac disease, or after radiation damage. Motility problems resulting in accelerated transit times may reduce absorption
3. **Adequate intake**
   This depends on both the motivation to maintain an adequate oral intake, often lacking in sick and elderly patients, and on the composition of the diet.

An inability to maintain nutrition is an indication to provide supplementation by one of three routes listed below. The underlying disease will determine which is appropriate:

- **Oral:** obviously the most simple form but relies on a conscious patient with an intact swallowing mechanism. High-protein or -carbohydrate drinks may be used to provide good nutritional intake in a small volume
- **Enteral:** useful when swallowing impaired (eg in neurological disease) or when high-volume intake is needed. May take the form of a simple nasogastric tube, or a percutaneous gastrostomy (PEG) or jejunostomy, which can be inserted endoscopically, radiologically or surgically. Can be for short- or long-term supplementation
- **Parenteral:** this is intravenous feeding, either to supplement enteral nutrition or to provide total support in the case of complete intestinal failure.

Refeeding syndrome

When re-establishing feeding (orally, enterally or parenterally) in malnourished patients with inadequate oral intake for more than 5 days, it is important to recognise the high risk of refeeding syndrome. Overenthusiastic feeding of these patients can precipitate surges in insulin levels, which in turn provoke large intracellular shifts in potassium, phosphate and magnesium, leading to low plasma levels of these ions.

Potential serious adverse clinical consequences of these preventable electrolyte deficiencies include:

- cardiac instability/arrhythmias and sudden death
- seizures
- delirium
- paraesthesia
- myopathy
- haemolysis
- paralysis

- oedema
- respiratory and cardiac failure.

A cautious approach to refeeding is therefore paramount, gradually increasing calorie intake and correcting electrolyte deficiencies. It is mandatory to monitor serum electrolytes (including potassium, phosphate, magnesium and calcium) daily in this situation. Also, during refeeding there is increased consumption of thiamine by cells, so at-risk patients should also receive thiamine replacement before starting nutritional support (oral, enteral or parenteral) as prophylaxis for Wernicke's encephalopathy.

Problems with parenteral nutrition

- **Central venous access needed**
- Patient/carer must be sufficiently motivated and competent to master aseptic techniques and care for venous line
- **Electrolyte abnormalities may occur** – need for careful monitoring; also need to monitor trace elements such as zinc and selenium
- **Risk of sepsis** – central venous catheter infections, right heart endocarditis

Examples of specific nutritional deficiencies are covered in Chapter 13, Metabolic Diseases.

6.7.2 Diarrhoea

Diarrhoea means different things to different people but medically is defined as >200 ml of stool per day. In lay terms, diarrhoea is used to describe increased frequency and/or decreased consistency of motions. There are several causes (as illustrated below), and these result in diarrhoea by differing mechanisms.

Various classifications can be used:

- Acute or chronic
- Large bowel (often smaller amounts, may contain blood or mucus)
- Small bowel (often voluminous, pale and fatty).

Causes of diarrhoea

- **Osmotic** (osmotic agents draw water into the gut)
  - Osmotic laxatives (lactulose, polyethylene glycol)
  - Magnesium sulphate
  - Lactase deficiency* (poorly absorbed lactose acts as a laxative)
  - *Stops with fasting*
- **Secretory** (failure of active ion absorption ± active ion secretion)

- Infection (eg *Escherichia coli*, cholera)
- Malabsorption
- Bile salts (↑ deposition into bowel after cholecystectomy)
- *Continues with fasting, nocturnal, high volume (> 1 l/day)*
- *Stool electrolytes and osmotic gap can be used to differentiate between secretory and osmotic diarrhoeas*

- **Altered motility** (altered peristalsis or damage to autonomic nervous system)
  - Irritable bowel syndrome
  - Thyrotoxicosis
  - Post-vagotomy
  - Diabetic autonomic neuropathy
  - *Stops with fasting*

*Lactase deficiency may be congenital (possibly severe) or acquired, and often occurs in the setting of viral gastroenteritis or coeliac disease. Complete exclusion of lactose from the diet is usually not necessary – there is often a threshold below which symptoms are absent.

Causes of bloody diarrhoea

- Ulcerative colitis
- Crohn's disease
- Colorectal cancer
- Ischaemic colitis
- Pseudomembranous colitis
- Schistosomiasis
- *Salmonella*
- *Shigella*
- Amoebiasis
- *Campylobacter*
- *Strongyloides stercoralis*
- Haemolytic uraemic syndrome (which can be caused by *E. coli* type O157, *Campylobacter*, *Shigella*, etc)

Investigations for diarrhoea

History and examination vital, including rectal examination

- History may be suggestive of large- or small-bowel cause; examination per rectum to exclude overflow or rectal tumour
- **Gut hormone assay**

- **Sigmoidoscopy/colonoscopy**
  If large-bowel cause suspected
- **B_{12}, folate, and iron assay**
  If small-bowel cause suspected
- **Gastroscopy**
  With duodenal biopsy if small-bowel cause suspected
- **Biochemistry**
  Electrolyte disturbance: include thyroid function tests, albumin and calcium
- **Stool examination**
  Including examination for ova, cysts and parasites, and laxative screen
- SeHCAT (selenium-75 homotaurocholic acid retention) test for bile salt malabsorption. This is a radiolabelled isotope scan for measuring bile acid loss from enterohepatic circulation
- **Faecal elastase**
  If pancreatic exocrine insufficiency suspected
- **Small-bowel radiology**
  If small-bowel cause suspected
- **Urine analysis**
  Laxative screen
  5-HIAA
- **Hydrogen breath test**
  Bacterial overgrowth in the small bowel can be identified by detection of exhaled hydrogen from ingested glucose or lactulose. False positives occur with rapid small-bowel transit that results in prolonged hydrogen release
- **Serology**
  Anti-endomysial antibody
- **Faecal calprotectin**
  Faecal calprotectin is a highly specific (96%) and sensitive (93%) screening test in patients with chronic diarrhoea, to exclude inflammatory bowel disease and support a diagnosis of irritable bowel syndrome (IBS) in patients with chronic lower gastrointestinal symptoms in whom cancer is not suspected. If there is no suspicion of malignancy, then faecal calprotectin, where available, can be considered as an initial investigation of choice where the results can inform the physician about the need for further (more invasive) investigations such as sigmoidoscopy or colonoscopy. (Van Rheenan *et al*. 2010) There is currently still some uncertainty as to appropriate cut-off levels and appropriate age range for use of this test.

Treatment of diarrhoea

This depends on the underlying disease process, which should be treated if possible. Loperamide or codeine increases gut transit time and so may control symptoms. Similarly, racecadotril, an oral enkephalinase inhibitor, reduces hypersecretion of water and electrolytes into the intestinal lumen and is now licensed in the UK for symptomatic treatment of acute diarrhoea in adults. This drug has effects comparable to loperamide but without the adverse effects such as constipation and abdominal

distension. Octreotide may be useful for chronic secretory diarrhoea, short-bowel symptoms and diarrhoea secondary to endocrine tumours. Cholestyramine can be useful in bile salt malabsorption

6.7.3 Malabsorption

Malabsorption may be defined as a failure to absorb sufficient exogenous nutrients or to reabsorb endogenous substances such as bile salts. It may be caused by several factors, because normal absorption depends on gut structure, motility and secretion of hormones and enzymes. Malabsorption usually results in diarrhoea. Clinical presentation depends on the type and site of defect, and includes weight loss and general ill health, osteomalacia, or specific nutritional deficiencies such as of B_{12} and folate.

Investigation of malabsorption

Investigation is as for diarrhoea. In addition, specific tests for malabsorption include:

- **Xylose absorption test**: 25 g of xylose is given orally. Urinary excretion of xylose is quantified. More than 20% should appear in the urine if small-bowel absorption is normal
- **Pancreatic function testing**: see Section 6.5
- **^{14}C breath testing**: to detect overgrowth (although the most accurate test remains quantitative bacteriological assay of jejunal aspirates)

Causes of malabsorption

- **Structural abnormalities**
  - Coeliac disease*
  - Crohn's disease*
  - Post-surgical resections*
  - Bacterial overgrowth due to blind loops or anatomical abnormalities
  - Whipple's disease
  - Tropical sprue
- **Motility abnormalities**
  - Thyrotoxicosis
  - Drugs (eg neomycin)
  - Diabetes
- **Secretory abnormalities**
  - GI tract infection (eg Giardia, amoebiasis)
  - Chronic pancreatitis*
  - Cystic fibrosis

*Common causes in the UK.

Bacterial overgrowth of the small bowel

This is common in patients who have undergone small-bowel resections or in those with jejunal diverticulae or systemic sclerosis. These bacteria are able to metabolise vitamin B_{12} and carbohydrate, but the serum folate usually remains normal or elevated. Patients usually have diarrhoea, and malabsorption may ensue. Treatment is with antibiotics such as metronidazole, tetracycline or ciprofloxacin, and recurrent courses of these antibiotics may be necessary.

6.8 LARGE-BOWEL DISORDERS

6.8.1 Crohn's disease and ulcerative colitis

Crohn's disease and ulcerative colitis are both chronic relapsing inflammatory diseases of the gastrointestinal tract.

Aetiology of inflammatory bowel disease

There is an undoubted genetic predisposition based on the identification of at least five susceptibility loci in family studies, and the recent discovery of the *NOD2/CARD15* gene on chromosome 16 which is clearly associated with the development of Crohn's disease. This gene codes for a protein which facilitates opsonisation of gut bacteria, and animal studies have confirmed that colitis does not develop in animals raised in a sterile environment. Putative infectious agents including *Mycobacterium paratuberculosis* have not been confirmed, and recent speculation about the role of measles or the measles vaccination in Crohn's disease has no epidemiological basis. The use of NSAIDs and the oral contraceptive pill have also been implicated, but mechanisms remain unclear.

The major similarities and differences between the two diseases are detailed in Table 6.2.

Treatment of inflammatory bowel disease (IBD)

Treatment is similar for both Crohn's disease and ulcerative colitis. Here we discuss the major treatment strategies and important differences between ulcerative colitis and Crohn's Disease management.

- **5-aminosalicylic acid (5-ASA) compounds** (mesalazine, olsalazine, balsalazide): these are used to treat mild-to-moderate relapses of ulcerative colitis and are taken long term to maintain remission. Oral 5-ASAs are targeted to the colon using pH-dependent or bacterial cleavage systems to release active 5-ASA from carrier molecules. Side-effects are common with sulfasalazine, and these include rash, infertility, agranulocytosis, headache, diarrhoea and renal failure. Interstitial nephritis is a rare side-effect of all 5-ASA drugs. Based on disease extent, patients with endoscopically confirmed distal colitis (inflammation only below the descending colon) may benefit from topical 5-ASA preparations via retention enemas and or suppositories. In contrast to ulcerative colitis, there is no evidence to support the use of 5-ASA drugs in Crohn's disease, either in maintenance or active disease

Table 6.2 Clinico-pathology of Crohn's disease and ulcerative colitis

	Crohn's disease	Ulcerative colitis
	Affects any part of the Gl tract from mouth to anus. Commonly terminal ileum (70%), colon (30%), anorectum (30%). May be 'skip lesions' of normal mucosa between affected areas	Always involves the rectum and extends confluently into the colon. Terminal ileum may be affected by 'backwash ileitis', but remainder of the gut unaffected
Pathology	Transmural inflammation Mucosal ulcers (in 30% only) Fissuring ulcers Lymphoid aggregates Neutrophil infiltrates	Mucosa and submucosa only involved Inflammatory cell infiltrate Crypt abscesses
Clinical	Abdominal pain prominent and frequent fever Diarrhoea blood per rectum Anal/perianal/oral lesions Stricturing common, resulting in obstructive symptoms	Diarrhoea, often with blood and mucus Fever Abdominal pain less prominent
Associations	Increased incidence in smokers (50–60% smokers) Skin disorders: Erythema nodosum (5–10%) Pyoderma gangrenosum (0.5%) Iritis/uveitis (3–10%) Joint pain/arthritis (6–12%) Cholelithiasis (common) Primary sclerosing cholangitis Clubbing Depression	Decreased incidence in smokers (70–80% non-smokers) Increased incidence of: Primary biliary cirrhosis Chronic active hepatitis Sclerosing cholangitis Other systemic manifestations occur but less common than in Crohn's disease
Diagnosis	Faecal calprotectin (raised) Ileocolonoscopy with biopsies: Cobblestoning of mucosa Rose-thorn ulcers Strictures Skip lesions Terminal Ileitis OGD (if upper GI symptoms) CT/MR enterography: assess small-bowel involvement	Faecal calprotectin (raised) Sigmoidoscopy (often initially) or colonoscopy (often later) with biopsies: Determine anatomical extent of colitis Determine disease activity - Mayo endoscopic score is widely used to describe mucosal appearances Mayo endoscopic score (ulcerative colitis): 0 = inactive (normal) 1 = mild (erythema, decreased vascular pattern, mild friability) 2 = moderate (marked erythema, absent vascular pattern, friability, erosions) 3 = severe (spontaneous bleeding,

		ulceration)
Complications	Fistulae: Entero-enteral Entero-vesical Entero-vaginal Perianal Carcinoma – slightly increased risk of colonic malignancy (see later)* B_{12} deficiency common (decreased absorption in terminal ileal disease) Iron deficiency anaemia Abscess formation Venous thromboembolism	Fistulae do not develop Toxic megacolon (uncommon – usually an indication for urgent colectomy) Increased risk of carcinoma* (risk increases with time since diagnosis, extent of disease and early age of onset) Iron-deficiency anaemia Venous thromboembolism

*See section 'Carcinoma complicating inflammatory bowel disease'.

- **Steroids**: this is the main treatment for active disease, and is available for topical, oral and intravenous administration. Terminal ileal Crohn's disease may be treated with topically acting oral budesonide, which is metabolised in the liver and has far fewer systemic side-effects. The use of steroids should be minimised to short tapering regimes to induce remission, and calcium and vitamin D supplementation should be co-prescribed
- **Immunosuppressants: azathioprine** or **mercaptopurine** are very effective as steroid-sparing agents in steroid refractory cases, those requiring frequent steroid courses for exacerbations or patients unable to wean off steroids. Their use as a monotherapy for active disease is limited by their slow onset of action. Their use is limited by gastrointestinal and systemic side-effects, and close monitoring for evidence of marrow suppression and hepatotoxicity is necessary. Pancreatitis is an uncommon but potentially serious idiosyncratic side-effect.
- **Methotrexate** is useful in patients with Crohn's disease but does not appear to be effective in patients with ulcerative colitis.
- **Intravenous ciclosporin** is sometimes effective in the treatment of acute, steroid-resistant colitis, but long-term benefit has not been established
- **Metronidazole and ciprofloxacin**, used in the treatment of perianal Crohn's disease
- **Anti-tumour necrosis factor-α (biologics)**: infliximab (chimeric [mouse/human] monoclonal antibody) and adalimumab (recombinant human IgG1 monoclonal antibody against TNF-α) are recommended by NICE in the treatment of severe active Crohn's disease refractory to conventional therapy (immunosuppressants and corticosteroids), or when conventional therapy is not tolerated/ contraindicated. A planned course is recommended until treatment failure (including the need for surgery) or 12 months, at which point disease activity should be reassessed to guide further management. Adalimumab can be administered subcutaneously. Infliximab is also recommended for fistulising Crohn's disease refractory to antibiotics, drainage and immunosuppression
- **Nutritional support and treatment**: patients with inflammatory bowel disease are often malnourished and require nutritional supplementation (enteral or parenteral), especially if

- surgery is planned. An elemental or polymeric diet may be as effective as steroids in inducing remission in Crohn's disease

Surgery: surgical resection is very effective for symptom relief in obstructive Crohn's disease, and colectomy offers a cure to patients with ulcerative colitis. Absolute indications for surgery in ulcerative colitis are exsanguinating hemorrhage, perforation and documented or strongly suspected carcinoma. Other indications for surgery are severe colitis with or without toxic megacolon unresponsive to conventional maximal medical therapy, and less severe but medically
- intractable symptoms or intolerable medication side-effects (ACG guidelines, 2010). The recurrence rate for Crohn's disease after surgery is approximately 50%. The role of postoperative medication (azathioprine, anti-TNF) in reducing risk of recurrence is being evaluated and debated. Current opinion is that treatment should be risk-stratified and given to those deemed to have high risk of recurrence. Ileoanal pouch surgery restores continence to patients undergoing colectomy

Immunisation: recent literature has highlighted that patients with inflammatory bowel disease are vulnerable to infections secondary to immunocompromise, both from the disease itself and potent immunosuppressive medications which they may be taking or may require in the future. It is therefore important that at the time of diagnosis of inflammatory bowel disease, immunity and
- serologic status should be determined and detailed vaccination history should be taken. Patients with inflammatory bowel disease should be recommended to recieve the following vaccinations: varicella, human papilloma virus, influenza, pneumococcal and hepatitis B vaccine. However, patients already on immunosuppresants or biological drugs and those with human immunodeficiency virus should avoid live-virus vaccines.

Management of acute severe colitis

- Defined by Truelove and Witts' criteria, more than six bloody stools/day PLUS one sign of systemic toxicity: heart rate >90/min, temperature >37.8°C, Hb <10.5 g/dl or ESR >30 mm/hr
- Exclude infective cause (stool cultures)
- Accurate recording of stool frequency (stool chart)
- Intravenous steroids 5-days, fluid and electrolyte replacement
- Prophylactic thromboprophylaxis
- Daily abdominal examination ± abdominal radiographs/ bloods (including inflammatory markers)
- Consider urgent flexible sigmoidoscopy (without bowel preparation)
- Colectomy rate relatively high – 30%; early surgical consultation and daily joint review with gastroenterologist is important
- Day 3: if no improvement: – consider surgery or 'rescue' medical therapy (ciclosporin/ infliximab) – stool frequency 8/day or CRP >45 predictor of colectomy in 85% cases

Colon diameter >5.5 cm (on abdominal radiograph) needs surgical referral.

Carcinoma complicating inflammatory bowel disease

The risk of carcinoma associated with inflammatory bowel disease is increased if:

- Onset of IBD occurs at less than 15 years of age
- Disease duration has been longer than 10 years
- There is widespread disease (eg total colitis)
- The disease takes an unremitting course
- Compliance with treatment and follow-up is poor.

Colonoscopic surveillance for inflammatory bowel disease

Current NICE guidelines (published March 2011) state that the risk of developing colorectal cancer for people with ulcerative colitis is estimated as 2% after 10 years, 8% after 20 years and 18% after 30 years of disease. The risk of developing colorectal cancer for people with Crohn's disease is considered to be similar to that for people with ulcerative colitis with the same extent of colonic involvement.

- Therefore patients with both Crohn's disease and ulcerative colitis are recommended to have an index surveillance colonoscopy 8-10 years after the onset of symptoms to assess disease extent and other endoscopic risk factors. Pancolonic dye spraying (chromoendoscopy) with targeted biopsies of abnormal areas is recommended. If chromoendoscopy is not used, two to four random biopsy specimens should be taken every 10 cm from the entire colon, with additional samples of suspicious areas
- The interval for surveillance colonoscopy depends on disease extent, duration, histology and additional risk factors
- **Low-risk patients** (extensive colitis with no active endoscopic or histological inflammation, left-sided colitis or Crohn's colitis involving <50% of the colon) should have surveillance every 5 years
- **Intermediate-risk patients** (extensive colitis with mildly active endoscopic or histological inflammation, post-inflammatory polyps, or a family history of colorectal cancer in a first-degree relative who was at least 50 years of age) should have surveillance every 3 years
- **High-risk patients** (extensive colitis with moderately active endoscopic or histological inflammation, a stricture in the preceding 5 years, dysplasia in the previous 5 years that was not treated surgically, primary sclerosing cholangitis or a family history of colorectal cancer in a first-degree relative aged <50 years) should have annual surveillance.

6.8.2 Pseudomembranous colitis

This is acute exudative colitis, almost always due overgrowth of *Clostridium difficile*. *Clostridium difficile* infection is usually precipitated by broad-spectrum antibiotics. It is common in elderly or chronically ill people, and the mortality rate may be as high as 20%. Patient-to-patient spread in hospital is common. Diagnosis is by demonstration of the *Clostridium difficile* toxin in stools in most cases, but rarely by endoscopy (which shows inflamed mucosa with yellow pseudomembranes) when the stool test is negative and there is a strong suspicion.

Treatment

- Discontinue inciting concomitant antibiotics as soon as possible and adopt infection control precautions
- Oral vancomycin or metronidazole for 10-14 days, depending on the severity of disease (Public Health England 2013 guidelines). Metronidazole is recommended for mild and moderate infections. Vancomycin is reserved for patients with severe infection defined by presence of one of the following severity markers:
  - WCC >15 10^9/L;
  - acutely rising blood creatinine (e.g. >50% increase above baseline);
  - temperature >38.5°C; or
  - evidence of severe colitis (abdominal signs, radiology)
- Patients with an underlying infection requiring prolonged duration of concomitant antibiotics should continue treatment throughout the antibiotic course, plus an additional week after its completion
- Recent evidence suggests that fidaxomicin, a macrocyclic antimicrobial (bactericidal to *C. difficile*), which is less disruptive to colonic microflora, should be considered in patients with either high risk of recurrence or recurrent infection
- Intravenous immunoglobulin (IVIg), which contains *C. difficile* antitoxin, is recommended as an appropriate adjunct to antibiotics in relapsing and severe *C. difficile* colitis (by the Department of Health and Public Health England guidance, 2013). Data on this treatment is, however, currently limited to case reports and small case series, which suggests an improvement in about two-thirds of intractable cases
- There is insufficient evidence to support the use of probiotics, and faecal transplantation is under evaluation
- Close monitoring of full blood count, CRP, electrolytes and albumin is necessary
- CT is used to detect toxic megacolon in severe cases, which may need a colectomy
- Recurrent cases may need a tapering regimen of vancomycin over a period of a few weeks

C. difficile can be detected in normal stools but is treated only when it causes diarrhoea.

6.8.3 Familial polyposis coli

This is an autosomal dominant condition, caused by mutation in the *APC* tumour suppressor gene which is located on the long arm of chromosome 5. Estimates of the incidence vary from 1 in 7000–30 000 of the population in the UK.

Multiple adenomata occur throughout the colon; if untreated, malignancy is inevitable, often when patients are aged only 30 or 40 years. Surveillance colonoscopy begins in adolescence and prophylactic colectomy usually follows at around the age of 20 years, in view of the high risk of malignant change. Many patients opt for an ileo-anal pouch. Screening of family members is essential.

6.8.4 Peutz–Jeghers syndrome

This is an autosomal dominant condition in which multiple hamartomatous polyps occur throughout the GI tract (particularly in the small bowel). Patients may have mucocutaneous pigmentation and perioral freckles. Lesions may lead to GI haemorrhage and may undergo malignant change (carcinoma is increased 12-fold in patients with this condition).

6.8.5 Hereditary non-polyposis colorectal cancer (HNPCC)

This is a dominantly inherited disorder of DNA mismatch repair genes located on chromosomes 2 and 3. Malignancies such as those affecting the colon, breast, ovary and endometrium occur at a young age. Relatives of affected patients require genetic counselling and cancer screening.

6.8.6 Colorectal cancer

This is the second most common cause of cancer death in the UK, with an incidence of approximately 44/100 000. A National Bowel Cancer Screening Programme based on faecal occult blood (FOB) testing at 60 years of age, followed by colonoscopy, has been introduced in the UK to good effect. The feasibility of screening using flexible sigmoidoscopy between ages 55 and 64 years is currently being considered.

Pathologically, it is an adenocarcinoma usually arising from tubular and villous adenomatous polyps (although in inflammatory bowel disease, malignant change arises directly from the mucosa). The commonest sites are the rectum and sigmoid colon.

Risk factors and clinical features of colorectal cancer

- **Increased incidence**
  - Male sex
  - Family history
  - Inflammatory bowel disease, especially ulcerative colitis
  - Familial polyposis coli
  - Diet low in fibre, fruit and vegetables
  - Diet high in fat and red meat
  - Cholecystectomy (bile salts 'dumped' in colon)
  - Obesity
- **Genetics**
  - Sporadic mutations may occur in the *p53*, *Ras* and *APC* genes. *p53* regulates the cell cycle and causes apoptosis in the event of DNA damage – its loss therefore leads to uncontrolled proliferation of cells
- **Clinical signs**
  - These depend on the site of the lesion; all can cause weight loss and obstructive symptoms

- Right-sided
  - Iron-deficiency anaemia
  - Abdominal pain
  - Abdominal mass
- Left-sided
  - Blood per rectum
  - Altered bowel habit
  - Abdominal mass
- Rectum
  - Blood per rectum
  - Tenesmus
  - Obstruction
- **Complications**
  - Local spread to organs and lymph nodes
  - Metastasis to liver, lung, brain and bone
  - Obstruction perforation

Treatment of colorectal cancer

This consists of surgery for cure or symptomatic relief, depending on **Duke's staging (Table 6.3)**.

- **Radiotherapy** may be used as an adjuvant, particularly to reduce tumour bulk before surgery
- **Adjuvant chemotherapy** (eg 5-fluorouracil post-operatively) has been shown to improve prognosis for patients at Duke's stages B and C; toxicity is low, so quality of life tends to be good
- Chemotherapeutic agents such as oxaliplatin plus fluorouracil, plus folinic acid (first-line) and irinotecan (second-line) have been used for advanced colorectal cancer. Biological treatments such as cetuximab, bevacizumab and panitumumab are not recommended by NICE in the UK as adjunctive therapies in advanced colorectal cancers that have progressed despite first-line chemotherapy
- Serial monitoring of carcinoembryonic antigen (CEA), a glycoprotein from gastrointestinal epithelia, may be of use in detecting recurrence. However, surveillance colonoscopies are indicated
- Isolated hepatic metastases to a single lobe of liver can be resected

Carcinoma complicating inflammatory bowel disease: this is discussed in Section 6.8.1, Crohn's disease and ulcerative colitis.

Table 6.3 Duke's classification and prognosis of colorectal cancer

Stage	5-year survival

A – confined to mucosa and submucosa	80%+
B – extends through muscularis propria	60–70%
C – regional lymph nodes involved	30–40%
D – distant spread	0%

6.8.7 Irritable bowel syndrome (IBS)

This is a chronic, relapsing, functional gut disorder with no recognisable pathological abnormality. In most cases the diagnosis is based on clinical presentation, although symptoms presenting in older patients require investigation to exclude other pathologies. Faecal calprotectin is a useful test to exclude inflammatory bowel disease and support a diagnosis of irritable bowel syndrome (IBS) in patients with chronic lower gastrointestinal symptoms in whom cancer is not suspected. IBS affects up to 10% of the population, with a ratio of 5:1 female : male. Strict diagnosis is based on the Rome III criteria, requiring recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months, associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool.

Full blood count, ESR, CRP, anti-endomysial antibody, TFTs and stool culture are useful screening investigations to exclude common diagnoses, and sigmoidoscopy provides reassurance for patients and clinicians that there is no underlying pathology.

- Bloating, borborygmi, excessive flatus, belching and mucorrhoea are common gastrointestinal symptoms
- IBS is often associated with variable bowel habit both in stool frequency and consistency, but may also present with ‘diarrhoea-dominant’ or ‘constipation-dominant’ symptoms
- Patients with IBS often complain of other ‘functional’ symptoms and have a higher prevalence of fibromyalgia, non-cardiac chest pain, tension headache, sterile cystitis, dyspareunia, back pain, myalgic encephalopathy, anxiety and depression
- There is a clear association with a history of childhood abuse
- In about a quarter of cases IBS is preceded by gastrointestinal infection, raising the possibility of damage to the neuroenteric innervation in some cases.

Treatment of irritable bowel syndrome

Treatment is usually symptomatic and until recently has been limited to antispasmodics, increased dietary fibre, laxatives, constipating agents, antidepressants, hypnotherapy and psychotherapy. The last therapies are particularly useful for patients whose symptoms occur on a background of significant psychological morbidity. Extensive research and clinical trials to improve patient phenotyping and development of novel treatment targets for IBS holds promise for more tailored treatment options in the future. One such treatment, prucalopride (a $5HT_4$ agonist), has NICE approval for treatment of ‘constipation-dominant’ IBS (IBS-C) in females who have persistent symptoms

despite having tried at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months. Another novel treatment licensed in moderate-to-severe IBS-C, linaclotide (guanylyl cyclase C receptor agonist), has the added advantage of improving visceral pain in addition to colonic transit.

6.9 GASTROINTESTINAL INFECTIONS

AIDS and the gut is covered in Chapter 8, Genitourinary Medicine and AIDS.

6.9.1 Gastroenteritis

Most gastrointestinal infections in the UK are viral or self-limiting bacterial infections such as *Staphylococcus aureus* or *Campylobacte*r. Most patients require no treatment, but antidiarrhoeals (such as loperamide) and oral rehydration therapy (ORT) may be required in patients who are at risk of dehydration. ORT utilises the capacity of the small bowel to absorb chloride, sodium and water via a glucose-dependent active transport channel that is not disrupted by infections. More intensive therapy is confined to those systemically unwell or immuno-suppressed.

The following are some of the more important gastrointestinal infections. (See also Chapter 11, Infectious Diseases and Tropical Medicine.)

Amoebiasis

- Infection is due to *Entamoeba histolytica* with faecal–oral spread
- The clinical spectrum ranges from mild diarrhoea to dysentery with profuse bloody stool; a chronic illness with irritable bowel-type symptoms may also occur. Colonic or hepatic abscesses occur, the latter commonly in the setting of a severe amoebic colitis
- Treatment is with metronidazole.

Campylobacter

This is due to a Gram-negative bacillus; spread is faecal–oral.

- Gram-negative rods
- Clinically, patients are often systemically unwell with headache and malaise prior to the onset of diarrhoeal illness. Abdominal pain may be severe, mimicking an acute abdomen
- Erythromycin may be indicated if symptoms are prolonged.

Cholera

- Infection is due to *Vibrio cholerae* (Gram-negative rods) which colonise the small bowel; spread is faecal–oral. A high infecting dose is needed as the bacteria are susceptible to gastric acid
- A severe toxin-mediated diarrhoea occurs with ‘rice-water’ stool which may exceed 20 litres per day. Dehydration is the main cause of death, especially in young or elderly, and mortality is

high without rehydration treatment
- Tetracycline may reduce transmission

Giardiasis

- Infection is due to *Giardia lamblia* (a flagellate protozoan) which colonises the duodenum and jejunum; spread is faecal–oral
- Bloating and diarrhoea (not bloody) occur and may be chronic. Malabsorption may occur with small-intestinal colonisation. Asymptomatic carriage is common and duodenal biopsy may be necessary to make the diagnosis in patients with chronic diarrhoea or malabsorption symptoms
- Treatment is with metronidazole

Salmonella

- A Gram-negative bacillus, *Salmonella Typhimurium*, with multiple serotypes divided into two main groups: those causing typhoid and paratyphoid (enteric fever), and those causing gastroenteritis (food poisoning). Spread is faecal–oral
- Diarrhoea (may be bloody) occurs, with or without vomiting and abdominal pain
- Rose spots tend to appear on the chest and abdomen about 2 weeks after the onset of symptoms
- Diagnosis is made by blood culture
- Treatment is supportive, but occasionally ciprofloxacin or trimethoprim may be required for chronic symptoms or severe illness in the very young or elderly.

Shigella

- Gram-negative rods. Spread is faecal–oral with a very low infecting dose of organisms needed owing to its high virulence
- The clinical spectrum ranges from diarrhoeal illness to severe dysentery, depending on the infecting type: *S. sonnei, S. flexneri, S. boydi, S. dysenteriae*
- Diarrhoea (may be bloody), vomiting, abdominal pain
- Treat if severe with ampicillin or tetracycline, although there is widespread resistance

6.9.2 Gastrointestinal tuberculosis

This is common in developing countries, and causes ileocaecal TB (mimicking Crohn's disease) or occasionally spontaneous TB peritonitis. There has been a recent increase in abdominal TB, particularly in patients with AIDS. The infection may occur secondary to pulmonary TB as a result of swallowing infected sputum or by haematogenous spread.

- Clinical features are often non-specific, such as malaise, fever and weight loss, as well as diarrhoea and abdominal pain
- Ultrasound, barium studies or CT may suggest the diagnosis, but biopsy, either by laparoscopy or endoscopy, is confirmative
- Treatment is with conventional anti-tuberculous therapy

6.10. HEPATOLOGY

6.10.1 Jaundice

Jaundice is one of the most common symptoms of liver disease, caused by the accumulation of bilirubin in the tissues. Bilirubin is formed as the end product of catabolism of haem-containing compounds and is clinically detectable at a level of >35 umol/l. The formation and excretion of bilirubin is shown in Figure 6.4.

The most common causes of jaundice in the UK are alcoholic liver disease, gallstones and tumours of the liver and pancreas.

Hyperbilirubinaemia may occur because of excess production or decreased elimination of bilirubin (Table 6.5). Jaundice can thus be broadly divided into three categories depending on the site of the pathology.

Causes of jaundice

The following classification is used (Table 6.4):

- **Pre-hepatic**: excess production of bilirubin or failure of uptake into the liver. Bilirubin is unconjugated and insoluble, so it does not appear in the urine–acholuric jaundice
- **Hepatic**: defect is at the level of hepatocyte. There is diminished hepatocyte function, and so both conjugated and unconjugated bilirubin appear in the urine
- **Post-hepatic**: there is impaired excretion of bile from liver into the gut. Conjugated bilirubin is therefore reabsorbed, which increases serum and urine levels and produces dark urine. The stools become pale due to lack of stercobilinogen; urobilinogen (produced in the gut – see Figure 6.4) becomes undetectable in urine.

Table 6.4 Causes of jaundice

Pre-hepatic	Haemolysis causing excess haem production Congenital hyperbilirubinaemia (eg Gilbert syndrome, Crigler–Najjar syndrome (see Table 6.5)
Hepatic	Alcoholic hepatitis Viral infection (eg hepatitis A, B, Epstein–Barr virus) Drugs (eg phenothiazines, augmentin and other antibiotics) Wilson's disease Rotor and Dubin–Johnson syndromes (see Table 6.5) Cirrhosis Multiple hepatic metastases Hepatic congestion in cardiac failure
Post-hepatic	Gallstones Carcinoma of pancreas or bile ducts Lymph nodes at porta hepatis (eg metastatic, lymphomatous) Primary biliary cirrhosis – small-bile-duct obliteration

Sclerosing cholangitis
Structural abnormality of the biliary tree – post-surgery, congenital (eg biliary atresia)

Investigation of jaundice

Figure 6.5 shows a typical systematic approach.

Figure 6.4 Enterohepatic circulation of bile.

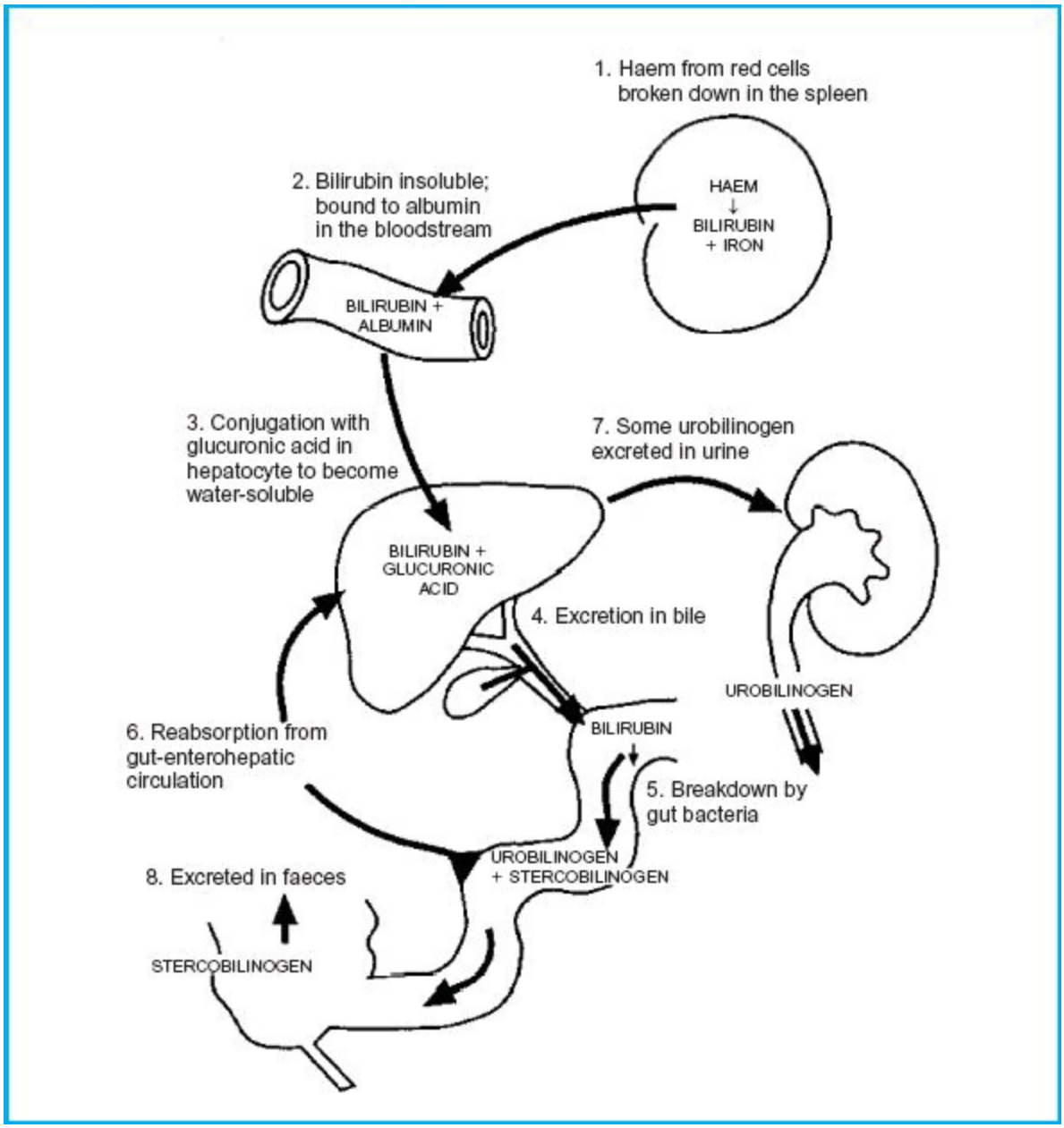
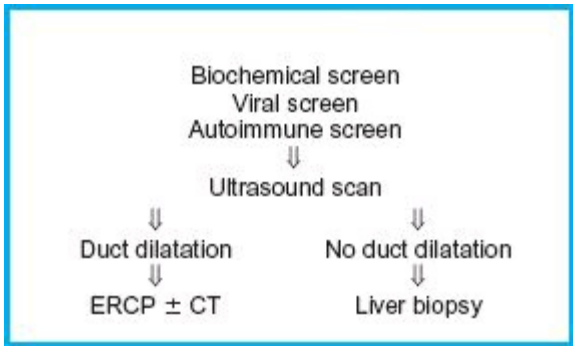


Figure 6.5 Investigation of jaundice



Blood tests

- **Liver function tests** (see Table 6.6) may indicate if jaundice is obstructive (elevated alkaline phosphatase from cells lining canaliculi) or hepatocellular (elevated transaminases). Patients with chronic liver disease may have normal enzyme levels but poor synthetic function (low albumin, prolonged prothrombin time) – will indicate a hepatic aetiology. Full blood count, reticulocyte count, haptoglobins, Coombs' test and blood film should be performed if haemolysis is suspected
- **Viral serology** (hepatitis A, B and C), **autoantibody titres** (antimitochondrial M2 for primary biliary cirrhosis and anti-smooth muscle for chronic autoimmune hepatitis), α_1-antitrypsin, α-fetoprotein (AFP), ferritin and copper studies are essential when investigating unexplained jaundice or chronic liver disease.

Imaging and biopsy

- **Liver ultrasound**: is the single most useful radiological test and will identify obstruction, metastases, cirrhosis and hepatoma
- **CT scanning**: is frequently used to complement ultrasound images, to define lesions more clearly and to diagnose lesions not seen on ultrasound
- **MRCP**: is non-invasive and is a highly accurate technique which has become the diagnostic test of choice in evaluating patients with biliary obstruction
- **Endoscopic ultrasound (EUS)**: is useful when non-invasive methods such as ultrasound and MRCP fail to yield a diagnosis for biliary duct dilatation, providing complete and detailed imaging of the biliary system, with a much lower complication risk than ERCP (0.03%)
- **ERCP**: is no longer used as a diagnostic test in obstructive jaundice due to the procedural risk of complications (>5%). It should always be interventional to stent obstructing tumours or remove obstructing gallstones identified on the above imaging modalities
- **Liver biopsy**: may be helpful in non-obstructive jaundice, but is contraindicated in the presence of uncorrected coagulation disorders, and is technically difficult if ascites is present.

Table 6.5 Classification of congenital hyperbilirubinaemia

Syndrome	Genetics	Defect	Clinical features	Treatment
	Autosomal	Defect in	Increased unconjugated bilirubin	

Gilbert	dominant	conjugation	Asymptomatic jaundice, increases with fasting	Nil as benign condition
Crigler–Najjar	Type 1 – autosomal recessive Type 2 – autosomal dominant	Both due to defective conjugation	Neonatal kernicterus and death Jaundice as neonate/child; survive to adulthood	None; fatal Phenobarbital to decrease jaundice
Dubin–Johnson	Autosomal recessive	Defect in hepatic excretion	Jaundice with right upper quadrant pain and malaise	Nil as benign condition
Rotor	Autosomal recessive	Defect in uptake and storage of bilirubin	Increased conjugated bilirubin	Nil as benign condition

Table 6.6 Liver function tests in jaundice

	Unconjugated bilirubin	Conjugated bilirubin	ALT/AST	Alkaline phosphatase	Gamma GT
Pre-hepatic	↑↑	Normal	Normal	Normal/↑↑	Normal/↑↑
Hepatic	Normal	↑↑	↑↑	↑	↑
Post-hepatic	Normal	↑↑	↑	↑↑	↑↑

↑ Moderately raised; ↑↑ raised.

6.10.2 Gallstone disease

Gallstones are one of the commonest causes of jaundice, usually presenting with right hypochondrial or epigastric pain and cholestatic liver function tests. Approximately 1 litre of bile is secreted by the hepatocytes each day. Half of this drains directly into the duodenum, whilst the remainder is stored and concentrated in the gall bladder by removal of sodium, chloride, bicarbonate and water. Cholecystokinin (CCK) then stimulates its release.

- Stones are found in 10–20% of the population (with a female preponderance), but are asymptomatic in the majority
- 70–90% of gallstones are a mixture of cholesterol and bile pigment and 10% are pure cholesterol. Pure pigment stones are rare except with chronic haemolysis (eg sickle cell disease, spherocytosis).

Risk factors for and clinical presentation of gallstones

- **Risk factors for stone formation**
  - Female sex

- Increasing age
- Drugs (eg oral contraceptive pill, clofibrate)
- Crohn's disease (terminal ileum)
- Short-bowel syndrome
- Haemolysis (pigment stones)

- **Clinical presentation**
  - Acute/chronic cholecystitis
  - Biliary colic
  - Cholestatic jaundice if duct obstruction
  - Pancreatitis
  - Cholangitis
  - Gallstone ileus

NB: Stones may form in the common bile duct even after cholecystectomy.

- Diagnosis in most cases may be established by ultrasound. MRCP has replaced ERCP as a useful, non-invasive investigation. EUS, where available, is the most sensitive test for diagnosing stones and is useful when noninvasive investigations fail to demonstrate a cause for biliary dilatation. ERCP is reserved to deal with stones that have been confirmed by other imaging investigations
- Definitive treatment is by cholecystectomy. ERCP with sphincterotomy and balloon clearance of the common bile duct is indicated for intraductal stones. Medical treatment with ursodeoxycholic acid can be used to dissolve cholesterol stones; however, this is extremely slow and should be reserved only for patients who are unfit for other treatment.

6.10.3 Ascites

Ascites is defined as the accumulation of free fluid within the peritoneal cavity. It can be subdivided into transudate or exudate (Table 6.7) depending on whether the protein content is less or greater than 30 g/l, respectively. The most common causes in the UK are cirrhosis and malignant disease.

The treatment of ascites depends on the aetiology.

- **Transudates** respond to fluid restriction, low sodium intake and diuretic therapy, to promote sodium and water excretion via the kidneys. Aldosterone antagonists (spironolactone) are first-line diuretics (BSG and EASL guidelines) with a starting dose of 100 mg, increasing stepwise every 7 days if there is no response up to a maximum of 400 mg/day. In failure of aldosterone antagonists (failure to lose 2 kg/week or development of hyperkalaemia), furosemide should be added 40 mg/day, increasing stepwise to a maximum of 160 mg/day. Patients should undergo frequent clinical and biochemical monitoring. Once ascites has largely resolved, doses should be reduced to the minimum required or discontinued. Paracentesis may be used for tense ascites or ascites that is not responding to diuretics. However, paracentesis may result in a further shift of fluid from the intravascular space into the peritoneal cavity with the risk of circulatory collapse.

This can be reduced by supporting the circulation using intravenous albumin. The drain should be removed at the earliest opportunity (typically after 6 hours) because of the risk of introducing infection, which can in turn lead to decompensation of liver disease

- **Exudates** can be safely paracentesed without protein replacement.

Table 6.7 Causes of ascites

Transudate	Portal hypertension Nephrotic syndrome Malnutrition Cardiac failure Budd–Chiari syndrome Myxoedema
Exudate	Hepatic or peritoneal malignancy Intra-abdominal TB Pancreatitis

Hepatorenal syndrome (HRS)

- Acute kidney injury can complicate chronic liver disease, but it can also occur with fulminant hepatic failure:
  - Type 1 HRS occurs as a rapidly progressive renal impairment, with a very high mortality rate, all patients dying within weeks without treatment
  - In Type 2 HRS renal impairment is more stable and some hepatic reserve is preserved. Mortality is again high, but some patients survive over 6 months
- The benefits of dialysis in hepatorenal syndrome are limited and it is not recommended in patients with decompensated cirrhosis who are not candidates for liver transplantation (Acute Dialysis Quality Initiative [ADQI] guidelines–2012).

Spontaneous bacterial peritonitis

Patients with cirrhosis and ascites are at risk of spontaneous bacterial peritonitis (SBP), which may present with local symptoms or features of peritonitis, signs of sepsis, deterioration in liver function, hepatic encephalopathy, renal failure and gastrointestinal bleeding. An ascitic fluid neutrophil count of ≥ 250 / mm^3 is diagnostic on paracentesis, and appropriate empirical antibiotics with Gram-negative cover should be started once diagnosis has been confirmed. Patients who present with SBP should be treated with intravenous albumin because this has been shown to decrease the incidence of hepatorenal syndrome and improve survival (European Association for the Study of the Liver [EASL] clinical practice guidelines – 2010).

6.10.4 Viral hepatitis

The six major hepatitis viruses are described below, but further types are already postulated. Hepatitis B and C in particular are major causes of morbidity and mortality worldwide, although

recent advances in treatment with interferon and other antivirals have improved the outcome in certain groups.

Hepatitis A

Spread: faecal–oral
Virus: RNA
Clinical: anorexia, jaundice, nausea, joint pains, fever
Treatment: supportive
Chronicity: no chronic state
Vaccine: yes

Hepatitis B

Spread: blood-borne (eg sexual, vertical, congenital transmission)
Virus: DNA
Clinical: acute fever, arteritis, glomerulonephritis, arthropathy
Treatment: supportive; EASL guidance recommends that patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ ml, serum ALT levels above the upper limit of normal and severity of liver disease assessed by liver biopsy showing moderate-to-severe active necroinflammation. Treatment options include interferon and the antiviral agents lamivudine, adefovir, tenofovir, entecavir and telbivudine (with an aim to acheive seroconversion to anti-HBe and achieve reduction in viral replication [HBV DNA levels] and reduce histological activity of chronic hepatitis)
Chronicity: 5% progress to chronic carriage (risk of cirrhosis and hepatocellular carcinoma)
Vaccine: yes

Hepatitis C

Spread: blood-borne, sexual
Virus: RNA
Clinical: acute hepatitis – less severe than A or B, fulminant failure rate
Treatment: pegylated interferon-alpha (interferon bound to polyethylene glycol) for chronic HCV. This may be more effective when used in combination with ribavirin
Chronicity: 60–80% develop chronic hepatitis, and 20% of these progress to cirrhosis (of whom a third will develop hepatocellular carcinoma). IV- drug-related hepatitis C represents a major public health problem in the UK
Vaccine: no

Hepatitis D (delta agent)

Spread: blood-borne (dependent on concurrent hepatitis B infection for replication)
Virus: incomplete
Clinical: exacerbates established hepatitis B infection and increases risk of hepatic failure and cirrhosis
Treatment: interferon of limited benefit
Chronicity: increases incidence of cirrhosis in chronic HBV

Vaccine: no

Hepatitis E

Spread: faecal–oral
Virus: RNA
Clinical: acute self-limiting illness, but there is a 25% mortality (fetal and maternal) in pregnancy, which increases in later stages of gestation
Treatment: supportive
Chronicity: no chronic state
Vaccine: no

Hepatitis G

Spread: blood-borne
Virus: RNA
Clinical: doubtful relevance; 20% of patients with chronic HCV are infected with hepatitis G
Treatment: viraemia may decline with interferon
Chronicity: unknown – may cause cirrhosis and hepatocellular carcinoma
Vaccine: no

Interferon in viral hepatitis

Virological response to treatment is defined as an HBV DNA concentration of less than 2000 IU/ml. It is usually evaluated at 6 months and at the end of therapy, as well as at 6 and 12 months after the end of therapy. Interferon is predominantly of benefit in patients suffering from chronic hepatitis B and C. In hepatitis B, there is a response in 40% of chronic carriers. The response is poorer in Asian patients. The response is likely to be very poor if the patient is also infected with HIV, and thus treatment is not usually indicated in this group. In hepatitis C, there is a response in 50% of chronic carriers, but 50% of these will relapse despite treatment.

Hepatitis B serology

Antigens/antibodies related to viral surface (**s**), envelope (**e**) and core (**c**) are useful for determining the stages, infectivity and chronicity of hepatitis B infection:

- **HBsAg**: present in acute infection; if present longer than 6 months, then 25% develop chronic hepatitis
- **HBeAg**: present in acute or chronic infection; signifies high infectivity
- **HBcAg**: present in acute or chronic infection; found only in liver tissue; present for life
- **Anti-HBs**: signifies immunity after vaccination or acute infection
- **Anti-HBe**: signifies declining infectivity and resolving infection
- **Anti-HBe IgM**: signifies recent acute infection; lasts less than 6 months
- **Anti-HBc IgG**: a lifelong marker of past acute or chronic infection; does not signify immunity or previous vaccination

6.10.5 Drug-induced hepatitis

Many drugs can cause hepatitis. Toxicity may be due to overdose (eg paracetamol), idiosyncratic (eg flucloxacillin) or may be related to dosage or duration of therapy (eg azathioprine). Three patterns of damage can occur:

- **Cholestasis**: some drugs produce a functional obstruction to bile flow by causing bile duct inflammation and interfering with excretory transport mechanisms. The commonest examples are flucloxacillin, erythromycin, chlorpromazine, oral contraceptives and anabolic steroids
- **True hepatitis**: some drugs produce direct hepatocellular damage which may be trivial or result in fulminant liver failure. Several mechanisms are responsible. Common examples include statins, anti-tuberculous drugs, immunosuppressants, ketoconazole and halothane
- **Hepatic necrosis**: if the ability of the liver to detoxify metabolites is overwhelmed, glutathione levels fall and toxic metabolites accumulate, causing liver necrosis. This is the pattern of damage with carbon tetrachloride ingestion and paracetamol overdosage.

Other causes of acute hepatitis include:

- alcohol
- other viruses (eg Epstein–Barr, yellow fever, CMV, rubella, herpes simplex)
- other infections (eg malaria, toxoplasmosis, leptospirosis, brucellosis).

6.10.6 Autoimmune hepatitis

This condition occurs predominantly in female patients. Other autoimmune disease is often present and patients are usually antinuclear antibody-positive. Other antibodies associated with autoimmune hepatitis include anti-smooth muscle and anti-liver kidney microsomal-1 antibody, and anti-double stranded DNA antibody is present in 15% of cases. Autoimmune hepatitis responds to steroids and azathioprine, but the majority progress to cirrhosis, although 90% are alive at 5 years and may be candidates for transplantation.

6.10.7 Cirrhosis

Cirrhosis is characterised by the irreversible destruction and fibrosis of normal liver architecture with some regeneration into nodules.

There are four stages of pathological change:

- liver cell necrosis
- inflammatory infiltrate
- fibrosis
- nodular regeneration.

Regeneration may be macronodular (eg alcohol- or drug-induced), micronodular (eg viral hepatitis)

or mixed, but a more useful categorisation is according to the aetiological agent.

Causes of cirrhosis

- Alcohol (most common in the UK, approximately 30% of all cases)
- Haemochromatosis
- Hepatitis B or C (most common worldwide)
- α1-antitrypsin deficiency
- Cryptogenic
- Primary biliary cirrhosis
- Wilson's disease
- Non-alcoholic steatohepatitis (NASH)
- Autoimmune hepatitis

Evidence of chronic liver disease may or may not be present.

Clinical features of cirrhosis

Clinical features are related to hepatic insufficiency:

- **Confusion/encephalopathy**: due to failure of liver to metabolise ammonium salts
- **Haemorrhage**: bruising/bleeding/petechiae secondary to deficiency in factors II, VII, IX and X, and thrombocytopenia
- **Oedema**: secondary to hypoalbuminaemia
- **Ascites**: due to portal hypertension, hypoalbuminaemia and secondary hyperaldosteronism
- **Jaundice**: failure to metabolise and/or excrete bilirubin
- **Other clinical features include**: palmar erythema, spider naevi, Dupuytren's contracture, caput medusae and splenomegaly (due to portal hypertension)
- **Gastrointestinal haemorrhage** secondary to varices (oesophageal, gastric or rectal)
- **Hepatorenal syndrome**

Diagnosis of cirrhosis

Cirrhosis may be suspected on ultrasonography but diagnosis can be confirmed histologically via ultrasound-guided liver biopsy, which may also help identify the aetiology. An ultrasound-guided approach to biopsy is mandatory because the liver is often very small. Rarely, a transjugular biopsy may be required, particularly if clotting is markedly deranged. The disadvantages of liver biopsy include its invasiveness and post-procedural risks such as pain and bleeding. Recently, transient elastography (Fibroscan) has been developed to determine the degree of liver fibrosis via a non-invasive technique. This involves passage of sound waves through the liver via a transducer at the end of an ultrasound probe; the velocity of these sound waves is then converted into a measure of liver stiffness. In addition to non-invasiveness, advantages include instantly available results.

Indications for liver biopsy (adapted from AASLD position paper Liver Biopsy – Hepatology, 2009)

- Guide management plans based on histological analysis (eg. viral hepatitis, autoimmune hepatitis)
- Persistently abnormal liver enzymes of unknown cause
- Prognosticate and stage known parenchymal liver disease
- Confirm a diagnosis of non-alcoholic fatty liver disease
- Focal liver lesions identified on imaging studies
- Multiple parenchymal liver diseases, eg overlap of PBC and autoimmune hepatitis or steatosis with viral hepatitis

Treatment of cirrhosis

Treatment is aimed at the removal of causal factors such as alcohol. Specific treatments include interferon for viral hepatitis and ursodeoxycholic acid for primary biliary cirrhosis. Transplantation is the best hope but many patients are not suitable.

Contraindications for liver transplantation include:

- Poor cardiac reserve
- Co-morbidity such as HIV infection or severe respiratory disease
- Failure to abstain from alcohol.

There is no definitive cut-off regarding age, but patients over 70 years are less likely to be suitable.

Conditions which may be amenable to hepatic transplantation

- **Fulminant hepatic failure** (eg due to hepatitis C or paracetamol toxicity)
- **Primary biliary cirrhosis**
- **Wilson's disease**
- **Hepatitis B** – although there is frequent recurrence after transplant; this can be reduced with pre-transplant treatment with interferon
- **Cholangiocarcinoma** – if unresectable at presentation
- **Alcohol** – following psychological review and if abstained for more than 6 months
- **Haemochromatosis**
- **Hepatocellular carcinoma** – if not multifocal, if <5 cm and no evidence of vascular invasion

6.10.8 Portal hypertension and varices

Portal hypertension occurs as a result of increased resistance to portal venous flow. Pressure in the

portal vein rises and is said to be pathological when >12 mmHg, although pressures of up to 50 mmHg may occur. The spleen enlarges and anastomoses may open between the portal and systemic circulation. Some of the collaterals, which most commonly occur at the oesophagogastric junction, umbilicus and rectum, may become very large, with a risk of bleeding.

A variety of conditions may cause portal hypertension; in the UK, the single most common is cirrhosis secondary to alcohol.

Causes of portal hypertension

- Cirrhosis due to any cause
- Portal vein thrombosis (congenital malformation, pancreatitis, tumour)
- Budd–Chiari syndrome (thrombosis or obstruction of hepatic vein due to tumour, haematological disease or the oral contraceptive pill)
- Intrahepatic tumours such as cholangiocarcinoma or hepatocellular carcinoma
- Constrictive pericarditis
- Right heart failure
- Splenic vein thrombosis (segmental portal hypertension)

Variceal haemorrhage

Thirty per cent of patients with varices will bleed at some point, with a mortality of 50% for that episode. The majority of survivors will rebleed, with a mortality of 30%. Bleeding is often catastrophic as many patients also have coagulopathy as a result of their underlying liver disease.

Primary prevention of haemorrhage

All patients with cirrhosis of the liver should have upper GI endoscopy to determine the presence or absence of varices. If there are none, or only very small varices, no treatment is required except regular endoscopic review every 2–3 years. Larger varices in patients with no history of variceal haemorrhage should be treated with prophylactic, non-selective β blockers (such as propranolol or carvedilol), alone or in combination with a nitrate (nitrates given alone are of no benefit). These reduce portal pressure and thus the risk of haemorrhage. Patients intolerant of β blockers and who are at high risk of bleeding may be considered for endoscopic variceal ligation.

Treatment of variceal haemorrhage (see Figure 6.3)

After resuscitation and correction of coagulopathy and thrombocytopenia, vasoactive drugs, such as terlipressin (Glypressin), should be concomitantly prescribed with antibiotics at presentation of suspected variceal bleeding. Confirmation of diagnosis and treatment of choice is early gastroscopy with band ligation of oesophageal varices (now shown to be superior to injection sclerotherapy). Gastric varices should be treated endoscopically with injection sclerotherapy using *N*-butyl-2-cyanoacrylate. Temporary balloon tamponade (Sengstaken–Blakemore tube) may be useful if endoscopy is not immediately available or bleeding cannot be stopped endoscopically. Bleeding that does not respond to these measures may be an indication for emergency transjugular intrahepatic

portosystemic shunting (TIPSS).

Secondary prevention of haemorrhage

Patients should undergo repeated band ligation until varices are eradicated. Beta blockers should be given as this reduces the risk of rebleeding by up to 40%. Recurrent haemorrhage may be an indication for TIPSS.

Transjugular intrahepatic portosystemic shunting (TIPSS)

This involves placement of a shunt under radiological screening which decompresses the portal venous system. Anatomically the shunt connects the portal vein (high pressure) to the hepatic vein (low pressure). As it is less invasive than surgery, it may be a useful rescue procedure for patients with recurrent or resistant haemorrhage who are not fit for surgery. The major problems are that shunting may precipitate hepatic encephalopathy (this occurs in up to 24%, but seems more responsive to treatment than encephalopathy from other causes), and shunt blockage. In the latter case, a second shunt may be 'piggy-backed' across the first. TIPSS may be particularly helpful as a palliative procedure in patients with recurrent haemorrhage due to malignancy.

6.10.9 Hepatic encephalopathy

Hepatic encephalopathy is a neuropsychiatric syndrome which may complicate acute or chronic liver disease from any cause. Symptoms include confusion, falling level of consciousness, vomiting, fits and hyperventilation. Acute kidney injury may often supervene – the chance of recovery from hepatorenal failure is extremely poor. The underlying mechanisms are complex, but the absorption of toxins, such as ammonia, from bacterial breakdown of proteins in the gut is thought to play a major part. Portosystemic shunting of blood occurs – toxins thus bypass the liver and cross the blood–brain barrier.

The most common causes of **acute hepatic encephalopathy** are fulminant viral hepatitis and paracetamol toxicity, which are potentially fully reversible. Indicators of poor prognosis are:

- worsening acidosis
- rising prothrombin time
- falling Glasgow Coma Scale score.

These patients should be referred to a specialist centre as they may need transplantation.

Chronic hepatic encephalopathy may supervene in chronic liver disease of any type. It is often precipitated by:

- alcohol
- drugs
- GI haemorrhage
- infections
- constipation.

It is characterised by a flapping tremor, decreased consciousness level and constructional apraxia.

Treatment of hepatic encephalopathy

- Screen for and treat sepsis aggressively – if ascites is present, consider bacterial peritonitis and perform a diagnostic ascitic tap. There should be a low threshold for prescribing antibiotics
- Strict fluid and electrolyte balance
- High protein diet
- Laxatives (lactulose) to clear the gut and thus reduce toxin absorption; neomycin is now rarely used
- Rifaxamin, a semi-synthetic antibiotic which decreases intestinal production and absorption of ammonia, has shown promise in clinical trials in maintaining remission in patients with hepatic encephalopathy. This drug is currently being appraised by NICE
- Remove or treat precipitants
- Mortality is high, especially if renal failure supervenes, when the mortality exceeds 50%

6.10.10 Primary biliary cirrhosis

Primary biliary cirrhosis accounts for approximately 5% of deaths due to cirrhosis. The cause is unknown although environmental and genetic factors and autoimmune aetiology are suggested in the literature, especially given the strong association with other autoimmune disease such as rheumatoid arthritis, Sjögren syndrome and CREST syndrome. Histologically, progressive inflammation and destruction of small intrahepatic ducts leads to eventual cirrhosis. Ninety per cent of patients are female, often in middle age. There are four stages of primary biliary cirrhosis:

1. Destruction of interlobular ducts
2. Small-duct proliferation
3. Fibrosis
4. Cirrhosis.

Primary biliary cirrhosis

- **Clinical features**
  - Cholestatic jaundice
  - Xanthelasmata due to hypercholesterolaemia
  - Skin pigmentation
  - Clubbing
  - Hepatosplenomegaly
  - Portal hypertension varices
  - Osteoporosis and osteomalacia
- **Diagnosis**

- Antimitochondrial (M2) antibody present in 95%
- Predominantly raised alkaline phosphatase – often raised in advance of symptoms/signs
- Raised IgM
- Liver biopsy showing the features listed above

Treatment is symptomatic; cholestyramine relieves pruritus. Ursodeoxycholic acid is widely used, but it is doubtful whether this agent either improves the prognosis or delays time to liver transplantation. Rising bilirubin levels are an indication that the disease is approaching end-stage, and as liver transplantation remains the only hope of cure, patients should be assessed for this later treatment at an appropriate stage of their disease process.

6.10.11 Other causes of chronic liver disease

Haemochromatosis: this is an autosomal recessive disorder of iron metabolism leading to deposition in the liver, pancreas, pituitary and myocardium. (See Chapter 13, Metabolic Diseases.)

Wilson's disease: this is an autosomal recessive disorder of copper metabolism causing deposition in the liver, basal ganglia and cornea (Kayser–Fleischer ring). (See Chapter 13, Metabolic Diseases.)

Non-alcoholic fatty liver disease (NAFLD): NAFLD is the most common cause of liver disease in the West and accounts for a growing proportion of liver transplant patients. Diagnosis requires demonstration of hepatic steatosis (imaging or histology) without significant alcohol consumption history. Histologically, NAFLD is divided into non-alcoholic fatty liver (NAFL), which is common (33% of UK population), and non-alcoholic steatohepatitis, inflammation with hepatocyte injury (ballooning) with or without fibrosis (NASH), which affects 2-5% of UK population.

Conditions associated with NAFLD:

- obesity
- type 2 diabetes mellitus
- dysplipidaemia
- metabolic syndrome.

Other causes of parenchymal liver disease should be excluded. Liver biopsy should be considered in patients with higher risk (eg metabolic syndrome) for steatohepatitis and advanced fibrosis, and those in whom coexisting chronic liver diseases cannot be excluded without biopsy. Patients often have no specific symptoms. Treatment should focus on managing lifestyle factors, cardiovascular and metabolic risk factors. In particular, there is evidence that exercise and loss of 3–5% of body weight can regress steatosis. The British Society of Gastroenterology advises that diabetic control must be optimised, including metformin and GLP-1 analogues, and consideration of thiazolidinediones (pioglitazone) Orlistat and Vitamin E. Patients with NASH cirrhosis will require surveillance for hepatocellular carcinoma, oesophageal varices and features of decompensation (ascites, jaundice, encephalopathy, malnutrition). Bariatric surgery is thought to be beneficial in NASH, with reports of improved liver histology and glycaemic control.

6.10.12 Parasitic infections of the liver

Hydatid disease

This is caused by *Echinococcus granulosus* (a dog tapeworm), and is most common in areas of sheep and cattle farming. Ingestion results from eating contaminated vegetables or as a result of poor hand hygiene. The parasitic embryos hatch in the small intestine and enter the bloodstream via the portal venous circulation to the liver, but there may also be spread to lung or brain.

- Many cases are asymptomatic, but right upper quadrant pain is the commonest symptom. Jaundice occurs if there is duct obstruction, and peritonitis will result from cyst rupture
- Diagnosis is confirmed using a haemagglutination test, but eosinophilia or the presence of cystic lesions on liver ultrasound in an at-risk individual is strongly suggestive of the disease
- Active infection is treated with albendazole followed by surgical resection of the intact cyst. Chronic calcified cysts can be left untreated.

Schistosomiasis

This affects about 250 million people worldwide. It is caused by *Schistosoma mansoni* (Africa, South America) or *Schistosoma japonicum* (Asia). Infection occurs when the parasite penetrates the skin during swimming or bathing in infected water contaminated by the intermediate host – the freshwater snail. The parasite migrates to the liver via the portal venous system where it matures, migrates back along the portal (and mesenteric) veins and produces numerous eggs which penetrate the gut wall and are excreted to continue the cycle. A chronic granulomatous reaction occurs in the liver leading to periportal fibrosis and cirrhosis.

- Early symptoms are related to the site of entry of the organism (swimmer's itch) and systemic effects, including malaise, fever, myalgia, nausea and vomiting
- Diagnosis confirmed by detecting ova in stool or liver biopsy. Liver function tests show raised alkaline phosphatase, and there is an eosinophilia
- Treatment is with praziquantel.

6.10.13 Hepatic abscesses

Pyogenic abscesses most commonly occur following intra-abdominal sepsis, but they can occur spontaneously. The most common organism isolated is *E. coli* but *Enterococcus, Proteus*, *Staphylococcus aureus* and anaerobes are recognised.

- Patients present with swinging pyrexia, weight loss, right upper quadrant pain and anorexia. Septic shock or jaundice may develop
- Diagnosis is confirmed by liver ultrasound, which is used to guide aspiration or insertion of a drain
- Broad-spectrum antibiotics are given until sensitivities are available; occasionally surgical resection is required.

Amoebic abscesses are caused *by Entamoeba histolytica* which spreads from the gut (where it can cause an acute diarrhoeal illness) via the portal system to the liver. Single or multiple abscesses may

be found on ultrasound and treatment is with metronidazole.

6.10.14 Hepatobiliary tumours

There are a number of types of primary hepatic malignancy, all of which are rare. Secondary tumours, however, are common, typically metastasising from the stomach, colon, breast and lung.

Treatment of metastatic tumours is usually not indicated as the disease process is far advanced, although chemotherapy may slow progression in selected patients.

Hepatocellular carcinoma

This is rare in the UK (1–2/100 000 population), but the incidence is increased 20–30 times in Africa, Asia and Japan.

Incidence is increased by:

- Hepatitis B (commonest cause worldwide) and hepatitis C virus
- Cirrhosis from any cause, particularly hepatitis B and C and haemochromatosis
- Aflatoxin – a carcinogen from the mould *Aspergillus flavus* which may contaminate food
- Long-term oral contraceptive use.

Raised serum α-fetoprotein (AFP) suggests the diagnosis and in association with ultrasound, has been suggested as an appropriate 6 monthly screening for patients with cirrhosis (EASL guidelines, 2012). The treatment and prognosis are outlined in Table 6.8.

Table 6.8 Treatment and prognosis of hepatocellular carcinoma

Treatment	Prognosis
Resection	Only 5–15% are suitable, with 20% operative mortality; 5-year survival <30%
Transplant	Very few patients are suitable – they should have single tumours smaller than 5 cm with no vascular or metastatic spread; 5-year survival 90%
Chemotherapy/ethanol injection into tumour/embolisation	Palliative with little survival benefit

Cholangiocarcinoma

This is an uncommon adenocarcinoma arising from the biliary epithelium. It usually presents with obstructive jaundice.

Predisposing factors:

- Sclerosing cholangitis

- Choledochal cyst or other biliary tract abnormality
- Liver fluke infection
- Caroli's disease (dilatation of the intrahepatic bile ducts predisposing to infection and stone formation).

The treatment and prognosis of cholangiocarcinoma are outlined in Table 6.9. Palliative stenting relieves jaundice and improves quality of life.

Carcinoma of the gallbladder

This adenocarcinoma occurs in the elderly, but is uncommon. It has usually invaded locally or metastasised by the time of diagnosis.

Benign hepatic adenoma

The incidence of this is increased in patients who have been taking oral contraceptives for longer than 5 years, and also with the use of anabolic steroids. It is usually asymptomatic but may, rarely, cause intraperitoneal bleeding or right upper quadrant pain.

Hepatic haemangioma

This is common, and is often an incidental finding on ultrasound. It is benign, but may occasionally rupture.

Table 6.9 Treatment and prognosis of cholangiocarcinoma

Treatment	Prognosis
No treatment	Average survival 2 months
Resection	Fewer than 20% of patients are suitable; average survival approximately 3 years
Transplant	Very few patients are suitable, but this gives the best prognosis

6.11. ACUTE ABDOMEN

An acute abdomen is one of the more frequent presentations to the Accident and Emergency department. Commoner causes are given in Table 6.10.

Table 6.10 Acute abdomen: causes

Bowel	Acute appendicitis Perforated viscus Inflammatory bowel disease Diverticular disease Bowel obstruction Mesenteric ischaemia

	Incarcerated inguinal hernia Incarcerated femoral hernia Volvulus Intussusception
Pelvic organs	Torsion of ovaries Pelvic inflammatory disease Endometriosis
Pancreas	Acute pancreatitis Acute on chronic pancreatitis
Gallbladder/ biliary system	Cholecystitis Cholangitis
Peritoneum	Peritonitis
Kidneys	Renal calculi
Spleen	Splenic infarcts

6.11.1 Investigations of acute abdomen

- Bloods: full blood count, urea and electrolytes, liver function tests, CRP, amylase, arterial blood gases, calcium
- Chest X-ray
- Abdominal X-ray
- ECG
- CT scan of abdomen
- Laparotomy.

Chapter 7
Genetics

CONTENTS

Genetics

7.1 CHROMOSOMES

Within the nucleus of somatic cells there are 22 pairs of autosomes and one pair of sex chromosomes. Normal male and female karyotypes are 46,XY and 46,XX, respectively. The normal chromosome complement is known as **diploid**. Genomes with a single copy of each chromosome are known as **haploid**, and those with three copies of each chromosome are known as **triploid**. A karyotype with too many or too few chromosomes, in which the total is not a multiple of 23, is called **aneuploid**. Chromosomes are divided by the centromere into a short 'p' arm ('petit') and long 'q' arm. **Acrocentric** chromosomes (13, 14, 15, 21, 22) have the centromere at one end.

Lyonisation is the process in which, in a cell containing more than one X chromosome, only one is active. Selection of the active X is usually random and each inactivated X chromosome can be seen as a Barr body on microscopy.

Mitosis is diploid-to-diploid cell division (Figure 7.1). This occurs in somatic cells, resulting in two diploid daughter cells with nuclear chromosomes that are genetically identical both to each other and to the original parent cell.

Meiosis is diploid-to-haploid cell division (Figure 7.2). This occurs in the germ cells of the gonads and is also known as 'reduction division'. It results in four **haploid** daughter cells, each containing just one member (homologue) of each chromosome pair. Meiosis involves two divisions (**meiosis I and II**). The reduction in chromosome number occurs during meiosis I and is preceded by exchange of chromosome segments between homologous chromosomes called **crossing over**. All four daughter cells are genetically different, due to **recombination** from these crossovers. In males, the onset of meiosis and spermatogenesis is at puberty. In females, replication of the chromosomes and crossing over begins in fetal life, but the oocytes remain suspended before the first cell division until just before ovulation.

Figure 7.1 Mitosis

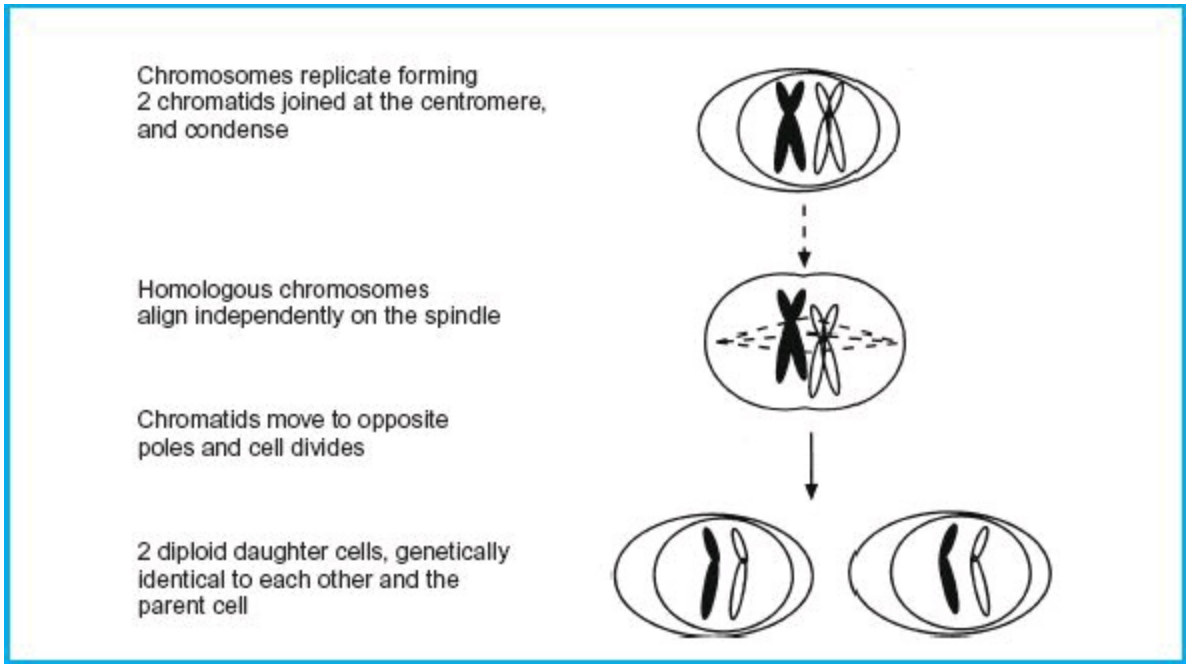
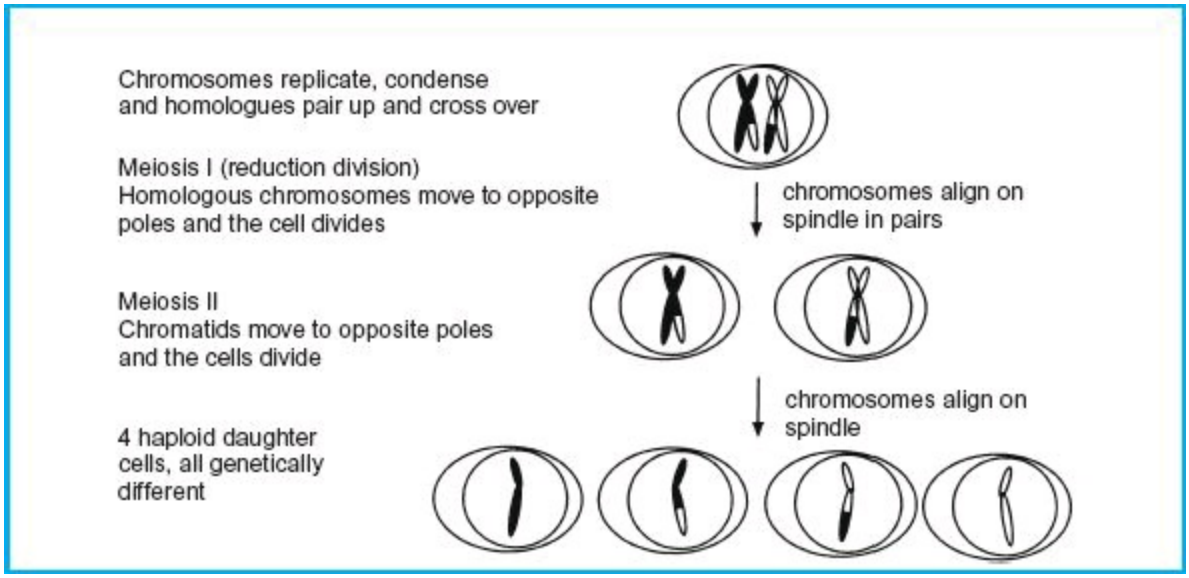


Figure 7.2 Meiosis



Translocations

- **Reciprocal**: exchange of genetic material between non-homologous chromosomes
- **Robertsonian**: fusion of two acrocentric chromosomes at their centromeres (eg 14;21)
- **Unbalanced**: if chromosomal material has been lost or gained overall
- **Balanced**: if no chromosomal material has been lost or gained overall.

7.1.1 Common sex chromosome aneuploidies

Turner syndrome (karyotype 45,X)

This affects 1 in 2500 live-born girls but it is a frequent finding among early miscarriages. Patients are usually of normal intelligence, but may experience specific cognitive difficulties, particularly with arithmetic and visuospatial tasks. They have streak ovaries which result in primary

amenorrhoea, low oestrogen with high gonadotrophins and infertility.

Normal secondary sexual characteristics may develop spontaneously or be induced with oestrogens. Short stature throughout childhood with failure of the pubertal growth spurt is typical. Final height can be increased by early treatment with growth hormone. Cardiovascular complications are very common, with up to 50% having congenital heart disease, particularly coarctation. Type 2 diabetes and hypertension are common late-onset complications, and aortic dilatation and rupture are also observed, which contribute to the excess mortality in this condition. Other features may include those in the box.

Features of Turner syndrome

- Webbed or short neck
- Shield chest with widely spaced nipples
- Renal abnormalities (eg horseshoe kidney, duplicated ureters, renal aplasia) in approximately 30%
- Cubitus valgus (wide carrying angle)
- Low hairline
- Autoimmune conditions, particularly coeliac disease
- Non-pitting lymphoedema in approximately 30%

When women with Turner syndrome are fertile, this is often due to the presence of 45,X/46,XX mosaicism. Their offspring may be at increased risk for 45,X (or other sex chromosome aneuploidy) and trisomy 21.

Triple X syndrome (karyotype 47,XXX)

Incidence of this karyotype is hard to estimate because patients show little phenotypic abnormality, but tend to be of tall stature, usually above the 75th centile. Intelligence is typically slightly reduced compared with siblings, by on average 10–15 IQ points, and therefore usually still falls within normal or low-to-normal limits. Speech delay is more common than in 46,XX; there may be higher chances of 47,XXX girls needing some help with this or other schooling needs (but usually in a mainstream school). Fertility is normal, but the incidence of premature ovarian failure is increased. There is a low risk of recurrence in offspring.

Klinefelter syndrome (karyotype 47,XXY)

This affects 1 in 600 newborn boys. Phenotypic abnormalities are rare prepubertally, other than a tendency for tall stature. At puberty, spontaneous expression of secondary sexual characteristics is variable but poor growth of facial and body hair is common. The testes are small in association with azoospermia, testosterone production of around 50% of normal and raised gonadotrophin levels (hypergonadotrophic hypogonadism). Gynaecomastia occurs in 30% and there is an increased (but still not high) risk of male breast cancer. Female distribution of fat and hair and a high-pitched voice may occur but are not typical. Intelligence is generally marginally reduced compared with siblings but

usually falls within normal or low-to-normal limits. Mild developmental delay (especially speech) and behavioural problems are more common.

47,XYY males

This occurs in approximately 1 in 1000 newborn boys. These boys are phenotypically normal but tend to be tall. Intelligence is usually within normal limits but there is an increased incidence of behavioural abnormalities. Fertility is usually normal, with a low risk for recurrence in offspring.

7.1.2 Common autosomal chromosome aneuploidies

In general, trisomy is tolerated better by the organism than monosomy. There are no whole autosome monosomies that are compatible with life. It is no coincidence that the three autosomal aneuploidies compatible with live birth involve the three least gene-rich chromosomes.

Down syndrome (trisomy 21)

Down syndrome affects 1 in 700 live births overall and is usually secondary to meiotic non-disjunction during oogenesis, which is more common with increasing maternal age. Of patients, 2% have an underlying Robertsonian translocation, most commonly between chromosomes 14 and 21. This arises anew in 50% and is inherited from a parent in 50%.

Around 3% of people with trisomy 21 have detectable **mosaicism** (a mixture of trisomy 21 and karyotypically normal cells), usually resulting in a milder phenotype.

Phenotypic features of Down syndrome

- Brachycephaly
- Protruding tongue
- Single palmar crease, fifth finger clinodactyly, wide sandal gaps between first and second toes
- Upslanting palpebral fissures, epicanthic folds, Brushfield's spots on the iris
- Hypotonia and moderate learning disability

The next box shows the more common features in patients with Down syndrome.

Common features of Down syndrome

- Cardiovascular malformations in 40%, particularly atrioventricular septal defects (AVSDs)
- Haematological abnormalities, particularly acute lymphoblastic leukaemia (ALL), acute myeloblastic leukaemia (AML) and transient leukaemias
- Gastrointestinal abnormalities in 6%, particularly duodenal atresia and Hirschsprung's disease
- Hypothyroidism
- Cataracts in 3%

- Alzheimer's disease in most by age 50 years

Edwards syndrome (trisomy 18)

This typically causes intrauterine growth retardation, a characteristic facies, prominent occiput, overlapping fingers (second and fifth overlap third and fourth), rockerbottom feet (vertical talus) and short dorsiflexed great toes. Malformations, particularly congenital heart disease, diaphragmatic hernias, renal abnormalities and dislocated hips, are more common. Survival beyond early infancy is rare and associated with profound learning disability.

Patau syndrome (trisomy 13)

Affected infants usually have multiple malformations, including holoprosencephaly and other central nervous system (CNS) abnormalities, scalp defects, microphthalmia, cleft lip and palate, post-axial polydactyly, rockerbottom feet, renal abnormalities and congenital heart disease. Survival beyond early infancy is rare and associated with profound learning disability.

7.1.3 Microdeletion syndromes

These are caused by chromosomal deletions that are too small to be seen microscopically but involve two or more adjacent genes. They can be detected using specific fluorescent probes (**f**luorescent **i**n **s**itu **h**ybridisation [**FISH**]), but may now more frequently be identified through array comparative genomic hybridisation or other methods of genome-wide testing.

The following are examples of microdeletion syndromes:

- **DiGeorge syndrome**: parathyroid gland hypoplasia with hypocalcaemia, thymus hypoplasia with T-lymphocyte deficiency, congenital cardiac malformations (particularly outflow tract abnormalities such as interrupted aortic arch and truncus arteriosus), cleft palate, learning disability; arises due to microdeletions at 22q11. There is an increased incidence of psychiatric disorders, particularly within the schizophrenic spectrum. Importantly, deletions may be inherited from phenotypically normal parents, demonstrating the variable effects of this deletion
- **Williams syndrome**: supravalvular aortic stenosis, hypercalcaemia, stellate irides, learning disability and chatty, sociable behaviour known as a 'cocktail party manner'; caused by microdeletions involving the elastin gene on chromosome 7. These deletions occur anew, because people with Williams syndrome are unlikely to have their own children.

7.2. MENDELIAN INHERITANCE

7.2.1 Autosomal dominant conditions

Autosomal dominant (AD) conditions result from mutation of one copy (allele) of a gene carried on an autosome. Each child of an affected person has a 50% chance of inheriting the mutation. Within a family the severity may vary (**variable expression**) and known mutation carriers may appear clinically normal (**reduced penetrance**). Some conditions, such as achondroplasia and neurofibromatosis type 1, frequently begin anew through new mutations arising in the egg or (more

commonly) in the sperm.

Examples of autosomal dominant conditions*

- Achondroplasia
- Ehlers–Danlos syndrome (most)
- Facioscapulohumeral dystrophy
- Familial adenomatous polyposis coli
- Familial hypercholesterolaemia
- Gilbert syndrome
- Hereditary non-polyposis colorectal cancer
- Huntington's disease
- Marfan syndrome
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Osteogenesis imperfecta (most)
- Porphyrias (except congenital erythropoietic and erythropoietic protoporphyria which are autosomal recessive)
- Tuberous sclerosis
- Von Willebrand's disease

*Conditions prefixed 'hereditary' or 'familial' are usually autosomal dominant. An important exception is hereditary haemochromatosis which is autosomal recessive (see section 7.2.2).

Noonan syndrome

This is an AD condition with an unknown incidence, which may affect around 1 in 2500 people. Around two-thirds of patients are the first affected person in their family. It is genetically heterogeneous, ie mutations at more than one gene locus can cause the Noonan phenotype. In around half the patients, the condition is caused by mutations in the *PTPN11* gene (protein tyrosine phosphatase non-receptor type 11) on chromosome 12. Mutations in several other genes (coding for other proteins that are members of the MAPK kinase pathway) have recently been identified in Noonan syndrome, whereas the genetic basis of the syndrome in some individuals still remains unclear. As for other single gene disorders, the karyotype would be expected to be normal.

Clinical features of Noonan syndrome

- **Cardiac**
  - Pulmonary valve stenosis
  - Hypertrophic cardiomyopathy
  - Septal defects (ASD, VSD)

    - Branch pulmonary artery stenosis
- **Musculoskeletal**
    - Webbed or short neck
    - Pectus excavatum or carinatum
    - Wide-spaced nipples
    - Cubitus valgus
    - Short stature in 80%
- **Other features**
    - Poor feeding and hypotonia in infancy
    - Ptosis
    - Low-set and/or posteriorly rotated ears
    - Small genitalia and undescended testes in boys
    - Coagulation defects in 30% particularly factors XI:C, XIIC and VIIIC deficiencies)
    - Von Willebrand's disease
    - Juvenile myelomonocytic leukaemia (rarely)
    - Thrombocytopenia
    - Mild intellectual disability in 30%

7.2.2 Autosomal recessive conditions

Autosomal recessive (AR) conditions result from mutations in both copies (alleles) of an autosomal gene. Where both parents are carriers, each of their offspring has a one in four (25%) risk of being affected, and a 50% chance of being a carrier.

Examples of autosomal recessive conditions

- Alkaptonuria
- Ataxia telangiectasia
- Congenital adrenal hyperplasia
- Crigler–Najjar syndrome (severe form)
- Cystic fibrosis
- Dubin–Johnson syndrome
- Fanconi's anaemia
- Galactosaemia
- Glucose-6-phosphatase deficiency (von Gierke's disease)[a]
- Glycogen storage diseases
- Haemochromatosis
- Homocystinuria

- Mucopolysaccharidoses (all except Hunter syndrome)
- Oculocutaneous albinism
- Phenylketonuria
- Rotor syndrome (usually)
- Sickle cell anaemia
- Spinal muscular atrophy
- β-Thalassaemia
- Wilson's disease
- Xeroderma pigmentosum

Most metabolic disorders are autosomal recessive – remember the exceptions:

- **X-linked recessive exceptions**: Hunter syndrome (mucopolysaccharidosis or MPS type 2), glucose-6-phosphate dehydrogenase deficiency (favism) and the childhood form of adrenoleukodystrophy. Ornithine transcarbamoylase deficiency, a urea cycle disorder, also shows X-linked inheritance, with affected males often having a severe neonatal onset, whereas carrier females may remain well into later life. They may, however, be at significant risk for dangerous hyperammonaemia in periods of stress or starvation
- **Autosomal dominant exceptions**: acute intermittent porphyria, variegate porphyria, familial hypercholesterolaemia

[a]Do not confuse with glucose-6-phosphate dehydrogenase deficiency (favism) which is X-linked recessive

Hereditary haemochromatosis

As stated previously, 'hereditary' or 'familial' conditions are usually autosomal dominant. However, hereditary haemochromatosis is autosomal recessive, due to mutation in the *HFE* gene, C282Y being much the most common mutation. The carrier frequency for this is high (>1 in 10), so **pseudodominant** inheritance has been observed. This occurs when the partner of an affected person is, coincidentally, a carrier so that, on average, 50% of his or her offspring will have a genotype predisposing to clinical haemochromatosis. An apparent vertical (dominant) transmission may therefore be observed. Only a small proportion of patients with mutations on both alleles will ever become symptomatic, and the penetrance is higher in males than females. (See also Chapter 6, Gastroenterology and Chapter 13, Metabolic Diseases.)

7.2.3 X-linked conditions

These conditions result from a mutation in a gene carried on the X chromosome and most commonly affect males, because they have just one copy of each gene on the X chromosome. X-linked inheritance is characterised by the following:

- No male-to-male transmission (an affected father passes his Y chromosome to all his sons)
- Daughters of an affected male are obligate carriers (an affected father passes his X chromosome to all his daughters)

- Sons of a female carrier have a 50% chance of being affected and daughters have a 50% chance of being carriers.

Females are usually unaffected by X-linked recessive conditions, but may have mild manifestations as a result of X-inactivation (Lyonisation). Many X-linked conditions do not fit neatly into a purely recessive or dominant pattern, but have more severe expression in males than females, for example:

- X-linked **Alport syndrome**, due to mutations in *COL4A5*, causes renal failure and deafness in boyhood. Carrier females may have haematuria from early in life, but generally remain clinically well unless they develop hypertension (as happens in a third) or renal failure (up to 15%), and deafness, later in life
- **Fragile X**, a trinucleotide repeat disorder, causes significant learning disability in affected boys, but up to half of female full-mutation carriers (see section 7.4.1) also have some learning or behavioural problems. These are usually, but not always, less severe than those seen in affected boys
- **Fabry's disease**, in which the long-recognised, mainly cardiovascular and renal phenotype in males is also seen in a milder form in significant numbers of female mutation carriers. These females have a reduced life expectancy compared with non-carriers as a result of the disease

X-linked recessive inheritance

Examples of X-linked recessive (XLR) conditions

- Becker muscular dystrophy
- Duchenne muscular dystrophy
- Fabry's disease
- Glucose-6-phosphate dehydrogenase deficiency (favism)
- Haemophilias A and B (Christmas disease)
- Hunter syndrome (MPS 2)
- Lesch–Nyhan syndrome
- Ocular albinism
- Red–green colour blindness
- Androgen insensitivity syndrome
- Wiskott–Aldrich syndrome

Note that recent evidence shows an increased risk of cardiac complications in female carriers of Duchenne muscular dystrophy (10% lifetime risk of overt cardiac failure) and Fabry's disease. This may warrant 5-yearly echocardiographic screening in asymptomatic individuals, and more frequently if symptoms are present.

X-linked dominant conditions

In X-linked dominant (XLD) conditions, both male and female mutation carriers are affected by a mutation in a gene on the X chromosome. Females are usually less severely affected because of lyonisation, and these disorders are frequently lethal in males, because they have only a single X

chromosome.

- All offspring of an affected female have a 50% chance of being affected; however, if the condition is embryonically lethal in males, as is the case for disorders such as **incontinentia pigmenti**, a skewed birth ratio may be observed, ie one affected female:one unaffected female:one unaffected male (and an excess of miscarriages may be observed, representing affected male conceptions).

The following are examples of XLD conditions:

- **Vitamin D-resistant rickets**: this results from mutations in the *PHEX* (phosphate-regulating gene with homology to endopeptidases, X-linked) gene. This is a non-lethal condition, such that males and females are affected, and either may pass the mutated X chromosome on to their children
- **Incontinentia pigmenti (IP)**: a disorder of girls causing vesicular skin lesions in infancy with variable hypodontia (small teeth), alopecia, and retinal and other abnormalities. This results from mutations in the *NEMO (*NFκB essential modulator) gene. Such mutations are embryonically lethal in males, meaning that only females are affected (and affected females may have increased rates of miscarriage, or affected male conceptuses)
- **Periventricular nodular heterotopia**: this is associated with epilepsy and occasional learning disability in females, and, similar to IP, with embryonic lethality in males. It results from certain mutations in the *FLNA (*filamin A) gene.
- **Rett syndrome** results from mutations in the *MeCP2* (methyl CpG-binding protein 2) gene. This is a disorder of girls associated with developmental regression, progressive microcephaly, stereotypical hand movements and irregular breathing patterns. Males with *MeCP2* mutations are exceptionally rare (due to embryonic lethality) and usually extremely severely affected. Such mutations generally arise anew in the individual, because Rett syndrome is a severe enough condition that affected individuals do not reproduce.

7.2.4 Genetic heterogeneity

This means that there is more than one gene which, when mutated, causes a particular phenotype. Examples are given in Table 7.1.

7.3. MOLECULAR GENETICS

7.3.1 DNA (deoxyribonucleic acid)

DNA is a **double-stranded** molecule composed of purine (adenine + guanine) and pyrimidine (cytosine and thymine) bases linked by a backbone of covalently bonded **deoxyribose sugar** phosphate residues. The two antiparallel strands are held together by hydrogen bonds, which can be disrupted by heating, and re-form on cooling.

- **Adenine (A)** pairs with **thymine (T)** by two hydrogen bonds
- **Guanine (G)** pairs with **cytosine (C)** by three hydrogen bonds

7.3.2 RNA (ribonucleic acid)

DNA is **transcribed** in the nucleus into messenger RNA (mRNA), which is **translated** by ribosomes in the cytoplasm into a polypeptide chain. RNA differs from DNA in that:

- it is **single-stranded**
- thymine is replaced by **uracil**
- the sugar backbone is **ribose**.

7.3.3 Polymerase chain reaction

The polymerase chain reaction (PCR) is a widely used method for generating large amounts of DNA from very small samples. PCR can be adapted for use with RNA provided that the RNA is first converted to DNA. (For a more detailed account see Chapter 14, Molecular Medicine.)

Table 7.1 The genetic heterogeneity of various conditions

Condition	Genes (modes of inheritance)
Alport syndrome	*COL4A5* (X-linked), *COL4A4 and COL4A3* (AR and AD)
Autosomal dominant polycystic kidney disease	*PKD1, PKD2* (AD)
Noonan syndrome	*PTPN11*, others (AD)
Retinal dystrophies (retinitis pigmentosa)	*RHO* (rhodopsin, accounts for 30% of cases, AR), 40 or more other genes (X-linked, AR and AD)
Tuberous sclerosis	*TSC1, TSC2* (AD)
Long QT syndrome	Genes coding for ion channel proteins (AD or AR)
Hypertrophic cardiomyopathy	Genes coding for components of the sarcomere (AD)
Hereditary motor and sensory neuropathy (Charcot–Marie–Tooth disease)	*PMP22* (AD), also several other genes (AD, AR and X-linked)
Hereditary non-polyposis colon cancer	Mismatch repair genes *MLH1, MSH2, MSH6* and others (AD, remember reduced penetrance)
Hereditary breast and ovarian cancer	*BRCA1, BRCA2* (AD, remember reduced penetrance)

AD, autosomal dominant; AR, autosomal recessive.

7.3.4 DNA sequencing: the changing landscape of genetic testing

Traditionally, genetic testing has been laborious, with DNA of individual exons (or lengths of DNA up to approximately 1–2 kilobases or kb in length) being amplified in single PCR reactions and then

sequenced using dideoxy (Sanger) sequencing. This made testing for mutations in large genes, and testing for genetically heterogeneous disorders, very difficult and expensive. Massively parallel sequencing technologies developed since the mid-2000s mean that many millions of bases of DNA can now be read in a single experiment, and the cost of sequencing has fallen dramatically as a result. This means that testing for genetically heterogeneous disorders such as hypertrophic cardiomyopathy or retinal dystrophy can now be achieved in a single investigation. Similarly, patients with undiagnosed conditions may now be offered sequencing of their whole exome (all the coding genetic material) to identify the mutation responsible for their phenotype. Although a major advance in the diagnostic repertoire, with implications for many branches of medicine, such sequencing requires significant infrastructure and bioinformatic expertise.

7.4 TRINUCLEOTIDE REPEAT DISORDERS

(See also Chapter 14, Molecular Medicine.) These conditions are associated with genes containing stretches of repeating units of three nucleotides and include those shown in the box.

Trinucleotide repeat disorders

- Fragile X syndrome, X-linked
- Huntington's disease, AD
- Spinocerebellar ataxia, AD
- Myotonic dystrophy, AD
- Friedreich's ataxia, AR

In normal individuals the number of repeats varies slightly but remains below a defined threshold. Affected patients have an increased number of repeats, called an **expansion**, above the disease-causing threshold. The expansions may be unstable and enlarge further in successive generations, causing increased disease severity ('**anticipation**') and earlier onset, eg **myotonic dystrophy**, particularly congenital myotonic dystrophy following transmission by an affected mother.

7.4.1 Fragile X syndrome

This causes learning disability, macro-orchidism and seizures, and is often associated with a cytogenetically visible constriction on the X chromosome. The inheritance is X-linked but complex. Among controls, there are between 6 and 55 stably inherited trinucleotide repeats in the *FMR1* gene. People with between 55 and 230 repeats are said to be premutation carriers, but are unaffected by fragile X syndrome. During oogenesis in female premutation carriers, the triplet repeat is unstable and may expand into the disease-causing range (230 to >1000 repeats), known as a **full mutation**. All males and around 50% of females with the full mutation are affected by fragile X syndrome.

The effects of being a premutation carrier do not usually include learning disability, but premutation carrier females are at increased risk of premature ovarian failure, compared with controls or full

mutation carriers. Males with premutations are at risk (estimated at 3%) of developing fragile X-associated tremor/ataxia syndrome, which includes symptoms of parkinsonism and cognitive decline, around 50 years of age.

7.5 MITOCHONDRIAL DISORDERS

(See also Chapter 14, Molecular Medicine.) Mitochondria are **exclusively maternally inherited**, deriving from those present in the cytoplasm of the ovum. They contain copies of their own **circular 16.5-kilobase genome**, which contains genes for several respiratory chain enzyme subunits and transfer RNAs. Mitochondrial genes differ from nuclear genes in having no introns and using some different amino acid codons. Within cells there may be a mixed population of normal and abnormal mitochondria known as **heteroplasmy**. Different proportions of abnormal mitochondria may be required to cause disease in different tissues, known as a **threshold effect**. Disorders caused by mitochondrial gene mutations include the following:

- **MELAS** (**m**itochondrial **e**ncephalopathy, **l**actic **a**cidosis, **s**troke-like episodes)
- **MERRF** (**m**yoclonic **e**pilepsy, **r**agged **r**ed **f**ibres)
- Mitochondrially inherited diabetes mellitus and deafness
- Leber's hereditary optic neuropathy (note that other factors also contribute, resulting in higher penetrance in males).

7.6 GENOMIC IMPRINTING

For most genes, both copies are expressed but, for some genes, either the maternally or the paternally derived copy is preferentially used, a phenomenon known as genomic imprinting. The best known examples are the **Prader–Willi** and **Angelman** syndromes, both caused by either cytogenetic deletions of the same region of chromosome 15q or by **uniparental disomy** of chromosome 15 (where both copies of chromosome 15 are derived from one parent with no copy of chromosome 15 from the other parent).

Each of the above conditions is described in Table 7.2.

Other well-recognised imprinting disorders include:

- Albright's hereditary osteodystrophy
- Beckwith–Wiedemann syndrome
- Russell–Silver syndrome
- Familial paraganglionoma

Albright's hereditary osteodystrophy

This results from deactivating mutations in the *GNAS* gene (α subunit of the adenylyl cyclase-stimulating G-protein, Gs) on chromosome 20q13. Mutations on the maternally derived *GNAS* allele result in an associated pseudohypoparathyroidism. The typical clinical features are as follows:

- Short adult stature with a tendency to obesity
- Round facies
- Mild-to-moderate learning disabilities
- Brachydactyly: short metacarpals, particularly fourth and fifth, and short distal phalanges (particularly the thumb)
- Ectopic ossifications.

Table 7.2 Genomic imprinting: comparison between Prader–Willi and Angelman syndromes

	Prader–Willi	**Angelman**
Clinical	Neonatal hypotonia and poor feeding	'Happy puppet', unprovoked laughter/clapping
	Moderate learning disability	Microcephaly, severe learning disability
	Hyperphagia + obesity in late childhood	Ataxia, broad-based gait
	Small genitalia	Seizures, characteristic EEG
Genetics	70% deletion on paternal chromosome 15	80% deletion on maternal chromosome 15
	30% maternal uniparental disomy 15 (ie no paternal contribution)	2–3% paternal uniparental disomy 15 (ie no maternal contribution)
	Many of remainder due to mutations in *UBE3A* gene	

Beckwith–Wiedemann syndrome

This is due to abnormal imprinting of the *IGF2/H19/p57^{KIP}/KvLqQT1* gene cluster on chromosome 11p15.

The following are the clinical features:

- Large birthweight
- Neonatal hyperinsulinism causing hypoglycaemia
- Omphalocele (exomphalos)
- Hemihypertrophy
- Facial nevus flammeus
- Increased risk of childhood abdominal tumours (particularly Wilms' tumour and hepatoblastoma).

Russell–Silver syndrome

- This condition has a prenatal onset with small stature and relative macrocephaly, very poor feeding is usual
- Patients also have a triangular face, asymmetry and fifth finger clinodactyly

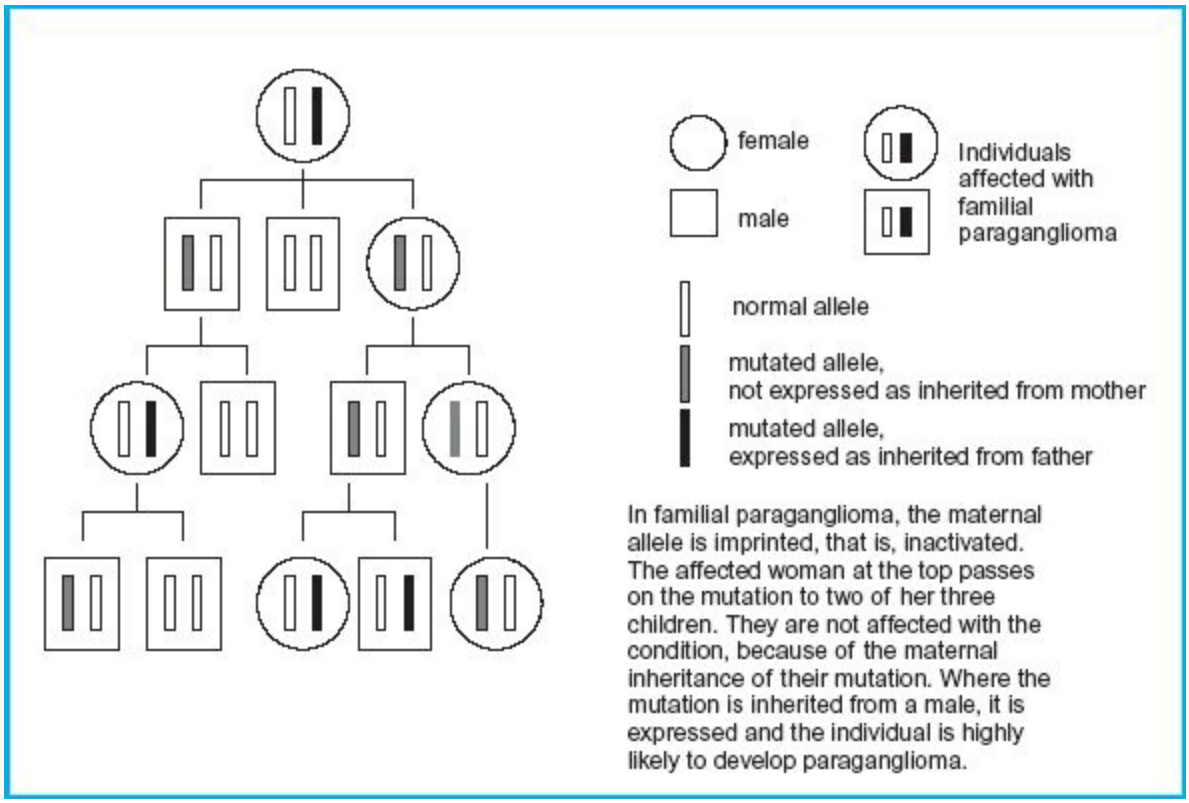
- Maternal uniparental disomy for chromosome 7 is seen in around 10% of cases, abnormalities of other imprinted regions are also observed.

Familial paraganglioma

In this condition, paragangliomas, including phaeochromocytomas and glomus jugulare tumours, occur throughout the body (most commonly in the head and neck). This is due to mutations in the *SDHB*, *SDHC* and *SDHD* genes, but the mutation causes disease only when it has been inherited from the father. This is because the maternally inherited allele is imprinted (ie inactivated), and hence will not cause disease in the individual who inherits a mutation from his or her mother (Figure 7.3).

The inheritance pattern of these conditions is in itself autosomal dominant, ie there is a 50% chance of the disease genotype being inherited by each child. However, whether the mutant allele is expressed depends on the parental origin of the allele, as shown in Figure 7.3.

Figure 7.3 Genomic imprinting



7.7 OTHER IMPORTANT GENETICS TOPICS

This section includes short notes on conditions that form popular exam topics. See also homocystinuria (Chapter 13, Metabolic Diseases) and muscular dystrophy (Chapters 14, Molecular Medicine, and 16, Neurology).

7.7.1 Cancer genetics

Details of the increasing number of inherited cancer predisposition syndromes now defined are

beyond the scope of this chapter (see also Chapter 6, Gastroenterology, re polyposis syndromes, Chapter 4, Endocrinology, re multiple endocrine neoplasia syndrome, and Chapter 14, Molecular medicine, re Li Fraumeni syndrome), general points to remember are:

- Nearly all have AD transmission (note the reduced penetrance, see below)
- Young age at diagnosis or unusual combinations of cancers raise the suspicion of a heritable cancer predisposition syndrome
- Penetrance is often reduced, eg 80% risk of breast cancer in female carriers of *BRCA1* or *BRCA2* mutations; colorectal cancer risk in hereditary non-polyposis colon cancer (HNPCC) is approximately 80% for males and 60% for females, with an approximately 50% risk of endometrial cancer in female *HNPCC* mutation carriers
- Even in a high-risk family, non-genetic lifestyle factors are important to an individual's cancer risk, such as smoking, diet (fresh fruit and vegetables, in particular resistant starch for bowel cancer risk) and maintaining a healthy body weight. For breast cancer risk, hormonal factors are also very important: late age of menarche, early age at birth of first baby, breastfeeding for more than 6 months and earlier menopause are all protective; being overweight, and combined oral contraceptive and hormone replacement therapy (HRT) use can all increase risk. In Gorlin syndrome (basal cell naevus syndrome), and other conditions predisposing to skin cancer, meticulous sun protection and avoidance of X-irradiation if at all possible is important
- The von Hippel–Lindau disease is nearly completely penetrant, ie it is unusual for a person who carries a mutation not to develop at least one feature of the condition (cerebellar or spinal haemangioblastoma, retinal angioma, phaeochromocytoma or renal cell carcinoma; cystic lesions in the kidneys and pancreas also occur)
- Certain tumours are unusual enough to be almost pathognomonic for a certain syndrome, eg transitional cell carcinoma of the renal pelvis in HNPCC, or sebaceous tumours in Muir–Torre syndrome (the name for HNPCC occurring with these skin tumours).

Screening may be recommended for at-risk individuals in several cancer-predisposing conditions, including the following:

- **HNPCC**: colonoscopy every 18–24 months for proven mutation carriers/those at 50% risk (frequency of colon [and upper gastrointestinal endoscopy] screening for other conditions may vary)
- **High-risk hereditary breast and ovarian cancer**: mammography, MRI breast screening where available (benefits of ovarian screening not proven)
- **Von Hippel–Lindau disease**: annual renal ultrasound, urinary catecholamines, ophthalmic review, 2- to 3-yearly MRI of brain and spine
- **Familial renal carcinomas**: annual renal ultrasonography.

Discussion of prophylactic treatment is indicated in certain conditions:

- **Colectomy** (as development of malignancy is almost inevitable) in familial adenomatosis polyposis (FAP) is often performed between 16 and 30 years (this does not usually need to be considered in HNPCC, because surveillance colonoscopy with polypectomy successfully prevents cancers)
- **Prophylactic mastectomy and oophorectomy** may be chosen (after appropriate counselling) by

- some women in high-risk breast cancer families. Oophorectomy reduces the risk of breast cancer as well as ovarian cancer
- **Prophylactic chemoprevention**, eg using tamoxifen, may now be indicated for certain subgroups of women at high risk of breast cancer.

7.7.2 Ambiguous genitalia

(See also intersex in Chapter 4, Endocrinology.)

The 6-week embryo has undifferentiated gonads, Müllerian ducts (capable of developing into the uterus, fallopian tubes and upper vagina), Wolffian ducts (capable of forming the epididymis, vas deferens and seminal vesicles) and undifferentiated external genitalia (Figure 7.4).

In the presence of a Y chromosome, the gonads become testes which produce testosterone and Müllerian inhibiting factor (MIF). Testosterone causes the Wolffian ducts to persist and differentiate and, after conversion to dihydrotestosterone (by 5α-reductase), masculinisation of the external genitalia. MIF causes the Müllerian ducts to regress.

In the absence of a Y chromosome, the gonads become ovaries which secrete neither testosterone nor MIF. In the absence of testosterone the Wolffian ducts regress and the external genitalia feminise. In the absence of MIF, the Müllerian ducts persist and differentiate.

The causes of **ambiguous genitalia** divide broadly into those resulting in undermasculinisation of a male fetus, those causing masculinisation of a female fetus, and those resulting from mosaicism for a cell line containing a Y chromosome and another that does not. They are summarised in Figure 7.5.

Figure 7.4 Outline of the normal development of the reproductive tract and external genetalia

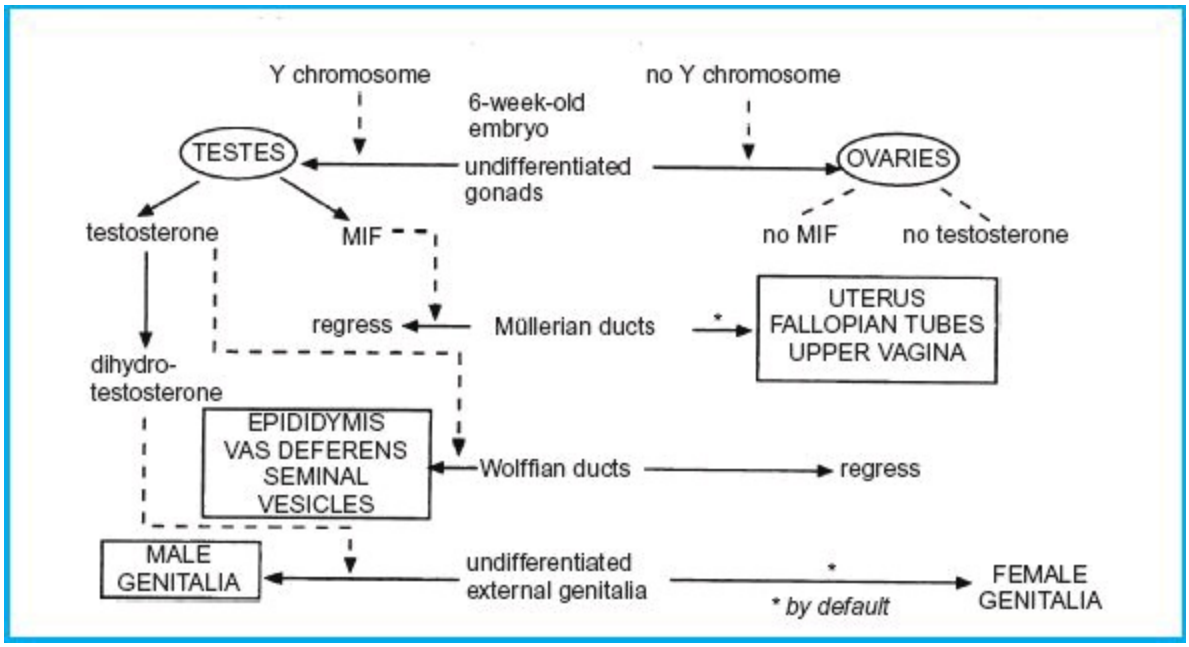
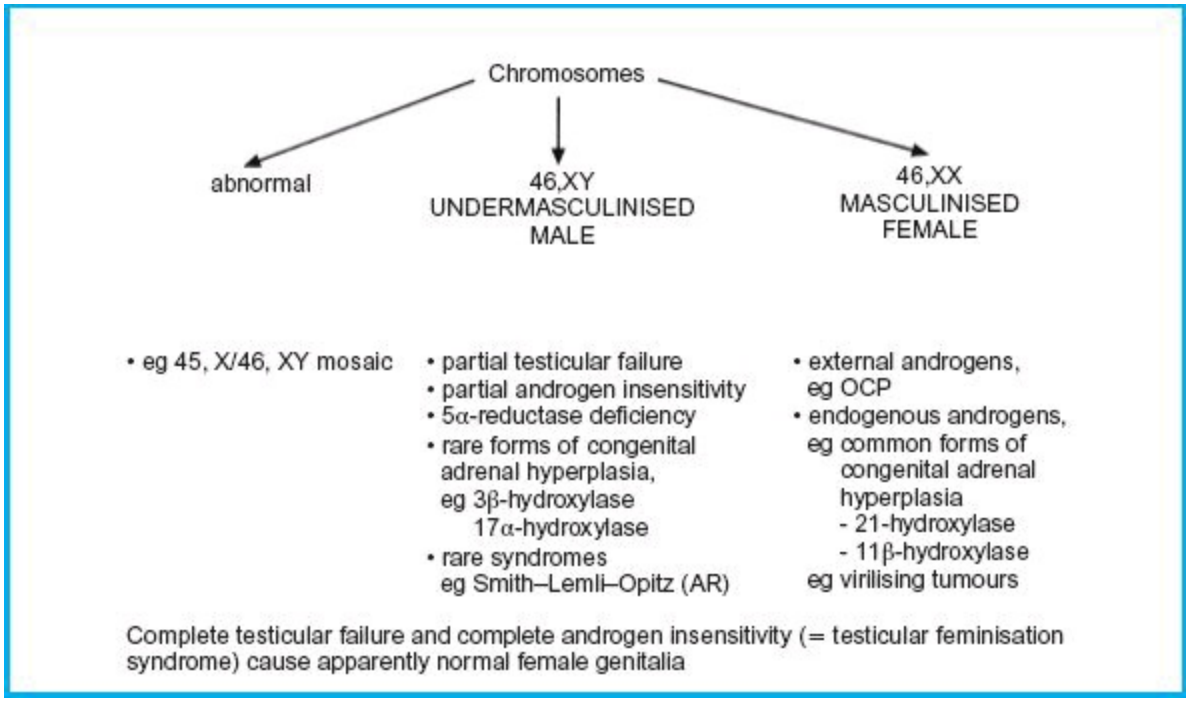


Figure 7.5 Outline of the causes of abnormal genitalia



7.7.3 Cystic fibrosis

This results from mutations in the ***CFTR*** (cystic fibrosis transmembrane conductance regulator) gene and the Δ***F508*** mutation (deletion of three nucleotides coding for a phenylalanine residue) account for 75% of mutations in White individuals. Around 15% of cystic fibrosis mutations cannot be detected on routine molecular testing, which tests for the most commonly identified mutations. Such testing cannot therefore exclude a diagnosis of cystic fibrosis (see also Chapter 19, Respiratory Medicine), but sequencing of the whole *CFTR* gene may be able to demonstrate rare alleles.

7.7.4 Neurofibromatosis

There are two forms of neurofibromatosis (NF) which are clinically and genetically distinct. Both demonstrate a high rate of new mutations, meaning that patients may not have a family history of the condition (Table 7.3).

7.7.5 Tuberous sclerosis

There are at least two separate genes that cause tuberous sclerosis (TS), one on chromosome 9 (*TSC1*, hamartin) and the other on chromosome 16 (*TSC2*, tuberin).

Table 7.3 Comparison of neurofibromatosis (NF) types 1 and 2

NF1	NF2
Major features	
≥6 café-au-lait patches (CALs)	Bilateral vestibular schwannomas
	Other cranial and spinal tumours, eg

Axillary/inguinal freckling	meningiomas
Lisch nodules on the iris	Lens opacities/cataracts
Cutaneous neurofibromas	Peripheral schwannomas
Subcutaneous neurofibromas	
Plexiform neurofibromas	
Minor features	
Macrocephaly	CALs (usually <6)
Short stature	Peripheral neurofibromas
Complications	
Plexiform neuromas	Deafness/tinnitus/vertigo
Optic glioma (2%)	Spinal cord and nerve compressions
Other cranial and spinal tumours	Malignant change/sarcomas
Pseudoarthrosis (especially tibial)	
Sphenoid wing dysplasia	
Renal artery stenosis	
Phaeochromocytoma	
Learning difficulties	
Scoliosis	
Spinal cord and nerve compressions	
Malignant change/sarcomas	
Gene	
Chromosome 17	Chromosome 22
Birth incidence	
1 in 2000	1 in 30 000

Clinical features of tuberous sclerosis

- **Skin/nails**
  - Ash-leaf macules
  - Shagreen patches (especially over the lumbosacral area)
  - Adenoma sebaceum (facial area)
  - Subungual/periungual fibromas
- **Kidneys**
  - Renal cysts
- **Neuroimaging**
  - Intracranial calcification (periventricular)
  - Subependymal nodules

- **Eyes**
  - Retinal hamartomas
- **Heart**
  - Cardiac rhabdomyomas, detectable antenatally, usually regressing during childhood
- **Neurological**
  - Seizures
  - Learning disability

7.7.6 Marfan syndrome

This results from mutations in the *fibrillin 1* gene on chromosome 15. Intelligence is usually normal. Of affected individuals, 25% are the first affected person in their family (due to a new mutation).

Clinical features of Marfan syndrome

- **Musculoskeletal**
  - Tall stature with disproportionately long limbs (dolichostenomelia)
  - Arachnodactyly
  - Pectus carinatum or excavatum
  - Scoliosis
  - High, narrow, arched palate
  - Joint laxity
  - Pes planus
- **Heart**
  - Aortic root dilatation and dissection
  - Mitral valve prolapse
- **Eyes**
  - Lens dislocation (typically upward)
  - Myopia
- **Skin**
  - Striae
- **Pulmonary**
  - Spontaneous pneumothorax
  - Apical blebs on chest radiograph
- **Radiological**
  - Protrusio acetabulae
  - Dural ectasia on spinal MRI

The diagnosis of Marfan syndrome is based on the modified Ghent criteria. These were revised recently to place greater weight on the cardinal clinical features of aortic dilatation and ectopia lentis, and to take into account the emerging spectrum of mutations in fibrillin-1 associated with disorders other than Marfan syndrome (e.g. familial ectopia lentis, and Weill-Marchesani syndrome). A systemic score is calculated according to the presence of musculoskeletal, radiological and skin findings, weighted according to their diagnostic specificity.

For patients without a family history, the following four conditions meet diagnostic criteria for Marfan syndrome:

- aortic dilatation (Z score greater than or equalling 2) and ectopia lentis
- aortic dilatation (as above) and fibrillin-1 mutation*
- aortic dilatation and systemic score greater than or equalling 7
- ectopia lentis and fibrillin-1 mutation.*

For patients with a first-degree relative (parent, sibling or child) with Marfan syndrome

- (according to the above scheme), the presence of either aortic dilatation, ectopia lentis, or a systemic score of greater than or equalling 7, is sufficient to meet diagnostic criteria.

* indicates that the mutation in fibrillin-1 should be known to be associated with Marfan syndrome.

Chapter 8
Genito-urinary Medicine and AIDS

CONTENTS

Genito-urinary Medicine and AIDS

8.1 SEXUALLY TRANSMITTED INFECTIONS

The incidence of sexually transmitted infections (STIs) has increased dramatically over the past 50 years, both globally and in the UK. As well as the more 'traditional' diseases such as syphilis and gonorrhoea, a wider spectrum of diseases transmitted by sexual contact has increasingly been recognised (eg oroanal transmission of enteric infections such as giardiasis and hepatitis A). Human immunodeficiency virus (HIV) infection arrived on the scene in the late 1970s.

8.1.1 Gonorrhoea

Transmission is primarily sexual; there is a large asymptomatic reservoir, mainly pharyngeal, rectal and cervical. *Neisseria gonorrhoea* is a capsulated organism, and it therefore resists phagocytosis. In the UK, >10% of isolates show resistance to penicillin and quinolones. This has resulted in cephalosporins currently being the first-choice antibiotic in uncomplicated gonorrhoea, currently intramuscular ceftriaxone. Treatment should be guided by the appropriate antibiotic sensitivities of the gonococcal isolates.

Disseminated (bacteraemic) infection is unusual but is more common in women. Responsible strains are nearly always highly susceptible to penicillin. Pharyngeal and rectal infection is often asymptomatic. Ophthalmia neonatorum is treated with systemic antimicrobials and appropriate eye drops.

8.1.2 Syphilis

Transmission is primarily sexual, although it may be congenital or, rarely, by blood transfusion. Penicillin is the drug of choice, with tetracycline as an alternative option. **Concurrent HIV infection may increase the risk of neurosyphilis**, and extended courses of treatment are required. Diagnosis is by:

- **Serology**: two specific treponemal tests, enzyme immunoassay (EIA) and *Treponema pallidum* haemagglutination assay (TPHA) (would use a specific treponemal antigen), plus a quantitative non-treponemal test, ie rapid plasma reagin (RPR) or Venereal Disease Reference Laboratory (VDRL). The latter are non-specific (cardiolipin antigen) and biologically false-positive results can be obtained in other conditions
- **Dark-ground microscopy**: of fresh material from chancres or lesions of secondary syphilitic rash

- **Treponemal PCR (polymerase chain reaction)**: a molecular test used to diagnose early syphilitic ulcers.

In early syphilis, during the secondary stage, there is haematogenous spread of treponemes, which can give the following clinical presentations:

- **Mucocutaneous**: widespread non-itchy rash affecting hands and feet, oral and anal mucosal erosions
- **Lymphadenopathy**: usually generalised, painless
- **Neurological**: syphilitic meningitis, cranial nerve palsies
- **Ocular**: anterior uveitis, retinitis
- **Gastrointestinal**: hepatitis, proctitis
- **Rheumatological**: polyarthritis, periostitis.

8.1.3 *Chlamydia* infections

Non-gonococcal urethritis (NGU) due to *Chlamydia trachomatis* is the most common bacterial STI in the Western world. Serovars D to K are responsible. It is also a major cause of pelvic inflammatory disease in women (frequently silent) and prostatitis/epididymitis in men. Neonatal conjunctivitis and, more rarely, diffuse interstitial pneumonia are both complications of serovars D to K; infection is acquired by passage through an infected birth canal.

- **Trachoma** (corneal scarring) is caused by serovars A, B and C
- **Lymphogranuloma venereum (LGV)** is due to serovars L1, L2 and L3 and is an emerging cause of rectal infection and proctitis in men who have sex with men (MSM).

Both neonatal pneumonia and conjunctivitis need systemic treatment with erythromycin. Tetracycline or azithromycin is the drug of choice for adults.

Molecular diagnostic NAATs (nucleic acid amplification tests) have the advantage of a higher sensitivity over culture and EIA tests, in addition to less invasive sampling.

The main disadvantage is culture confirmation and antibiotic sensitivities required in case of gonorrhoea-positive NAATs.

Current NAATs for STIs:

- Gonorrhoea: can be used on urine sample in men and vaginal swab in women
- *Chlamydia trachomatis*: urine in men and vaginal/cervical swab in women
- Herpes simplex virus: direct from ulcer sample able to type virus 1 or 2
- Syphilis: primary anogenital ulcers or mucosal lesions of secondary syphilis
- *Trichomonas vaginalis*: swab test on vaginal sample in women.

8.2 BASIC EPIDEMIOLOGY AND VIROLOGY OF HIV/AIDS

8.2.1 Epidemiology

HIV/AIDS is a global disease. Of the estimated 34 million people infected with HIV, 23 million (69%) are from sub-Saharan Africa. Figures from the World Health Organisation (WHO) also indicate an emerging epidemic in the former Soviet Union and eastern Europe. In the UK there were approximately 96 000 prevalent HIV patients in 2011. In 2011 there were 6280 newly diagnosed cases, with 50% presenting with late HIV disease (CD4 count <350 mm) and 25% with advanced HIV disease (acquired immune deficiency disease or AIDS; CD4 <200 mm).

The following are the estimated routes of transmission in the current UK HIV population:

- Sexual intercourse between men (42%)
- Sexual intercourse between men and women (49%) – mainly acquired abroad
- Injecting drug abuse (2.7%)
- Blood and blood products (5%).

Risk factors facilitating sexual transmission include:

- Seroconversion and advancing stage of disease
- Concurrent STIs, particularly ulcerative disease of the genitalia
- Hepatitis C co-infection
- High viral load.

Maternofetal transmission occurs in 15–20% of non-breastfed and 33% of breastfed infants of patients with HIV/AIDS without medical intervention.

The risk of transmission from mother to baby can be reduced by:

- Antiretroviral therapy (this can reduce transmission to only 0.5% if therapy is started before the third trimester)
- Avoidance of breastfeeding
- Delivery by caesarean section (if detectable VL at 36 weeks).

8.2.2 The virus

Human retrovirus is a member of the lentivirus family. It contains RNA that is transcribed to DNA via a reverse transcriptase enzyme. The main target sites of action of antiretroviral drugs are reverse transcriptases, proteases and integrases. There are two types of human immunodeficiency virus:

- **HIV-1**: (previously known as HTLV III) is prevalent worldwide
- **HIV-2**: is common in West Africa.

Pathogenesis

The HIV virus has tropism for the following CD4 cells:

- T-helper lymphocytes
- B lymphocytes
- macrophages
- central nervous system (CNS) cells.

HIV infection causes progressive immune dysfunction, characterised by CD4 cell depletion. Impairment of immunity is primarily cell-mediated, but as the disease progresses there is general immune dysregulation.

The following laboratory markers are associated with disease progression:

- Decreased CD4 lymphocyte count (normal >500/mm^3 or 0.5 × 10^9/l). In the USA, a CD4 count of <200/mm^3 is regarded as AIDS, irrespective of the presence of clinical disease
- High HIV viral load, using HIV polymerase chain reaction (PCR) assay (note that CD4 and HIV viral load are the only markers monitored in clinical practice which help to predict progression as well as the response to treatment).

8.2.3 Seroconversion and the HIV antibody test

After inoculation, the window or seroconversion period can be up to 3 months; HIV antibody may not be detectable during this time. The HIV p24 antigen becomes detectable during seroconversion. Current fourth-generation antibody tests/p24 antigen tests can detect HIV-1 as early as a month after exposure. Approximately 30% of patients develop clinical seroconversion illnesses of variable severity, and which are often diagnosed retrospectively. HIV PCR (viral load) and p24 antigen are used to diagnose HIV infection during this window period, and they are then confirmed by a positive confirmatory panel of antibody tests. If the seroconversion illness is severe, then antiretroviral combination treatment should be used. Whether such early treatment improves long-term prognosis is unknown.

Seroconversion illnesses

- Fever
- Malaise
- Diarrhoea
- Meningoencephalitis
- Rash
- Sore throat
- Lymphadenopathy
- Arthralgia

Constitutional symptoms in early infection:

- Fatigue, night sweats, diarrhoea, dry itchy skin

8.2.4 Centers for Disease Control and Prevention (CDC) classification of HIV/AIDS

The CDC classification is adopted in the USA and most developed countries. HIV infection is not

synonymous with AIDS – the latter is a stage of severe immunodeficiency characterised by opportunistic infections and/or tumour.

CDC classification of HIV/AIDS

- **Stage 1**
  - Primary seroconversion illness
- **Stage 2**
  - Asymptomatic
- **Stage 3**
  - Persistent generalised lymphadenopathy
- **Stage 4a**
  - AIDS-related complex (ie advanced HIV disease, but having none of the features of stages 4b–d)
- **Stages 4b–d**
  - AIDS: patient may have opportunistic infection or tumours, which are termed 'AIDS indicator' illnesses

8.3 RESPIRATORY DISEASES ASSOCIATED WITH HIV/AIDS

8.3.1 *Pneumocystis jirovecii (carinii)* pneumonia (PCP)

Pneumonia is the most common opportunistic infection and clinical presentation of AIDS. *Pneumocystis jirovecii* (*carinii*) pneumonia (PCP) constitutes 40% of all AIDS-defining illness.

The symptoms of PCP include dry cough, dyspnoea, fever and malaise. There are remarkably few abnormal signs on chest examination.

Investigations for PCP

- **Chest X-ray**: the typical appearance of PCP is bilateral mid- and lower zone interstitial shadowing. Atypical chest X-ray findings are found in 10% of PCP cases and include: cavitation, upper zone opacities, pneumothorax or unilateral consolidation. The chest X-ray may be normal and effusions are rare
- **Pulse oximetry**: hypoxia with low/normal *P*CO2 is typically seen in moderate-to-severe infection. If O_2 saturation is normal, then exercise-induced oxygen desaturation (O_2 saturation falling by >5% and/or to a saturation of <90%, with exercise) will support the diagnosis of PCP
- **Identification of *pneumocystis* cysts**: samples obtained by inducing sputum or from bronchoalveolar lavage (BAL) can be stained with silver or immunofluorescent antibody, or molecular detection tests such as PCR

- The combination of an HIV-positive person (usually with CD4 <200/mm^3) who is not taking PCP prophylaxis and who has a typical radiological appearance and hypoxia is sufficient for a confident diagnosis to be made. Empirical treatment with co-trimoxazole should be started. It is now unusual to have to resort to lung biopsy for PCP diagnosis.

Poor prognostic features in PCP include poor response to treatment, co-infection, requirement for assisted ventilation and pneumothorax.

Treatment for PCP

- Treatment is with high-dose co-trimoxazole or intravenous pentamidine for severe cases. Clindamycin/primaquine, atovaquone and dapsone/trimethoprim are alternative treatments
- Intolerance to co-trimoxazole is common, with nausea, vomiting, rash, leukopenia and thrombocytopenia
- Steroids have been shown to improve prognosis in those with PO_2 <8 kPa (60 mmHg)

There is a 50% risk of recurrence within 12 months. **PCP prophylaxis** (co-trimoxazole, nebulised pentamidine, dapsone or atovaquone) is always given to patients with a CD4 count <200/mm^3 and to those who have already had an episode of PCP. Prophylaxis is continued until the CD4 count is increased above 200/mm^3 with the use of highly active antiretroviral treatment (HAART).

8.3.2 Pulmonary tuberculosis

The incidence of infection depends upon the prevalence of tuberculosis (TB) in the rest of the general population and it is therefore much more common in African patients. In some areas of the UK up to a quarter of patients with TB are HIV positive.

Atypical features include:

- Extrapulmonary involvement
- Normal or atypical appearances on chest X-ray
- Occurs at any stage of HIV disease, and at any level of CD4 count
- Atypical mycobacterial infections (when CD4 count <50/mm^3) – usually *Mycobacterium avium intracellulare*. The usual presenting features are fever, anaemia, anorexia and the disease is commonly extrapulmonary.

8.3.3 Other respiratory diseases in HIV/AIDS

Other causes of respiratory disease in HIV/AIDS

- **Viral**
  - Cytomegalovirus (CMV) pneumonitis
- **Fungal**

  - *Candida*
  - Histoplasmosis
  - *Cryptococcus*
  - *Nocardia*
- **Bacterial**
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
  - *Mycobacterium tuberculosis*
  - *Mycobacterium avium intracellulare*
- **Protozoal**
  - *Toxoplasma*
- **Tumour**
  - Kaposi's sarcoma (see Section 8.6.1)
  - Non-Hodgkin's lymphoma

Radiological appearance of other infections

- Cavitation: *M. tuberculosis*, *Nocardia*, *S. aureus*
- Consolidation: *S. pneumoniae*, *Toxoplasma*
- Effusion: TB (Kaposi's sarcoma may also cause effusion).

8.4 GASTROINTESTINAL DISEASES IN PATIENTS WITH HIV/AIDS

There are four main presentations:

- oral/oesophageal disease
- abdominal pain/diarrhoea
- biliary/pancreatic disease
- anorectal symptoms.

8.4.1 Oral/oesophageal conditions

Ninety per cent of patients will develop an oral/oesophageal condition:

- oral and oesophageal candidiasis
- periodontal disease (including gingivitis)
- herpes simplex
- lymphoma
- oral hairy leukoplakia (caused by EBV)
- aphthous ulcers

- Kaposi's sarcoma
- cytomegalovirus.

These conditions may be asymptomatic, or patients may have dysphagia or odynophagia.

8.4.2 Diarrhoea/abdominal pain

Weight loss, diarrhoea and malnutrition are very common in patients with any stage of HIV infection, and can be due to specific infection or advanced disease. Approximately 50% of diarrhoeal illnesses are infective in origin (due to specific enteropathogens or opportunistic infections).

Enteropathogens found in HIV

- **Bacteria**
  - *Salmonella*
  - *Shigella*
- **Protozoal**
  - *Giardia lamblia*
- **Viral**
  - CMV
- **Opportunistic organisms**
  - Bacterial
    - Atypical mycobacteria (*M. avium intracellulare* with CD4 <100/mm^3)
  - Protozoal
    - *Isospora belli*
    - Cryptosporidia (intracellular protozoan)
    - Microsporidia

Clinical presentation can be with watery diffuse diarrhoea as exemplified by *Cryptosporidium*, or abdominal pain and bloody diarrhoea (eg CMV proctocolitis).

- **Cryptosporidiosis**: this is a coccidian parasite of the gastrointestinal tract which is responsible for 10–15% of HIV-associated diarrhoeas, particularly occurring in patients with advanced HIV disease
- ***Salmonella***: much more frequent in HIV-infected patients than in the general population. More likely to cause bacteraemia, and recurrence is common.

The investigation of infective diarrhoea includes the following:

- Identification of organisms in stool samples: microscopy and culture for pathogens, ova and parasites
- If stool specimen negative, stain with modified Ziehl–Neelsen for *Cryptosporidium*

- Sigmoidoscopy/colonoscopy with biopsy: with culture or PCR detection of the specimen for viruses, mycobacteria, bacteriology and mycology. Histological appearances are often important.

Gastrointestinal tumours

These may also cause abdominal pain and diarrhoea.

- **Kaposi's sarcoma**: may cause rectal bleeding
- Intra-abdominal lymphoma (often high-grade non-Hodgkin's B-cell lymphoma).

8.4.3 Biliary and pancreatic disease

The two most common presentations are **cholangiopathy** and **pancreatitis**.

- **Cholangiopathy**: due to *Cryptosporidium*, CMV, or *Microsporidium*
- **Pancreatitis**: this can be induced by drugs used in HIV treatment (eg DDI (didanosine), or DDC (zalcitabine), which are both reverse transcriptase inhibitors), or by the biliary organisms listed previously.

8.4.4 Anorectal conditions

These usually present with proctitis.

Symptoms and infective causes of anorectal conditions

- **Symptoms**
  - Anal discharge
  - Tenesmus
  - Pruritus ani
  - Rectal bleeding
  - Diarrhoea
- **Causative organisms**
  - Herpes simplex virus
  - Cytomegalovirus
  - *Neisseria gonorrhoeae* (gonorrhoea)
  - Non-specific/*Chlamydia*
  - Wart virus
  - *Treponema pallidum* (syphilis)
  - *Chlamydia* serovars 1–3, LGV

8.5 HIV/AIDS-RELATED NEUROLOGICAL DISORDERS

Neurological disease is the first presentation of AIDS in 10% of HIV patients. An acute self-limiting lymphocytic meningitis may occur at the time of seroconversion. Chronic neurological syndromes or opportunistic infections occur later in the course of HIV infection. The most common cause is the neurotropic effect of the virus itself.

Clinical presentation may be:

- **Focal**: hemiparesis, fits
- **Generalised**: drowsiness, confusion, behavioural change
- **Asymptomatic**: in early HIV disease.

Patients may also develop proximal myopathy, or drug-induced neuropathy (eg didanosine) and myopathy (eg zidovudine).

8.5.1 Direct neurotropic effects of HIV

These include:

- AIDS dementia complex (see below)
- vacuolar myelopathy
- neuropathy (see below)

Neurotropic disorders are diagnosed with the help of:

- **CSF analysis**: raised protein, and pleocytosis
- **MRI brain scan**: cerebral atrophy
- **Nerve conduction studies**: distal symmetric sensory neuropathy.

AIDS dementia is the most frequent neurological condition of HIV infection, and is directly caused by the virus. Impairment of concentration and memory leads to progressive decline in widespread cognitive function. Occasionally psychiatric symptoms may be prominent. The EEG shows generalised slowing with no specific features, and imaging demonstrates cortical atrophy.

Sensorimotor neuropathy associated with HIV/AIDS usually has mild sensory symptoms and signs. Less commonly, a mononeuritis multiplex or a chronic painful myelopathy may develop. HIV-associated neurocognitive dysfunction (HAND) may present as minor cognitive impairment at all stages of infection. There is an association with detectable virus in cerebrospinal fluid (CSF), even in presence of full virological suppression in plasma.

Consideration of CSF penetration of antiretroviral drugs is sometimes indicated.

8.5.2 Neurological infections

Opportunistic infections of the CNS are common.

Causes of focal neurological disease

- ***Toxoplasma gondii***
  - Cerebral abscess
- ***Mycobacterium tuberculosis***
  - Meningitis
  - Tuberculosis abscess

Causes of generalised neurological disease

- ***Cryptococcus neoformans***
  - Meningitis
- **Virus family (papovavirus)**
  - Progressive multifocal leukoencephalopathy
- **Cytomegalovirus**
  - Encephalitis/retinitis
  - Peripheral neuropathy

Specific CNS infections

Cerebral toxoplasmosis is the most common CNS infection (90% of focal lesions) and occurs in 10% of AIDS patients. The organism is the crescentic trophozoite form of *Toxoplasma gondii*.

- Investigations: CT brain scan shows solitary or multiple ring-enhancing lesions. *Toxoplasma* IgG serology is positive in >90% of cases
- First-line anti-*Toxoplasma* therapy is pyrimethamine plus sulfadiazine (with folinic acid to prevent bone marrow suppression)
- Prognosis: 10% mortality with first episode; 25% of patients have residual neurological deficit
- It is important to differentiate from primary CNS lymphoma causing a space-occupying lesion.

Cryptococcal meningitis is due to a 'budding' yeast; it occurs in 5–10% of AIDS patients. It presents with a subacute meningitic illness.

- Cryptococcal antigen is present in blood and CSF in most cases
- **India ink stain**: positive in 70% of CSF samples.

Neurosyphilis: the coexistence of HIV and syphilis can result in aggressive and atypical neurosyphilis. Previous syphilis infection may reactivate. The following features are recognised:

- myelopathy
- retinitis
- meningitis

- meningovascular.

Diagnosis: from syphilis serology (rising VDRL and TPHA) and CSF, although serology may be modified by immune dysfunction.

Treatment: The first-line therapy is intramuscular procaine penicillin and oral probenecid for 17 days.

8.5.3 Ophthalmic disorders

AIDS may affect the lids or any layer of the eye.

Ophthalmic features of AIDS

- **Molluscum contagiosum of lids**
- **Episcleritis and keratitis**
- **Uveitis**
- **Choroidal granulomata**
- **CMV retinitis**
- **Neuro-ophthalmic manifestations** (eg cranial nerve palsies, optic neuritis, sequelae to CNS infection or space-occupying lesion)
- **Kaposi's sarcoma of the eyelids or conjunctiva**
- **Retinal changes**: haemorrhages, cotton wool spots, oedema and vascular sheathing
- **Toxoplasmosis**: may develop acquired disease or reactivation of pre-existing disease
- ***Candida* endophthalmitis**

Retinitis is common and may be caused by HIV itself (non-specific microangiopathy which is present in 75% of HIV patients) or by CMV.

CMV retinitis usually occurs when the CD4 count is $<50/mm^3$. This is the most common AIDS-related opportunistic infection in the eye (occurring in 25% of patients).

- **Symptoms**: blurred or loss of vision; floaters
- **Signs**: soft exudates, and retinal haemorrhages
- **Prognosis**: initially unilateral eye involvement; ultimately both eyes are affected.

8.6 MALIGNANT DISEASE IN PATIENTS WITH HIV/AIDS

Despite the introduction of HAART, the incidence of malignant disease in patients with HIV/AIDS has increased in recent years. The most frequently occurring malignancies are:

- Kaposi's sarcoma (83%)

- Non-Hodgkin's lymphoma (13%)
- Primary CNS lymphoma (4%)
- Other non-AIDS malignancies at increased risk are anal cancer and cervical cancer, both associated with oncogenic HPV type 16/18.

8.6.1 Kaposi's sarcoma (KS)

This occurs in 10–15% of HIV patients as the first AIDS-defining presentation. The tumour is derived from vascular or lymphatic endothelial cells and is due to infection with human herpesvirus type 8 (HHV8). This virus is closely related to EBV and is transmitted sexually, vertically and via organ transplantation.

- **Clinical presentation**: Kaposi's sarcoma (KS) can have cutaneous and visceral involvement. Lesions appear as purple plaques or nodules. The most common systems involved are the gastrointestinal tract (30% of patients with KS of the skin also have gastrointestinal involvement), lymph nodes and the respiratory system. Patients with pulmonary KS have cough, dyspnoea and infiltrates, lymphadenopathy or effusion on chest X-ray. KS is now quite uncommon owing to the effect of the new antiretroviral combination therapies
- **Diagnosis**: clinical appearance (or biopsy in difficult cases)
- **Prognosis**: depends on stage of sarcoma: tumour (T), extent of systemic involvement (ie gastrointestinal, pulmonary) and level of immune status, immunosuppression (I), as indicated by level of CD4 lymphocyte count. The best prognosis occurs when disease is confined to skin or lymph nodes, when there is minimal oral disease, and when the CD4 lymphocyte count is >150/mm^3.

8.7 HIV/AIDS-RELATED SKIN DISEASE

Dermatological diseases are extremely common in HIV patients (affecting 75%), especially in those who have AIDS. During the acute HIV illness, patients may develop an asymptomatic maculopapular eruption affecting the face and trunk. During seroconversion, they may also develop marked seborrhoeic dermatitis. As the disease progresses to AIDS, the development of tumours and atypical infections is seen.

Dermatological associations of HIV disease

- **General inflammatory dermatoses**
  - Psoriasis
  - Eczema
  - Seborrhoeic dermatitis
  - Folliculitis
- **Fungal/yeast infections**
  - *Pityrosporum ovale**

- Candidiasis*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*

- **Malignancy**
  - Kaposi's sarcoma
  - Lymphomas
  - Cervical intraepithelial neoplasia*
- **Viral infections**
  - Herpes zoster/herpes simplex
  - Human papilloma virus*
  - Cytomegalovirus
  - Molluscum contagiosum*
- **Bacterial infections**
  - Tuberculosis
  - Syphilis
  - Bacillary angiomatosis
  - *Staphylococcus aureus*

*Features common in HIV patients.

Other skin diseases that are recognised include:

- **Generalised maculopapular rash** (due to drugs): co-trimoxazole (25%), nevirapine (14%), efavirenz (4%), abacavir (5%), dapsone (5%)
- **Nail pigmentation**: zidovudine, indinavir
- **Stevens–Johnson syndrome** (due to drugs): nevirapine, co-trimoxazole.

8.8 DRUG THERAPIES IN HIV/AIDS PATIENTS

8.8.1 Specific therapy of common opportunistic infections

Opportunistic infections in HIV/AIDS and their treatment are outlined in Table 8.1.

8.8.2 Antiretroviral therapy

Antiretroviral therapy is usually given as combination therapy with the following aims:

- Suppression of viral replication to undetectable levels (<40 copies/ml)
- Reducing the risk of viral resistance emerging with three or more drugs
- Improving patient immunity with reduction of morbidity and mortality.

Highly active antiretroviral treatment (HAART)

This involves combinations of at least three drugs; for example, two different nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) in addition to a protease inhibitor (PI), or a non-nucleoside reverse transcriptase inhibitor (NNRTI).

There are three main classes of antiretroviral drugs currently licensed in the UK. Their modes of action are by inhibition of the viral reverse transcriptase enzyme or by inhibition of protease enzymes.

Table 8.1. Opportunistic infections, their treatment and side-effects in HIV/AIDS

Infection	First-line drugs	Side-effects
Pneumocystis pneumonia	Co-trimoxazole (oral, or IV for moderate-to-severe infection) Pentamidine (IV)	Rash, bone marrow toxicity, nausea and fever Hyper/hypoglycaemia, pancreatitis, hypotension
Cerebral toxoplasmosis	Pyrimethamine and sulfadiazine (in combination)	Bone marrow suppression, fever, gastrointestinal reactions, rash
Cryptococcal meningitis	Amphotericin and flucytosine (in combination)	Chills, fever, gastrointestinal reactions, renal impairment (amphotericin), bone marrow toxicity, liver toxicity
CMV retinitis	Ganciclovir or valganciclovir Foscarnet Cidofovir	Bone marrow suppression Renal impairment Nephrotoxicity

- Between 20% and 25% of ward admissions in patients with known HIV are due to drug toxicity
- Patients who fail combination therapy switch to salvage regimens, which might include drugs from all classes (sometimes combinations of four to six drugs are used).

Reverse transcriptase inhibitors

- **Nucleoside/nucleotide analogues** (NRTI): zidovudine, lamivudine, didanosine, abacavir, tenofovir
- **Non-nucleoside analogues (NNRTI)**: efavirenz, nevirapine, etravirine, rilpivirine
- **Protease inhibitors (PI)**: these act by inhibiting a protease that is needed to make the virus viable outside the cell. Particular PIs include saquinavir, ritonavir, fosamprenavir, lopinavir, atazanavir, darunavir.

Other drugs used as antiretrovirals

Interleukin-2: this is used to boost CD4 counts in those patients who have had good HIV

- suppression with therapy, but who have failed to recover CD4 counts. The agent has little effect on HIV viral load
- **Enfuvirtide (T-20)**: amino acid peptide (GP41) competes with the HIV viral envelope protein for fusion to the cell membrane (therefore, a fusion receptor inhibitor). This is used in conjunction with HAART salvage therapy.

Newer antiretroviral drug classes currently licensed for use

- Integrase inhibitors (inhibit cellular integration of viral DNA), eg raltegravir and elvitegravir
- CCR5 inhibitors (classed as entry uptake inhibitors), eg maraviroc.

Side-effects of antiretroviral drugs

- **Nucleoside/nucleotide analogues**
  - Zidovudine: myopathy, anaemia, fatigue, bone marrow toxicity, nail changes
  - Tenofovir: renal tubular dysfunction
  - Lamivudine: peripheral neuropathy, fatigue
  - Abacavir: hypersensitivity reaction (can be fatal on rechallenge)
  - Didanosine: pancreatitis, peripheral neuropathy
- **Non-nucleoside analogues**
  - All agents: potential for drug interactions via the CYP450 cytochrome family; they can act as inhibitors or inducers
  - Nevirapine: rash, hepatitis
  - Efavirenz: rash, vivid dreams, hallucinations and depression
- **Protease inhibitors**
  - All agents: diabetes, hypertriglyceridaemia and hypercholesterolaemia (except atazanavir), central adiposity, buffalo hump, peripheral fat loss (lipodystrophy syndrome also associates with nucleoside analogues, eg zidovudine and stavudine); there is also great potential for drug interaction via the CYP450 cytochrome family (ritonavir is the most potent inhibitor known)
  - Atazanavir: no effect on lipids, but hyperbilirubinaemia occurs in 5%

Monitoring of HIV patients on treatment

- **Clinical assessment**: examination of mouth (for ulcers and candidiasis), skin, lymph nodes, chest, fundoscopy and weight
- Renal and hepatic function
- CD4 lymphocyte count
- HIV viral RNA load
- Viral resistance assay
- HLA-B5701 – a genotypic allele which is carried in up to 4–6% of the population (lower in African origin ~1%) which can predict severe abacavir hypersensitivity

- Cholesterol, blood sugar, triglycerides
- Lactate if symptoms of lactic acidosis (muscle pains, malaise, gastrointestinal symptoms, breathlessness) are present
- **Adherence to treatment**: >90–95% of therapy must be taken to maintain adequate viral suppression, and this will also reduce the chance of resistance developing to therapy. If there is evidence of virological failure (increased viral load on >2 tests), then HIV **resistance testing** is indicated. The latter involves viral genotype assay of point mutations associated with antiretroviral resistance to specific drugs
- **R5 tropism assay**: genotype to assess suitability for CCR5 uptake inhibitors.

8.8.3 Prognosis of patients with HIV/AIDS

HIV was previously the leading cause of death in the USA in people aged 25–40 years (40 deaths/100 000). The prognosis of HIV/AIDS patients has now been revolutionised by HAART (introduced 1997) and the death rate has reduced.

- Life expectancy may surpass 25 years after diagnosis; can now be same as in uninfected individuals if HAART is started promptly (nadir CD4 count >350 mm)
- The new antiretroviral agents also significantly reduce mother-to-baby transmission of the virus from 20% to <1% (if breastfeeding is avoided)
- Individual prognosis depends on viral resistance (10% of new infections in Europe involve a resistant virus), side-effects and adherence to treatment; prognosis is worse if treatment is started when the CD4 count is below 200 cells/mm^3
- Evidence from the SMART Study suggests that the optimum time to commence HAART is when the CD4 count falls to around 350/mm^3. Prognosis is worse in patients who present late with AIDS (mainly heterosexuals who may have no obvious risks); death is due to delay in diagnosis
- Coronary heart disease, end-stage liver failure (due to co-infection with hepatitis B and C) and malignancy (lymphoma) are now common causes of death in patients with HIV/AIDS.

HIV has now become a treatable chronic illness rather than a fatal disease.

8.8.4 New strategies for reduction of HIV transmission

- **Post-exposure prophylaxis after sexual exposure (PEPSE)**: a short course of antiretrovirals (4 weeks of Truvada [emtricitabine/tenofovir]/Kaletra [*lopinavir*/ritonavir]) is taken within 72 h of 'high-risk' exposure and may reduce transmission by 70–80%
- **Pre-exposure prophylaxis (PrEP)**: in high-risk, non-infected individuals, long-term adherence to HIV drugs (Truvada) may reduce acquisition of HIV, but is limited by adherence and tolerability
- **Treatment as prevention (TAP)**: virological suppression on ARVs can significantly reduce risk of transmission to an uninfected discordant partner (96% in heterosexual couples), and can now be recommended in asymptomatic patients with higher CD4 counts
- **Expanded HIV testing**: to reduce late diagnosis in areas of high HIV prevalence (>0.2%), it is

- recommended that routine testing should be offered across medical admissions and newly registered GP patients. Such early diagnosis will encourage behavioural and therapeutic interventions felt to reduce the burden of the global HIV epidemic.

Chapter 9
Haematology

CONTENTS

Haematology

9.1 ANAEMIAS

9.1.1 Definition and clinical features

Anaemia is defined as a reduction in the concentration of circulating haemoglobin. The British units of haemoglobin measurement changed from grams per decilitre (g/dL) to the SI units of grams per litre (g/L) in 2013; the decimal point has moved one place to the right but the numbers are otherwise unchanged. The normal haemoglobin level varies with age and sex, neonates having higher levels than adults, infants lower levels and women having lower levels than men.

Clinical features of anaemia

- Pallor – examine mucous membranes
- Decreased oxygen-carrying capacity (shortness of breath on exertion, tiredness)
- Increased cardiac output (palpitations, 'haemic' ejection murmurs, cardiac failure in elderly people)

Unless the cause of anaemia is known it is usually classified by red cell size using the mean (red) cell volume (MCV), each type of anaemia being associated with a different list of differential diagnoses:

- Macrocytic: large red cells
- Normocytic: normal size red cells
- Microcytic: small red cells.

9.1.2 Causes of macrocytosis

Normal maturation of erythroid cells is termed 'normoblastic erythropoiesis'.

Many causes of macrocytic anaemia are associated with a series of morphological changes in the bone marrow, which include a lacy appearance to the nuclear chromatin of developing erythroblasts, premature appearance of haemoglobin in their cytoplasm (pink colour), giant metamyelocytes and (in the blood) hypersegmented neutrophils. Put together these changes are termed 'megaloblastic erythropoiesis'.

Causes of macrocytosis with megaloblastic erythropoiesis

- **Vitamin B_{12} deficiency**: vitamin B_{12} is found in liver, red meat and fish, and bound to intrinsic factor secreted by the parietal cells of the stomach. This delivers it to the absorption receptors in the terminal ileum. Measurement of holocobalamin-bound or 'active' vitamin B_{12} is a more reliable predictor of deficiency than total vitamin B_{12}, much of the latter being irreversibly bound to carrier proteins
- **Folic acid deficiency**: folic acid is found in fruit and vegetables ('foliage'), destroyed by cooking, absorbed in the jejunum. Measurement of red cell folate provides a longer look back at folate status than serum folate which reflects only recent folic acid intake
- **Drugs affecting bone marrow nucleic acid synthesis**: methotrexate, hydroxycarbamide, azathioprine and many other chronically administered cytotoxics.

Causes of vitamin B_{12} deficiency

- Lack of intake: vegans
- Lack of intrinsic factor: pernicious anaemia, gastrectomy
- Lack of absorption ability: inflammatory bowel disease affecting the terminal ileum, surgical resection of terminal ileum
- Competitive consumption (rare): colonisation of small bowel by bacteria that consume vitamin B_{12}

Pernicious anaemia

- The most common cause of macrocytic anaemia, often positive family history for autoimmune disorders and more frequent in northern races
- Autoimmune attack against gastric parietal cells that secrete intrinsic factor and acid
- May be associated with other autoimmune disorders such as vitiligo or myxoedema
- Vitamin B_{12} is required for nervous tissue so peripheral neuropathy, subacute combined degeneration of the cord, dementia and optic atrophy are associated
- Presence of intrinsic factor antibodies in serum strongly supports the diagnosis of pernicious anaemia (PA). Parietal cell antibodies are also commonly found but are not specific for PA
- Shilling test for B_{12} absorption is, sadly, no longer generally available in the UK
- Simple and cheap to treat with lifelong quarterly hydroxocobalamin B_{12} injections; anaemia improves in weeks/months but neurological damage may take years.

Causes of folic acid deficiency

- Lack of intake: poverty, crank diets
- Lack of absorption: inflammatory bowel disease or surgical resection
- Increased requirement: pregnancy, haemolytic anaemias

Macrocytosis with a normoblastic bone marrow

- **High reticulocyte count**: young cells are big cells. Most commonly seen in recovery from surgical blood loss and in haemolytic anaemias
- **Liver disease**: interference with hepatic manufacture of lipids for the red cell envelope, one cause of target cells on the blood film
- **Alcohol**: direct toxic effect of alcohol on the bone marrow; may also be a cause of liver disease and associated with dietary folate deficiency
- **Myxoedema**: check not due to the associated autoimmune disease PA!
- **Pregnancy**: usually mild.

Macrocytosis associated with haematological diseases having their own special features

- **Myelodysplasia**: associated with cytopenias, monocytosis and **dysplastic changes** in blood and bone marrow cells, sometimes with increased myeloblasts if transforming to acute myeloid leukaemia
- **Myeloma**: look for paraprotein, high erythrocyte sedimentation rate (ESR), leukoerythroblastic blood picture
- **Myeloproliferative disorders**: polycythaemia (high haemoglobin, haematocrit, red cell count, white cell count), essential thrombocythaemia (high platelet count), myelofibrosis (anaemia, leukoerythroblastic film, teardrop poikilocytes), chronic myeloid leukaemia
- **Aplastic anaemia**: pancytopenia with low reticulocyte count and hypoplastic marrow.

9.1.3 Causes of microcytosis

- **Iron deficiency**: look for pencil cells, hypochromia (pale staining red cells), check serum iron/total iron-binding capacity (TIBC) or ferritin
- **Thalassaemia trait**: look for Mediterranean/Asian origin, check HbA2 level (elevated in most cases of β thal. trait)
- **Anaemia of chronic disease**: often normocytic, usually obvious disease, and raised inflammatory markers
- **Sideroblastic anaemia**: the MCV may be low, normal or high (see Section 9.2.2).

9.1.4 Red cell morphology

Sometimes morphological changes reported on the blood film are sufficiently characteristic to suggest a diagnosis (Table 9.1).

Dimorphic red cell populations

The dimorphic red cell picture refers to the presence of two populations of red cells. These differ in cell size and/or staining intensity, and may be detected by modern blood counters and film examination. Causes are:

- After transfusion of normal donor red cells into a patient with a microcytic or macrocytic anaemia
- Haematinic deficiency responding to treatment. The new normal cells contrast with the persisting abnormal cells characteristic of the anaemia
- Mixed deficiencies separated in time (eg folatedeficient patient then develops iron deficiency)
- In the early stages of primary sideroblastic anaemia the clone of abnormal erythroblasts may produce abnormally sized red cells; these contrast with the persisting normal-sized red cells which are a product of normal erythropoiesis.

9.1.5 Sickle cell disease

Haemoglobin consists of haem, an iron-containing part, and globin, a protein-containing part. Globin consists of two polypeptide chains. The normal human haemoglobins differ in the nature of these globin chains. At birth most haemoglobin is fetal Hb (HbF), containing two α and two γ globin chains. During the first year of life there is a gradual switch to production of adult haemoglobin (HbA) which contains two α chains and two β chains. Up to 3.5% of normal haemoglobin is the second adult haemoglobin HbA2, which contains two α chains and two β chains.

Table 9.1 Characteristic morphological changes found in red cells

Changes in shape (poikilocytosis)	**Found in**
Teardrops	Myelofibrosis
Fragmented cells and helmet cells	Microangiopathic haemolysis
Pencil cells	Iron deficiency (with hypochromic microcytes)
Elliptocytosis	Hereditary elliptocytosis
Sickle cells	Sickle cell disease
Changes in staining characteristics	
Spherocytes	Any cause of haemolysis but particularly warm autoimmune haemolysis and hereditary spherocytosis
Target cells	Liver disease, post-splenectomy, iron deficiency, thalassaemias and haemoglobinopathies
Polychromasia	Young red cells, implying a high reticulocyte count, if this is measured
Changes in arrangement of red cells	
Rouleaux	Any cause of a high erythrocyte sedimentation rate
Agglutinates	Presence of cold agglutinins

In the haemoglobinopathies one or other of the polypeptide chains of globin has an abnormal structure, eg in sickle cell disease valine is substituted for glutamic acid in position six of the β chain. In the thalassaemias the globin chains are normal in structure but one or other of them is not made in sufficient quantity.

Sickle cell disease is the most common serious inherited disease in England; 13,500 suffer from the disorder and there are 240,000 carriers of sickle trait. The sickle cell diseases consist of homozygous sickle cell anaemia (HbSS), haemoglobin SC disease (HbSC), and haemoglobin S β-thalassaemia trait (HbSThal). More than two-thirds of cases of sickle cell disease are sickle cell anaemia. The clinical manifestations of sickle cell disease are caused by the occlusion of small blood vessels by logjams of sickled red cells, resulting in local tissue hypoxia and subsequent infarction. Precipitating causes may be hypoxia, dehydration and infection, but often no cause can be determined for a vaso-occlusive crisis.

Clinical syndromes found in sickle cell disease

- **Simple pain crisis**: due to infarction of red bone marrow, a common problem in sickle cell disease. Red marrow is active haemopoietic marrow, which in normal adults is confined to skull, sternum, spine and pelvis – in the axial skeleton of adults with haemolytic anaemia, the red marrow may extend into the long bones, and normal babies may have red marrow to their fingertips (see sickle dactylitis below). Deep-seated bone pain often requires opiate analgesia, preferably with diamorphine. Visual analogue scoring, patient-controlled analgesia, non-steroidal anti-inflammatory drugs (NSAIDs) and nitrous oxide have a role to play. Vigorous hydration may shorten the duration of crisis and oxygen therapy should be given for hypoxaemia demonstrated by good quality pulse oximetry. Infection is treated with antibiotics after appropriate cultures have been taken
- **Pulmonary infarction (chest syndrome)**: may be associated with infection. A serious complication of sickle cell disease often requiring exchange transfusion
- **Localised areas of splenic infarction**: results in pleuritic pain in the left hypochondrium often radiating to the left shoulder and may be associated with an audible rubover the affected area. The spleen is responsible for removing senescent red cells from the circulation at the end of their lifespan and the older the red cell the more likely it is to undergo irreversible sickling, so sickled red cells may accumulate in the splenic vasculature leading to local hypoxia and infarction. The spleen in most sickle cell patients atrophies by repeated infarction during childhood, resulting in hyposplenism (see Section 9.9)
- **Vaso-occlusive stroke**: a rare but serious complication of sickle cell disease requiring urgent and repeated exchange transfusion
- **Priapism**: painful sustained penile erection due to sickling of red cells in the corpora cavernosa, which may lead to long-term impotence. Perineal ice packs and walking up and down stairs may be helpful while waiting for urological opinion, and an exchange transfusion is often required
- **Sickle dactylitis**: infarction of the small bones of the hands or feet (which contain red active marrow in childhood) may be the earliest manifestation of sickle cell disease. Local pain and swelling result with possible long-term deformity
- **Splenic sequestration crisis**: in children the spleen and liver may rapidly enlarge (over hours)

- and become painful. This is associated with massive retention of sickled cells in the spleen, resulting in severe anaemia with a requirement for urgent top-up transfusion. The bilirubin and reticulocyte count (already elevated in sickle cell disease) are higher than usual and the haemoglobin lower

- **Aplastic crisis**: this is a syndrome of severe anaemia with a lower reticulocyte count and bilirubin level than usual for the patient. It is usually due to parvovirus B19 infection (now renamed erythrovirus). In normal people this infection results in a mild febrile illness ('slapped cheek' or fifth disease), with infection of red cell precursors in the marrow causing a temporary shutdown of red cell production. In patients with an increased red cell turnover, such as sickle cell disease, a precipitous drop in haemoglobin level may result from a short interruption of erythropoiesis. Aplastic crisis may be found in other congenital haemolytic anaemia associated with a high red cell turnover

- **Other areas of sickle infarction**: no tissue is immune. Infarction of the retina, particularly in haemoglobin SC disease may lead to retinal detachment and blindness. Infarction of the placenta may lead to fetal loss and small-forgestation babies. Intractable leg ulcers are common in countries where protective footwear is not worn. Avascular necrosis of the head of femur may be seen in adults.

Transfusion in sickle cell disease

As the oxygen dissociation curve of HbS is shifted to the right in comparison with HbA, oxygen is more easily released from haemoglobin to the tissues. Anaemia is therefore well tolerated and red cell transfusion for the correction of anaemia is rarely required, except in aplastic or sequestration crises. For severe sickle problems, exchange transfusion with non-sickling, HbA-containing red cells is required. To be effective the percentage of HbA needs to be raised to 80–90% and care needs to taken not to increase the haematocrit, which may lead to stagnation, increased sickling and increased vascular occlusion. Using ABO-compatible red cells matched for Rhesus and Kell antigens will inhibit the development of atypical red cell antibodies which may otherwise complicate future transfusions. The following are commonly accepted indications for exchange transfusion:

- Frequent severe sickle pain crisis
- Central nervous system sickling
- Priapism
- Chest syndrome not responding to conservative management
- Preoperatively or in pregnancy if there is a bad sickling history or a large operation is required.

Haemoglobin F in sickle cell disease

Elevated levels of HbF protect against sickling, hence clinical manifestations of sickle cell disease are not seen before 1 year of age, after which the physiological switch from HbF to HbS becomes complete. Hydroxycarbamide, an oral cytotoxic mainly used for the treatment of myeloproliferative diseases, has the side-effect of increasing HbF levels and is sometimes used for the amelioration of sickle cell disease; however, this use has to be balanced against its other possible effects of marrow suppression, reduction of fertility and teratogenicity. New drugs without these side-effects are in development.

9.1.6 Thalassaemias

In these disorders the structure of the globin chains is normal, but **not enough** of the globin chains of haemoglobin can be produced. The disorder may affect α chains (**α-thalassaemia**) or β chains (**β-thalassaemia**). Both types of thalassaemia may be severe (homozygous, major) or mild (heterozygous, trait). Thalassaemia is the most common inherited genetic disorder in the world, with 5% of the world population carrying α-thalassaemia and 1.5% β-thalassaemia trait. In England, there are approximately 215,000 carriers of β-thalassaemia trait and 1000 suffer from β-thalassaemia major. Thalassaemias orginate from the areas of the world with historically high incidence of malaria, but with increasing immigration, the incidence in Europe is increasing.

Alpha-Thalassaemia

Alpha chains are required for the production of HbF, HbA and HbA2. As α-chain production is controlled by four genes, various degrees of clinical severity can be seen. With one α gene affected there is a mild microcytosis without anaemia. Three α genes affected results in a microcytic/hypochromic anaemia with splenomegaly. In this situation, unpaired β chains may complex together to form a tetramer of β chains which is called HbH. HbH may be detected by routine haemoglobinopathy screening methods or seen in red cells stained by an incubated reticulocyte stain. When four α genes are affected, death in utero results.

In β-thalassaemia major the blood is normal at birth, because β chains are not required for the production of fetal haemoglobin. During the first year of life there is failure to switch over from HbF to HbA production and the syndrome of anaemia, growth-stunting and hepatosplenomegaly arises.

Management of β-thalassaemia major

- Effective treatment depends on regular (every 3–6 weeks) blood transfusions of ABO, Rhesus and Kell–matched red cells, which leads to iron overload
- Iron overload results in cardiomyopathy, endocrine failure and cirrhosis, but can be prevented by iron chelation therapy. The aim of chelation therapy is to maintain the ferritin level <1000 μg/L
- **Desferrioxamine**: given by overnight subcutaneous infusion (using a syringe driver or balloon pump) on 2–5 nights of the week, depending on the degree of iron overload
- **Deferasirox**: an orally active iron chelator that removes iron mostly in the bile and faeces. As a result of its cost, it is available in the UK only for desferrioxamine treatment failures
- Inheritance of β-thalassaemia major is autosomal recessive. Screening for the heterozygous (trait) by blood count and haemoglobinopathy screening is performed routinely in pregnancy. Intrauterine diagnosis of thalassaemia major by chorionic villous sampling is possible, allowing the option of therapeutic abortion of an affected fetus.

β-Thalassaemia trait

The variable clinical presentation of α-thalassaemia has been remarked upon above. Beta-Thalassaemia trait is associated with minor suppression of β-chain manufacture and a mild microcytic/hypochromic anaemia with a haemoglobin usually >90 g/L. Besides assessing iron status

(see Section 9.2.1), an elevated HbA2 level is a useful marker of this trait.

9.1.7 Aplastic anaemia

This is a pancytopenia (reduction in white cell count, haemoglobin and platelet count) secondary to marrow hypoplasia. The reticulocyte count measured by high precision (automated) techniques is lower than normal.

Aetiology of aplastic anaemia

- **Idiopathic**: most cases are in fact autoimmune
- **Drugs**: an idiosyncratic reaction to drugs such as gold, phenylbutazone and chloramphenicol
- **Post-hepatitis**: viruses that are toxic to hepatocytes may also kill bone marrow stem cells. The aplasia may supervene after recovery from the hepatitis.
- As a predictable reaction to **chemotherapy or radiation**. About 1 in 300 of the general population has low levels of thiopurine methyl transferase (TPMT), the main enzyme responsible for degradation of the immunosuppressants azathioprine and mercaptopurine. Measurement of serum TPMT allows suitable reduction in dose of these drugs to prevent severe myelosupression in deficient patients

Management of aplastic anaemia

- **Remove possible causes** (eg stop possible offending drugs)
- **Supportive**: red cell transfusion for the correction of anaemia, antibiotics for infections, platelet transfusion for thrombocytopenia bleeding. Granulocyte colony-stimulating factor (G-CSF) does not improve stem cell numbers but may boost the numbers and function of maturing myeloid cells
- **Immunosupression**: usually with a combination of high-dose steroids, anti-lymphocyte globulin and ciclosporin
- **Stimulation of residual bone marrow activity**: anabolic steroids
- **Bone marrow transplantation**: in severe cases; most successful in children with an HLA-matched sibling. A reduced intensity conditioning regimen is used, avoiding the toxicity of total body irradiation, because the bone marrow is already empty and there are no malignant cells to eradicate.

9.2 IRON METABOLISM

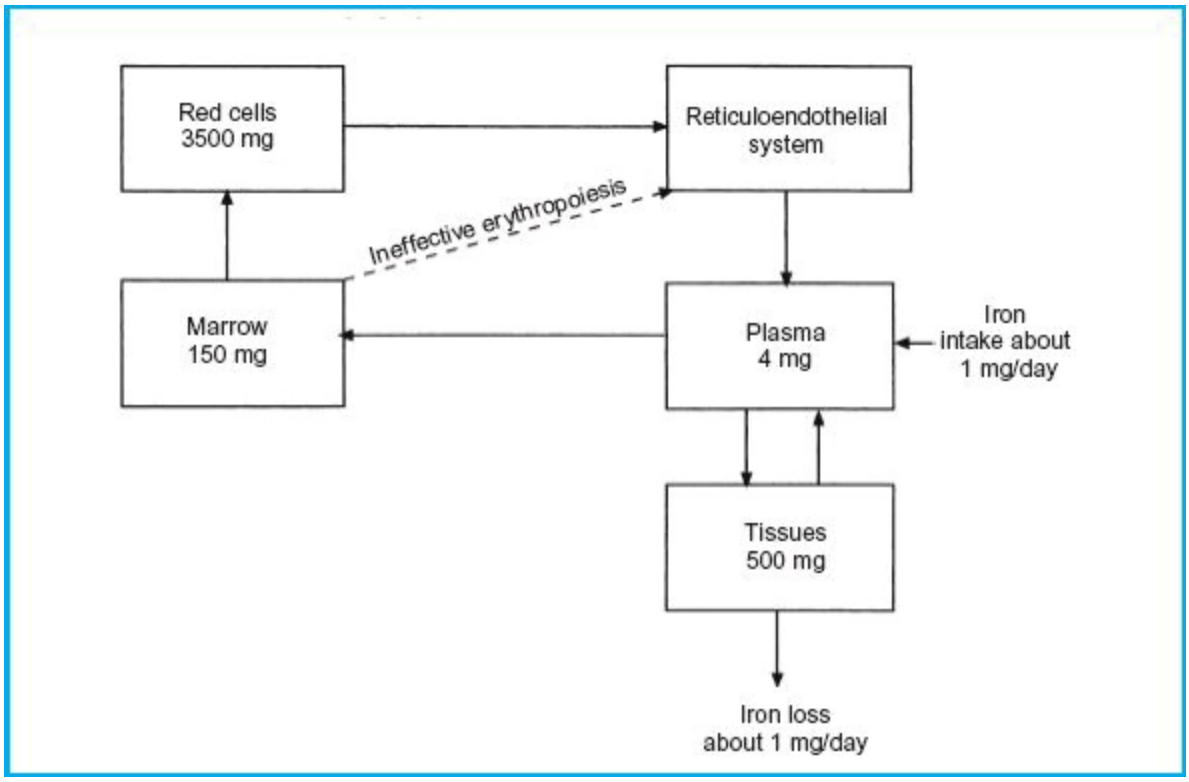
A representation of the body's iron economy is shown in Figure 9.1.

Iron absorption may be greatly increased in iron deficiency, but iron excretion cannot be increased in the case of iron overload. Most iron in the body is contained within red cells, so chronic bleeding is a potent cause of iron deficiency.

The marrow normally contains stainable iron stores, but it is possible to have no stainable iron in the bone marrow but a normal haemoglobin level. The converse is not true – in anaemia due to iron

deficiency, the marrow will not contain stainable iron. In megaloblastic anaemias, haemoglobinopathies and myelodysplasia, red cells may die and enter the reticuloendothelial recycling system without leaving the bone marrow – this is termed 'ineffective erythropoiesis'.

Figure 9.1 Iron economy in the body



9.2.1 Assessment of iron status

- **Transferrin saturation**: may be calculated by dividing the serum iron by total iron-binding capacity (TIBC) and multiplying by 100%. Neither the serum iron nor the TIBC is particularly helpful on its own, so transferrin saturation should always be requested. This is low in iron deficiency and high in iron overload
- **Serum ferritin**: a major transport and storage form of iron that is high in iron overload states and low in iron depletion. It is one of the acute phase proteins, and so, similar to C-reactive protein (CRP), fibrinogen and immunoglobulins, is released in inflammatory illness. If the ESR is increased then the ferritin may be falsely high. Ferritin is also released from damaged liver cells, and so will also be falsely elevated in the presence of a transaminitis
- **Iron stain on bone marrow particles**: this is the gold standard, but invasive and expensive, so rarely performed in the diagnosis of iron deficiency
- **Serum-soluble transferrin receptor**: the latest index for measuring iron status, being high in iron deficiency and low in iron overload. It is available only in some laboratories
- **Trial of oral iron**: In some patients it is difficult to establish the cause of an anaemia with certainty and a trial of oral iron for about a month is justified, and will do harm if the patient is not iron overloaded.

Functional iron deficiency

- Despite normal iron stores assessed by stainable marrow iron and normal serum ferritin, iron is not transferred to the developing erythroblast
- Functional iron deficiency (FID) is a major contributor to the anaemia of chronic disease
- Inflammation causes increased levels of hepcidin, a polypeptide hormone made by the liver, to be secreted. This prevents iron release from macrophages for use by developing red cells
- Diagnosis by specialist red cell indices – raised percentage of hypochromic red cells and low reticulocyte haemoglobin content (CHr); also increased red cell zinc protoporphyrin level (ZPP)
- FID results in failure to respond to erythroidstimulating agents such as erythropoietin
- Diagnosis of FID is an indication for intravenous iron supplementation, despite normal or raised ferritin.

9.2.2 Sideroblastic anaemia

In this disorder there is a failure to incorporate iron into the haemoglobin molecule, due to a biochemical block, and it accumulates in the mitochondrial factories. These become poisoned and are visible as iron granules lying in a ring around the erythroblast nucleus. Hence the diagnostic feature is **ring sideroblasts** in the bone marrow iron stain.

Causes of sideroblastic anaemia

- **Congenital**: rare, usually sex linked, responsive to pyridoxine
- **Acquired primary**: one of the myelodysplastic disorders
- **Acquired secondary**: alcohol, malignancy in the body, drugs (eg anti-tuberculous), connective tissue disorders, heavy metal poisoning

Management of sideroblastic anaemia

- **Remove the cause** if known
- **High doses of pyridoxine and folic acid** may act as a coenzyme in the incorporation of iron into haemoglobin
- **Erythropoietin** may improve the haemoglobin level
- **Red cell transfusion**: this may worsen iron overload.

9.3 HAEMOLYSIS

Destruction of red cells may occur in the:

- circulation (intravascular)
- reticuloendothelial system (extravascular).

Mild intravascular haemolysis liberates haemoglobin from red cells which the body tries to conserve by binding to plasma proteins. Initially this will be haptoglobin, so haptoglobin levels will be

reduced as the iron-laden haptoglobin is collected by the liver. Then albumin will bind free haemoglobin, forming methaemalbumin, which may be detected by a positive Schumm test. Without a protein to bind to, the haemoglobin will pass through the glomerulus to appear in the urine – **haemoglobinuria**. This will give a positive stick test for haemoglobin, but in contrast to **haematuria**, red cells will not be seen on urine microscopy. In extravascular haemolysis, the red cells are engulfed by macrophages mainly in the spleen and liver. In cases of severe haemolysis both mechanisms may occur together.

9.3.1 General features and causes of haemolysis

The anaemia is commonly macrocytic and associated with:

- **Elevated reticulocyte count**: >2%

  Jaundice: pre-hepatic, unconjugated, water-insoluble bilirubin, so **not** found in the urine.
- However, **urobilinogen** may be found in the urine – due to increased breakdown products of porphyrins secreted into the bile and reabsorbed from the bowel. Detected by simple stick test
- **Abnormal red cell morphology**: particularly spherocytes (see Section 9.1.4).

Causes of haemolysis

- **Mainly intravascular**
  - Immediate and some delayed haemolytic transfusion reactions
  - Paroxysmal cold haemoglobinuria
  - Microangiopathic haemolytic anaemia
  - Red cell enzyme deficiencies including glucose-6-phosphate dehydrogenase deficiency and phosphokinase deficiency
  - Infections – malaria (Blackwater fever)
  - Paroxysmal nocturnal haemoglobinuria
- **Mainly extravascular**
  - Warm autoimmune haemolytic anaemia
  - Cold haemagglutinin disease
  - Haemolytic diseases of the newborn
  - Red cell membrane disorders: hereditary spherocytosis, elliptocytosis, pyropoikilocytosis
  - Some delayed haemolytic transfusion reactions
  - Haemoglobinopathies, eg sickle cell disease

9.3.2 The antiglobulin (Coombs') test

This is divided into **direct** and **indirect** tests. The direct antiglobulin test (DAT) **detects antibody on**

the patient's red cells. This coating may be as follows:

- **Opsonising**: making the reticulocytes attractive to the phagocytes of the reticuloendothelial system
- **Complement fixing**: causing a local enzymatic explosion, blowing a hole in the red cell envelope
- **Agglutinating**: in which case the clumping of red cells may be visible in the blood sample vial when it has cooled to room temperature, or on the blood film, without resorting to a DAT.

The indirect antiglobulin test detects antibody in the patient's serum. This involves incubation of the patient's serum with ABO-compatible test red cells bearing a variety of minor blood group antigens. This test is most frequently used as part of the 'crossmatch' or compatibility testing. Donor red cells are incubated with recipient plasma and, if there are incompatibility antibodies in the plasma, they will stick to the donor's red cells and give a positive indirect antiglobulin test.

9.3.3 Microangiopathic haemolytic anaemia

As might be expected from the name – micro (small), angio (blood vessel), pathic (disease of) – the essential mechanism of this condition is the laying down of fibrin strands in the capillary bed. These chop up passing red cells (similar to a wire cheese-cutter). If not too badly damaged these may reseal themselves and circulate as helmet (half) red cells or if multitudinously chopped, as fragmented cells. These may be seen on the blood film – the microangiopathic blood picture. All the usual features of intravascular haemolysis will also be present, including a reticulocytosis. Depending on the cause of the microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and consumption coagulopathy may also be present.

Causes of MAHA

- Disseminated intravascular coagulation (DIC) (see Section 9.7.4)
- Haemolytic uraemic syndrome (HUS)
- Thrombotic thrombocytopenic purpura (TTP)
- Malignant (accelerated phase) hypertension
- Severe pre-eclampsia

Thrombotic thrombocytopenic purpura

In addition to the general features of MAHA there is often fever, cerebral and cardiac dysfunction. Renal impairment is less marked than in HUS. (See also Chapter 15, Nephrology.)

There is an excess of sticky high-molecular-weight von Willebrand's factor in the plasma, which causes the platelets to adhere to vascular endothelium. This results in consumption thrombocytopenia and the blockage of small capillaries in the brain and kidney by platelet thrombi. Activation of the coagulation system causes fibrin strands to be laid down and these shred passing red cells, resulting in the classic features of microangiopathic haemolysis.

In normal plasma, high-molecular-weight vWF is cleaved to less sticky vWF by a plasma protease, ADAMST13. Low levels of this protease (<10% of normal) have been found in many cases of TTP, and antibody directed against the protease has been demonstrated. In contrast to disseminated intravascular coagulation (DIC), the screening tests of coagulation (but not platelet count) are normal. ADAMST13 levels can be measured in plasma but this investigation is not commonly available enough to dictate initial management.

Haemolytic uraemic syndrome

HUS is the commonest cause of acute renal failure in childhood. It is most commonly caused by infection with shigatoxin-producing strains of enteropathogenic *Escherichia coli* 0157 due to contamination of food (particularly meat) or of hands by animal faeces (diarrhoea-associated HUS). When not associated with diarrhoea (about 10% of cases) it is termed atypical or diarrhoea-negative (aHUS) and is most commonly due to defects in the regulation of complement activation. Complementmediated damage to endothelial cells causes platelet activation and adhesion with laying down of fibrin strands that damage passing red blood cells - a microangiopathic picture identical to TTP.

Atypical HUS may be sporadic or familial. Sporadic aHUS is commonly triggered by illness such as bacterial or viral infections, particularly *Strep. pneumoniae*. Most sporadic cases can be demonstrated to have a genetic predisposition due to mutations in complement regulatory proteins.

Treatment of HUS

Supportive therapy is the mainstay of treatment for diarrhoea-associated HUS, including maintenance of electrolyte balance and control of hypertension, with no particular role identified for antibiotic treatment unless the patient is clinically septic. Dialysis may be required with renal transplantation if the renal failure becomes irreversible.

Atypical HUS is treated similarly to TTP, with highvolume plasma exchange. The anti-complement C5 monoclonal antibody eculizumab is effective (See PNH below)

Treatment of TTP and HUS

- **Large-volume infusion of fresh frozen plasma (FFP)** (which contains the vWF-cleaving protease and complement components) is the mainstay of treatment, coupled with plasma exchange. The latter has the advantage of removing any antibodies and toxins involved in the pathogenesis of the disease. Cryo-poor FFP (from which cryoprecipitate, a useful blood product, has been removed) may be used for the plasma exchange and solvent-/detergent-inactivated FFP may confer less risk of transfusion-transmitted infection
- **High-dose steroids** may be of benefit in cases with an autoimmune aetiology and are often given (except in the epidemic form of HUS)
- **Low-dose aspirin** may be used to inhibit further adhesion of platelets to vascular endothelium once the platelet count has exceeded 50×10^9/L
- **Rituximab**, a monoclonal anti-CD20 antibody, is effective in cases with an autoimmune aetiology

Other specific therapies may be required for specific disease sequelae (eg dialysis for acute

- renal failure).

9.3.4 Paroxysmal nocturnal haemoglobinuria

This is a rare acquired disorder that may affect all haematological cells. There is increased sensitivity of the cell membranes to the action of the patient's own complement, which damages red cells, white cells, platelets and stem cells. This results in intravascular haemolysis with haemoglobinuria, leukopenia, thrombocytopenia and (sometimes) pancytopenia with a hypoplastic marrow – aplastic anaemia. The following are other clinical features:

- The release of tissue thromboplastin from damaged cells leads to an acquired thrombophilia when thrombosis may present in unusual sites such as the hepatic or portal veins. Paroxysmal nocturnal haemoglobinuria (PNH) should be considered as an underlying diagnosis in the Budd–Chiari syndrome
- There is an increased incidence of acute myeloid leukaemia.

Pathogenesis and diagnosis of PNH

A transmembrane glycoprotein is missing from the cell surface in PNH, and this 'fence post' would normally carry molecules that inactivate complement approaching the cell membrane. These molecules include the CD antigens CD55 and CD59, which are missing from the cell surface in PNH. This allows diagnosis by the immunophenotyping of red cells, white cells or platelets. Unlike many other causes of haemolysis, which may be associated with iron overload, iron deficiency is common in PNH because of chronic haemoglobin loss in the urine. A minor clone of PNH cells can be demonstrated by immunophenotyping of blood in haematological diseases associated with a 'stressed' marrow, such as aplastic anaemia.

Treatment of PNH

- **Red cell transfusion**: the correction of anaemia often requires the use of washed red cells, as the transfusion of complement in the donor plasma may exacerbate haemolysis
- **Anticoagulation**: thrombosis is the most common cause of death, so anticoagulation with warfarin is usual if the platelet count is $>50 \times 10^9$/L
- **Eculizumab**: a monoclonal antibody directed against the complement component C5, this reduces haemolysis, rendering most patients transfusion independent, and decreases thrombosis. As a result of its high cost, its use in the UK is limited to special PNH clinics who receive central funding
- **Other therapies**: erythropoietin, steroids and danazol are of unproven value, although folic acid (and sometimes iron) supplements should be given. Bone marrow transplantation is curative but risky, and so usually reserved for patients developing acute myeloid leukaemia.

9.4 MEASUREMENT OF INFLAMMATION

Many medical disorders are associated with inflammation, and measurement of inflammatory markers

is useful in screening for disease and following the clinical progress of inflammatory disease. The three most popular measurements are ESR, CRP and plasma viscosity.

9.4.1 Erythrocyte sedimentation rate

An increased concentration of inflammatory proteins affects the dielectric of the suspending plasma so that red cells can approach each other more closely. Normally their surface negative electrical charge causes them to repel each other and remain in suspension. If they touch, they adhere face to face, forming stacks of red blood cells similar to piles of coins – rouleaux. These rouleaux may be seen on the blood film, when they suggest the presence of an inflammatory process or paraprotein. Alteration in the volume:surface area ratio means that rouleaux sediment more rapidly than individual red cells. When spherocytes are present, rouleaux cannot form, so the ESR may be falsely depressed.

- Despite the complex underlying mechanism, the ESR is a simple test to do and can be performed in the clinic using long, thin, citrated, bloodtaking tubes placed vertically in a rack. The ESR is measured as the depth in millimetres that the red cell meniscus has dropped after 1 hour
- The normal ESR is 2–20 mm/h. The normal range is age related, rising with advancing years. The upper limit for a normal ESR is often quoted as 0.5 × age in years for men and 0.5 × age + 5 in women. An ESR >100 mm/h is usually due to a paraprotein, collagen disease or tuberculosis
- There will be a delay of a few weeks, after cure of an inflammatory condition, before a return of the ESR to normal levels
- The ESR is not stable overnight in citrate tubes but EDTA (ethylenediamine tetra-acetic acid) (blood count) tubes can be used for up to 24 hours, provided that citrate anticoagulant is added in the laboratory at the time of the test
- The ESR is frequently used as a screening test to distinguish diseased from non-diseased patients – a normal ESR does not exclude disease, but an elevated one suggests an inflammatory process
- In the diagnosis of headache, a normal ESR does not exclude temporal arteritis, but an elevated one (usually >60 mm/h) supports the diagnosis. CRP may be more useful but is not always available as an out-of-hours investigation.

9.4.2 C-reactive protein

The name refers to the original finding of a protein that reacted with the C-polysaccharide of pneumococci, but CRP is released by hepatocytes and fat cells in response to high levels of the cytokine interleukin-6 (IL-6) and appears to attach to dead and dying cells and bacteria, assisting in their removal by macrophages that bear receptors for CRP. The assay is relatively complex and performed in the laboratory. CRP levels rise in a few hours in response to inflammation and reach their peak in 2 days. CRP levels drop more rapidly than ESR as inflammation improves.

A modest sustained elevation of CRP level is also a marker for increased cardiovascular risk.

9.4.3 Plasma viscosity

Providing a viscometer is available this is a reliable and inexpensive way of assessing acute phase

proteins, which include relatively large molecules such as fibrinogen and immunoglobulins. The sample is stable for several days at room temperature.

9.5 WHITE CELL DISORDERS

9.5.1 Leukocytosis

An elevated white cell count may be due to an increase in any of the individual types of white cells in the blood and should prompt a differential count to determine whether there is a neutrophilia, lymphocytosis or, more rarely, an increase in the number of other white cell types causing the leukocytosis. The only types of white cell present in normal blood (in order of decreasing frequency) are neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Neutrophilia (>7.5 × 10^9/L)

This is by far the most common cause of a leukocytosis. If acute it may be associated with young neutrophils (band cells, metamyelocytes) in the blood or 'left shift'.

Causes of neutrophilia

- Bacterial infections: localised or generalised
- Trauma
- Metabolic disorders: uraemia, acidosis, gout, eclampsia, poisoning
- Malignant neoplasms: particularly when associated with tissue necrosis
- Inflammation or infarction: myocardial infarction, burns, vasculitis
- Corticosteroid therapy
- Myeloproliferative disorders: chronic myeloid leukaemia, myelofibrosis, essential thrombocythaemia, primary polycythaemia

Lymphocytosis (>4.0 × 10^9/L)

The morphology of the lymphocytes may give valuable clues, eg in acute viral infections the lymphocytes may show morphological abnormalities termed 'reactive changes', and in chronic lymphocytic leukaemia the mature-looking small lymphocytes characteristic of the disease are fragile and become crushed during the spreading of the blood film – 'smear cells'.

Causes of lymphocytosis

- Acute viral infections: influenza, glandular fever, rubella, mumps, acute HIV
- Chronic lymphocytic leukaemia
- Chronic infections: tuberculosis (TB), *Brucella* spp., hepatitis, syphilis
- Hyposplenism

- Low-grade lymphomas with blood spill of lymphoma cells
- A lymphocytosis is normal in infancy

Eosinophilia (>0.5 × 10^9/L)

In the developed world allergic disorders are the main cause of eosinophilia.

Causes of eosinophilia

- Allergies: asthma, hay fever, drug reactions
- Skin diseases: eczema, psoriasis, dermatitis herpetiformis
- Parasite infections: most parasitic infections cause eosinophilia with the exception of malaria and threadworm. 'Tropical' eosinophilia is usually the result of multiple parasitic infections
- Myeloproliferative disorders: as part of the granulocytosis of chronic myeloid leukaemia, and in the rare myeloproliferative disorder associated with the *FIP1L1/PDGRF* translocation, which responds to imitanib
- Neoplasms: Hodgkin's lymphoma, interleukin-5-secreting T-cell lymphomas
- Miscellaneous conditions: sarcoidosis, polyarteritis nodosa, eosinophilic granuloma

Hypereosinophilia

Prolonged eosinophilia from any cause may damage tissues mainly as a result of eosinophils degranulating toxic cationic proteins on endothelium and serous surfaces. In the heart, mural thrombi may form and be the source of systemic emboli. Chronic damage to the endocardium may lead to endomyocardial fibrosis. If the eosinophil count is chronically (>6 months) >1.5 × 10^9/L and the cause cannot be removed, consideration should be given to reducing it by steroid or hydroxycarbamide treatment and regular cardiac ultrasonographic assessments.

Monocytosis (>0.8 × 10^9/L)

Monocytes are tissue macrophages ('dustbin lorries') en route to the tissues to phagocytose and digest dead cells and other debris.

Causes of monocytosis

- Recovery from tissue-damaging procedures: chemotherapy, radiotherapy, trauma, surgery
- Chronic inflammatory disease: sarcoidosis, Crohn's, ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus (SLE)
- Myelodysplastic syndromes including chronic myelomonocytic leukaemia
- Infections: TB, *Brucella* spp., kala-azar, typhus, bacterial endocarditis, malaria, *Trypanosoma* spp.
- Acute myelomonocytic leukaemia: when it will be associated with increased blast cells

9.5.2 Leukoerythroblastic change

This is defined as the presence of nucleated red cells and primitive white cells of any type in the peripheral blood. There are two major causes: either the normal cells inhabiting the bone marrow are being evicted by a marrow infiltration or the patient has an acute severe illness.

Causes of a leukoerythroblastic blood picture

- **Invasion of bone marrow space**
  - Metastatic carcinoma: particularly breast, prostate, lung, kidney and thyroid
  - Haematological malignancy: leukaemia, lymphoma, myeloma, myelofibrosis
  - Lipid storage diseases: eg Gaucher's
  - Bone disorders: eg osteopetrosis
- **Severe acute illness**, eg massive trauma, septicaemia, severe haemolysis

9.5.3 Neutropenia

This is defined as a neutrophil count of $<2 \times 10^9$/L. Below $<1 \times 10^9$/L some risk of bacterial infection exists, and $<0.5 \times 10^9$/L may be severe and such patients, if in hospital, will usually be isolated and subject to a routine of neutropenia care, including prophylactic antiseptic mouthwashes, antifungal agents and avoidance of food with a high bacterial load. In the event of significant fever, a broadspectrum intravenous antibiotic regimen reserved for 'febrile neutropenia' is instituted.

Causes of neutropenia

- Associated with intercurrent viral infection: usually mild neutropenia; reactive lymphocytes may be seen on the blood film
- Idiosyncratic drug reactions, eg clozapine, carbimazole
- Collagen diseases, eg SLE, rheumatoid arthritis
- Myelodysplasia: dysplastic changes such as hypogranularity or hypersegmentation often present
- After chemotherapy or radiotherapy
- Benign ethnic neutropenia: in Black or Arab individuals, whose neutrophils are held in the tissues rather than circulating in the blood
- Hypersplenism: usually a low platelet count and haemoglobin as well
- Marrow infiltration: usually associated with low platelet count and haemoglobin; sometimes a leukoerythroblastic blood picture

9.6 HAEMATOLOGICAL MALIGNANCIES

These may be broadly divided into the following categories:

- leukaemias
- lymphomas
- myelodysplasias
- myeloproliferative disorders.

Acute leukaemias are characterised by an excess of primitive blast cells in the marrow, spilling into the blood. Chronic leukaemias show an excess of more mature cells in the marrow and blood. In leukaemias, the malignant cells lie mainly in marrow and blood, whereas in lymphomas they lie mostly in lymph nodes. There is an overlap, however, so many cases of lymphoblastic lymphoma have marrow involvement by cells of the disease in addition to enlargement of lymph nodes and thymus.

9.6.1 Leukaemias

Acute leukaemias
• Acute myeloid leukaemia (AML) • Acute lymphoblastic leukaemia (ALL)
Chronic leukaemias
• Chronic myeloid leukaemia (CML) • Chronic lymphocytic leukaemia (CLL)

Acute myeloblastic leukaemia

- Predominantly affects adults
- Chemotherapy sufficient to induce marrow hypoplasia is usually required to induce remission
- Central nervous system (CNS) involvement rare
- More than 30% cure rate with chemotherapy
- May be further classified by morphological appearance (see below).

Acute lymphoblastic leukaemia

- Predominantly affects children
- Remission may be induced by non-myelosuppressive chemotherapy

- CNS involvement is common, requiring prophylactic intrathecal cytotoxic therapy
- More than 80% cure rate with chemotherapy
- Further classified by immunological surface markers.

How to identify the leukaemic blast cell

As treatment and prognosis differ between AML and ALL, it is important to be sure which disease it is. This may be determined by the following:

- **Morphology**: sometimes this is not helpful because lymphoblasts look similar to myeloblasts. One give-away is the presence of Auer rods, stick-like crystallisations of myeloid granules that may be found in the cytoplasm of myeloblasts
- **Immunological surface markers**: particularly useful in ALL, allowing classification into T-cell, B-cell and other immunological subtypes
- **Cytochemistry**: the leukaemic cells are stained for their biochemical activities. Important cytochemical tests in acute leukaemia are: Sudan black (stains lipid material in myeloblasts); periodic acid–Schiff (PAS) (stains carbohydrate material in ALL); non-specific esterase (stains the monocytic variants of AML).

Treatment strategies in acute leukaemia

Chemotherapy treatment in acute leukaemia is usually divided into phases:

- **Induction**: inpatient chemotherapy designed to remove the bulk of leukaemic cells, allowing restoration of normal bone marrow function and remission (<5% blasts in the marrow)
- **Consolidation therapy**: chemotherapy designed to remove residual leukaemia cells
- **Maintenance chemotherapy**: applied in ALL rather than AML – low doses of oral chemotherapy given for 1–3 years.

Stem cell transplantation is a powerful treatment for acute leukaemia because it combines the leukaemia-killing effect of conditioning treatment with strong chemotherapy and radiotherapy, which removes all the recipient's marrow cells with an immunological attack of the donor's transplanted immune system against residual leukaemia (graft-versus-leukaemia effect). However, stem cell transplantation is a risky treatment, and this risk increases with age. Total body irradiation, often employed as a conditioning regimen, results in sterility. Powerful chemotherapy also carries major risks, so patients are stratified by risk of relapse. This allows the selective application of stronger, and hence riskier, chemotherapeutic regimens for those patients who require them, and less stringent chemotherapy in patients with a better prognosis (see below).

Prognostic factors in acute leukaemias

Acute lymphoblastic leukaemia

- Age: <1 year or >10 years worsens prognosis; adults do particularly badly
- Height of highest pretreatment white cell count (a higher count = a higher tumour load and worse prognosis, particularly in children)
- Cytogenetics (see Section 9.6.2)

- Sex – in children boys do worse
- Immunophenotype (T-cell ALL usually has high presenting white cell count – see Section 9.6.3)

Response to treatment is measured by blast cell count in the marrow, or by assessment of minimal residual disease (MRD). Morphological remission is defined as <5% blasts in the bone marrow. MRD assessment uses the polymerase chain reaction (PCR) to amplify clonal rearrangements of immunoglobulin genes (in B-cell ALL) or T-cell receptor genes (in T-cell ALL) that are characteristic of that patient's disease. PCR allows reliable detection of 1 leukaemic cell in 10,000 marrow cells, a sensitivity which cannot be approached by morphological examination. In children the persistence of more than one malignant cell per 10^4 marrow cells after 1 month into chemotherapy mandates the use of a more intensive chemotherapy protocol.

Acute myeloid leukaemia

- cytogenetics (see below)
- age (over-60s do worse)
- response to the first course of induction chemotherapy.

9.6.2 Specific chromosome abnormalities in leukaemia/lymphoma

Cytogenetic abnormalities are found in two-thirds of cases of AML and three-quarters of cases of ALL. Chromosome abnormalities are important in leukaemia and lymphoma for the following reasons:

- They act as a marker of the disease, indicating remission or relapse

Some have a prognostic significance. If the prognosis is especially bad (eg Philadelphia chromosome in childhood ALL), then a high-risk treatment such as stem cell transplantation may be employed early in treatment. If the prognosis is good (eg t(8;21) in adult AML), then conventional chemotherapy may be employed without a transplantation unless the patient relapses

Some of the abnormal DNA sequences that result from chromosomal translocation can be amplified by PCR to allow the detection of very small amounts of residual leukaemia, allowing adjustment of chemotherapy regimen (see MRD above).

Many of the chromosomal abnormalities in leukaemia and lymphoma are translocations, involving the exchange of material between chromosomes (Table 9.2), eg t(9;22) involves a reciprocal translocation between chromosomes 9 and 22. Chromosome 22 comes off worse in this exchange, gaining only a small amount of extra material. The abnormally truncated short arms of this chromosome are recognisable as the Philadelphia chromosome (see Section 9.6.4).

9.6.3 The French–American–British morphological classification of acute leukaemia

Acute leukaemia is associated with a massive increase in primitive blast cells in the marrow. Some

of these cells may start differentiating along one of the myeloid pathways, and this can be assessed morphologically and is the basis of the French–American–British (FAB) classification. In ALL this has been largely supplanted by the immunophenotype. In AML there are eight morphological subtypes recognised as M0–M7. In general these are treated similarly, but two subtypes are worthy of special mention.

Table 9.2 Cytogenetic abnormalities associated with malignant haematological disease

Cytogenetic abnormality	Found in
t(9;22)	Philadelphia chromosome (Ph) in CML – see section 9.6.4
t(15;17)	Acute promyelocytic leukaemia (M3) – see section 9.6.3
t(8;21)	AML with some differentiation (M2) – better prognosis
inv 16	Inversion of the long arm of chromosome 16 in acute myelomonocytic leukaemia with bone marrow eosinophilia (AML M4Eo) – better prognosis
Hyperdiploidy	(>47 chromosomes) childhood ALL – better prognosis Burkitt's lymphoma (loss of part of the long arm of chromosome 5) Myelodysplastic syndrome (refractory anaemia) with abnormal megakaryocytes – lenalidomide-responsive
t(8;14) 5q-	
t(14;18)	Follicular NHL – found in three-quarters of cases

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; NHL, non-Hodgkin's lymphoma.

Acute promyelocytic leukaemia (AML M3)

Promyelocytic leukaemia is associated with DIC during the early phases of chemotherapy, as procoagulant granules are released from the dying abnormal promyelocytes. Heavy support with platelet transfusion and fresh frozen plasma is therefore required.

- Most leukaemic cells are abnormal hypergranular promyelocytes
- Auer rods and bundles of Auer rods (faggots) are common
- Strongly Sudan black/peroxidise-positive
- The characteristic t(15;17) chromosome abnormality involves the retinoic acid receptor gene (*RARA*)
- All-*trans*-retinoic acid (ATRA), a synthetic vitamin A analogue, can induce differentiation and apoptosis of the promyelocytes, inducing remission without chemotherapy
- Variant M3 is **hypo**granular but otherwise the same.

Acute monocytic leukaemia (AML M5)

- Morphological evidence of monocytic differentiation
- Strongly non-specific esterase-positive
- Often significant tissue infiltration of gums, liver/spleen, lymph nodes and skin
- Release of the microbicidal enzyme lysozyme from the malignant cells damages the renal tubules,

causing a potassium leak so that hypokalaemia may be found at presentation.

9.6.4 Chronic myeloid leukaemia

CML is mainly a disease of middle age, with most patients presenting with tiredness, weight loss and sweating. Splenomegaly is found in 90% of cases. If the white blood cell count (WBC) is very high (>500 × 10^9/L) then problems associated with hyperleukocytosis may be found: visual disturbance, priapism, deafness, confusion. As with other myeloproliferative diseases, gout may be a presenting symptom. Treatment with tyrosine kinase inhibitors (particularly imatininb) has revolutionised the prognosis of this disease, and reduced in particular the frequency of transformation into an acute phase (blast crisis), which is very difficult to treat.

The following are blood and marrow features of CML:

- High white cell counts (100–500 × 10^9/L)
- Massive neutrophilia with left shift (ie some myelocytes, metamyelocytes)
- Absolute basophilia and eosinophilia
- Anaemia in relation to the height of the WBC
- Platelet count may be low, normal or high
- Increased blood colony-forming cells (stem cells)
- High serum vitamin B_{12} due to production of a vitamin B_{12}-binding protein by the white cells
- *BCR-ABL*/Philadelphia chromosome, a diagnostic marker for the disease (see below)
- Marrow hyperplasia, sometimes with increased reticulin (fibrosis).

Philadelphia chromosome and *BCR-ABL*

The Philadelphia chromosome (Ph) is an abnormally truncated chromosome 22 that has lost part of its long arms, which have become attached to chromosome 9, with a much smaller portion of chromosome 9 being attached to 22. There is thus a translocation between chromosomes 9 and 22, termed t(9;22). More than 95% of cases have the Ph chromosome; the breakpoints are at the *BCR* gene on 22 and the *ABL* gene on 9. Most Ph-negative CML cases have a *BCR-ABL* translocation at the **molecular** level, although abnormal chromosome morphology is not present.

Ph is also found in the following:

- 5% of childhood ALL cases
- 25% adult ALL cases
- 1% adult AML cases.

It carries a bad prognosis if found in these acute leukaemias. The protein product of the hybrid gene has tyrosine kinase activity.

Treatment of CML

The aims of treatment are as follows:

- Clinical remission: reduction of hypercatabolic symptoms and splenomegaly

- Haematological remission: normalisation of the blood count
- Cytogenetic remission: disappearance of the Ph chromosome from marrow cells
- Molecular remission: non-detectability of the *BCR-ABL* fusion gene by PCR.

Tyrosine kinase inhibitors, of which the most used is imatinib, produce haematological remission in 90% of cases, cytogenetic remission in 60% and molecular remission in 20%. These results may improve with continued therapy.

Hydroxycarbamide does not modify the underlying cytogenetic/molecular abnormality or prevent transformation into acute crisis, but is used to normalise the blood count and shrink splenomegaly while conformation of Ph status is being obtained.

Quarterly measurements of blood *BCR-ABL* are usually performed, with excellent cytogenetic response being defined as a three log reduction in *BCR-ABL* percentage, ie <0.1% (assuming 100% at presentation). Patients who fail to respond to imatinib should be assessed for mutations of *BCR-ABL* associated with imatinib resistance and can be treated by the newer tyrosine kinase inhibitors such as dasatinib or nilotinib.

The tyrosine kinase inhibitors are going through trials for the treatment of many other malignancies.

Stem cell transplantation remains a curative option for young and fit patients who are not fully responsive to imatinib and who have a suitable donor.

9.6.5 Chronic lymphocytic leukaemia

This is the most indolent of the chronic leukaemias. Many cases are discovered as an incidental finding when blood counts are done for some other reason, such as health screening.

- The most common cause of a lymphocytosis in patients aged >60 years
- Of cases, 95% are of B-cell lineage
- Diagnosis is confirmed by immunophenotyping – the cells express B-cell markers CD19 and CD23, but paradoxically also express a T-cell antigen CD5
- The blood film shows mature-looking small lymphocytes with smear cells
- Progression is through lymphocytosis to lymphadenopathy, hepatosplenomegaly and marrow failure, although patients may skip stages and this disease may remain unchanged for years
- Increased incidence of certain antibody-mediated autoimmune diseases, such as warm autoimmune haemolytic anaemia and immune thrombocytopenia

Treatment of CLL

Many patients with CLL require no treatment, living at peace with their lymphocytosis to die of an unrelated complaint. Early antibiotic treatment of intercurrent infection is indicated because of the associated immunoglobulin deficiency, and some patients with recurrent infections may benefit from immunoglobulin administration, particularly during the winter months. Annual flu immunisation should be given.

Chemotherapy is indicated for the following:

- Patients with bulky disease or B symptoms (see under Hodgkin's lymphoma below)
- Cytopenias due to marrow infiltration
- A short lymphocyte doubling time (ie rapid progression).

If treatment is anticipated, an assessment of the *p53* (tumour-suppressor) gene on chromosome 17p of the lymphocytes should be made by fluorescent in situ hybridisation (FISH). Deletions or mutations of *p53* are associated with a worse prognosis and failure to respond to conventional chemotherapies such as chlorambucil, cyclophosphamide and fludarabine.

- **Fludarabine, cyclophophamide and rituximab** (FCR) is the most popular treatment option for fit patients who require therapy. Rituximab is a monoclonal anti-CD20 antibody. Fludarabine is highly immunosuppressive and pneumocystis prophylaxis with low-dose co-trimoxazole should accompany its use
- **Single-agent oral chlorambucil or fludarabine** may be used in less fit patients who will not tolerate the myelosupression of FCR
- **High-dose methylprednisolone** is effective at shrinking bulky disease and can be combined with rituximab
- **Alemtuzumab**, another monoclonal antibody directed against the CD56 antigen, is useful in cases with resistance to chemotherapy or demonstrated to have deletions or mutations of *p53*. It is effective at clearing marrow-based disease but less so for lymph-node disease. As the CD56 antigen is present on both T cells and B cells this treatment is very immunosuppressive and weekly monitoring for cytomegalovirus by PCR is appropriate
- **Local radiotherapy** will effectively shrink enlarged nodes causing a local problem
- **Stem cell transplantation with reduced intensity conditioning** may benefit young patients who require treatment and have a suitable donor

The antibody-mediated autoimmune disorders are treated along conventional lines when they occur.

9.6.6 Hodgkin's lymphoma

The prognosis of Hodgkin's lymphoma is related to clinical stage (Table 9.3), bulk of tumour and histopathological type.

The clinical stage may be given the letter suffix A or B, to reflect presence or absence of systemic symptoms:

- A: no 'B' symptoms
- B: B symptoms consist of significant fever (>38°C), night sweats (drenching), weight loss of >10% in the last 6 months.

Pruritis and alcohol-induced pain are not B symptoms, although they are useful indicators of relapse.

Investigation

- Many patients have neutrophilia, thrombocytosis and anaemia of chronic disease; some have an eosinophilia

- The ESR and other inflammatory markers are elevated
- Lactate dehydrogenase (LDH) is elevated and provides a useful guide to volume of disease in high-grade lymphomas; 'bulky disease' is a node mass >10 cm in diameter
- Clinical examination and CT are used to establish clinical stage; there is almost no role for staging laparotomy if suitable imaging facilities are available
- Residual masses are common after treatment and it is often difficult to decide whether or not they represent active disease. Positron emission tomography (PET) using radioactive glucose helps distinguish tissue that is metabolically active
- False-positive results may be found if the PET scan is performed within 6 weeks of completion of chemotherapy, due to healing activity within the nodes.

Table 9.3 Ann Arbor clinical staging of lymphomas

Stage 1	One involved lymph node group
Stage II	Two nodal areas on one side of the diaphragm
Stage III	Lymph nodes on both sides of the diaphragm
Stage IV	Involvement of extranodal tissues such as liver or bone marrow[a]

[a]The spleen is an honorary lymph node, ie if involved this is not necessarily stage IV.

Histological types of Hodgkin's disease

The Reed–Sternberg (RS) cell is the most useful diagnostic feature. This is a giant cell, often with twin mirror-image nuclei and prominent 'owl's eye' nucleoli. Histological typing depends on the other cells within the diseased tissue:

- Lymphocyte-predominant: there is an infiltration with reactive T lymphocytes
- Nodular sclerosing (NS): bands of fibrous tissue separate nodules of Hodgkin's tissue
- Mixed picture
- Lymphocyte depleted: no infiltrating lymphocytes.

The prognosis worsens through the histological types from lymphocyte-predominant (best) to lymphocyte-depleted (worst). With the benefit of modern immunophenotyping methodology (which uses monoclonal antibodies) many cases of Hodgkin's lymphomas that were historically classified as lymphocyte-predominant Hodgkin's disease are now recognised to be non-Hodgkin's lymphoma. More than two-thirds of cases of Hodgkin's disease are of the NS type; this category can be subdivided into grade I and grade II NS Hodgkin's lymphoma, depending on the number of RS cells and other histological features.

Treatment

Clinical stage I Hodgkin's lymphoma can be treated with radiotherapy, and more advanced stages with combination chemotherapy. The dividing line depends on national and institutional preferences. Currently the most used used chemotherapy is ABVD which contains **A**driamycin (doxorubicin), **b**leomycin, **v**inblastine and **d**acabazine.

Many relapsed patients can be salvaged with second-line chemotherapy and stem cell autografts, particularly if the relapse occurs more than 1 year after completion of initial treatment. The most popular second-line chemotherapy is ESHAP (**e**toposide, cytosine **a**rabinoside, methyl prednisolone [**h**ighdose steroid] and cis**p**latin).

9.6.7 Non-Hodgkin's lymphomas

Despite several international reclassifications of the histology, the categorisation of NHL remains in a state of flux. For clinical purposes the NHLs are divided into three groups: indolent, high grade and lymphoblastic.

Indolent NHL

- The cells are relatively mature and the disease pursues an indolent course without treatment. In many cases it is acceptable to watch and wait for symptoms or evidence of organ failure
- Local radiotherapy to involved nodal regions is effective and usually given in stage I disease (infrequent) because some patients can be cured by this
- Rituximab anti-CD20 monoclonal antibody is effective as most cases are of B-cell lineage. It is commonly given with other chemotherapy regimens for both aggressive and indolent B-cell lymphomas, and its addition usually improves the response by about 10%
- Single-agent chemotherapy (eg chlorambucil) is often used for diffuse disease
- Interferon may prolong remission duration.

High-grade NHL

- The cells are immature and the disease is rapidly progressive without treatment
- Combination chemotherapy is usual from the outset; the most used regimen is R-CHOP (**r**ituximab, **c**yclophosphamide, Adriamycin (**h**ydroxydaunorubicin), vincristine (**O**ncovin) and **p**rednisolone)
- It is usual to give four to eight (3-weekly) courses depending on the response, although bone marrow suppression may cause a delay
- Maintenance therapy with rituximab may be used
- Multi-agent, alternating and hybrid regimens may be advantageous.

Lymphoblastic NHL

- The cells of the disease are very immature and have a propensity to involve the CNS
- Treatment is similar to that of ALL, with CNS prophylaxis.

High-dose chemotherapy with stem cell rescue may salvage some younger patients with aggressive chemotherapy-responsive lymphomas.

Prognosis

Low-grade (indolent) lymphomas are readily controllable initially, but relapse usually occurs even

after many years of remission. Approximately 40% of high-grade lymphomas are cured.

9.6.8 Myeloma

In myeloma there is a clonal proliferation of plasma cells and the clinical manifestations of disease are related to substances secreted by the plasma cells as much as to the effects of marrow infiltration. **Clonality** (all cells of the disease originating from one parent plasma cell) may be confirmed by either of the following:

- The presence of paraprotein (**m**onoclonal) band on serum electrophoresis
- Immunophenotyping the increased numbers of plasma cells in the bone marrow, and demonstrating that they all express κ or λ light chains rather than a mixture of the two, which would be seen in a normal plasma cell population
- Imbalance in the ratio of κ to λ light chains in cases where these are secreted into the blood or urine (see below).

The incidence of the different types of myeloma is related to the relative numbers of molecules of the different immunoglobulins in the blood, ie because IgG is present in the highest concentration it is the most common type of myeloma, with IgA next, IgM rare and IgE/IgD very rare.

Plasma hyperviscosity syndrome may be found when plasma viscosity exceeds 4 cP (centipoise). This consists of confusion, capillary bleeding, oedema and renal impairment. The incidence of hyperviscosity syndrome relates to the size of the immunoglobulin molecule as well as its concentration. As IgM is the largest immunoglobulin molecule, this syndrome is seen relatively frequently in IgM myeloma, less frequently in IgA myeloma and is rare in IgG myeloma. However, see the comment above about the relative incidence of the different types of myeloma. Red cell transfusion should be avoided if possible in patients with plasma hyperviscosity syndrome, because it will cause a big increase in whole blood viscosity.

Investigations used in the diagnosis of myeloma:

Investigation	**Purpose**
Serum protein electrophoresis	Detect the monoclonal immunoglobulin band present in three quarters of cases
Immunoglobulin levels	Ig levels **other than** the actual paraprotein class are supressed in myeloma; all are supressed in "non secretory myeloma"
Blood count	Cytopenias due to marrow infiltration (CRAB – see above)
Bone chemistry	Hypercalcaemia. In contrast to many other causes of lytic bone disease, alkaline phosphatase is normal in the absence of fractures.
Renal function	Renal failure due to hypercalcaemia, tubular blockage by light chains, renal amyloid
Serum-free light chains	Useful when there is no intact paraprotein but other evidence of

(SFLC) in selected cases	myeloma – see BJP above
Urine Bence Jones protein	Identifies ‘‘light chain only’’ myeloma – see above BJP is not identified by conventional urine dipstick
Skeletal survey to include skull, chest, spine, pelvis, femur and any symptomatic area	Looking for lytic lesions/osteopenia; rarely a single isolated plasmacytoma Isotopic bone scans not of value in myeloma due to lack of osteoblastic (as opposed to osteoclastic) activity. MRI better, PET-CT very good but limited availability
Bone marrow aspirate and trephine	Normally <5% plasma cells, up to 20% in reactive inflammatory conditions, >20% = myeloma However, % plasma cells depends on whether a lytic lesion is hit or missed – further diagnostic confidence from morphological appearance, κ and λ staining to establish clonality (see above)

- **Cryoglobulin**: rarely the paraprotein may be a cryoglobulin, so that the protein precipitates from the plasma in the cold. This may be a cause of vasculitis. Do not confuse cryoglobulin with cold agglutinin – the latter has antibody activity against red cells, causing them to agglutinate in the cold. The antigenic target of cryoglobulin paraprotein is usually unknown
- **Bence Jones protein**: sometimes the malignant plasma cells are so defective that they cannot make a complete immunoglobulin molecule and are able to make only light chains. The latter are small enough to be filtered within the glomerulus and to appear in the urine as Bence Jones proteinuria. They may obstruct the renal tubules and contribute to the renal failure that is often found in myeloma (see Chapter 15, Nephrology). Light chains may also precipitate in the tissues as one type of (AL) amyloid. Measurement of light chains in serum is now commonly available and allows detection and progression monitoring of myeloma not associated with a serum paraprotein, in which the myeloma cells produce only light chains – ‘light chain myeloma’. Even many so-called ‘non-secretory’ myelomas can be found to have an imbalanced ratio of κ and λ light chains in their serum, pointing to a clonal proliferation of plasma cells.

Role of cytokines in myeloma

Osteoclast-activating factors stimulate the normal osteoclasts to dissolve bone, and lead to bone pain, hypercalcaemia and pathological fractures in myeloma. In other myeloma cases, interleukin-6 (IL-6) may be produced in excess by bone marrow stromal cells infected with human herpes virus 8 (HHV8).

Treatment of myeloma

Treatment is indicated for patients who have evidence of myeloma-related tissue damage – ‘CRAB’ – any of: hyper**c**alcaemia, **r**enal impairment, **a**naemia or **b**one disease. Stem cell transplantation should form part of treatment once a low bulk of disease has been achieved, although many patients will not be suitable for this procedure because of age or co-morbidities. Drugs used in patients likely to be suitable for autologous transplantation include combinations of the following:

Thalidomide or its analogue lenalidomide: the mechanism of action of thalidomide includes

- anti-angiogenesis, inhibition of tumour necrosis factor secretion and stimulation of interferon production. As its use as a sedative antiemetic in pregnancy resulted in the birth of many children with severe limb defects, there is a strict programme of prescription control to prevent use in patients who might become pregnant. Sideeffects of somnolence, peripheral neuropathy and skin rash can be troublesome. Lenalidomide causes less sedation but more myelosupression
- **Cyclophosphamide**
- **Dexamethasone**
- **Bortezomid** targets the proteasome enzyme complex within the plasma cell, encouraging apoptosis and inhibiting plasma cell adhesion. Peripheral neuropathy and thrombocytopenia are major side-effects.

Melphalan (often given with prednisolone) is a proven drug in myeloma, but it kills marrow stem cells, so is not used in patients for whom autologous stem cell recruitment is likely to be required. It is used in high doses as a conditioning regimen for autologous stem cell transplantation, when the stem cells have been safely stored.

Bisphosphonates for bone disease and hypercalcaemia

A number of bisphosphonates, such as monthly intravenous pamidronate, have an important role in the prevention of pathological fractures and the treatment of myeloma hypercalcaemia.

Prognosis in myeloma

Almost all patients with myeloma will die of their disease, except for the small minority of young, fit patients who can access allogeneic stem cell transplantation after successful disease bulk reduction.

Differentiation of myeloma from MGUS

MGUS	Myeloma
• Low level of paraprotein (<20 g/L for an IgG paraprotein)	• High level of paraprotein
• Paraprotein level remains stable over a period of observation (months or years)	• Level rises with continued observation
• Levels of other immunoglobulins are normal	• Other immunoglobulin levels depressed
• No evidence of bone, kidney or marrow involvement	• Clinical evidence of myeloma

The median 5-year survival rate is about 40%. The following factors worsen the prognosis:

- Elevated β_2-microglobulin level
- Low serum albumin
- Cytogenetic abnormalities; presence of deletions of 17p, t(4;14), t(14;16)
- High degree of plasma cell infiltration in marrow

- High level of paraprotein
- Elevated creatinine
- Low presenting haemoglobin and platelet count

Monoclonal gammopathy of undetermined significance

A common clinical problem is the differentiation between myeloma and a benign monoclonal gammopathy in patients found to have a paraprotein. Of patients with monoclonal gammopathy of undetermined significance (MGUS), 1% will develop myeloma each year. It is probable that most of these patients would eventually develop myeloma but die of other causes before this develops. MGUS does not require treatment but needs regular monitoring of paraprotein level, blood count, renal function and bone chemistry to detect the progression to myeloma.

9.6.9 Monoclonal antibodies in the treatment of haematological diseases

Monoclonal antibodies that are directed against various CD antigens on haematopoietic cells are now established in the treatment of a variety of haematological diseases (Table 9.4). In many cases these are being used on a trial basis. Such antibodies may be administered in their native state or after conjugation to cell poisons or radioactive isotopes.

9.6.10 Polycythaemia

Polycythaemia is an increase in red cell count, haematocrit and (usually) haemoglobin. Polycythaemia may divided into the following:

- True polycythaemia: an increase in red cell mass. True polycythaemia may be either primary (polycythaemia rubra vera, myeloproliferative disease) or secondary to other causes
- Relative (pseudo-)polycythaemia: a decrease in plasma volume.

Primary true polycythaemia (rubra vera)

This is one of the myeloproliferative disorders. There is uncontrolled production of red cells by the bone marrow, even though erythropoietin is switched off.

- **Clinical features**: hypertension, splenomegaly, arterial and venous thromboses, pruritis, plethoric features, peptic ulceration, gout

  Laboratory features: high red count, haemoglobin, haematocrit, whole blood viscosity and urate. The neutrophil count and platelet count are also often increased and this helps distinguish primary polycythaemia from secondary polycythaemia where these are usually normal. Of primary polycythaemia patients, 90% have a gene mutation, *JAK*-2, detectable by PCR on blood cells. This test is a useful initial screening test for new cases of polycythaemia because, if positive, it obviates the requirement to perform more complex investigations to discover the cause of a secondary polycythaemia.

Table 9.4 Monoclonal antibodies used in haematology

Antibody	Disease treated	Antibody specificity	Comments
Rituximab	B-cell non-Hodgkin's lymphoma, autoimmune disorders	CD20	In routine use
Campath	Lymphoproliferative disorders. Immunosuppression in stem cell transplantation	CD56	In routine use
Gemtuzumab	Acute myeloid leukaemia	CD33	Coupled to an anthracycline cell poison
Eculizumab	Complement-mediated thrombotic mico-angiopathies (HUS) and paroxysmal nocturnal haemoglobinuria	Complement C5	Expense limits use
Anti-D	Prevention of Rhesus D sensitisation in pregnancy	Anti-D	In trial – unlike donor-derived anti-D, no risk of infectious disease transfer

Investigation of polycythaemia

In addition to clinical history and examination, cases of *JAK-2*-negative polycythaemia will often require the following:

- Pulse oximetry
- Abdominal ultrasonography for kidneys, liver and spleen
- Plasma erythropoietin
- Renal function tests and urate
- Vitamin B_{12} (elevated in the myeloproliferative disease)
- Isotopic measurement of red cell mass/plasma volume to confirm true rather than relative polycythaemia.

Secondary true polycythaemia

This common condition is associated with increased levels of erythropoietin which are produced by either the kidney or ectopic secretion by a tumour. It is often a physiological response to hypoxia. Pathological causes of secondary true polycythaemia are given in Table 9.5. Pharmacological causes are erythropoietin doping, and use of anabolic steroids for bodybuilding and post sex-change.

Relative polycythaemia

A reduction in circulating plasma volume can be due to pyrexia, diarrhoea, vomiting and diuretic

therapy. The blood count abnormalities resolve after rehydration.

'Stress polycythaemia' refers to a relative polycythaemia found mainly in middle-aged men who have stressful occupations and a chronically reduced plasma volume of uncertain cause.

Treatment of polycythaemia

Treatment is indicated for polycythaemia because high blood viscosity leads to increased incidence of thrombosis, hypertension, stroke and atherovascular disease.

Table 9.5 Causes of secondary polycythaemia

Due to hypoxia	
Physiological	Adaption to altitude, in neonates
Congenital cyanotic heart disease	eg tetralogy of Fallot, Eisenmenger's complex
Respiratory related	COPD, smoking[a]
High-affinity haemoglobinopathies (rare)	eg haemoglobin M[b]
Due to inappropriate erythropoietin production	
From the kidney	eg pyonephrosis, renal cysts, renal artery stenosis, after renal transplantation[c]
From a tumour	eg carcinoma of the kidney, hepatoma, giant uterine fibroids, cerebellar haemangioblastoma

[a]Inhaled carbon monoxide combines irreversibly with haemoglobin, forming carboxyhaemoglobin, which is then unavailable for oxygen transport.

[b]An abnormal structure of the globin chains decreases the ability of the haemoglobin to release oxygen to hypoxic tissues (including the kidney), so more erythropoietin is produced.

[c]All these pathologies result in decreased oxygen delivery to the juxtaglomerular apparatus, by either increasing the pressure within the renal capsule or reducing the blood supply to the whole kidney.
COPD, chronic obstructive pulmonary disease.

The following are the main treatment options:

- **Venesection** to a target haematocrit: the packed cell volume is more closely related to blood viscosity than the haemoglobin. In primary polycythaemia target haematocrit is <50, in secondary polycythaemia <55, but clinical factors such as history of thrombosis need to be taken into account. Repeated venesection may result in iron-deficient red cells with a low haemoglobin content. Venesection may be conventional (as in normal blood donation) or isovolaemic (with saline replacement). The latter is used in patients with cardiovascular risk factors (eg angina or hypertension) or in those who are taking drugs that may impair physiological response to venesection (angiotensin-converting enzyme [ACE] inhibitors, β blockers)
- **Cytotoxic agents**, particularly hyroxycarbamide: this suppresses erythropoiesis and causes a macrocytosis that is not related to vitamin B_{12} or folate deficiency. Unlike the alkylating agents (eg busulphan, chlorambucil), it does not appear to be associated with secondary leukaemia

- **Aspirin and anticoagulants**: if the patient has presented with thrombosis.

9.6.11 Thrombocytosis

This may be primary (essential) thrombocythaemia or a secondary thrombocytosis. Most cases where the platelet count is over 1000 × 10^9/L are due to essential thrombocythaemia unless there is a clinically obvious secondary cause.

Causes of secondary (reactive) thrombocytosis

- Bleeding
- Infection
- Trauma
- Thrombosis
- Infarction
- Iron deficiency (even if not due to bleeding)
- Hyposplenism

Primary thrombocythaemia

A common problem is the distinction between primary thrombocythaemia and a secondary thrombocytosis. There may be markers of a myeloproliferative disorder (polycythaemia, splenomegaly, basophilia, increased marrow reticulin, cytogenetic abnormality or hyposplenism caused by multiple splenic infarcts). The patient's previous blood count records may show a normal platelet count before an event such as surgery/infection that triggered a thrombocytosis. Elevated inflammatory markers suggest a reactive cause, whereas these are often normal in essential thrombocythaemia. Measurement of ferritin may confirm iron deficiency, which should be treated before presuming essential thrombocythaemia. Treatment most commonly employs hydroxycarbamide. As this is potentially teratogenic, pregnant patients or those who may become pregnant are treated with interferon. Aspirin and anticoagulants may be required for thrombosis treatment.

Table 9.6 Classification of the myelodysplastic syndromes (MDSs)

MDSs	Special features
Refractory anaemia	Dysplastic morphological features seen (see text) but difficult to diagnose with certainty in early stages – other cause of anaemia need excluding
Refractory anaemia with excess of blasts (RAEB)	As above plus increased numbers of blast cells in the marrow (5–20%; normal <5%)
Refractory anaemia with excess of blasts in transformation (RAEB-t)	As above but 20–30% blasts in marrow – more than this is acute myeloid leukaemia

Chronic myelomonocytic leukaemia (do not confuse with the myeloproliferative disorder chronic myeloid leukaemia, which is associated with granulocytosis rather than monocytosis)	Monocytosis in blood and marrow
Primary acquired sideroblastic anaemia	Ring sideroblasts in marrow (see section 9.2.2)

9.6.12 Myelodysplasias (myelodysplastic syndromes)

This group of haematological malignancies is being seen with increasing frequency as the mean age of the population rises and screening blood counts are performed more often. As a group (Table 9.6), they hang together less well than other haematological malignancies but they do have the following features in common:

- More common in elderly people, but no age is exempt
- Cytopenias: normocytic or macrocytic anaemia most common, also neutropenia and thrombocytopenia, or combinations of these
- Dysplastic changes seen in blood and bone marrow. These include hypogranular neutrophils, abnormal neutrophil nuclear lobulation and changes in red cell marrow precursors mimicking megaloblastic change
- Monocytosis: this may be found in all the myelodysplastic disorders but is most marked (>1 × 10^9/L) in chronic myelomonocytic leukaemia
- A preleukaemic condition – about a third of cases will transform into acute myeloid leukaemia. Increased numbers of blast cells may be found in the marrow heralding this change
- Cytogentic abnormalities, as seen in AML, may be seen in MDS. A rare variant of MDS with a relatively good prognosis is 5q– syndrome, found mainly in women with a normal or high platelet count, increased number of dysplastic megakaryocytes in the marrow and deletion of part of the long arm of chromosome 5. This subtype of MDS responds well to thalidomide/lenolidamide therapy
- Mainstay of treatment for most patients is support: transfusion/erythropoietin for anaemia, antibiotics for infection, platelet transfusion for bleeding.

9.6.13 Stem cell transplantation

Haematopoietic stem cells for transplantation are now routinely obtained from donors by leukopheresis after treatment with G-CSF and/or other cytokines (see below), obviating the requirement for the general anaesthesia needed for marrow harvesting. Stem cell transplants work by using a strong (myeloablative) treatment such as high-dose cyclophosphamide with total body irradiation to wipe out residual malignant disease. In addition, the donor's transplanted immune system may recognise malignant cells and destroy them – graft-versus-leukaemia (GVL) effect. The downside of GVL is that the donor's immunity may attack the recipient's tissues, particularly the liver, skin, intestine and haematopoietic cells, causing graft-versus-host disease (GVHD). In general, the worse the GVHD the better the GVL effect.

Peripheral blood stem cells

In the rebound after marrow recovery from chemotherapy, stem cells appear in the peripheral blood. They can be made to appear in larger numbers by using growth factors such as G-CSF. Plerixafor binds to the CXCR4 receptor on stem cells, preventing their attachment to bone marrow and increasing the number that can be harvested by leukopheresis on a cell separator and frozen. Peripheral blood stem cells (PBSCs) are further down the differentiation pathway to mature cells than marrow stem cells, so their use is associated with quicker haematological recovery than seen when bone marrow is used. A slight disadvantage is the inadvertent harvesting of more donor T lymphocytes with the PBSCs, theoretically increasing the incidence of GVHD. The types of donor and stem cells used are shown in Table 9.7.

The following are conditions in which a stem cell allograft is a useful treatment if a matched sibling is available and the recipient is fit enough for the procedure:

- **Acute myeloid leukaemia**: in first or subsequent remission. However, if good prognosis cytogenetics are present (see section 9.6.2) and the patient is in remission after the first course of chemotherapy, then a stem cell transplantation is not performed. Also, in elderly patients or those with significant co-morbidities, the risks may outweigh the benefits and conventional chemotherapy may be a more prudent course
- **Acute lymphoblastic leukaemia**: in second or later remissions, unless adverse prognostic features (such as age beyond childhood or adverse cytogenetics) are present, in which case bone marrow transplantation should be performed at first remission
- **Chronic myeloid leukaemia**: in the first chronic phase, if imatinib or an alternative tyrosine kinase inhibitor does not induce a major cytogenetic response and a donor is available with a recipient fit enough for the procedure

Table 9.7 Types of donor and stem cells used

Type	Advantages	Disadvantages
Autologous	Donor available!	Poor GVL; possibility of residual bone marrow disease being harvested and returned to patient
Syngeneic (identical twin)	Full-house HLA match – no GVHD	Reduced GVL effect
HLA-matched sibling	Controllable GVHD but some GVL	GVHD unpredictable. Only one in four of our siblings will be an HLA match
Matched volunteer, unrelated donor	Available if no family match and HLA type is not rare	GVHD unpredictable but more than HLA-matched sibling

GVHD, graft-versus-host disease; GVL, graft-versus-leukaemia.

Other indications: stem cell transplantation for thalassaemia major and sickle cell disease

- remains controversial
- **Others**: storage diseases, some lymphomas responsive to second-line chemotherapy.

9.7 COAGULATION

9.7.1 The coagulation mechanism and detection of coagulation factor deficiencies

A representation of the coagulation cascades is shown in Figure 9.2. These consist of an **extrinsic pathway** (in which tissue thromboplastin plays an important part, and the physiologically important one), and an **intrinsic pathway** (intrinsic to the blood itself – what happens when the blood clots away from the body in a test tube). These two pathways share a final **common pathway** resulting in the production of a fibrin clot.

The system can be divided into boxes, each box representing one of the following three basic screening tests of coagulation:

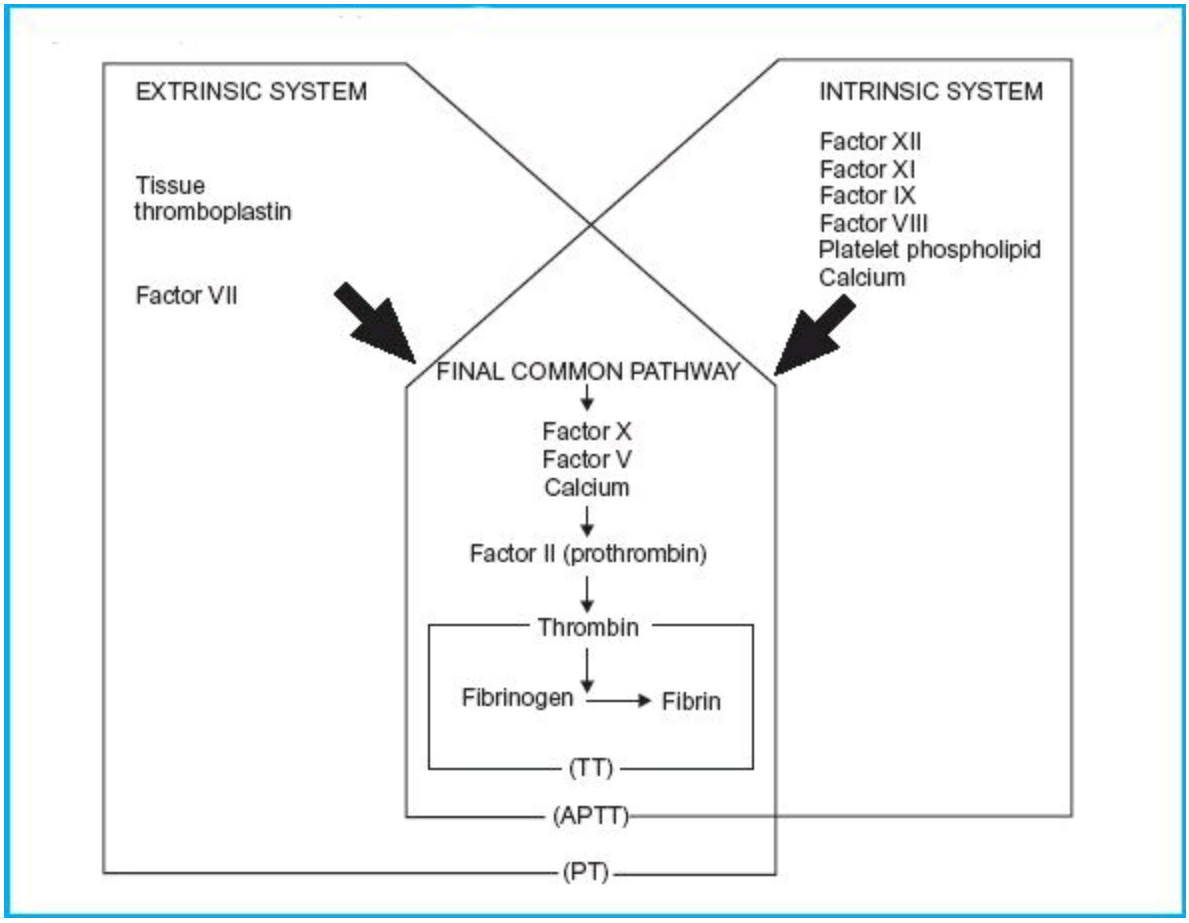
- **Prothrombin time** (PT) measures the extrinsic system and final common pathway. The international normalised (prothrombin) ratio (INR) is derived from the PT and measures the same thing
- **Activated partial thromboplastin time** (APTT) measures the intrinsic system and final common pathway
- **Thrombin time (TT)** measures the final part of the final common pathway. It is prolonged by lack of fibrinogen to convert to fibrin, and by inhibitors of this conversion, including heparin and high levels of fibrin degradation products.

Figure 9.2 shows which factors should be assayed after finding a prolonged coagulation time, eg an isolated prolonged APTT should prompt assay of factors XII, XI, IX and VIII. If the clinical picture is suggestive of haemophilia, then starting with factors VIII and IX may save time.

Coagulation inhibitors

If one of these screening tests of coagulation is significantly prolonged, then it should be repeated using a mixture of 50% normal plasma and 50% patient plasma. If the cause of the prolonged time is factor deficiency, the abnormal time should correct more than halfway back to the control value. If it does not, this suggests the presence of a coagulation inhibitor such as the lupus anticoagulant, antibodies against coagulation factors (eg anti-factor VIII antibodies developing in someone with haemophilia) or heparin.

Figure 9.2 Representation of the coagulation cascade



9.7.2 Haemophilias

These diseases are characterised by deep muscular haematomas and haemarthroses with prolonged bleeding after trauma or surgery. There is a deficiency of factor VIII (classic haemophilia) or factor IX (Christmas disease). The disease is classified as severe if the factor level is <1% of normal (<1 unit/dL). Inheritance is sex-linked, although a third of cases have no family history and are due to a spontaneous mutation. Carriers may be detected because they have half the amount of coagulation factor measured by a coagulation assay than they have measured by an immunological assay. Also, restriction fragment polymorphisms (RFLPs) can track the affected chromosome. Diagnosis is by prolonged APTT (but normal PT and TT), which corrects with normal plasma. Factor VIII or IX levels are low. The range of treatments is shown in Table 9.8. Complications of treatment include hepatitis, HIV, development of antibodies against the administered coagulation factors and opiate addiction.

9.7.3 Von Willebrand's disease

This is the most common inherited coagulopathy in the UK, with up to 1% of the population having the disorder on unselected testing. Most of these cases are mild. Von Willebrand's factor (vWF) is coded for on chromosome 12 – hence inheritance is autosomal dominant. It is caused by a quantitative or qualitative deficiency of vWF production. The vWF is made in endothelial cells and forms variablesized polymers in plasma.

Table 9.8 Treatment of haemophilia

Treatment	Rationale
Virally inactivated coagulation factor concentrate	Should be given early in the course of a bleed, ideally home treatment
DDAVP (a synthetic antidiuretic hormone analogue)	Releases factor VIII from storage sites in endothelial cells so can temporarily boost blood levels in mild haemophilia A (not effective in Christmas disease)
Fibrinolytic inhibitors (eg tranexamic acid)	Delay dissolution of fibrin clot; useful for bleeding wounds but avoid in haemarthrosis, muscle haematomas and urinary bleeding as may lead to resolution by local fibrosis
Ancillary treatments (part of 'total haemophilia care')	Physiotherapy, hydrotherapy, immunisation against hepatitis B, dental and orthopaedic advice

The vWF acts as a protective carrier for factor VIII in the circulation and is also responsible for gluing the platelets to exposed vascular subendothelium. Hence, the factor VIII level in vWD is often reduced, but not to the very low levels seen in haemophilia A. Also, in contrast to the haemophilias, the disease manifests as a platelet-type bleeding disorder with bruising, superficial purpura, menorrhagia, nosebleeds, and bleeding from cuts and mucous membranes.

Diagnosis

- Low factor VIIIc (c for 'clotting' activity – a functional assay)
- Low vWFAg (von Willebrand's factor antigen measured in an immunological assay)
- Low vWF:RCo (ristocetin cofactor) – a functional assay of vWF
- Prolonged in vitro bleeding time (PFA100 test).

Ristocetin is an antibiotic that clumps platelets in normal plasma but fails to clump them in vWF-deficient plasma, and this is the basis for a functional assay of vF:, the vWF:RCo ratio. The levels of vWF in normal persons vary according to blood group, group O individuals having less, and this needs to be taken into account when interpreting tests. vWD may divided into subtypes depending on whether the deficiency is quantitative (type I) or qualitative (type II) and on the size of vWF multimers present.

Treatment is with DDAVP if mild, and with intermediate purity factor VIII concentrates, which also contain vWF, if the bleeding or the disease is more severe.

9.7.4 Disseminated intravascular coagulation

This disorder is caused by the release into the circulation of tissue factor released from dying cells and activated leukocytes that promote coagulation. There is massive activation of coagulation factors

and platelets, with laying down of fibrin. This fibrin clot is immediately removed because the fibrinolytic system is also put into overdrive, worsening the haemorrhagic tendency. Treatment is to remove the cause, if possible, and transfuse with red cells, platelets, FFP and cryoprecipitate.

Features and causes of disseminated intravascular coagulation

- **Laboratory features of DIC**
  - Prolongation of all coagulation times (prothrombin, APTT and thrombin)
  - Activation of the fibrinolytic system leading to low fibrinogen and high levels of fibrin degradation products
  - Consumption thrombocytopenia
- **Obstetric causes**
  - Retroplacental haemorrhage
  - Retained dead fetus
  - Amniotic fluid embolus
  - Severe pre-eclampsia
- **Other causes**
  - Crush injury
  - Septicaemia, particularly with Gramnegative and some Gram-positive including toxin-producing *Staph. aureus* and *Clostridia*
  - Haemolytic blood transfusion reaction
  - Malignancy, particularly associated with necrosis of tumour cells

9.7.5 Vitamin K-dependent coagulation factors (II, VII, IX and X)

Vitamin K is a fat-soluble vitamin essential for the carboxylation of inactive coagulation factors into their active functional form. These coagulation factors are manufactured in the liver, so levels are low in liver disease, obstructive jaundice and when there is fat malabsorption (loss of vitamin K). Levels are also low in the neonate due to liver immaturity – this can lead to haemorrhagic disease of the newborn (not haemolytic disease!), particularly when breastfed. These coagulation factors are also reduced by warfarin anticoagulation. Deficiency causes a prolonged PT and APTT.

9.7.6 Thrombocytopenia

There is overcapacity in haemostasis, including the platelet count (Table 9.9) (this assumes normal platelet function).

Young platelets tend to be relatively large and efficient compared with old platelets. Hence bleeding at a given platelet count is more severe in **underproduction** thrombocytopenia than in **peripheral destruction** thrombocytopenia. In the latter the bone marrow produces more young platelets and if the

platelet count is <50 × 10^9/L, an elevated **reticulated** platelet count is a useful marker of peripheral destruction, diminishing the need to examine the number of megakaryocytes in the marrow.

When thrombocytopenia is associated with other blood count abnormalities, there is a wide differential diagnosis, including most of the haematological malignancies described in Section 9.6.

When it is associated with abnormalities of coagulation, the differential diagnosis includes DIC (see section 9.7.4).

Isolated thrombocytopenia is usually the result of increased platelet destruction.

Causes of isolated thrombocytopenia

- **Artefactual**: clot in the sample or platelet clumping. This can be confirmed by examination of the sample and the blood film. When platelets are clumped, sometimes a more accurate count can be obtained by using citrateor heparin-anticoagulated blood sample tubes, or performing an 'instant' blood count on a blood counter located close to the patient
- **Idiopathic or immune thrombocytopenia**: very common – see below
- **Drugs**: heparin, abciximab, quinine, valproate, sulfonamides, dopa, interferons
- **Hypersplenism**: the spleen contains about a third of the circulating platelets, and if the spleen is enlarged from any cause this may be associated with thrombocytopenia (see Section 9.9.1 for the causes of splenomegaly)
- **Gestational thrombocytopenia**: the platelet count is usually >70 × 10^9/L, and the patient is clinically well with no symptoms of preeclampsia or abnormality of liver function. HELLP syndrome (**h**aemolysis with **e**levated **l**iver enzymes and **l**ow **p**latelet count) manifests as haemolytic anaemia with liver function abnormality and thrombocytopenia, is associated with pre-eclampsia and should be included in the differential diagnosis.

Table 9.9 Clinical risks of different degrees of thrombocytopenia

Platelet count × 10^9/L	Clinical effect
140	Lower limit of normal range
100	Normal haemostasis, including surgery
50	Normal haemostasis unless challenged
20	Minor risk of bleeding
<10	Significant risk of bleeding

Immune thrombocytopenia

This is the most common cause of an isolated thrombocytopenia and is an autoimmune disease. However, obtaining sufficient platelets to prove this is difficult in the context of thrombocytopenia, so a diagnosis immune thrombocytopenia (ITP) is often made by the absence of other causes of thrombocytopenia. When the platelet count is >100 × 10^9/L, without evidence of other disease, it is reasonable not to perform marrow examination but to observe the platelet count at follow-up, (with

decreasing frequency if it is stable). The following medical disorders are associated with ITP and need to be excluded:

- SLE
- autoimmune haemolytic anaemia (with ITP is Evans' syndrome)
- viral infection: HIV, Epstein–Barr virus (EBV), hepatitis C
- antiphospholipid syndrome (Hughes' syndrome)
- Helicobacter gastritis.

When the platelet count is $<20 \times 10^9$/L or associated with significant bleeding, treatment is indicated and it is usual to examine the bone marrow to confirm normal or increased numbers of megakaryocytes. Sometimes, however, the immune reaction is directed against megakaryocytes, so marrow examination is important for excluding other haematological diseases as the cause of thrombocytopenia.

Initial treatment is usually with prednisolone 1 mg/kg per day. The dose may be reduced to decrease side-effects when the platelet count is haemostatic ($>20 \times 10^9$/L). Gastroprotection in the form of an H_2-receptor antagonist is usual and aspirin/NSAIDs should obviously be avoided. Sometimes steroids need to be continued for up to 3 months for maximum effect. The addition of azathioprine may have a useful steroid-sparing action.

For steroid-resistant cases, other treatments are as follows:

- **Splenectomy**: about two-thirds of patients benefit from splenectomy, because either this enables discontinuation of steroid or lower doses are then required to achieve a haemostatic platelet count (see section 9.9 for post-splenectomy precautions)
- **High-dose intravenous immunoglobulin** will improve the platelet count in a few days, but its effects are often short-lived; it is indicated before surgery and for emergency treatment
- **Intravenous anti-D**: applicable to only the 80% of patients who are Rhesus D positive. The administered anti-D coats their red cells, which are preferentially destroyed by the spleen and reticuloendothelial system, sparing the platelets. A drop of 10–20 g/L in the haemoglobin level is to be anticipated, and note that anti-D seems to be ineffective in splenectomised patients
- **Rituximab**: this anti-CD20 antibody has an emerging role in the treatment of refractory cases.

9.8 THROMBOSIS

There are many well-recognised risk factors for venous thromboembolism and in these situations it may be appropriate to take prophylactic measures.

General clinical risk factors for venous thrombosis

- Previous thrombosis
- Increasing age
- Immobility

- Obesity
- Major abdominal and hip operations
- Oestrogen/contraceptive pill
- After a myocardial infarction or stroke
- Nephrotic syndrome
- Smoking
- Varicose veins
- Family history of thrombosis
- Cancer
- Trauma/surgery on the lower limbs
- Pregnancy and the puerperium
- Diabetic hyperosmolar state
- Paroxysmal nocturnal haemoglobinuria
- Thrombophilia (see Section 9.8.3)

Therapeutic INR ranges for warfarin anticoagulation

The necessary degree of anticoagulation will vary depending on the indication (Table 9.10) and whether the causes (eg bed rest, fracture) can be removed.

Table 9.10 Therapeutic INR ranges for warfarin anticoagulation

Indication	INR range
Atrial fibrillation, treatment of DVT/PE, systemic embolism, post-MI, transient ischaemic attacks	2.0–3.0
Recurrent DVT/PE, arterial disease including MI, mechanical prosthetic valves	3.0–4.5

DVT, deep vein thrombosis; INR, international normalised ratio; MI, myocardial infarction; PE, pulmonary embolism.

9.8.1 Venous thrombo-embolism (VTE) prophylaxis

In 2005 it was estimated that 25,000 patients per annum suffered hospital acquired VTE. All adults admitted to hospital should have VTE risk assessment on admission.

Risk factors for VTE in medical patients

- Critical care admission
- Age >60 years
- Likely reduced mobility for 3 days or more
- Obesity BMI >30 kg/m^2

- Congenital or acquired thrombophilia (see below)
- Oestrogen/contraceptive pill
- After a myocardial infarction or stroke
- Significant medical illness – eg nephrotic syndrome, heart failure, myocardial infarction, diabetic hyperosmolar state
- Cancer diagnosis
- Varicose veins with phlebitis, or history of VTE
- pregnancy and the puerperium

Such patients should be offered pharmacological VTE prophylaxis, most commonly with daily subcutaneous LMW heparin (see above) or fondaparinux, unless risk factors for bleeding are present (see below).

Risk factors for bleeding with anticoagulant prophylaxis in medical patients

- Congenital or acquired bleeding disorder eg von Willebrand disease, synthetic liver disease
- Lumbar puncture due within 12 hours, or performed less than 4 hours ago
- Acute stroke
- Thrombocytopenia, platelets $<75 \times 10^9$/L
- Uncontrolled hypertension

Non-pharmacological VTE prevention measures, applicable to all patients, include encouraging mobilisation, avoiding dehydration and physical methods to increase venous return from the legs eg antiembolism stockings, calf compression devices.

A full consideration of hospital VTE prophylaxis can be found on the NICE website, or in local hospital guidelines.

9.8.2 Thrombosis and the pill

Administration of oestrogen-containing pills:

- Increases fibrinogen and vitamin K-dependent clotting factors
- Decreases antithrombin levels
- Gives a four times greater risk of thromboembolism.

The risk of thromboembolism is increased by eight times if factor V Leiden is present; it is important to screen all women with a history of thrombosis if starting on the combined oral contraceptive pill.

Hormone replacement therapy is also associated with a small risk of thrombosis and women with a history of thromboembolism should be screened for thrombophilia.

9.8.3 Thrombophilia

Congenital thrombophilia

The blood contains clotting factors that promote the formation of thrombus when activated. This system is in balance with a group of natural anticoagulants that inhibit clot formation:

- Antithrombin: the most common inherited natural anticoagulant deficiency
- Protein C: vitamin K-dependent natural anticoagulant
- Protein S.

A congenital deficiency of these factors results in a tendency to thrombosis, so they are measured when testing for inherited thrombophilias

Normally, activated factor V is inactivated by the anticoagulant protein C. Approximately 3–5% of Europeans have an abnormal structure to their factor V, caused by a single point mutation in the factor V gene. This means that protein cannot bind to and inactivate it. This abnormal factor V is called factor V Leiden after its place of discovery; it is found in 30% of patients with recurrent thrombosis. Screening for factor V Leiden may be done by PCR on blood.

The following are other causes of inherited thrombophilia:

- Prothrombin gene mutation: similar to factor V Leiden, can be detected by PCR
- Dysfibrinogenaemia
- Fibrinolytic defects.

Acquired thrombophilias

- Polycythaemia and essential thrombocythaemia
- Lupus anticoagulant/antiphospholipid antibodies.

Antiphospholipid antibodies include lupus anticoagulant, anticardiopin antibodies and anti-beta 2 glycoprotein 1 antibodies. They have a strong association with each other and with immune thrombocytopenia. Paradoxically, lupus anticoagulant, causing venous thrombosis, is detected by a prolonged coagulation test such as the APTT, or the more sensitive DRVVT (**d**ilute **R**ussell **v**iper **v**enom **t**ime). The coagulation times are prolonged because antiphospholipid antibodies neutralise phospholipids that are essential for the coagulation reaction. Although it may be found in patients with SLE, most patients with lupus anticoagulant do not have SLE. The disorder may present with recurrent venous thromboembolism or recurrent miscarriages. (See also Chapter 12, Maternal Medicine.)

Strict criteria for the diagnosis of lupus anticoagulant require confirmation by a repeat test 12 weeks after the first (some lupus anticoagulants are a temporary phenomenon associated with intercurrent illness). The prolonged DRVVT should fail to correct with the addition of normal plasma, but should correct when an excess of phospholipid is added to the plasma.

9.8.4 Therapeutic fibrinolysis

Therapeutic fibrinolysis

- **Action**
  - Conversion of plasminogen to plasmin which dissolves fibrin to fibrin degradation products
- **Indications**
  - Early stages of myocardial infarction, young patients with proximal deep venous thrombosis eg iliofemoral, survivors of massive pulmonary embolism, peripheral arterial thrombosis
- **Drugs**
  - Sreptokinase, urokinase, tissue plasminogen activator (tPA), anisoylated plasminogen streptokinase activator (APSAC)
- **Unwanted effects**
  - Bleeding
- **Reversal**
  - Administration of tranexamic acid, cryoprecipitate

9.8.5 Low-molecular-weight heparin

Conventional heparin is a mixture of different-sized polymers. Low-molecular-weight fractions can be separated by various chemical and physical methods. Low-molecular-weight heparin (LMWH) has a molecular weight of 5000 Da, compared with average 15 000 Da for unfractionated heparin. LMWH has strong anti-factor Xa and relatively weak antithrombin action compared with conventional heparin. It is claimed that this gives it more antithrombotic effect with less risk of bleeding. It certainly means that no significant prolongation of the APTT is found, so this test is not used for monitoring therapy. Measurement of its anti-factor Xa effect is possible, although this is necessary only if prolonged treatment is required.

Advantages of LMWH

- Long half-life – once or at most twice daily administration
- Laboratory assays are not required for short-term administration
- Less heparin-induced thrombocytopenia and osteopenia than conventional heparin.

Disadvantages of LMWH

- No easy antidote for reversal in the event of bleeding
- Expensive, but allows outpatient-based antithrombotic therapy
- Different doses for different brands
- When given for more than a few weeks (eg in pregnancy) requires (relatively) complicated anti-factor Xa assay for monitoring.

9.8.6 Direct-acting oral anticoagulants

Unlike warfarin, which works through the inhibition of hepatic synthesis of active coagulation factors, these new oral anticoagulants directly inhibit coagulation factors, eg dabigatran inhibits thrombin, rivaroxaban and apixaban inhibit Xa.

Advantages in comparison to warfarin

- Rapid action, peak concentration in circa 3 hours
- Rapid elimination in circa 12 hours
- Much fewer drug and food interactions
- No requirement for coagulation test monitoring. Although the Xa inhibitors prolong the prothrombin time, and thrombin inhibitors prolong the thrombin time and APTT, the relationship between clotting time and clinical effect/bleeding risk is too approximate and assay-dependent for routine use. For dabigatran, measuring drug level may reduce bleeding episodes in the elderly
- Efficacy equivalent or superior to warfarin; in the context of AF, less intracerebral bleeding but more GI bleeds with higher dose of dabigatran.

Disadvantages in comparison to warfarin

- Expensive – usually restricted to warfarin failures in NHS practice
- No universally accepted antidote in the event of bleeding – but levels drop in hours and prothrombin complex concentrate has been used
- Dose adjustment required in renal failure
- Shorter half life results in rapid decline in anticoagulation if doses are missed and requires multiple daily dosing.

9.9 THE SPLEEN

9.9.1 Causes of spenomegaly

- **Myeloproliferative disorders**
  - Myelofibrosis
  - Chronic myeloid leukaemia
  - Primary polycythaemia
  - Essential thrombocythaemia (splenic atrophy also common)
- **Portal hypertension**
  - Cirrhosis
  - Congestive cardiac failure
- **Bacterial infections**
  - Typhoid, brucella, TB, subacute bacterial endocarditis

- **Viral infections**
  - Glandular fever, hepatitis
- **Collagen diseases**
- **Chronic haemolytic anaemias**
  - Warm autoimmune haemolytic anaemia
  - Cold haemagglutinin disease
- **Lymphoproliferative disorders**
  - Most lymphomas
  - Chronic lymphocytic leukaemia
  - Hairy cell leukaemia
- **Tropical**
  - For example, malaria, kala-azar
- **Storage diseases**

9.9.2 Splenectomy

Often performed because of traumatic injury or haematological disease, this operation results in a characteristic blood film appearance and a well-recognised predisposition to sudden overwhelming infection with capsulated organisms such as *Pneumococcus* or *Haemophilus* spp.

Clinical indications for splenectomy

- **Traumatic rupture**: although surgeons may preserve splenic function by surgical repair of capsular tears, omental patches and sometimes implantation of some splenic tissue in the retroperitoneum
- **Autoimmune destruction of blood cells**: immune thrombocytopenia and warm autoimmune haemolytic anaemia after failure of steroid therapy
- **Haematological malignancies**: low-grade lymphoproliferative disorders associated with painful splenomegaly, hypersplenism and not much disease outside the spleen. Also sometimes performed in the myeloproliferative disorders, particularly in myelofibrosis when an enlarged or painful spleen is destroying more blood cells than it is producing
- **Congenital haemolytic anaemias**: particularly the red cell membrane disorders such as spherocytosis and elliptocytosis and some cases of hypersplenism in β-thalassaemia major.

Haematological and immune changes after splenectomy

- Howell–Jolly bodies: nuclear remnants in the red cells – the spleen is responsible for removing particulate material from red cell cytoplasm – pitting function
- Enhanced neutrophilia in response to infection
- Target cells, thrombocytosis, occasional spherocytes and increased red cell aniso- and poikilocytosis

- Decreased IgM levels
- Mild polyclonal T-cell lymphocytosis.

9.9.3 Causes of hyposplenism

- Splenectomy (see Section 9.9.2)
- Sickle cell disease
- Coeliac disease
- Myeloproliferative diseases associated with splenic infarcts, particularly essential thrombocythaemia
- Congenital asplenism (rare)

Infection prophylaxis in hyposplenic patients

- Pneumococcal vaccine
- *Haemophilus influenzae* vaccine (Hib)
- Meningitis C vaccine
- Prophylactic lifelong oral phenoxymethylpenicillin twice daily (or erythromycin if patient is penicillin-allergic)
- Meticulous anti-malarial prophylaxis, including insect repellant and mosquito net
- A warning card for the patient to carry is available from the Department of Health.

The above applies to hyposplenic patients as well as previously splenectomised patients recognised by the film comment 'Howell–Jolly bodies' on routine blood count. If penicillin prophylaxis is declined, then they should keep a supply of amoxicillin at home to take at the first sign of infection.

9.10 BLOOD TRANSFUSION

9.10.1 Better blood transfusion

The British government's 'Better blood transfusion' initiatives have promoted the importance of reduced blood product consumption in several ways:

- Routine pre-admission assessment including blood count and preoperative correction of haematinic deficiencies before elective surgery
- Establishment of maximum blood order schedules (MBOS) with agreed quantities of cross-matched blood being provided for specified operations. In general, if the chance of blood being needed for an elective operation is <30%, then only a 'group and screen' need be performed. If the screen for atypical red cell antibodies is negative, then there should be no problem obtaining compatible blood in an emergency
- Increased use of 'group and screen' with accelerated compatibility testing rather than the issuing of cross-matched blood for operations

- Adoption of lower haemoglobin thresholds for post-operative transfusion. There is usually no indication for red cell transfusion if the haemoglobin is >100 g/L. Transfusion is usually given if the haemoglobin is <70 g/L, in otherwise fit patients, or Hb <90 g/L in patients with cardiovascular disease or aged >70 years
- Intraoperative and post-operative red cell salvage is encouraged
- Use of erythropoietin in diseases associated with anaemia such as myelodysplasia, myeloma, myelofibrosis and advanced chronic kidney disease. Measurement of serum erythropoietin level may provide a guide to likely response – <100 IU/L likely to respond, >500 unlikely to respond, 100–500 discuss a trial of erythropoietin.

9.10.2 Transfusion-transmitted infection

Periodically, transfusion-transmitted infections hit the headlines, resulting in patients' reluctance to accept blood products. The infection of most concern was variant Creuzfeldt–Jakob disease (vCJD) or 'mad cow' disease, the prion protein of which is not destroyed by conventional heat-detergent viral inactivation procedures. A screening test for carriers of this disease is being developed, although it is feared that introduction of such a test may shrink the donor pool, because potential donors may not wish to have a test for a disease for which no treatment is currently available.

All cellular blood products issued by the UK blood service are leukodepleted at source. Leukodepletion by filtration has the following advantages:

- Reduced possibility of vCJD transmission
- Reduced incidence of non-haemolytic febrile transfusion reactions
- Decreased transmission of cytomegalovirus (CMV) to CMV-negative blood transfusion recipients
- Reduced incidence of third-party GVHD, which is usually fatal and caused by the transfusion of immunocompetent lymphocytes to immunodeficient recipients.

Testing donations for transfusion-transmitted infection in the UK

- HIV antibodies: there remains a very small risk of viral transmission from infected donors, when they donate in the 8-week window after HIV infection and before antibody production
- Hepatitis B surface antigen
- Hepatitis C nucleic acid (antigen)
- Syphilis screen
- Human T-lymphotrophic virus (HTLV) antibody
- CMV antibody (some donations only) to ensure enough CMV-negative products for transfusion to premature neonates and immunosuppressed patients who would be at risk of transfusion-transmitted CMV.

9.10.3 Platelet transfusion in marrow failure

Platelet transfusion is usually administered when the platelet count is $<10 \times 10^9$/L in cases of

thrombocytopenia due to marrow failure after chemotherapy or radiotherapy. The platelet transfusion threshold may be reduced as a result of clinical criteria such as bleeding, fever, splenomegaly or planned surgical procedures.

- Platelet transfusions should not be used in conditions with peripheral platelet destruction (eg immune thrombocytopenia), except in cases of haemorrhagic emergency. Efforts should be directed at reducing platelet destruction with immunosuppression
- Platelet transfusion is contraindicated in TTP and HUS because it will contribute to the microvascular occlusion in the brain and kidneys that is associated with these conditions
- Platelet concentrates are obtained by the thrombocytopheresis of donors who have a high platelet count on the cell separator. One adult dose of platelets contains more than 2×10^{11} platelets
- Less commonly, the unit of platelets is prepared by pooling the platelets extracted from 4–6 units of fresh blood.

Platelet refractoriness is defined as an increment of platelet count $<20 \times 10^9$/L 1 hour after transfusion of an adult dose. This may be due to the following:

- Non-immune consumption (eg bleeding, DIC, hypersplenism)
- Immune consumption due to HLA antibodies directed against class I HLA antigens present on platelets (90% of cases). Give HLA-matched, cell-separated platelets and consider plateletpheresis of relatives
- Immune platelet-specific antibodies (10% of cases): use double doses of random platelets.

9.10.4 Indications for the transfusion of fresh frozen plasma

- Correction of multiple coagulation factor deficits as in DIC or after massive transfusion
- Correction of single coagulation factor deficiency where a virus-inactivated concentrate is not available
- Emergency correction of warfarin over-anticoagulation where prothrombin complex concentrate is not available and intravenous vitamin K would be too slow (a few hours)
- Treatment of TTP or HUS with or without large-volume plasma exchange.

The formula replacement of coagulation factors by FFP after large-volume blood transfusion is no longer recommended – it is better to perform a coagulation screen, and give FFP as required.

Chapter 10
Immunology

CONTENTS

Immunology

10.1 INTRODUCTION

The immune system must be credited as one of the most remarkable feats of engineering in the human body.

The ability to provide a robust defence against the enormous array of pathogens to which we are exposed during our lifespan, combined with a reassuringly low incidence of serious mistakes, represents a truly phenomenal achievement.

What makes immunology particularly fascinating is that, in recent years, there has been a vast increase in our understanding not only of immunity but also our ability to manipulate it to our advantage in clinical practice. In fact, one might argue that we have learnt to run before we can walk in respect to this latter point!

10.1.1 An overview

The primary function of the immune system is to provide host defence against invading pathogens.

The system can be broken down into two key components:

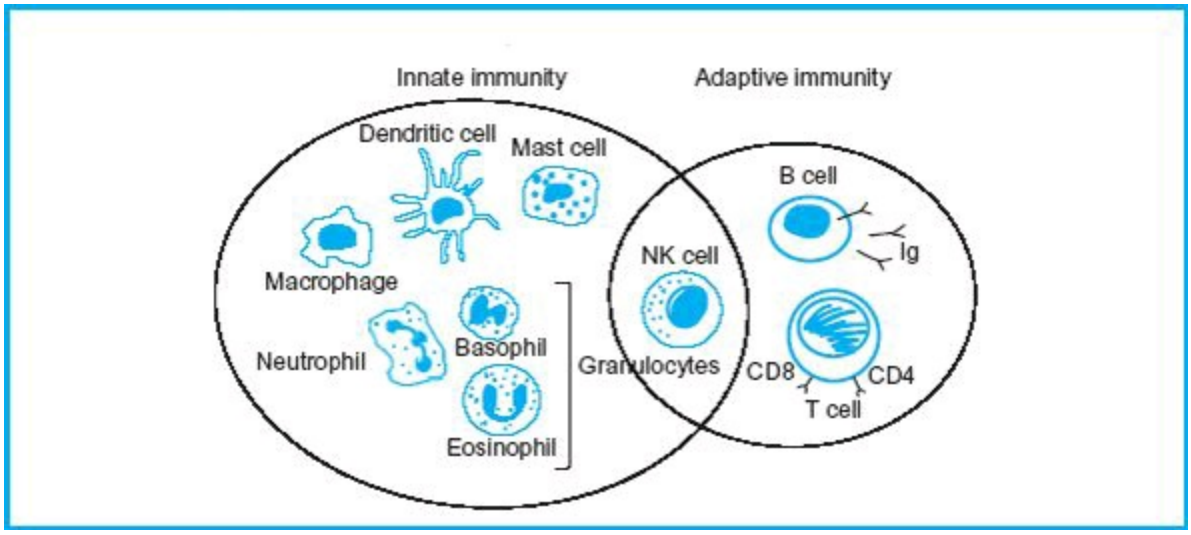
- Innate immunity
- Adaptive immunity.

The innate immune system (including antigen-presenting cells, eg dendritic cells) is typified by a rapid response to pathogens, but this response is not specific and lacks any 'memory'.

The adaptive system (including B and T cells) takes longer to respond; however, responses are highly specific and a lasting memory exists.

Although these two systems are described in more detail in this chapter, it is important to remember that the different components of the immune system do not function in isolation – but rather act in concert, with a vast array of communication networks (comprising chemokines and cytokines) enabling crosstalk between the different cells. Figure 10.1 highlights some of the key cellular components of the immune system.

Figure 10.1 The cells of the innate and adaptive immune systems



10.1.2 Innate immunity

The innate immune system is the first line of defence against infection. The most obvious example of a component of the innate immune system is the skin; however, at a cellular level this includes monocytes, neutrophils, mast cells and complement proteins. The innate immune response is not specific and lacks any memory. Phagocytic cells located at sites of invasion (typically a resident macrophage) use pattern-recognition receptors (eg toll-like receptors) to identify antigenic motifs referred to as pathogen-associated molecular patterns (PAMPs). Recognition of a PAMP will trigger a series of steps:

- Complement activation (to kill invading pathogens)
- Chemokine release (increase adhesion molecule expression)
- Cytokine release (recruit adaptive immune cells).

After phagocytosis of a pathogen, antigen-presenting cells (APCs) can then express the pathogenic peptides on their cell surface for recognition by adaptive immune cells.

10.1.3 Adaptive immunity

The adaptive immune system is found only in vertebrate organisms, and provides a highly specific response to invading infection. In humans, the adaptive immune system subdivides into cellular and humoral systems. The hallmarks of the adaptive immune response are **specificity** and **memory**.

The humoral system refers to the 'circulating' immunity: B cells produce antibody that can recognise specific pathogens; however, these pathogens must be visible in the circulating fluids (blood, lymph) of the body. Once the humoral immune system has encountered a pathogen, it is able to produce memory cells that would be able to mount a more rapid and effective response should that pathogen ever be encountered again (Figure 10.2).

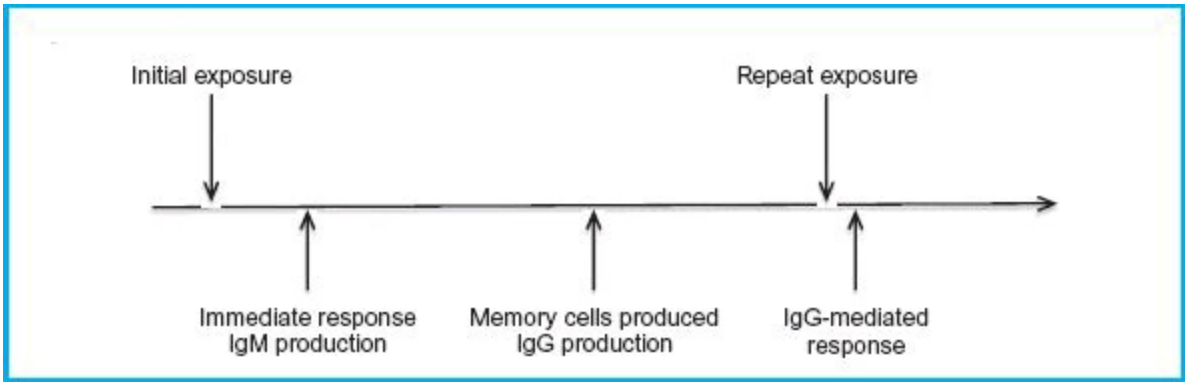
Many pathogens evade the humoral immune system by residing inside cells (eg viruses). In order to recognise intracellular pathogens, a 'cellular' immune system has evolved. Almost all cells are able to express samples of their intracellular contents on their cell surface using machinery referred to as the human leukocyte antigen (HLA) presentation system (encoded on chromosome 6 in the major

histocompatibility complex [MHC] region).

Most cells express class I HLA, which can be thought of as a form of housekeeping; a small number of 'professional' APCs express class II HLA: these are the cells of the innate immune system that spend their days phagocytosing extracellular material for the purpose of antigen expression.

The cellular immune system (T cells) can then interact with HLA to determine whether the peptides expressed are self or non-self.

Figure 10.2 Memory with the adaptive immune system



HLA

- Coded for on the short arm of chromosome 6
- Class I expression (recognised by CD8 T cells) on most cells
- Except red blood cells (RBCs) and trophoblasts
- Class II expression (recognised by CD4 T cells) on 'professional' APCs

10.2 COMPLEMENT

This is a plasma protein cascade (akin to the clotting cascade) that, once triggered, leads to the formation of the membrane attack complex (MAC). The MAC is one of the key mechanisms by which the immune system can destroy an invading entity, by creating a pore in the cell membrane. Exposure of the highly osmolar intracellular milieu to the extracellular fluid leads to rapid influx of fluid and ultimately osmotic cell lysis.

Complement can be activated by one of three distinct pathways:

1. Classic
2. Alternative
3. Lectin-binding.

Each pathway produces protein complexes capable of cleaving the C3 component into its active metabolites, C3a and C3b, which in turn activate the terminal complement components (C5–9) which join to form a rosette-like structure: the MAC. This structure forms on cell surfaces and will cause

cell lysis unless specific inhibitors are present. These inhibitors are generally ubiquitously expressed, except in disease states, such as in paroxysmal nocturnal haemoglobinuria. Here, the absence of a red cell complement inhibitor as a result of a genetic mutation, is the cause of uncontrolled RBC lysis.

Complement pathways are activated during infection (bacterial, viral, fungal) and it is unlikely that any particular pathway is predominant. The classic pathway is thought to be the most recently evolved, and is the only pathway to require antibodies for activation. The alternative and lectin-binding pathways can activate MAC in the absence of antibody by binding directly to polysaccharide components of cell walls of bacteria and yeasts.

The complement cascade slowly ticks over and is never completely inactive. This produces small quantities of active complement components. Positive feedback loops would be triggered and cause immune complex activation if it were not for important regulatory components (eg C1q deficiency predisposes to the development of systemic lupus erythematosus [SLE] – the archetypal immune complex disease).

The biologically active complement products have three main effects:

1. Opsonisation
2. Chemotaxis and inflammation
3. Cell lysis (MAC).

In clinical practice, measurement of components C3 and C4 are used to detect diseases in which complement activation is occurring. Depletion of C3 and C4 would suggest an immunologically driven disease. Typical examples of diseases associated with hypocomplementaemia for the MRCP include the following:

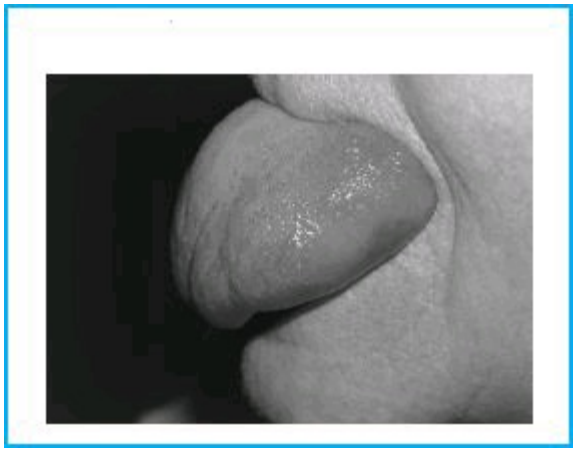
- SLE
- Mesangiocapillary glomerulonephritis
- Chronic infections (eg endocarditis, quartan malaria).

Complement

- The classic pathway is activated by antibody
- Inherited C1q deficiency is a risk factor for SLE
- Deficiency of the glycophosphatidylinositol anchor results in a failure of red cells to inhibit complement lysis: this is the pathogenesis of paroxysmal nocturnal haemoglobinuria
- The alternative pathway can be activated directly by pathogen-associated molecular patterns
- The final common pathway involves C5–9 forming an MAC, resulting in osmotic cell lysis
- Final common pathway deficiencies result in recurrent *Neisseria* spp. infections

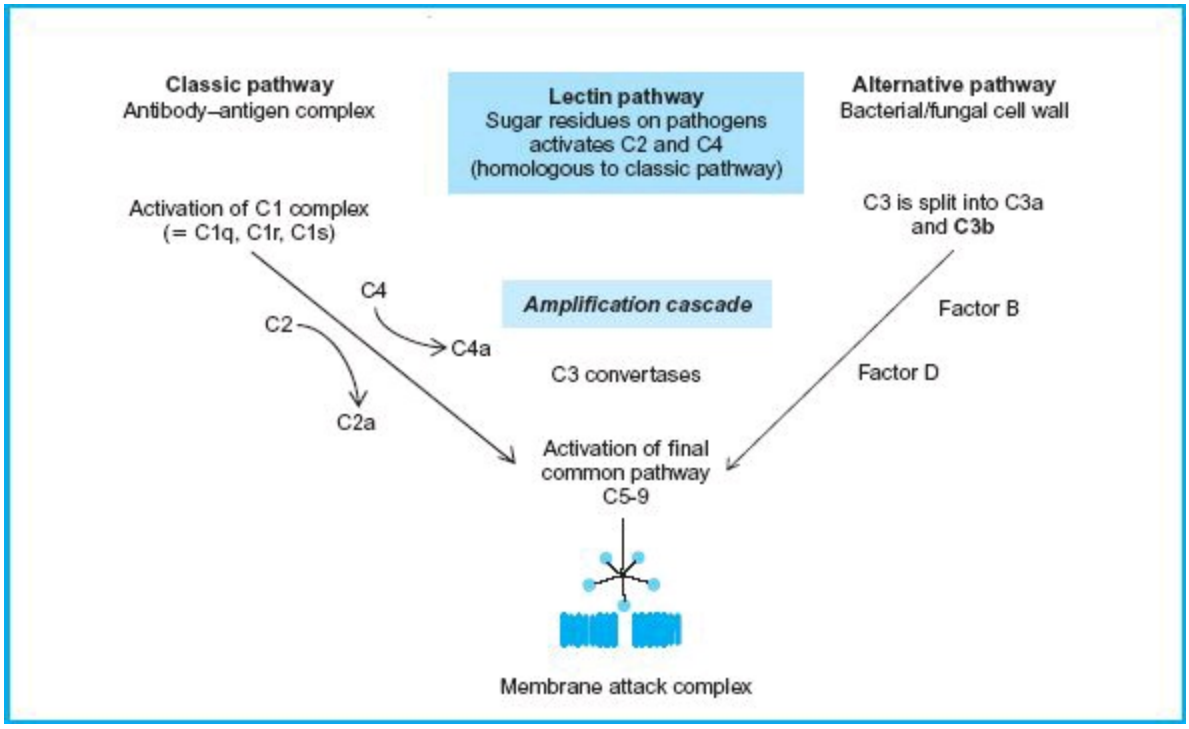
10.2.1 Hereditary angioedema

Figure 10.3 Angioedema on the tongue



This is an autosomal dominant disease caused by a mutation in the C1 inhibitor gene. The role of C1 inhibitor is as a regulator of the classic complement pathway (Figure 10.4), and also an inhibitor of kallikrein, which in turn can liberate bradykinin.

Figure 10.4 The complement cascade



Deficiency of C1 inhibitor results in recurrent attacks of bradykinin-driven angioedema. These episodes are distinguishable from anaphylaxis because hereditary angioedema attacks do not cause urticaria or hypotension.

10.3 CELLS OF THE INNATE IMMUNE SYSTEM

The innate immune system cells are primarily those of myeloid lineage (with the exception of some natural killer cells):

- Neutrophils – polymorphonuclear cells (PMNs) are the principal cells that are able to engulf and then directly kill invading microorganisms through the production of intracellular reactive oxygen species using NADPH oxidase

- Macrophages – they begin their life as monocytes. Upon exiting the lymphatic circulation into tissues, monocytes differentiate into macrophages. Alongside dendritic cells, these represent one of the 'professional' APCs
- Natural killer (NK) cells – these are lymphoid lineage cells that are able to recognise virally infected cells. NK cells also play a role in tumour surveillance. They share some features in common with both innate and adaptive immune systems (hence their inclusion in the overlap in Figure 10.1)
- Eosinophils – these are granular cells that are important in allergy and defence against parasite invasion.

You may notice that basophils have not been mentioned in this list. For MRCP purposes, it is perhaps worth mentioning that you are very unlikely to ever encounter an isolated basophilia outside the setting of a leukaemic process (usually chronic myeloid leukaemia or CML).

10.4 CYTOKINES AND CHEMOKINES

Cytokines and chemokines are signalling proteins that enable crosstalk between the components of the immune system, and drive cellular movement and action. There are vast numbers of these proteins; however, for the purpose of the MRCP it is useful to consider only the clinically relevant ones (Table 10.1).

Table 10.1 Key cytokines and their clinical relevance

Name	Function	MRCP relevance
IL-1	Proinflammatory produced by innate immune cells	Upregulated in many 'autoinflammatory' diseases, eg periodic fever syndromes. Can be blocked by anakinra (which can be an effective treatment for periodic fever syndromes)
IL-2	Drives T-cell proliferation	IL-2 inhibition is clinically useful for suppressing T-cell-driven disease, eg transplant rejection. Examples include the calcineurin inhibitors ciclosporin and tacrolimus
IL-6	Proinflammatory cytokine that is key driver of acute-phase response (especially CRP production)	IL-6 inhibition (eg tocilizumab) is a treatment for rheumatoid arthritis. Patients on this therapy are unable to mount a CRP response during infection (and so a normal CRP would not be reassuring in this setting)
IL-10	Anti-inflammatory cytokine: downregulates other cytokine production, suppresses HLA class II expression	Not much really – but one of the few truly 'anti-inflammatory' cytokines

IL-17	Stimulates production of Th17 cells	Th17 cells are a recent discovery and manipulation of this proinflammatory pathway is likely to become very important in the coming years
TNF	Proinflammatory cytokine produced primarily by macrophages to recruit T cells. Central to granuloma formation	TNF inhibition (eg adalimumab) has become a mainstay of therapy in rheumatoid arthritis. Side-effects include reactivation of granulomatous disease (ie tuberculosis).
IFN	Proinflammatory cytokine important in response to viral infections	IFNs are administered clinically as a treatment for chronic viral infections (hepatitis C) and also multiple sclerosis. Most common side-effects are flu-like symptoms

CRP, C-reactive protein; IFN, interferon; IL, interleukin; TNF, tumour necrosis factor.

10.5 CELLS OF THE ADAPTIVE IMMUNE SYSTEM

When considering the cells of the adaptive immune system, think of lymphocytes.

10.5.1 B cells and antibodies

B cells develop and mature in the bone marrow. Their name derives from their original discovery in the **b**ursa of Fabricius in birds, despite the fallacious etymology that is often taught in medical schools.

During the maturation phases, B cells are important APCs. As they mature they also begin to express immunoglobulin. The terminally differentiated B cell is the plasma cell, which is able to secrete immunoglobulin (antibody).

Antibodies (or immunoglobulins) are large glycoproteins that can identify and neutralise pathogens.

Antibodies comprise two basic structural units: a pair of large heavy chains and a pair of small light chains. At the very tip of the antibody structure is the ‘hypervariable region’. This is the section that determines to which unique antigen the antibody will bind. Antibodies are grouped into isotypes depending on the heavy chain that they possess. These isotypes and their function are listed in Table 10.2. Antibodies can vary isotype in a process called ‘class switching’ which changes the base of the heavy chain to another.

Cryoglobulins

These are immunoglobulins that precipitate out upon exposure to cold temperatures. Cryoglubulinaemia can be subdivided into three types, depending on whether the cryoprecipitate is monoclonal, polyclonal or a combination:

Table 10.2 Antibody isotypes

Antibody	Structure	Function	MRCP notes
IgG	Monomeric	Most abundant Ig (>75%), responsible for most antibody-based responses to infection. Four subclasses: IgG1–4	IgG is the only antibody to cross the placenta. Deficiency predisposes to recurrent bacterial infection
IgM	Pentameric	First antibody isotype to respond to a new infection	Useful in serodiagnosis: IgM confirms recent infection
IgE	Monomeric	Binds allergens, triggers mast cell degranulation, provides defence against parasite infections	Involved in type I hypersensitivity reactions (including anaphylaxis). A monoclonal antibody (omalizumab) against IgE is NICE-approved for use in severe allergic asthma
IgA	Dimeric	Important in host defence in mucosal tissues, eg respiratory tract and gut	IgA deficiency is associated with autoimmune disease (eg coeliac disease)
IgD	Monomeric	A puzzle. If you find out, a *Nature* paper awaits you	Hyper-IgD syndrome is a rare autosomal recessive periodic fever syndrome

NICE, National Institute for Health and Care Excellence.

Types of cryoglobulins

- **Type 1**: monoclonal IgM cryoglobulin: seen in Waldenström's macroglobulinaemia; clinical features primarily related to hyperviscosity
- **Type 2**: mixed monoclonal/polyclonal cryoglobulin: seen in chronic infections, eg hepatitis C
- **Type 3**: polyclonal cryoglobulin: seen in connective tissue diseases, eg Sjögren syndrome/SLE

Patients with type 2 and 3 cryoglobulinaemias may present clinically with vasculitis (palpable purpura, renal failure, arthritis). It is common to see a positive rheumatoid factor in these patients.

Cold agglutinin disease

This should not be confused with cryoglobulinaemia. Cold agglutinin disease is a form of haemolytic anaemia. It can be either idiopathic or acquired. For the MRCP, the two most important acquired causes are lymphoproliferative disease and *Mycoplasma pneumoniae* infection.

Rituximab

Rituximab is a chimseric monoclonal antibody that causes complement-mediated lysis of cells

expressing the CD20 antigen – which is present on immature, mature and some memory B cells. Rituximab does not deplete haematopoietic stem cells nor does it destroy plasma cells or immunoglobulin.

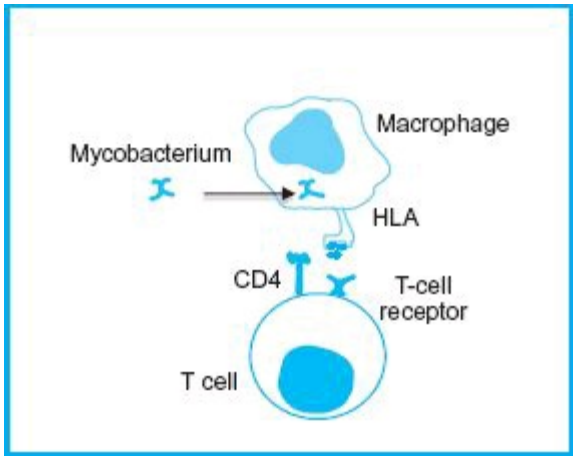
Rituximab was first developed as a targeted therapy for diffuse large B-cell lymphoma (in combination with CHOP – **c**yclophosphamide, Adriamycin [**h**ydroxydaunorubicin], vincristine [**O**ncovin] and **p**rednisolone) – but has subsequently been found to be efficacious in the treatment of rheumatoid arthritis, systemic vasculitis, idiopathic thrombocytopenic purpura (ITP) and other autoimmune diseases. It is currently in trials for the prevention of type 1 diabetes mellitus. Congratulations to anyone who foresaw this success in 1996 and bought shares when it was first licensed.

10.5.2 T cells

T cells make up around two-thirds of the circulating lymphocyte population. Similar to the B cell they are manufactured in the bone marrow; however, maturation takes place in the thymus gland. During the maturation phase, autoreactive cells are removed and then develop into either T-helper (recognising class II HLA) or cytotoxic (recognising class I HLA) T cells (Figure 10.5).

T cells all look much the same under light microscopy, and therefore, to distinguish them, flow cytometry is used to identify clusters of surface antigen that differentiate them (ie clusters of differention or 'CD' markers). All T cells express CD3, whereas CD4 is conserved among helper cells and CD8 is found on cytotoxic cells.

Figure 10.5 Example of T-cell recognition of antigen via HLA



T-helper cells

T-helper cells can further be separated out into subtypes including Th1, Th2 and Th17 cells.

Th1

Think of this as a more 'aggressive' phenotype, with a prominent inflammatory response, triggered by cytokines such as IFN, and resulting in a hostile environment for pathogens.

Th2

The Th2 phenotype represents a more tolerant response, with cytokines such as IL-10 present (see Table 10.1), and is associated with a humoral response, driving antibody class switching. Pregnancy

is a good example of when the Th2 phenotype predominates.

Th17

This is a relatively recently described Th subtype, and seems pivotal in driving autoimmune disease. IL-17 is the key driving cytokine, and both Th17 and IL-17 are the current subjects of pharmaceutical trials across a broad range of diseases. Watch this space!

T cells provide the immune system a 'window' into other cells, and are an especially important defence against intracellular pathogens. In the same way, the normal function of T cells is essential to prevent autoimmunity: unsurprisingly many of the genetic predictors of autoimmune disease lie in the genetic code for HLA on chromosome 6 (eg HLA-DR4 in rheumatoid disease, HLA-Cw6 in psoriasis).

HIV infection

HIV is the archetypal T-cell deficiency state. Specifically, the HIV virus leads to progressive depletion of the CD4 cell population. It is important to recognise the patterns of infections seen in HIV as a model of T-cell deficiency, and at this point refer to Table 10.1 – where you will recall IL-2 is a cytokine central to T-cell proliferation. Suppression of IL-2 effectively induces a T-cell-deficient state: one might rightly predict the same patterns of opportunistic infection in patients on tacrolimus and ciclosporin as we observe in HIV (tuberculosis, *Pneumocystis jirovecii*, disseminated viral disease).

10.6 HYPERSENSITIVITY

Hypersensitivity reactions are immunological responses with excessive or undesirable consequences that may result in tissue or organ damage. There are five types (there used to be only four, but there was concern that the list was not long enough for MRCP candidates) (Table 10.3).

10.6.1 Latent tuberculosis screening

Screening for latent tuberculosis (TB) relies on the tuberculin skin test (using either the Mantoux or the Heaf method). This was an example of a type IV hypersensitivity reaction – and highlights the delayed nature of the response. If an individual reacts to a tuberculin skin test in the first 24 hours, it implies allergy to protein rather than latent TB. After innoculation, patients need to return for the skin test to be read 48–72 hours after injection, and only if the response is delayed does it imply latent TB.

A complicating factor in skin testing for latent TB is that many people have been exposed to the BCG immunisation, which is a live attenuated *Mycobacterium bovis* strain. Prior BCG immunisation can result in false-positive skin tests.

To get around these issues, the interferon-γ release assays (IGRAs) have been developed (eg Quanti-FERON or T Spot). These tests offer an in vitro alternative to the skin test, and use proteins that are unique to *M. tuberculosis* (and not present in *M. bovis*) to stimulate cytokine (IFN) release. IGRAs are NICE (National Institute for Health and Care Excellence) approved for screening for latent TB (but are not currently recommended for use in diagnosing active TB).

Table 10.3 Hypersensitivity reactions

Type	Pathophysiology	Example	MRCP notes
I	Mast cell degranulation, histamine release, IgE	Anaphylaxis, hay fever, asthma	Immediate onset
II	Direct antibody-driven cytotoxicity	Autoimmune haemolytic anaemia, Goodpasture syndrome	Beware Graves' disease[a]
III	Immune complex deposition	Extrinsic allergic alveolitis, SLE	Hypocomplementaemia often present
IV	Cell-mediated (ie T-cell driven)	BCG immunisation, graft-versus-host disease	Delayed onset
V	Stimulating/inhibiting	Graves' disease, myasthenia gravis	Tissue damage does not occur

[a]In Grave's thyroid disease, antibodies stimulate the thyroid gland (as oppose to destroy it) – therefore Grave's disease is classed as a type V reaction. However, Grave's eye disease does involve cytotoxicity, and is an example of a type II reaction.
BCG, bacille Calmette–Guérin; SLE, systemic lupus erythematosus.

10.7 TRANSPLANTATION

Transplantation has evolved enormously over the last 50 years. A xenograft is a transplant across different species (eg porcine heart valve), an allograft is within species, whereas an autograft is within the same individual.

From an immunological perspective it is important to consider whether the transplant is immunogenic. Cardiac valve transplants are non-immunogenic and therefore do not require immunosuppression.

Almost all other tissues transplanted are potentially immunogenic, and will usually require some form of immunosuppression. In the setting of organ transplantation, this will prevent host rejection. In the setting of a bone marrow transplant (where effectively the immune system is the organ that has been transplanted), immune suppression is to prevent graft-versus-host disease.

A key principle in minimising the risk of rejection is to transplant tissue from an individual with as closely matched HLA genotypes as possible. The importance of HLA matching depends upon the immunogenicity of the tissue being transplanted. HLA matching is very important for renal transplantation, whereas it is relatively unimportant for liver transplantation (Table 10.4).

10.8 IMMUNODEFICIENCY

Primary immunodeficiency is rare, and usually the diagnostic remit of paediatricians. However, it is important to remember that secondary immunodeficiency due to disease or medication is common, encountered by adult physicians on a daily basis in routine practice.

10.8.1 Patterns of infection in immunodeficiency

Neutrophil defects

These result from recurrent bacterial or fungal skin infections (cellulitis/abscesses).

Examples

- Primary: chronic granulomatous disease
- Secondary: diabetes mellitus.

Complement deficiency

Complement deficiency may be uncovered incidentally, and is not always symptomatic. The most important clinical associations with complement deficiency include hereditary angioedema and SLE. When infections occur it usually implies a final common pathway defect manifesting with recurrent/invasive *Neisseria* spp. infections.

Table 10.4 Transplant rejection key facts

Type	Mechanism	Timing of onset	Clinical features
Hyperacute	Pre-existing humoral immunity	Immediate (ie while still on the operating table)	Severe systemic inflammatory response
Acute	T-cell driven	Weeks to months	Most patients experience some form of rejection. In its severe form it is characterised by photosensitive rash, abdominal pain and jaundice
Chronic	Variable (including non-compliance with medication)	Months to years	Occurs after repeated episodes of acute rejection. A problem especially in lung transplantation

Examples

- Primary: inherited final common pathway deficiencies
- Secondary: eculizumab (C5 inhibitor used for treatment of paroxysmal nocturnal haemoglobinuria [PNH]).

B-cell/antibody deficiency

This results in sinopulmonary infections/bronchiectasis.

Examples

- Primary: common variable immunodeficiency, selective IgA deficiency, Bruton's hypogammaglobulinaemia
- Secondary: chronic lymphocytic leukaemia, rituximab, gold, phenytoin.

T-cell deficiency

These include opportunistic infections, eg *Pneumocystis jirovecii*, invasive viral infections (cytomegalovirus [CMV]), intracellular bacterial infections (eg salmonellae) and mycobacterial infections.

Examples

- Primary: DiGeorge syndrome, severe combined immune deficiency (SCID), ataxia telangectasia
- Secondary: HIV infection, ciclosporin, anti-CD3 therapy.

Job syndrome (hyper-IgE syndrome)

This rare disease acquired its name after Job in the Bible, who was plagued with boils. The syndrome is characterised by multiple immune failures affecting both innate and adaptive responses. A common mnemonic used to remember the symptoms is FATED: coarse or leonine facies, cold *Staphylococcus* spp. abscesses, retained primary teeth, increased IgE, and dermatological problems (eczema). The key abnormality is a failure of intracellular signalling in the *JAK-STAT* pathway. Clinical manifestations are heterogeneous; however, it is one of the very few diseases that is associated with cryptococcal pneumonia (*Cryptococcus neoformans* usually invades only the CNS tissue).

The reason for mentioning this is that the *JAKSTAT* pathway has been earmarked as the next major immune pathway to inhibit in the treatment of autoimmune diseases. The US Food and Drug Administration (FDA) licensed the first *JAK* inhibitor in 2012, and there have already been reports of cryptococcal pneumonia.

10.9 IMMUNISATION

The principles underpinning immunisation date back to the nineteenth century when Edward Jenner published the first description of vaccination against smallpox. Vaccination or immunisation has contributed immeasurable benefits to society, while continuing to remain a controversial topic in the public eye. Scandal has surrounded the use of vaccine for over a century. For those who scorn sceptics of the MMR (measle, mumps, rubella) vaccine, it is worth remembering that vaccine supporters have not always been on the right side of the fence, eg in 1906 a cholera vaccine study accidentally muddled vaccine serum with bubonic plague serum, and infected and killed 13 study participants. However, there is no need to dwell on that. Instead remember the near eradication of

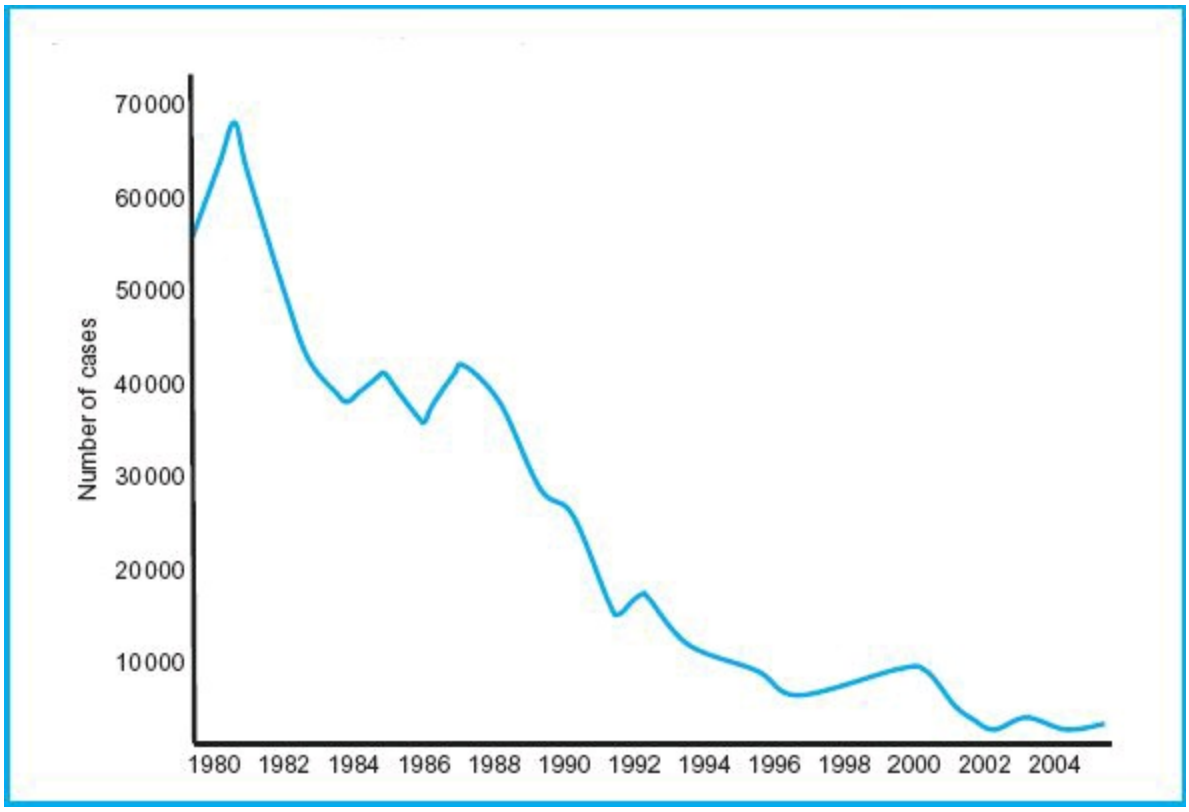
polio in the world (Figure 10.6).

10.9.1 Principles of immunisation

Immunity against a specific pathogen can be artificially generated either actively or passively.

Passive immunisation involves the administration of preformed antibodies against a particular agent, eg varicella or rabies immunoglobulin. This approach has the advantage of providing instantaneous (within 24–48 hours) immunity – hence this approach is used as an immediate post-exposure prophylaxis.

Figure 10.6 Worldwide annual incidence of polio (data from the World Health Organization)



The disadvantages of passive immunity are twofold:

1. Immunity only lasts for the half-life of the immunoglobulin (30 days)

2. As a blood-derived product, there is a risk of transmissible disease.

The principle of active immunisation is to expose the adaptive immune system to a stimulus (virus, bacteria or toxin) to generate a lasting response. The most common vaccines use killed whole organisms (the annual flu jab) or subunits or organisms (the polysaccharide pneumonococcal vaccine: Pneumovax).

Some antigens are inherently less immunogenic, and in these settings a live virus is sometimes used (yellow fever vaccine, BCG vaccine, MMR). However, live vaccines must NOT be given to people who are immunodeficient (primary or secondary immunodeficiency).

Another approach to improving the immunogenicity response of a vaccine is to conjugate a polysaccharide vaccine with a protein (eg conjugate pneumococcal vaccine – Prevenar). Conjugation stimulates a cellular immune response, improving the likelihood of protective immunity.

For a list of the important vaccines for MRCP, see Table 10.5.

Finally, remember no vaccine is 100% effective, and most immunisations rely on the principles of herd immunity. The concept of herd immunity relies on the premise that for infections to gain ground in a population they need to spread in chains from one person to the next. If a significant proportion of the population has reduced susceptibility, then these chains fail to develop and infection rates diminish in both vaccinated and unvaccinated individuals.

Table 10.5 Design of vaccines in common use

Passive	**Active**		
Preformed antibodies	**Live vaccines**	**Killed vaccines**	**Subunit vaccines**
Tetanus	Yellow fever	Seasonal flu	Pneumococcus
Varicella	MMR	Typhoid	Hib
Rabies	BCG	Rabies	Hepatitis B
Hepatitis B	Varicella	Pertussis	Meningococcus
Botulism Diphtheria	Oral polio (no longer available in the UK)	Cholera Parenteral polio	HPV

Hib, *Haemophilus influenzae* type b; HPV, human papilloma virus.

Chapter 11
Infectious Diseases and Tropical Medicine

CONTENTS

Infectious Diseases and Tropical Medicine

11.1 CLASSIFICATION OF BACTERIA AND VIRUSES

11.1.1 Bacteria

Classification is largely based on microscopic appearance, staining characteristics and biochemical tests. For example, Gram staining differentiates bacteria based on differences in cell wall thickness and therefore retention of the stain. Some relevant bacteria are classified here; more clinical detail is given in other sections as infections affecting the systems are discussed.

Classification according to Gram staining and aerobic/anaerobic metabolism is shown in Table 11.1.

Table 11.1 Gram staining and aerobic/anaerobic metabolism

	Gram positive	**Gram negative**
Aerobic cocci	Staphylococci[a] (in clusters) Streptococci[b] (in chains) Enterococci	*Moraxella* sp. *Neisseria* sp. (eg *N. meningitidis*, *N. gonorrhoeae*, both Gram-negative diplococci)
Aerobic bacilli	*Listeria monocytogenes Nocardia* spp. *Corynebacterium diphtheriae Bacillus cereus*	*Enterobacter* sp. *Escherichia coli Klebsiella* sp. *Proteus*
		Salmonellae (including *S. typhi*) *Shigella* sp. *Yersinia* sp.
Anaerobic bacilli	Clostridia (including *C. difficile*, *C. perfringens*)	*Bacteroides* sp.

[a]Staphylococci are further classified, by the coagulase test, into *S. aureus* (coagulase-positive) and 'coagulase-negative staphs', often skin contaminants when grown in blood cultures, most commonly *S. epidermidis*, but can cause pathology. Staphs are mostly resistant to penicillins due to production of β-lactamases and are treated with β-lactamase-resistant penicillins such as meticillin and flucloxacillin, or with antibiotics including a β-lactamase inhibitor, such as co-amoxiclav. Meticillin-resistant *S. aureus* (MRSA) requires treatment with other antibiotics, including the glycopeptides **vancomycin** and **teicoplanin**, which are also active against other Gram-positive organisms.

[b]Streptococci are further classified by the type of haemolysis seen on blood agar: α, β or γ haemolysis. Viridans-type streptococci are mostly α-haemolytic and commonly cause endocarditis. α-Haemolytic streptococci (and others) are classified using Lancefield groups.

The most important β-haemolytic streptococci are given in Table 11.2.

Table 11.2 Lancefield classification of important β-haemolytic streptococci

Lancefield

group	Name	Clinical relevance
A	*S. pyogenes*	Cellulitis Necrotising fasciitis Pharyngitis and tonsillitis Rheumatic fever (immunological reaction to pharyngeal infection) Glomerulonephritis (post-streptococcal infection, >1 week after infection) Scarlet fever (toxin-mediated)
B	*S. agalactiae*	Puerperal and neonatal sepsis (therefore intrapartum antibiotics are given in some circumstances if detected in pregnancy)
D	Previously 'enterococci'	Includes *S. bovis*, which causes infective endocarditis associated with colonic cancer

Bacteria that are not identified by Gram stain are often diagnosed by serology or other stains (Table 11.3).

Table 11.3 Classification by serology or stains other than Gram stain

Obligate intracellular bacteria	*Chlamydia* spp. *Coxiella* spp. *Rickettsia* spp. *Legionella* spp.
No cell wall	*Mycoplasma* spp.
Spirochaetes (coiled bacteria)	*Borrelia burgdorferi* *Leptospira* sp. Treponemes (eg *T. pallidum*, which causes syphilis)

11.1.2 Viruses

Viruses are classified according to whether their genetic material is DNA or RNA, aspects of their structure and replication cycle. Important examples are given here.

The herpes viruses are double-stranded DNA viruses and include herpes simplex viruses 1 and 2 (HSV1 and HSV2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV) and human herpesvirus 8 (HHV8). Diagnosis is by polymerase chain reaction (PCR) or serology. Their clinical associations are described in Table 11.4. Pox viruses are also double-stranded DNA viruses and include smallpox ('variola'; declared eradicated in 1979) and the molluscum contagiosum virus.

Table 11.4 Clinical associations of herpesviruses

HSV1	Initial infection may be asymptomatic or present with gingivostomatitis; leads to lifelong latency and recurrence as herpes labialis (cold sores)
HSV2	Genital herpes with lifelong latency and recurrences
	HSV1 and -2 (1>2) cause aseptic meningitis or encephalitis, localised to the temporal lobes. Diagnosis of encephalitis is by PCR for HSV on CSF, along with MRI of the brain. Treatment is with intravenous aciclovir. In utero infection can cause severe malformations and neonatal infection has a high mortality
VZV	Primary infection is chickenpox (varicella) with an incubation period of around 14 days. The virus is then latent in the sensory ganglia Reactivation causes shingles (more common in immunocompromised individuals) Complications of chickenpox are more common in adults and include pneumonitis, especially in smokers. Permanent calcification can be seen on the chest radiograph. Cerebellar ataxia (due to VZV encephalitis) is rare
CMV	Primary infection is often asymptomatic (or causes a glandular fever-type syndrome, which may be complicated by Guillain–Barré syndrome or Bell's palsy) and seroprevalence is >80% by age 60. CMV is problematic if the individual becomes immunosuppressed, eg after a transplantation or chemotherapy, or due to HIV infection. In HIV-infected individuals with low CD4 counts, CMV can cause sight-threatening retinitis, oesophagitis, colitis, hypoadrenalism, neuritis, CNS disease and cholangitis. Treatment is with antivirals, eg ganciclovir
EBV	Primary infection causes glandular fever (infectious mononucleosis or IM) and the virus is then latent in B cells, sometimes causing transformation to lymphoma. Adult seroprevalence is >90% and around 50% of acute infections cause symptomatic IM. It is associated with Burkitt's lymphoma and lymphoma in HIV, nasopharyngeal carcinoma and oral hairy leukoplakia (white lesions of the lateral tongue borders in HIV)
HHV8	Also known as 'Kaposi's sarcoma-associated virus', this sexually transmitted virus is found in Kaposi's lesions in HIV and in endemic Kaposi's sarcoma. It is also associated with primary effusion lymphoma and Castleman's disease in immunosuppressed individuals

Retroviruses include the human immunodeficiency viruses (HIV-1 and HIV-2), plus human T-cell lymphotropic virus (HTLV-1). They are single-stranded RNA viruses, which replicate using reverse transcriptase and have DNA in their replication cycle. Proviral DNA integrates into the host genome, precluding eradication of these viruses to date.

Hepatitis B and C have similarities in clinical disease, but are from different families: Hepatitis B is a DNA virus and hepatitis C is an RNA flavivirus.

The term arbovirus is an abbreviation of 'arthropod-borne virus', and includes a varied group of organisms such as yellow fever and dengue viruses (RNA flaviviruses) and various causes of encephalitis (such as the flaviviruses causing West Nile and Japanese encephalitis, and the alphaviruses causing St Louis and Eastern equine encephalitis).

11.2 TREATMENT AND PREVENTION OF INFECTIONS

11.2.1 Antibacterial agents

Antimicrobial groups, their mechanisms of action, indication, side-effects and mode of excretion are given in Table 11.5 (see also Chapter 2, Clinical Pharmacology, Toxicology and Poisoning).

Table 11.5 Characteristics and uses of the main groups of antibacterial agents

Antimicrobial group or name	Mechanism of action	Indications	Side-effects
Penicillins (eg benzylpenicillin)[1]	Block cell-wall synthesis	Streptococci, respiratory infections, syphilis	Anaphylaxis, interstitial nephritis (rare), encephalopathy (rare)
Sulfonamides (eg sulfamethoxazole in co-trimoxazole)	Inhibit enzymes converting *p*-aminobenzoic acid (PABA) into folic acid (antifolate)	Co-trimoxazole in pneumocystis pneumonia prophylaxis and treatment. Sulfadiazine in combination for toxoplasmosis	Agranulocytosis, bone marrow suppression, Stevens–Johnson syndrome
Aminoglycosides (eg gentamicin)	Inhibit bacterial protein synthesis	Gram-negative infections, synergistic action in streptococcal endocarditis. Tobramycin used for *Pseudomonas* and amikacin for mycobacteria	Ototoxicity, renal tubular damage (monitor levels to avoid toxicity)
Tetracyclines (eg doxycycline)	Inhibit bacterial protein synthesis	Respiratory infections, *Rickettsia* sp., Q fever, malaria prophylaxis	Photosensitivity, renal impairment, deposition in growing teeth and bones, dental hypoplasia
Cephalosporins (eg ceftriaxone)	Block cell-wall synthesis	Streptococci and Gram-negative infections, meningitis	Anaphylaxis
Macrolides (eg erythromycin)	Inhibition of bacterial protein synthesis	Gram-positive infections, atypical pneumonias, *Mycobacterium avium* (clarithromycin, in	Thrombophlebitis, cholestatic hepatitis

		combination)	
Glycopeptides (eg vancomycin)	Inhibit cell-wall synthesis	Gram-positive infections, MRSA, *C. difficile* (vancomycin)	Nephrotoxicity, ototoxicity, 'red man' syndrome (vancomycin)
Quinolones (eg ciprofloxacin)	Inhibit bacterial DNA synthesis	Gram-negative infections, TB in combination, gastrointestinal infections	Hallucinations, psychosis, reduced seizure threshold, tendon damage and inflammation
Carbapenems (eg meropenem)	Block cell-wall synthesis	Severe or resistant infections including extended spectrum betalactamase (ESBL)-producing bacteria. Meropenem used for central nervous system infections	Imipenem can induce seizures
Clindamycin	Inhibits protein synthesis	Skin and soft tissue infections including necrotising fasciitis; bone and joint infections	Antibiotic-associated colitis
Oxazolidinones (eg Linezolid)	Inhibits protein synthesis	Effective against Gram-positive organisms including MRSA. Skin and soft tissue infections, pneumonia	Cytopaenias/bone marrow suppression
Metronidazole and tinidazole	Production of free radicals in anaerobic microorganisms	Anaerobic infections including abdominal sepsis. Amoebiasis, giardiasis, *C. difficile*	Disulfiram-like effect with alcohol. Cytopaenias
Daptomycin	Blocks cell membrane function	Gram-positive skin and soft tissue infections; *S. aureus* bacteraemia or endocarditis, including MRSA	Creatine kinase elevation: measure CK at baseline and regular intervals during therapy
Tigecycline (a newer tetracycline)	Inhibits bacterial protein translation	Skin and soft tissue infections; abdominal sepsis (without bacteraemia)	Pancreatitis, elevated transaminases
Fidaxomicin	Inhibits RNA synthesis	*C. difficile* associated diarrhoea	Nausea, vomiting

[1] Antipseudomonal penicillins (eg piperacillin-tazobactam) used for severe *Pseudomonas* infections, often in combination. Pivmecillinam effective against Gram negatives, including *E. coli*, and used for uncomplicated urinary tract infections.

11.2.2 Other agents used to counteract infection

Immunoglobulins

Normal human immunoglobulin has many applications, particularly in passively immunising patients with humoral immunodeficiency. Kawasaki's disease (possibly due to an infectious agent) is one application. There are also specific immunoglobulins for specific situations (eg tetanus, rabies, diphtheria, hepatitis B and varicella-zoster immunoglobulin).

Vaccines

The UK vaccination schedule aims to provide protection for children against the following infections:

- Diphtheria
- Tetanus
- Pertussis
- *Haemophilus influenzae* type b
- Polio
- *N. meningitidis* serogroup C
- Measles
- Mumps
- Rubella
- *S. pneumoniae*
- Human papillomavirus types 16 and 18
- Rotavirus.

Older adults are offered influenza and shingles vaccine.

Immunisation of individuals with chronic medical conditions

HIV infection: inactivated vaccines are given according to schedule although response may be suboptimal, depending on CD4 count. Some live vaccines (BCG, oral polio) are contraindicated in HIV infection. Others (yellow fever, MMR, varicella) are given only if the individual is asymptomatic and the current CD4 count is >200 cells/mm^3.

Chronic respiratory, heart, renal, liver disease and diabetes: annual influenza vaccine; single pneumococcal vaccine.

(See also Chapter 10, Immunology.)

11.3 INFECTIONS IN SPECIFIC SITUATIONS

11.3.1 Pregnancy and congenital infections

Infections exacerbated by pregnancy

- Urinary tract infection
- *Salmonella* spp.
- *Listeria* spp.
- Varicella (pneumonitis is life-threatening, especially in third trimester)
- Hepatitis E (25% mortality rate)
- Falciparum malaria

Other infections important in pregnancy

Transplacental transmission may lead to fetal damage.

- ***Rubella***: adults may be symptomatic of infection, with headache, fever, upper respiratory symptoms and a rash. First trimester infection leads to congenital rubella syndrome, with deafness, cataracts and patent ductus arteriosus. Some have less severe features initially but may have developmental delay
- ***Toxoplasmosis***: infection in early pregnancy can cause miscarriage, and in later pregnancy, chorioretinitis, intracerebral calcification, psychomotor retardation and learning disability, jaundice and fever (see Section 11.8.4)
- ***CMV***: often asymptomatic and mild in pregnant women, primary CMV infection infects 30–40% of fetuses, with increased risk of fetal injury in early pregnancy. It may cause intracerebral calcification, hepatosplenomegaly, retinitis and pulmonary infiltration
- ***Varicella (chickenpox)***: infection in early pregnancy causes congenital varicella syndrome, with limb hypoplasia and scarring of dermatomes. Pregnant women with varicella have a higher risk of pneumonitis than other adults. If a pregnant woman is exposed to varicella and is unsure of her history, serum should be tested for varicella IgG and, if negative, varicella-zoster immunoglobulin (VZIg) can be given to prevent infection
- ***Parvovirus B19***: first trimester infection causes fetal anaemia, hydrops fetalis and fetal death.

11.3.2 Intravenous drug use

- ***Endocarditis***: repeated injection into veins carries a risk of right-sided endocarditis. Infections in intravenous drug users can be polymicrobial – often *Staphylococcus aureus*, less commonly streptococci and enterococci. Tricuspid valve endocarditis can lead to septic embolisation into the pulmonary circulation, causing pneumonia with patches of consolidation in both lungs (which may cavitate). See Section 11.5.4 and Chapter 1, Cardiology
- **Blood-borne viruses**: sharing of needles or any other equipment leads to transmission of HIV, hepatitis B and hepatitis C. Up to half of people who inject drugs in the UK have been infected with hepatitis C (antibody positive). A positive hepatitis C PCR test, detecting viral RNA, is

required to diagnose current infection (a positive antibody test only indicates exposure). (See also Chapter 6, Gastroenterology)

- **Soft tissue infections**: infections at injection sites, such as groin abscesses, are common, as is limb cellulitis, and there is a risk of gas gangrene (see Section 11.5.5)
- **Clostridial infections**: although more commonly seen in other groups, disease due to the Gram-positive bacilli, *C. botulinum* and *C. tetani*, has recently increased in incidence among intravenous drug users

  Botulism: *C. botulinum* produces a toxin that causes the clinical syndrome of botulism. It is usually transmitted through food contaminated with the toxin. However, wound botulism can occur in intravenous drug users when the toxin is produced at the wound site. It causes an acute, descending (unlike Guillain–Barré syndrome), symmetrical, flaccid paralysis affecting primarily cranial and autonomic nerves, without fever. The incubation period (IP) is usually 12–72 hours and presenting symptoms may be blurred vision, diplopia, weakness, vomiting or urinary retention, progressing to respiratory failure requiring ventilation. There may be ophthalmoplegia and specific muscle weakness. Diagnosis is by detection of toxin and treatment with antibiotics (penicillin/clindamycin and metronidazole), plus supportive management

  Tetanus: tetanospasmin is the toxin produced by *C. tetani*, which travels via motor neurons to the central nervous system (CNS) where it blocks neurotransmitter release. *C. tetani* is a soil commensal and tetanus may be seen in elderly people, intravenous drug users or other individuals who have been incompletely immunised. The IP is 3–21 days. Trismus (lockjaw) may be followed by restlessness, irritability, dysphagia, opisthotonus (extreme hyperextension of the neck, back and lower limbs caused by spasm of skeletal muscles) and seizures. Diagnosis is clinical, plus culture or PCR to detect the organism. Treatment is with anti-tetanus immunoglobulin, wound debridement if required and antibiotics with action against anaerobes. Immunisation is by three doses of tetanus toxoid as a primary course, and then repeat doses every 10 years until five doses in total have been given.

11.3.3 Splenectomy

The spleen accounts for approximately 25% of all lymphatic tissue; absence of its function causes particular vulnerability to systemic infection with capsulate organisms, such as:

- *S. pneumoniae*
- *H. influenzae*
- *N. meningitidis*
- *Capnocytophaga canimorsus*, a Gram-negative bacillus characteristically acquired from dog bites.

Splenectomised patients are also vulnerable to malaria and **babesiosis** (*Babesia* spp.), a protozoal infection transmitted by ixodid ticks (as is Lyme disease, see Section 11.8.2) from an animal reservoir comprising small rodents (North America) or cattle (Europe). Babesiosis causes a mild malarialike disease in immunocompetent individuals, but is potentially life-threatening in splenectomised individuals. Diagnosis is by blood film.

Immunisations and prophylaxis in splenectomised individuals

- Immunisation against *H. influenzae* type b, *N. meningitidis* group C and *S. pneumoniae* is recommended, as is an annual influenza vaccine
- Antibiotic prophylaxis with penicillin (or erythromycin if allergic) is required until at least age 16 or for at least 2 years after a splenectomy. Appropriate malaria prophylaxis is vital if travelling to an endemic area.

11.3.4 Sickle cell disease

Sicklers (ie those who are SS homozygotes) often have functional hyposplenism and also a reduction in complement-mediated serum-opsonising activity. This gives rise to vulnerability to:

- Pneumococcal infection (and other encapsulated organisms such as meningococci)
- Other forms of bacterial sepsis – pneumonia and meningitis in particular
- Osteomyelitis (due to *Salmonella* spp.)
- Morbidity and mortality from falciparum malaria, which precipitates haemolytic and infarctive crises (in contrast to AS heterozygotes, who are relatively resistant to malaria)
- Parvovirus B19 can cause life-threatening aplastic anaemia in sickle cell homozygotes.

11.3.5 Other factors predisposing to specific infections

There are some host factors conferring susceptibility to sepsis of particular cause:

1. Deficiency of mannose-binding lectin and pneumococcal sepsis
2. Terminal complement deficiencies and meningococcal sepsis
3. Agammaglobulinaemia and pneumococcal and *H. influenzae* type b sepsis
4. Chédiak–Higashi syndrome (a rare autosomal recessive condition with recurrent bacterial infections)
5. Leukocyte adhesion deficiency syndromes (genetically determined conditions with recurrent, severe bacterial infections)
6. Job's syndrome (also known as hyperimmunoglobulin E syndrome: a primary immunodeficiency associated with bacterial, especially staphylococcal, viral and fungal infections).

11.4 SYSTEMIC INFECTIONS AND SEPSIS

11.4.1 Sepsis

Sepsis is a systemic, deleterious host response to infection. To aid immediate clinical management, grades of severity are defined as follows:

SIRS (systemic inflammatory response	2 or more of: Fever >38 or <36°C Heart rate >90 beats/minute Respiratory rate >20 breaths/minute or *p*CO2 <32mmHg White cell

syndrome)	count >12,000/μL or <4,000/μL or >10% immature forms
Sepsis	The association of SIRS with evidence or suspicion of a microbial origin
Severe sepsis	Acute organ dysfunction secondary to documented or suspected infection
Septic shock	Severe sepsis plus hypotension not reversed with fluid resuscritation

SIRS is therefore not always associated with bacteraemia and bacteraemia does not always cause SIRS.

Shock is the result of a cascade of inflammatory mediators such as tumour necrosis factor (TNF) and interleukin-1 (IL-1), and the origin is usually bacterial, although often not confirmed by culture, but can be due to other infectious agents (eg fungi) or non-infectious causes.

Early antibiotic treatment and supportive care are the mainstays of management. International guidelines from the "Surviving sepsis campaign" recommend early goal-directed therapy in the first 6 hours to improve outcomes, plus completion in the first hour after presentation of the 'sepsis six'.

Sepsis six

1. High-flow oxygen
2. Blood cultures (and other relevant samples)
3. Broad-spectrum antibiotics
4. Intravenous fluid challenge
5. Measure serum lactate and Hb
6. Commence accurate hourly urine-output measurement

11.4.2 Toxic shock syndrome

Toxic shock syndrome is an acute, multisystem, toxin-mediated illness, with fever, rapid-onset hypotension and multiorgan failure. The majority of cases are caused by toxin-producing strains of *Staphylococci* or *Streptococci*.

Toxic shock has been associated with tampon use in menstruating women, but can be due to other staphylococcal foci, eg surgical wound infection or abscess. Toxin-producing *Staphylococcus aureus* (producing, for example, toxic shock syndrome toxin-1 [TSST-1] or staphylococcal enterotoxin B) is usually implicated, but a similar syndrome can follow infection with exotoxin-producing streptococci (eg invasive group A streptococci/*S. pyogenes*).

- **Clinical features**: fever, diffuse macular rash (followed by desquamation after 10-21 days in staphylococcal TSS), hypotension, plus evidence of multiorgan involvement such as vomiting or

diarrhoea, renal failure, thrombocytopenia or altered mental state

- **Diagnosis**: organisms may not be identified on culture, particularly in staphylococcal TSS, so treatment is on suspicion and exclusion of other causes of shock, eg meningococcaemia
- **Treatment**: Antibiotic therapy should include agents targeting suspected organisms, including consideration of drug-resistant organisms such as MRSA, plus an agent that suppresses toxin production, such as clindamycin or Linezolid. Urgent surgical debridement may be required if there is necrotising fasciitis or myositis. Supportive care is the mainstay of treatment. There is some evidence for the use of intravenous immunoglobulin and this can be considered if other approaches are failing in the initial hours of treatment.

11.5 INFECTIONS OF MAJOR SYSTEMS

11.5.1 Respiratory infections

Most respiratory conditions are covered in Chapter 19, Respiratory Medicine. Some specific infections are covered here. For mycobacterial infections, see Section 11.6.

Infectious mononucleosis

(See also Section 11.1.2.)

Infectious mononucleosis (IM) (also known as glandular fever) is caused by EBV, which is transmitted by saliva. Asymptomatic viral shedding is common and the IP is 30–45 days. Symptoms are sore throat, fever and malaise, with signs of exudative tonsillitis, lymphadenopathy and sometimes splenomegaly or a widespread maculopapular rash. An associated EBV hepatitis can cause jaundice. Treatment with ampicillin (often for presumed streptococcal infection) causes a maculopapular rash. Possible complications include thrombocytopenia, haemolytic anaemia, traumatic rupture of an enlarged spleen and, rarely (<1%), Guillain–Barré syndrome, cerebellar ataxia, aseptic meningitis, encephalitis, pneumonitis, pericarditis or lymphoma.

Diagnosis

IM causes a lymphocytosis, with atypical lymphocytes seen on the blood film, positive monospot (Paul–Bunnell) test for heterophile antibodies, and increased transaminase and bilirubin levels if there is associated hepatitis. Specific tests for EBV are also positive, including antiviral capsid IgM in recent infection.

Treatment

There is no specific treatment. Steroids are given if tonsillitis threatens airway obstruction.

Differential diagnosis of glandular fever (IM)

Includes acute CMV, toxoplasmosis, primary HIV infection, plus other causes of pharyngitis such as group A streptococcal infection or diphtheria

Diphtheria

Corynebacterium diphtheriae (or *C. ulcerans* in some cases) is a spore-forming, Gram-positive bacillus that can produce an exotoxin. It is transmitted by respiratory droplets. It is very rare in the UK due to the immunisation schedule, which includes diphtheria immunisation along with tetanus, polio, *Haemophilus influenzae* type b (Hib) and pertussis before 12 months of age. It occurs more frequently in countries with lower immunisation coverage.

The IP is 2–5 days and infection presents with fever, anterior cervical lymphadenopathy and soft tissue oedema, giving a 'bull neck' appearance and a membranous pharyngitis; the grey, fibrinous 'pseudomembrane' may cause airway obstruction. In immunised individuals, milder infection may resemble streptococcal pharyngitis. The exotoxin can rarely cause paralysis (peripheral neuritis) and myocarditis. Cutaneous diphtheria presents with a skin ulcer that may have an eschar.

Diagnosis
Culture of throat swab for corynebacteria should be specifically requested if infection is suspected. If cultured, organisms are sent for toxigenicity testing by PCR. Suspect infection in those who have travelled to endemic countries, had animal contact, are unvaccinated or are laboratory workers.

Treatment
Specific diphtheria antitoxin for suspected or confirmed cases, plus penicillin or erythromycin for 14 days. Immunise if this has not previously been done. Isolate the patient and notify public health authority so that contacts can be managed appropriately.

Lemierre's disease

Tonsillitis caused by the anaerobe *Fusobacterium necrophorum* can spread to cause internal jugular thrombosis and secondary abscesses elsewhere, eg lungs. Diagnosis is by culture of pus or blood and prolonged antibiotics ± anticoagulation is required.

'Atypical' pneumonia

This term is usually applied to pneumonias not conforming to a lobar pattern and 'typical' clinical features (symptoms and signs of acute lower respiratory tract infection, fever, focal chest signs and, if diagnosed in hospital, radiological features) and includes pneumonia caused by the following organisms:

- *Mycoplasma pneumoniae*
- *Legionella pneumophila*
- *Chlamydia pneumoniae*
- *Chlamydia psittaci* (psittacosis)
- *Coxiella burnetii* (Q fever).

Investigations for these infections differ from those for 'typical' pneumonia in that the organisms are not cultured from blood or sputum. Serological tests are required, ideally acutely and during convalescence, demonstrating an increasing antibody titre due to the infection.

Urinary antigen detection is useful for *L. pneumophila*, particularly as it can give a rapid diagnosis, as early as 1 day after symptoms although it detects only serogroup 1, *L. pneumophilia*.

For Q fever, see Section 11.8.3 Clinical features of pneumonia are described in Chapter 19,

Respiratory Medicine, Section 19.3.1.

11.5.2 Neurological infections

Infections of the brain and spinal cord can cause focal, space-occupying lesions, meningitis or encephalitis. The peripheral nerves are less susceptible to direct bacterial infection (with the exception of leprosy). Most bacterial infections that affect peripheral nerves do so by the action of specific toxins (eg botulinum, diphtheria). Some viruses (particularly enteroviruses, eg poliovirus) can damage peripheral nerves.

Meningitis

Acute meningitis presents with headache, fever and meningism. The level of consciousness is normal unless there is encephalitis. Urgent treatment (ceftriaxone or cefotaxime) is required for bacterial meningitis and UK guidelines now recommend glucocorticoid treatment (dexamethasone) with antibiotics; evidence is strongest for benefit in pneumococcal meningitis. Meningococcal disease may be in the form of meningitis or septicaemia, or both. In meningococcal septicaemia the diagnosis is made by blood culture and/or blood PCR for *Neisseria meningitidis*. Coagulopathy due to disseminated intravascular coagulation (DIC) may preclude lumbar puncture.

Common causes of acute bacterial meningitis in adults are *N. meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*. *Listeria monocytogenes* is an important, although less common, cause in elderly or very young people, and ampicillin should be added to cover this for adults over 55 years old. (See Section 11.1.1 for Gram-staining characteristics.) Spread from local ear, nose or throat infections is often implicated in pneumococcal meningitis.

Cerebrospinal fluid (CSF) characteristics in meningitis are given in Table 11.6.

Other causes of meningitis

- **Viral meningitis due to**:
  - Enteroviruses (Coxsackieviruses A and B, echoviruses)
  - Herpesviruses (HSV1 and 2, EBV, VZV)
- **More rarely** and characteristically **with lymphocytic CSF**
  - Leptospirosis (*Leptospira* spp.)
  - Syphilis (*Treponema pallidum*)
  - Lyme disease (*Borrelia burgdorferi*)
  - Fungal meningitis (eg *Cryptococcus neoformans, Histoplasma capsulatum*)

Note on prophylaxis of contacts

Antibiotic prophylaxis with rifampicin (licensed) or single-dose ciprofloxacin (unlicensed) is offered

to close (household) contacts of an individual with meningococcal disease as soon as possible, ideally within 24 hours, after diagnosis of the index case, and to those who have had contact with respiratory droplets/secretions at the time of admission to hospital, eg staff involved in airway management

Table 11.6 CSF characteristics in meningitis

	Appearance	Cells	Glucose	Protein	Organisms
Acute bacterial	Cloudy, turbid	Neutrophils	↓	↑	On Gram stain/culture
Viral	Clear	Lymphocytes ↑	↔	↑ or ↔	Not seen
Tuberculous	Cloudy/turbid	Lymphocytes ↑	↓	↑↑	On Ziehl–Neelsen/auramine stain/culture
Cryptococcal[a]	Clear	Lymphocytes ↑	↑ or ↔	↑ or ↔	India ink

[a]Often high opening pressure.

Encephalitis

Encephalitis is inflammation of the brain parenchyma, often due to infection, including viruses, bacteria and fungi. There is an altered level of consciousness. In the UK, the most common cause is HSV (1>2). Prognosis with HSV encephalitis is much improved with prompt aciclovir treatment.

Clinical features

There may be fever and headache with focal (often temporal lobe) signs, or seizures or coma.

Diagnosis

Viral encephalitis is diagnosed by PCR on CSF. The EEG may show abnormalities in the temporal lobes and magnetic resonance imaging (MRI) may show enhancement of the temporal lobes. HIV testing is recommended for all individuals with possible encephalitis.

Treatment

Autoimmune encephalitis is an important differential if tests for infections are negative. Prompt treatment with aciclovir (requiring dose adjustment in renal impairment) reduces the mortality rate from up to 70% to around 25%. It also reduces long-term neurological disability.

Infective causes of encephalitis

- **Viral**
  - Herpes simplex (high mortality/morbidity, mainly type 1)
  - Measles, mumps
  - Enteroviruses, flaviviruses (eg Japanese encephalitis, West Nile)
  - VZV

- HIV
- Rabies
- CMV and EBV in the immunocompromised

- **Others**
  - Listeria (brainstem encephalitis)
  - Toxoplasmosis
  - African trypanosomiasis

Space-occupying lesions

Brain abscesses

They often have an identifiable route of infection, such as recent surgery, parameningeal infection (otitis media, sinusitis, dental abscess) or metastatic spread from, for example, endocarditis, suppurative lung disease or congenital heart disease with right-to-left shunt.

Organisms

Often mixed, including one or more of: *Staphylococcus aureus*, *Streptococcus milleri* group, coliforms, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, anaerobes. *Listeria monocytogenes* causes brainstem abscesses or rhombencephalitis.

Treatment

Broad-spectrum initially, eg cephalosporin plus metronidazole, then antibiotic therapy guided by results of aspiration.

Other focal lesions

Neurocysticercosis (see Section 11.7.8), neuroschistosomiasis (see Section 11.7.4) and hydatid (see Section 11.5.3).

Toxoplasmosis or cryptococcoma in immunocompromised individuals; tuberculomas; aspergillomas in those with disseminated aspergillus infection.

(See also Chapter 16, Neurology.)

11.5.3 Gastrointestinal infections

Bowel

Most gut infections cause diarrhoea (Table 11.7); as a general rule, small-bowel infection usually manifests as toxin-mediated, watery diarrhoea with no blood whereas large-bowel infections (with exceptions) may be invasive of colonic mucosa and cause bloody diarrhoea with mucus and sometimes pus – 'dysentery'. (See also Chapter 6, Gastroenterology.)

Table 11.7 Organisms causing vomiting and/or diarrhoea

Symptom	Organisms	Incubation Period	Source

Vomiting	*Bacillus cereus*	1–6 hours	Toxin from rice or meat
	Staphylococcus aureus	2–7 hours	Toxin from dairy or meat products
Diarrhoea	*Escherichia coli* (enterotoxigenic)	12–72 hours	From milk, salads, water (major cause of travellers' diarrhoea)
	Campylobacter jejuni	1–10 days	From meat, especially poultry, dairy products
	Salmonella spp.	8–48 hours	From eggs, poultry
	Shigella spp.	12–96 hours	Faecal contamination
	Yersinia enterocolitica	3–7 days	From pork, dairy products

- Food poisoning should be notified to public health on suspicion. Other notifiable diseases include malaria, meningococcal disease, measles, enteric fever, TB, viral hepatitis, tetanus and diphtheria

Escherichia coli O157

Verotoxin-producing; may lead to epidemics of haemolytic uraemic syndrome.

Amoebiasis

See Section 11.7.3.

Giardiasis

The protozoon *Giardia lamblia* causes a minority of travellers' diarrhoea. It is transmitted by ingestion of cysts from faecally contaminated water or person-to-person. The IP is 3–20 days and symptoms may persist for several weeks. Initially causing diarrhoea, symptoms may progress to nausea, cramps, abdominal pain, bloating and burping. Some individuals develop chronic diarrhoea with significant weight loss.

Diagnosis

Cysts seen on stool microscopy or trophozoites seen on biopsy of small-bowel mucosa.

Treatment

Tinidazole (2 g single dose) or metronidazole (eg 2 g daily for 3 days; different regimens vary from 3 days to 10 days) plus supportive treatments.

Tropical sprue

Also known as post-infective malabsorption. *E. coli*, and *Klebsiella* and *Enterobacter* spp. are implicated in causing this chronic (>2 months) malabsorption of nutrients, which may lead to haematinic and protein deficiency states. It is mostly found in south and south-east Asia.

Cryptosporidiosis

This is a protozoal infection (*Cryptosporidium parvum*) that causes watery diarrhoea. The IP is 2–14 days. It occurs in water-borne epidemics worldwide but may cause severe, prolonged, watery diarrhoea in immunosuppressed, particularly HIV-infected, individuals. There is no reliable antimicrobial therapy and, in HIV, treatment is aimed at restoring T-cell levels with antiretroviral therapy. Nitaxozanide has some effect in immunocompetent individuals and may be considered in the immunosuppressed, although evidence is weak.

Diagnosis

Red cysts on Ziehl–Neelsen staining of stool.

Antibiotic-related diarrhoea and *C. difficile*

Antibiotic-associated diarrhoea is mostly due to toxin-producing *C. difficile*, growth of which is increased by the reduction in normal bowel flora. *C. difficile* is a spore-forming, anaerobic bacterium. Spores are found in hospital environments and are secreted by affected patients or asymptomatic individuals. Severe disease can cause pseudomembranous colitis, toxic megacolon and perforation.

C. difficile infection is an important issue in NHS hospitals, with targets for prevention, mandatory reporting and root-cause analysis of individual cases. It is associated with high levels of morbidity and mortality and optimal management is essential, including supportive management of patients with the disease.

Risk factors for disease should be minimised in hospitalised patients where possible and include the following:

- Older age
- Antibiotic use, including in the community (particularly broad-spectrum agents clindamycin, co-amoxiclav, ciprofloxacin, cephalosporins)
- Proton-pump inhibitors/other acid-suppressing agents.

Markers of severe disease are as follows:

- White cell count $>15 \times 10^9$/L
- Acutely raised creatinine (50% above baseline)
- Temperature >38.5°C
- Evidence of severe colitis (eg abdominal signs, bowel distension on radiology).

Elevated blood lactate is associated with very poor prognosis.

Diagnosis

Diarrhoeal stool should be sent for 2-stage testing for the presence of *C. difficile* and for toxin production. The first stage is a molecular (PCR) test or enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH) to indicate the presence of the *C. difficile* organism. If this is positive, an EIA for toxin is done, indicating whether diarrhoea-producing toxin is present. Those with toxin present are treated for disease as shown below. Infection control measures are required for those with organism present but negative tests for toxin, who may have the potential to transmit *C. difficile*.

Management
Treatment includes supportive measures and antibiotic therapy, and severity should be reassessed frequently. Frequency and severity of diarrhoea can be monitored using the Bristol stool chart. Patients should be isolated if *C. difficile* infection is suspected and stool sent for testing immediately. Those with suspected severe disease should have surgical input.

Treatment, according to severity, is summarised in the following Table 11.8, according to national guidelines.

There is increasing trial evidence for the use of faecal transplant ('faecal microbiota transplantation' or enteric infusion of donor faeces) in recurrent *C. difficile* infection and NICE recommends consideration of such therapy for those failing to respond to other treatments. However, faecal transplant is not available in most centres. It requires donor screening for transmissible infections.

Liver

Amoebic liver abscess

- See Section 11.7.3.

Hydatid disease

Echinococcus granulosus is a dog tapeworm. Ingested eggs from contact with dogs or contamination of food hatch into larvae and penetrate the bowel wall into the portal bloodstream. They mature into liver cysts and can also disseminate to other sites, eg lung, brain. Liver cysts present insidiously as a liver mass. Rupture can cause life-threatening anaphylaxis, and cysts must not be aspirated due to the risk of spreading the protoscolices around the body. People working with dogs or in sheep farming may be at risk.

Table 11.8 Grades of severity or *C. difficile*

Severity	Stools (Bristol stool chart)	White cell count	Treatment
Mild	<3 of type 5–7	Not raised	Oral metronidazole 400–500 mg tds for 10–14 days
Moderate	3–5/day	Raised but $<15 \times 10^9$/L	
Severe	Not a reliable indicator	$>15 \times 10^9$/L	Oral vancomycin 125mg qds for 10–14 days Consider fidaxomycin if high risk for recurrence In life-threatening cases, oral vancomycin up to 500mg qds for 10–14 days plus iv metronidazole 500mg tds

Diagnosis
Liver ultrasound, serology.

Treatment
Surgical removal of the cysts (with care not to spill contents into the abdominal cavity, because this can cause recurrence) and anthelmintic drugs, albendazole/mebendazole, praziquantel, pre- and post-operatively. Asymptomatic cysts may not need treatment.

Leptospirosis

This zoonotic spirochaete infection is transmitted by contact with the urine of infected mammals (dogs, rats) through broken skin, usually in contaminated water. There is often a history of occupational (sewage or agricultural workers) or recreational (fishing, water sports) exposure. *Leptospira interrogans* is the species responsible for disease. The IP is 7–12 days.

Clinical features
Usually headache, fever, myalgia, rigors and neck stiffness for 4–5 days due to leptospiraemia. Some recover after this phase, but for others, as the organism localises and causes vasculitis and capillary injury, further fever, suffused conjunctivae, aseptic meningitis and jaundice with renal impairment and proteinuria (Weil's disease) follow. Some have cardiac involvement with arrhythmias or cardiac failure. There is typically a neutrophilia, raised creatine kinase (CK) and lymphocytic CSF.

Diagnosis
Culture of blood/CSF/urine, serology, PCR.

Treatment
Penicillin, tetracycline with supportive measures.

(See Section 11.8 for other zoonoses.)

Viral hepatitis

See Chapter 6, Gastroenterology.

11.5.4 Cardiac infections

Infective endocarditis

Infective endocarditis is most commonly caused by bacterial infection affecting damaged or prosthetic heart valves, particularly streptococci, which colonise the mouth and upper respiratory tract. For example, viridans-type streptococci, a group including *S. sanguis* and *S. oralis*, are the most common cause of native valve endocarditis. Organisms may originate from dental disease or intravenous lines. Streptococcal endocarditis presents more indolently than staphylococcal endocarditis. Right-sided, staphylococcal endocarditis occurs in intravenous drug users, as above. Endocarditis is less commonly caused by the HACEK group of organisms (*Haemophilus aphrophilus* and *H. paraphrophilus*, *Actinobacillus hominis, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* and *K. denitrificans*); fastidious Gram-negative organisms, or by Bartonella spp. or Q-fever (*Coxiella burnetii*).

UK guidelines state that infective endocarditis must be considered in patients fulfilling the following

criteria:

- Fever and a murmur of new valvular regurgitation
- Fever and a pre-existing at-risk cardiac lesion and no other apparent source of infection
- Fever and:
  - Predisposition and recent intervention with associated bacteraemia
  - Evidence of congestive cardiac failure
  - Vascular of immunological phemonema: embolic events, Roth spots, splinter haemorrhages, Jameway lesions, Osler's nodes
  - A new stroke
  - Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause
- A protracted history of sweats, weight loss, anorexia or malaise, and an at-risk cardiac lesion
- Any new, unexpected embolic events
- Unexplained, persistently positive blood cultures
- Intravascular catheter-related bloodstream infection with persistently positive blood cultures 72 hours after catheter removal.

Echocardiogram should routinely be done in patients with *S. aureus* bacteraemia or candidaemia, in view of the higher likelihood of endocarditis.

Diagnosis of infective endocarditis can be made using Duke's criteria (see box). The importance of positive blood cultures in diagnosis and treatment means that samples must be taken before antibiotics are given. In those with chronic or subacute presentations, three sets of blood cultures should be taken with at least 6 hours between them, to confirm continuous bacteraemia. In very unwell patients, two sets with 1 hour between them should be taken before empirical therapy is started.

Transthoracic echocardiogram (TTE) is the initial imaging of choice, to be followed by transoesophageal echocardiogram (TOE) if there is a prosthetic valve, if the TTE is of poor quality, positive, or negative in the context of continuing clinical suspicion.

If blood cultures are negative, serology for *Coxiella* and *Bartonella* should be done, followed by *Chlamydia*, *Legionella* and *Mycoplasma* if these are negative, and *Brucella* if there is a history of potential exposure.

Cases are 'definite' if they fulfil two major Duke's criteria, one major and three minor, or five minor; 'possible' if they fulfil one major and one minor or three minor criteria:

Major Duke's criteria

- **Microbiological**
  - Typical infective endocarditis organism from two separate blood cultures (viridans-type streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, community-acquired enterococcal bacteraemia without obvious source)

  OR
  - Organism consistent with infective endocarditis from persistently positive blood cultures

OR

- Single positive blood culture for *Coxiella burnetii* or serology positive for *C. burnetii*

- **Cardiological**
  - New valvular regurgitation

  OR
  - Positive echocardiogram

Minor Duke's criteria

- Predisposition to infective endocarditis (intravenous drug use, cardiac abnormality)
- Fever
- Vascular phenomena
- Immunological phenomena
- Positive blood cultures not meeting major criteria

Treatment

Empirical treatment for native valve endocarditis with indolent presentation, unless staphylococcal infection is suspected, is intravenous amoxycillin with synergistic doses of gentamicin (1mg/kg twice daily). For prosthetic valve endocarditis, vancomycin and gentamicin plus rifampicin are currently recommended. Regimens can be rationalised once the organism is identified and sensitivity testing completed. The duration of treatment depends on the organism; for some cases (eg uncomplicated streptococcal disease), 2 weeks of intravenous antibiotic may be sufficient. In staphylococcal endocarditis with a sensitive organism, flucloxacillin is recommended, and with likely or confirmed MRSA, vancomycin and rifampicin can be given.

Antibiotic prophylaxis against endocarditis

NICE guidelines recommend that antibiotic prophylaxis is no longer given routinely for invasive procedures, including dental, gastrointestinal or genitourinary procedures due to lack of proven efficacy.

Pericarditis and myocarditis

Pericarditis and myocarditis present with chest pain and typical widespread, concave ST elevation on the ECG. They are caused by viruses, including enteroviruses (eg Coxsackie viruses A and B and echoviruses). Pericarditis may be caused by bacteria in individuals with severe septic illness or by *Mycobacterium tuberculosis*, often in combination with pulmonary tuberculosis.

Rheumatic fever

Rheumatic fever is very rare in the UK, but occurs in developing countries. It is an immunological response to group A streptococcal infection. Although not a cardiac infection in itself, it is included here because of its association with later risk of endocarditis and initial carditis, which may include valvular disease.

Diagnosis can be made according to the Jones' criteria, by the presence of evidence of streptococcal infection plus either two major criteria or one major and two minor criteria, as shown in the following box.

A	**Evidence of recent group A streptococcal infection**

- Positive throat swab culture or streptococcal antigen test
- Elevated or rising streptococcal antibody titre

B	**Major manifestations**

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

C	**Minor manifestations**

- Arthralgia
- Fever
- Elevated acute-phase response (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR])
- Prolonged PR interval in ECG

Q fever

For Q fever, see Section 11.8.3.

11.5.5 Skin and soft tissue infections

Staphylococcus aureus and *Streptococcus pyogenes* (Lancefield group A β-haemolytic streptococci, as in Table 11.2) are mainly responsible for community-acquired soft tissue infection in otherwise healthy patients.

Necrotising fasciitis

This is an acute necrotising infection of the skin, subcutaneous tissues and superficial fascia. It may involve muscle. Clinically there is soft tissue erythema or dusky appearance with severe pain. Risk factors are diabetes, advanced age, obesity and intercurrent illness. It is often a mixed infection, with *Streptococcus pyogenes*, anaerobes and coliforms. It requires aggressive surgical debridement as well as antibiotics (covering anaerobes, Gram negatives and streptococci; clindamycin may have

benefit in inhibiting production of streptococcal toxins). Fournier's gangrene is a type of necrotising fasciitis involving the male genitalia.

Clostridial gas gangrene

Muscles are involved in this infection with *Clostridium perfringens* or other clostridia. There is systemic illness and gas in the tissues. It often follows trauma or surgery with wound contamination. The organisms are anaerobic and so impaired perfusion increases risk of disease. Urgent debridement is required.

11.6 MYCOBACTERIAL INFECTIONS

11.6.1 Tuberculosis

Mycobacterium tuberculosis disease, although most commonly pulmonary, can affect any organ. *M. tuberculosis* can also produce latent infection, said to affect a third of the world's population, with the potential to reactivate and cause disease years later.

Transmission is by respiratory droplets from an individual with smear-positive ('open') TB. Globally, TB control has been hampered by the HIV pandemic, which increases the risk of TB disease by impairing cell-mediated immunity. Other risk factors include contact with a known case of pulmonary TB, history of living in an institution (eg prison) and originating from a country with high incidence of TB disease.

Current UK case notifications are around 14 per 100,000 population/year and have been stable since 2005 after previous increases. Around 1.5-2% of these are multidrug resistant, with 7.5% resistant to any one first-line drug.

Note on drug-resistant tuberculosis

Multidrug-resistant (MDR) TB is defined by resistance to at least isoniazid and rifampicin. Extensively drug-resistant (XDR) TB is MDR plus resistance to a fluoroquinolone (eg moxifloxacin, ciprofloxacin) and one of three injectable agents (kanamycin, capreomycin, amikacin).

Drug-resistant TB occurs if treatment has been wrongly prescribed, intermittent or incomplete, with the strongest risk factor being previous TB treatment. The highest proportions of drug resistance among TB cases are found in eastern Europe, Russia and central Asia

Diagnosis

The mainstay of diagnosis is identification of acid-and alcohol-fast bacilli (AAFBs) in sputum, fluid (eg pleural fluid, pus) or tissue by Ziehl–Neelsen or auramine staining, and by culture to confirm *M. tuberculosis* (rather than a non-tuberculous mycobacterium) and to establish drug susceptibility. Culture is on Löwenstein–Jensen solid medium (taking up to 6 weeks) or in liquid culture media, in which mycobacteria grow more quickly, in up to 2 weeks, allowing faster confirmation of diagnosis.

PCR is increasingly being used on some samples (sputum, CSF). Rapid PCR-based tests for genes

conferring rifampicin and isoniazid resistance can give early indication of susceptibility. A test for a gene conferring rifampicin resistance (rpoB) is a useful indicator of probable MDR TB, as rifampicin monoresistance is rare. These tests do not replace culture and drug-susceptibility testing, which must also be done.

Interferon-γ tests

These blood tests measure the release of IFN-γ in the laboratory in response to antigens found only in *M. tuberculosis* (and not BCG or non-tuberculous mycobacteria). They are used to differentiate latent TB from a positive Mantoux test due to previous exposure or immunisation, but do not distinguish between active disease and latent infection. Their use is principally in assessing contacts of an index case or diagnosing latent TB in those at risk of reactivation, for example certain HIV-positive individuals and those planning immunosuppressive treatment, eg infliximab for rheumatoid arthritis. Latent infection can then be treated with isoniazid ± rifampicin. Interferon-γ tests are not useful in diagnosing active TB.

Treatment

Drug-susceptible TB is treated with rifampicin and isoniazid for 6 months, adding pyrazinamide and ethambutol for the first 2-month intensive phase ('RIPE'). The exception is central nervous system TB disease, in which case the total treatment is 12 months, with a 2-month intensive phase and a 10-month continuation phase (see Section 11.5.2 for CSF values in TB meningitis). Pyridoxine (vitamin B_6) can be added to prevent peripheral neuropathy due to isoniazid. First-line anti-tuberculous drugs and their side-effects are summarised in Table 11.9.

Drug-resistant TB is treated with individualised regimens comprising at least four second-line drugs to which the organisms is known or presumed to be susceptible. Regimens should contain fluoroquinolones, an injectable agent, prothionamide and other drugs depending on susceptibility testing. New anti-tuberculous agents are now finally emerging after decades with no or very little development.

Table 11.9 First-line anti-tuberculous drugs

	Pharmacokinetics	Side-effects	Use
Rifampicin	Potent liver enzyme inducer – interactions with HIV drugs, methadone, steroids, anticoagulants	Drug-induced hepatitis, orange secretions, influenza-like syndrome	TB, meningococcal prophylaxis, staphylococcal infections, *Legionella* spp.
Isoniazid	Potentiates phenytoin, carbamazepine	Peripheral neuropathy, hepatitis	TB (treatment and prophylaxis)
Pyrazinamide	Good meningeal penetration (for TB meningitis)	Liver toxicity, arthralgia, gout	TB
		Optic neuritis, leading to impaired colour vision,	

Ethambutol	Renal excretion – reduce dose in renal failure	scotomata and reduced visual acuity (check baseline vision and monitor on treatment)	TB and other mycobacteria

Steroids in TB treatment

The addition of glucocorticoids is currently recommended for meningeal and pericardial TB.

BCG immunisation

BCG immunisation contains live, attenuated *Mycobacterium bovis*. UK BCG policy no longer recommends immunisation at age 10–14; since 2005, the policy is targeted immunisation of high-risk individuals. Those for whom BCG is recommended include:

- Neonates born in, or with parents or grandparents from, an area with TB notification rates ≥40/100 000 per year
- Neonates with a recent family history of TB
- Mantoux-negative (tuberculin skin test) close contacts of those with active TB
- Mantoux-negative new entrants to the UK, aged >16, from an area with notification rates ≥40/100 000
- Unvaccinated, Mantoux-negative individuals at occupational risk (eg health-care workers).

BCG is contraindicated in:

- Immunocompromised individuals, eg receiving oral steroid treatment, HIV infection, haematological malignancies.

11.6.2 Non-tuberculous mycobacteria

Also called opportunistic atypical or 'mycobacteria other than tuberculosis' (MOTT), this group includes mycobacteria other than *M. tuberculosis* complex (which includes *M. tuberculosis*, *M. africanum* and *M. bovis*). Some clinical associations of the more common opportunistic mycobacteria are given in Table 11.10.

Diagnosis

UK guidelines for management of these infections give guidance on assessing the significance of a laboratory isolate, depending on the sample from which it is cultured, the number of isolates, degree of growth and the patient's clinical condition. Those with established, chronic lung disease, such as emphysema, bronchitis or cavitation from previous TB, are at increased risk of opportunistic mycobacterial disease, as are immunocompromised individuals, eg those with HIV infection. Pulmonary disease is diagnosed when two specimens, at least 7 days apart, are isolated from a patient whose chest radiograph is consistent with mycobacterial disease, with or without symptoms or signs.

Table 11.10 Clinical associations of more common opportunistic mycobacteria

Pulmonary disease resembling tuberculosis	*M. kansasii* *M. malmoense* *M. avium* complex *M. xenopi* *M. fortuitum*
Lymphadenitis	*M. avium* complex *M. malmoense* *M. scrofulaceum*
Cutaneous disease	*M. marinum* (fish-tank granuloma) *M. ulcerans* (Buruli ulcer) *M. fortuitum*
Disseminated disease	*M. avium* complex (particularly in advanced HIV infection) *M. kansasii*

Treatment

Treatment is with combinations of antimycobacterial drugs, depending on the site of disease, HIV status of the patient and the organism isolated. Treatment regimens are longer than for TB, and may be up to 2 years or longer if a patient remains immunosuppressed or continues to have positive cultures.

Mycobacterium avium complex

This subgroup of opportunistic mycobacteria includes *M. avium*, *M. intracellulare* and a few other minor species, but is usually referred to as 'MAC' or MAI (*Mycobacterium avium intracellulare*). These are ubiquitous environmental organisms and are not acquired by person-to-person spread.

In immunocompetent people, MAC can cause pulmonary infection in one of two patterns:

1. Disease resembling tuberculosis in elderly smokers with chronic lung disease
2. Nodular infiltrates and a bronchiectasis-like pattern in those without chronic lung disease ('Lady Windermere syndrome'), with a productive cough but no systemic symptoms.

Paediatric infection can cause lymphadenopathy.

Since the start of the HIV pandemic, MAC is commonly seen in HIV-infected individuals with low CD4 counts. It causes systemic symptoms, fever and sweats. A full blood count may show pancytopenia. It can be cultured from blood or bone marrow in addition to sputum and stool. Consideration of primary prophylaxis with azithromycin is recommended for those with a CD4 count <50 cells/mm^3 until the CD4 count is improved by antiretroviral therapy. MAC is treated using combinations of anti-mycobacterial drugs as above.

Mycobacterium leprae

For *Mycobacterium leprae*, see Section 11.7.5.

11.7 SPECIFIC TROPICAL INFECTIONS

This is not a comprehensive review of tropical medicine and more extensive information on a greater range of illnesses can be sought by those interested. However, the main differentials, focusing on those most likely to appear in membership exams, and most important imported infections are included here.

11.7.1 Malaria

Four *Plasmodium* species commonly affect humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae* (A fifth of *P. knowlesi* is increasingly recognised as a human infection in south-east Asia). *P. falciparum* is the only one of these four commonly to cause severe disease, and therefore the majority of deaths. All are transmitted by female anopheles mosquitoes, which require blood for the development of their eggs, and all can be transmitted by blood transfusion. Worldwide, the majority of malaria mortality is in sub-Saharan Africa, but it occurs throughout the tropics. IPs vary between species: for *P. falciparum* it is usually 7–14 days, but may be longer. IPs are longer for other species.

Diagnosis

Thick-film examination (higher sensitivity), then thin-film examination (to determine species and, if *P. falciparum*, parasitaemia). Trophozoites are the form seen on blood films, inside red cells. Schizonts seen on a film are a marker of severity. Antigen tests are used in most labs and can differentiate between species. Repeat films are required if negative and there is a high clinical suspicion.

Falciparum malaria

Falciparum malaria is defined as severe if the parasitaemia (percentage of red cells on a thin film that contain malaria parasites) is 2% or more, or if there are complications (evidence of multisystem involvement, as below).

Clinical features

Clinical features are fever, headache, rigors, myalgia and thrombocytopenia (common in non-severe malaria). It may present with gastrointestinal symptoms and commonly presents with jaundice, which is mostly pre-hepatic, due to haemolysis (the jaundice often leads to initial misdiagnosis as acute hepatitis, a potential trap in clinical practice and MRCP questions). It may be complicated by:

- *Cerebral malaria*: reduced level of consciousness (strictly defined as ‘coma’), seizures, focal neurological disorders, but not meningism
- *Renal failure*: which may be severe and require haemodialysis, with blackwater fever or haemoglobinuria due to haemolysis
- *Pulmonary oedema* and acute respiratory distress syndrome (ARDS): It is vital not to overload with fluid
- *Severe anaemia*: due to haemolysis and bone marrow suppression, particularly in children
- *Hypoglycaemia*: regular glucose monitoring is important, particularly as quinine can also cause hypoglycaemia

- *Algid malaria*: malaria complicated by sepsis due to infection with Gram-negative organisms
- *Coagulopathy*: in addition to thrombocytopenia
- *Hyperreactive malarial splenomegaly* ('tropical splenomegaly syndrome'): massive splenomegaly secondary to malaria, which may resolve with continuing antimalarial therapy.

Treatment

Artesunate is the most effective therapy for severe falciparum malaria, used intravenously. Quinine may still be used, intravenously for severe and oral for non-severe falciparum, for 5 days or until blood films are negative. This must be followed by a second agent: doxycycline 200 mg daily for 7 days, is preferable to Fansidar (pyrimethamine and sulfadoxine) single dose.

Chloroquine is no longer recommended for falciparum malaria due to widespread resistance.

Benign malaria

P. vivax, *P. ovale* and *P. malariae* present with symptoms similar to falciparum malaria, but lack the complications or high parasitaemia. Most West Africans are protected against *P. vivax* by lack of the Duffy antigen, the receptor via which the merozoite stage of the parasite gains entry to red blood cells. The survival advantage conferred by the lack of this antigen accounts for the widespread absence of *P. vivax* in this region. Treatment is with oral chloroquine, followed with primaquine for 14 days to eliminate liver hypnozoites in *P. vivax* and *P. ovale* (but not *P. malariae*). Before giving primaquine, glucose-6-phosphatase dehydrogenase (G6PD) deficiency and pregnancy should be excluded. Primaquine can cause severe haemolysis in those G6PD deficiency; if it is required, then dose-and-interval adjustments can be made to avoid haemolysis.

Prophylaxis against malaria

Drugs used for prophylaxis of malaria when travelling to endemic areas include: doxycycline, mefloquine, Malarone (atovaquone and proguanil), and chloroquine and proguanil. The latter is not recommended for travel to sub-Saharan Africa due to resistance. Bite prevention, including use of insect repellents and bed nets, is an essential part of risk reduction.

11.7.2 Enteric fever ('typhoid')

Enteric fever is caused by *Salmonella typhi* and *S. paratyphi*, and is common in travellers returning from Asia, with around 350 cases per year reported in the UK, most associated with travel to the Indian subcontinent.

Incubation period

The IP is 1–3 weeks, depending on inoculating dose.

Transmission

Transmission is by ingestion of contaminated food or water. Enteric fever is endemic in areas with poor sanitation. Risk is increased with gastric acid suppression.

Clinical features

Enteric fever is a syndrome of fever, myalgia, cough, constipation, abdominal pain and headache. Features worsen with time and peak in the third week. Deafness and diarrhoea can occur and there is a classically described 'relative bradycardia'. Hepatosplenomegaly and 'rose spots' (pale pink, blanching spots on the trunk) may be found. Complications include psychosis or altered mental state, hepatitis, cholecystitis, pneumonia, pericarditis and meningitis. Leukopenia is typical. Untreated, mortality is from septicaemia or gastrointestinal perforation.

Diagnosis

Diagnosis is made by culture of the organism, a Gram-negative bacillus, from blood, bone marrow, stool or urine. Serology/Widal test is not useful.

Treatment

Prompt antibiotic therapy reduces mortality. Fluoroquinolones (eg ciprofloxacin) are the most effective treatment if the organism is susceptible, but there is widespread resistance in Asia and azithromycin is preferred for uncomplicated disease in those with recent travel to Asia. Intravenous ceftriaxone is an alternative for more severe disease. Treatment is for 14 days. Relapse is relatively common and the organism can persist in the gallbladder. Chronic secretion of the organism occurs occasionally and such individuals can transmit to others.

Immunisation

Polysaccharide vaccine is given intramuscularly; protection (*S. typhi* but not *S. paratyphi*) is incomplete and lasts for 3 years (alternatives are oral live, attenuated or killed whole-cell injectable vaccines). It is recommended for travellers to endemic areas.

11.7.3 Amoebiasis

The protozoon *Entamoeba histolytica* is transmitted by ingestion of food or water contaminated by amoebic cysts secreted in the faeces of asymptomatic individuals. It is found wherever sanitation is poor. Amoebae multiply in the gut and can cause invasive colitis and amoebic dysentery or amoebic liver abscess (containing 'anchovy sauce' pus), which if untreated can discharge into a cavity such as the peritoneum, pleural cavity or pericardium. It can also cause extraintestinal disease, eg abscesses in the lung or brain. The IP can be as long as several months.

Clinical features

Amoebic dysentery with blood and mucus in stools. Amoebic liver abscess can cause right upper quadrant pain and tenderness, right shoulder tip pain, with fever and leukocytosis. There may be hepatomegaly or signs of rupture of the abscess into a cavity, such as peritonitis or pericardial effusion.

Diagnosis

Amoebic trophozoites seen on microscopy of fresh stool, though repeat specimens may be required as

sensitivity is poor. Aspirates from abscesses may also be examined for trophozoites. Serology is used for invasive disease and imaging is useful

Treatment

Metronidazole with diloxanide furoate to eradicate intestinal cyst carriage. Aspiration of abscess if large or causing severe pain or swelling.

11.7.4 Schistosomiasis ('bilharzia')

These trematode, or blood fluke, infections cause much mortality and morbidity worldwide. Schistosomiasis is most common in Africa, particularly in freshwater lakes, and in the Middle East. The three main species affecting humans are *S. mansoni* (Africa, South America); *S. haematobium* (principally Africa, particularly the Nile valley) and *S. japonicum* (east Asia).

Transmission to humans occurs by exposure to fresh water infested with larvae (cercariae) from infected snails. The cercariae penetrate the skin and migrate as developing worms towards the venous plexus of the bladder or mesenteries, depending on the species, where they remain as adult pairs and lay eggs, which are in turn passed in the urine or faeces. Principal organs affected are:

- *S. haematobium* (urinary tract)
- *S. mansoni* and *S. japonicum* (bowel and liver), although CNS, pulmonary and other sites can become involved.

Clinical features

- **Acute**: cercarial dermatitis ('swimmers' itch') is an acute reaction to cercarial penetration, causing a self-limiting, pruritic, papular rash, within 24 hours of freshwater exposure. Katayama fever, or acute schistosomiasis, is less common but more severe and develops between 4 and 8 weeks after exposure, when the first eggs are produced. Features of an immune complex-mediated syndrome may include fever, urticaria, eosinophilia, diarrhoea, hepatosplenomegaly, cough and wheeze
- **Chronic**: the large numbers of eggs produced by adult worms are the cause of pathology in chronic schistosomiasis. The eggs cause granulomatous reactions and fibrosis in affected organs, leading to pathology as follows:
  - *Urinary tract*: haematuria ('terminal haematuria') as eggs pass through the bladder epithelium, fibrosis and calcification of the bladder (visible on plain radiograph), obstructive uropathy and, usually after at least 20 years of infection, squamous cell carcinoma of the bladder
  - *Bowel and liver*: haemorrhagic polyps and colitis, hepatomegaly, periportal fibrosis causing portal hypertension (with splenomegaly, varices and ascites)
  - *Other sites*: eggs can transit via the pulmonary and systemic circulation to cause pathology in other organs, such as pulmonary hypertension (eg *S. haematobium*), paraparesis (from transverse myelitis, eg *S. mansoni*), or seizures due to space-occupying lesions or encephalopathy (eg *S. japonicum*)

Diagnosis

Microscopic identification of eggs in the urine (terminal urine sample) or faeces, or in a tissue biopsy. Serological diagnosis is useful and would usually (but not always) be positive in Katayama fever.

Treatment

Praziquantel with steroids and anticonvulsants for CNS disease.

11.7.5 Leprosy

Leprosy (Hansen's disease) is caused by the slowgrowing, intracellular, acid-fast bacillus *Mycobacterium leprae*, which is transmitted person-to-person by respiratory droplets from the nasal mucosa. It is associated with overcrowding and poverty, and most cases are found in south Asia (more than in Africa and South America). Unlike TB, the risk of developing leprosy is not greatly increased by HIV infection. BCG offers some protection.

Incubation period

The IP is 2–12 years (shorter for tuberculoid leprosy, longer for lepromatous leprosy). Of those who are infected, 95% develop an effective immune response and clear the organism; others develop disease.

Clinical features

The organism grows well at lower temperatures and thus affects the skin, upper respiratory mucosa, superficial nerves, anterior chamber of the eye, lymph nodes and testes. Features are depigmented, anaesthetic skin patches or other, sometimes nodular, skin lesions, thickened superficial nerves (eg ulnar nerve), or signs of involvement of other organs, such as visual impairment.

There is a **spectrum** of disease from tuberculoid (paucibacillary) to lepromatous (multibacillary) types, depending on the degree of the T-cell-mediated immune response to the organism, as shown in Table 11.11.

Diagnosis

Diagnosis is based on the clinical features in a patient from an area where leprosy is endemic, plus a skin smear from a lesion, stained for mycobacteria. *M. leprae* cannot be grown in vitro.

Treatment

The World Health Organization recommends combination drug treatment of rifampicin, dapsone and clofazimine for 12 months for multibacillary leprosy, and rifampicin and dapsone for 6 months for paucibacillary leprosy. Clofazimine can cause abnormal skin pigmentation and ichthyosis.

Other aspects of care, such as protection of anaesthetic feet and hands, are also important.

Reactions

These are due to a shift in the individual's immune response, usually during treatment, either up or down the spectrum.

Reversal reaction (type 1)

Erythematous skin lesions and nerve damage with pain and loss of function occur in patients with delayed-type hypersensitivity and an increasing cell-mediated immune response to *M. leprae*. Prednisolone treatment can reduce nerve damage.

Erythema nodosum leprosum (type 2)

This occurs in patients at the lepromatous end of the spectrum. Reactions comprise fever, erythema nodosum leprosum (ENL) and occasionally life-threatening glomerulonephritis and renal failure due to immune complex deposition. Chronic or severe ENL can lead to amyloidosis. Treatment is with prednisolone or, in chronic reactions, higher-dose clofazimine or thalidomide.

11.7.6 Lymphatic filariasis

Filarial worm larvae, most commonly *Wuchereria bancrofti* or *Brugia malayi*, are transmitted throughout the tropics by mosquitoes and cause debilitating deformities of the limbs as a result of lymphatic damage. This can lead to 'elephantiasis' of the limbs. Microfilariae produced by adult worms can cause tropical pulmonary eosinophilia.

Diagnosis

Diagnosis is made by clinical appearance, microfilariae on blood film, serology and the presence of an eosinophilia.

Treatment

Diethylcarbamazine (DEC) and supportive treatment for lymphoedema.

Table 11.11 Spectrum of disease in leprosy

Tuberculoid	Brisk T-cell responses	Well-defined lesions or one/few nerves affected
Borderline	Some cell-mediated immunity	Multiple lesions, widespread nerve involvement, with sensory and motor function loss
Lepromatous	Poor T-cell responses; humoral immune response	Numerous, nodular lesions, not anaesthetic, thickened skin

11.7.7 Filariasis, including onchocerciasis

Onchocerciasis ('river blindness') is a form of filariasis caused by *Onchocerca volvulus* and transmitted by simulium black flies. It occurs mainly in west and central Africa (but also in south and

central America) near fast-flowing rivers. Clinical features include: subcutaneous nodules containing adult worms (onchocercomas); thickened, itchy, inelastic, wrinkled skin with lymphoedema, leading to 'hanging groin'; and eye lesions leading to blindness. Eye lesions involve the cornea, anterior chamber and iris.

Diagnosis

Skin snips to detect microfilariae are the gold standard, but not widely available. Serological tests are more commonly used outside specialist centres.

Treatment

Ivermectin, single dose, is used in the treatment of individuals and in mass eradication campaigns in Africa.

11.7.8 Cysticercosis

The pork tapeworm *Taenia solium* differs from the beef tapeworm, *T. saginata*, in that it can cause invasive disease in the human host. Intestinal infection with adult tapeworms is caused by ingestion of larval cysts in undercooked pork. In addition, ingestion of eggs from faecal–oral contamination can cause migration of the parasite to the tissues, most notably the muscles and CNS. Neurocysticercosis is a common cause of epilepsy worldwide.

Clinical features

Calcified subcutaneous or muscle cysts, visible on radiograph; epilepsy or spinal symptoms from CNS lesions.

Diagnosis

Diagnosis is made by imaging and serology for cysticercosis (eggs on stool microscopy for intestinal tapeworm infection).

Treatment

Albendazole or other anthelmintic drugs for intestinal tapeworm infection. Neurocysticercosis may require anticonvulsants and steroids before using anthelmintic drugs.

11.7.9 Trypanosomiasis

African trypanosomiasis

Trypanosoma brucei spp. (*gambiense* [West Africa] and *rhodesiense* [East Africa]) are transmitted by tsetse flies and cause sleeping sickness, which occurs in sub-Saharan Africa. In the first stage, trypanosomes multiply in blood and lymphatic tissues, producing fever, headaches, joint pains and itching. Later, trypanosomes invade the CNS from the blood and cause a meningoencephalitis, ultimately causing death in weeks or up to years, depending on the subtype. It is rarely seen in the UK,

although imported cases are usually associated with travel to national parks in Africa.

Diagnosis
Trypanosomes seen on blood or CSF microscopy; serology.

Treatment
The WHO recommends treatment of the first stage with pentamidine (W. African) or suramin (E. African), and the second stage with nifurtimox plus eflornithine (W. African) or the toxic arsenical compound melarsoprol (E. African)

South American trypanosomiasis

Trypanosoma cruzi is transmitted by reduviid bugs and causes Chagas' disease, which occurs in Central and South America. It can also be transmitted by blood transfusion.

Clinical features
Acute infection gives non-specific symptoms. Chronic complications include megaoesophagus, megacolon and cardiomyopathy with arrhythmias.

Diagnosis
Serology, or trypanosomes seen on blood films.

Treatment
Benznidazole or nifurtimox. Surgery for gastrointestinal complications or symptomatic treatment for cardiac disease.

Note on eosinophilia

In parasitic infections, eosinophilia is related to the tissue-migration phase of the life cycle of a multicellular parasite. It therefore occurs in schistosomiasis, strongyloidiasis and filariasis, but not in malaria, amoebiasis or giardiasis. Also note the non-infective causes of eosinophilia, including some malignancies and connective tissue diseases, drug reactions and allergies

11.7.10 Leishmaniasis

The many species of unicellular, protozoan leishmania parasites, transmitted by sandflies from animal reservoirs, cause cutaneous, mucocutaneous and visceral (kala-azar) leishmaniasis. Cutaneous leishmaniasis occurs mostly in central and south Asia and South America, and is relatively common in returning travellers in the UK. Visceral leishmaniasis occurs mostly in south Asia, Brazil and north-east Africa, but is rarely seen in travellers from the UK; there is an association with HIV infection.

Cutaneous leishmaniasis: skin lesions, including ulcers, nodules or plaques, with local lymphadenopathy, occur weeks to months after exposure. Diagnosis is by biopsy of lesions with appropriate staining to visualise the amastigote stage of the parasite and culture if available.

Treatment is with sodium stilbogluconate.

Mucocutaneous leishmaniasis: certain *Leishmania* spp. cause a destructive mucosal lesion, often at the mucocutaneous junction of the nose, with secondary bacterial infection. Diagnosis is by biopsy of the edge of a lesion for histological examination. Treatment is with sodium stilbogluconate as for cutaneous disease.

Visceral leishmaniasis (kala-azar): a systemic illness with fever, weight loss, hepatosplenomegaly and, in some cases, bone marrow involvement, with cytopenias. Diagnosis is by biopsy of lesions, lymph nodes, bone marrow or, where appropriate skills are available, spleen. Treatment is with liposomal amphotericin B and prognosis is very poor if untreated, particularly in those with HIV co-infection.

11.7.11 Hookworm

Ancylostoma duodenale and *Necator americanus* are helminths, transmitted by penetration of larvae in the soil through the skin. Infection is common where sanitation is poor, and hookworm is a common cause of anaemia worldwide. The worms mature in the intestines then attach to the mucosal surface, causing bleeding and iron-deficiency anaemia.

Diagnosis

Characteristic eggs are seen on stool microscopy.

Treatment

Anthelmintic drugs, such as mebendazole.

11.7.12 Strongyloidiasis

An intestinal helminth found throughout the tropics and subtropics, *S. stercoralis* has a life cycle that can be completed entirely within the human host and therefore cause illness many years after original exposure. Primarily an intestinal disease (diarrhoea, eosinophilia) with cutaneous manifestations (larva currens), in the context of immunosuppression, usually with steroids, can lead to a hyperinfection syndrome with widespread larvae included in respiratory secretions and disseminated disease with Gram-negative sepsis and organ failure. *Strongyloides* spp. are associated with human T-cell lymphotrophic virus-1 (HTLV-1) infection.

Diagnosis

Larvae seen in stools (or elsewhere in hyperinfection syndromes), or serology.

Treatment

Ivermectin or albendazole.

11.7.13 Dengue fever

Dengue fever is caused by a mosquito-borne flavivirus prevalent throughout the tropics, with greater risk in south-east Asia and the Caribbean. The IP is 5–8 days and symptoms are fever, rigors, headache (characteristically retro-orbital pain), with blanching, maculopapular rash and lymphadenopathy. There may be leukopenia, thrombocytopenia and mild transaminitis. The illness is usually mild and self-limiting. Dengue haemorrhagic fever is thought to result from subsequent infection with a second of the four serotypes

Diagnosis

In practice, the diagnosis is clinical in the context of the travel history. Serology confirms, but results take time.

Treatment

No specific treatment is available: supportive measures only. Mild disease is self-limiting, but there is substantial mortality in Dengue haemorrhagic fever (rare in the UK).

11.7.14 Viral haemorrhagic fevers

The main viruses of relevance here, to consider in returning travellers to the UK from Africa, are the arenavirus, Lassa, and the filoviruses, Marburg and Ebola. Crimean-Congo haemorrhagic fever is more widespread geographically, occurring in Africa, but also parts of the Middle East, Asia and Europe. These viruses can transmit person-to-person via blood and body fluids, including indirectly via contamination of the environment, and isolation measures for suspected cases are essential to protect health-care workers. Case fatality rates are high.

Viral haemorrhagic fevers (Lassa, Ebola, Marburg) should be considered in returning travellers with fever developing within 21 days of visiting endemic countries in west and central Africa, particularly if they have visited rural areas. A risk assessment should be undertaken and special isolation procedures are required for suspected cases and their blood specimens until a viral haemorrhagic fever is excluded. Malaria is an important and much more common differential diagnosis, and imported viral haemorrhagic fevers are very rare. Management of suspected cases should be in collaboration with public health. Those with confirmed disease should be managed at a high-security infectious disease unit.

Other viruses (including those causing dengue fever, Chikungunya and yellow fever) can have haemorrhagic manifestations, but most are less severe and do not transmit person-to-person, so are not managed in the same way.

Diagnosis

A malaria film would usually be done to exclude malaria before moving on to testing for viral haemorrhagic fever. Diagnostic tests are by serology or PCR at a national reference laboratory. All specimens need to be handled in collaboration with the local laboratory to reduce risk to laboratory staff.

Treatment

Ribavirin is recommended for confirmed Lassa fever. No specific antivirals are effective for Ebola or Marburg.

11.7.15 Rickettsial infections

African tick-bite fever typhus (*R. africae*) is the main rickettsial infection to consider in returning travellers, particularly from Africa (others include Rocky Mountain spotted fever, Mediterranean spotted fever and scrub typhus [*O. tsutsugamushi*] in Asia). Travel to game parks in southern Africa is a particular risk factor for *R. africae*.

IP is 5–14 days and symptoms are non-specific, with fever, headache and myalgia. An eschar may be present at the site of a tick bite, with local lymphadenopathy, maculopapular rash and conjunctival infection.

Diagnosis

Serology.

Treatment

Doxycycline.

11.7.16 Approach to fever in the returning traveller

Priorities when assessing a returning traveller are to detect and treat potentially life-threatening conditions, and to consider and manage infection control issues. A thorough travel history is essential, including destinations visited before the most recent travel, whether rural or urban setting, and activities undertaken. Details of pre-travel immunisations and malaria prophylaxis used are required. Viral haemorrhagic fever must be considered initially in travellers returning from endemic areas with symptom onset within 21 days of leaving.

Examination will give an indication as to the focus of fever. Initial investigations (having excluded viral haemorrhagic fever) include malaria film, blood count, biochemistry, blood culture, urinalysis and chest radiograph. Serological tests can be done for specific infections thought likely. Returning travellers would normally be isolated for infection control reasons until a diagnosis has been made.

The main important differentials in those returning from sub-Saharan Africa are viral haemorrhagic fever, malaria, rickettsial infections and HIV (including primary HIV infection/seroconversion). From Asia, they are malaria, enteric fever, dengue fever and HIV. In many returning travellers, a specific diagnosis is not made. Alternatively, a non-infectious diagnosis or one unrelated to the recent travel may be the cause of fever.

11.8 IMPORTANT ZOONOSES

11.8.1 Brucellosis

Brucella spp. (*B. abortus* from cattle, *B. melitensis* from goats or sheep, *B. suis* from pigs) are Gram-negative coccobacilli that can cause disease if humans come into contact by handling animal carcasses, ingesting unpasteurised milk or inhaling aerosols from infected animal carcasses or laboratory isolates. The majority of UK cases are acquired abroad. The organisms spread through the blood and lymphatics, and localise in the reticuloendothelial system, causing granulomas. It is most common in Mediterranean and Middle Eastern countries and South America, and rare in the UK.

Clinical features

The IP may be 5–60 days and presenting features include fever, malaise, sweats and weight loss. Hepatosplenomegaly and lymphadenopathy may be present. Less commonly there is arthritis, osteomyelitis, orchitis, meningoencephalitis, endocarditis or granulomatous hepatitis. The acute phase may be followed by a relapsing–remitting course ('undulant fever').

Diagnosis

The organism may be grown in prolonged culture of blood or bone marrow. Serology is an alternative and more commonly positive than cultures.

Treatment

Doxycycline and rifampicin or, if more severe, then intravenous aminoglycosides. Treatment is for 3–6 weeks.

11.8.2 Lyme disease

Lyme disease is caused by the spirochaete *Borrelia burgdorferi*, transmitted by hard ticks (ixodid ticks) from an animal reservoir. It is found in large parts of Europe, including the UK (forest areas) and the USA (north-east), China, Japan and Australia.

Clinical features

Early features (with variable IP of a few days to a month) include a characteristic rash at the site of the tick bite, called erythema migrans, which is an expanding erythematous plaque with central clearing. There may be local lymphadenopathy and fever. Later features (weeks to months later) follow direct or haematogenous dissemination and may include focal neurological symptoms (eg Bell's palsy), encephalitis, meningitis, cardiac involvement with atrioventricular block, or arthritis with effusion. Around 90% present with erythema migrans and 10% with other features, including neuroborreliosis and arthritis.

Diagnosis

Serology (most positive after 4 weeks) in an accredited laboratory, or PCR of CSF, synovial fluid or tissue. CSF is lymphocytic in Lyme meningitis.

Treatment

Doxycycline or erythromycin for erythema migrans, which can be treated without serological confirmation. Intravenous ceftriaxone for neurological or cardiac manifestations.

11.8.3 Q fever

Q fever refers to syndromes caused by infection with the rickettsial organism, *Coxiella burnetii*. It is usually transmitted by exposure to cattle or sheep, by aerosol or direct contact, or from contaminated milk. It occurs worldwide.

Clinical features

Fever, pneumonia or hepatitis. A few individuals suffer a chronic infection with 'culture-negative' endocarditis and possibly myocarditis. Other features or less common presentations include rash, arthralgia, meningoencephalitis and glomerulonephritis.

Diagnosis

Acute and convalescent serology.

Treatment

Tetracyclines for 2–3 weeks. Longer, combination therapy is required for cardiac involvement.

11.8.4 Toxoplasmosis

Toxoplasma gondii is a common parasite infection in Europe, with adult parasite forms in the cat. The life cycle involves humans by ingestion of oocysts from food contaminated with cat faeces or consumption of undercooked meat (eg beef, pork).

Clinical features

Primary toxoplasmosis infection can be asymptomatic or manifest as an infectious mononucleosis-like illness, with fever, lymphadenopathy, myalgia and fatigue. Reactivation in the context of immunosuppression, especially HIV with low CD4 count, can cause intracerebral lesions resulting in focal neurology and an encephalitis. Primary infection during early pregnancy has severe sequelae for a minority, with fetal retinochoroiditis, encephalomyelitis, and hydrocephalus or microcephaly. With infection in later pregnancy, most infants develop retinochoroiditis in infancy, having been normal at birth.

Diagnosis

Serology (IgG represents previous exposure and IgM acute infection) and/or PCR on appropriate specimens.

Treatment

No specific treatment for primary infection in immunocompetent individuals. Pyrimethamine, sulfadiazine and folinic acid for reactivation diseases in immunocompromised individuals. Spiramycin is sometimes used for suspected infection in pregnancy to reduce the risk of transmission to the fetus.

Chapter 12
Maternal Medicine

CONTENTS

Maternal Medicine

12.1 PHYSIOLOGY OF NORMAL PREGNANCY

Pregnancy impacts upon every system in the body, and each system adapts in order to accommodate the demands of the fetoplacental unit. Consequently, pregnancy can adversely affect many preexisting medical conditions and, likewise, many pregnancy complications arise because physiological adaptation does not occur.

12.1.1 Cardiovascular system

- There is an increase in plasma volume from 2600 mL to approximately 3800 mL, reaching a plateau by 32 weeks' gestation
- Cardiac output rises by about 40%, from about 4.5 L/min to 6 L/min, reaching a plateau by 24–30 weeks' gestation. This occurs because of an increase in heart rate (from approximately 80 beats/min to 90 beats/min) and an increase in stroke volume
- Left ventricular hypertrophy and dilatation facilitate this change in cardiac output but contractility remains unchanged. The structural changes revert to normal early post-partum and definitely by 6 weeks
- Together with the upward displacement of the diaphragm, the apex of the heart is moved anterior and to the left
- These changes may result in ECG findings of left axis deviation, depressed ST segments and inversion or flattening of the T wave in lead III
- Echocardiogram may show a small pericardial effusion and mild valvular regurgitation. The valvular regurgitation is a reflection of dilatation
- There is a decrease in total peripheral resistance that outstrips the increase in cardiac output, and this results in a fall in blood pressure (between 8 and 36 weeks' gestation). This generalised vasodilatation accommodates the increased blood flow to the uterus and other organs. A nadir in diastolic BP is typically seen at about 16 weeks' gestation, coincident with second-wave spiral artery dilatation
- Symptoms of pregnancy may mimic cardiac disease, such that dyspnoea, peripheral oedema and palpitations are all common complaints in normal pregnancy
- A benign ejection systolic murmur occurs in 96% of pregnant women – due to increased blood volume and flow, together with anaemia.

12.1.2 Respiratory system

Vital capacity does not change during pregnancy but the tidal volume expands into the expiratory and inspiratory reserve volume.

Consequently, ventilation increases by 40% in pregnancy. This increase in ventilation exceeds the increase in oxygen consumption and there is a proportional fall in *P*CO2.

The bicarbonate level falls to maintain a normal pH and there is a concomitant fall in sodium.

12.1.3 Haematological system

- There is an increase in red cell mass, from a non-pregnant level of 1400 mL to 1650–1800 mL
- Plasma volume increases proportionately more than red cell mass, resulting in a fall in the haematocrit and haemoglobin concentration in normal pregnancy, such that a haemoglobin level of 1.05 g/L may be within 'normal' limits and represents a physiological anaemia
- There is an increased demand for iron, mainly to meet the demands of the increased red cell mass and to a lesser extent the requirements of the developing fetus and placenta. This demand is not quite matched by an increase in dietary absorption
- There are increases in the levels of factors VII, VIII and X, and in the level of plasma fibrinogen, such that in late pregnancy the fibrinogen concentration is at least double that in the non-pregnant state
- White blood cell count increases and may peak at >20 × 10^9/L in stressful conditions such as labour. This can make the diagnosis of infection difficult in pregnancy
- A decrease in platelet concentration to around 100–150 × 10^9/L can also be seen.

12.1.4 Renal system

- Kidneys increase in length by about 1 cm in pregnancy
- Ureters become dilated, secondary to increased progesterone and to the obstructive effect of the gravid uterus
- Renal blood flow increases from about 1.2 L/ min in the non-pregnant state to at least 1.5 L/ min in pregnancy. This results in an increase in glomerular filtration rate (GFR)
- Increased GFR leads to a fall in blood urea (from 4.3 mmol/L to 3.1 mmol/L) and creatinine (from 73 µmol/L to 47 µmol/L)
- Increased GFR also increases the filtered load of glucose and benign glycosuria is common in pregnancy.

12.2 PHARMACOKINETICS IN PREGNANCY

The physiological changes of normal pregnancy profoundly affect pharmacokinetics.

Physiological changes in pregnancy which affect drug pharmacokinetics

- Renal blood flow increases and leads to increased renal clearance
- Increased plasma volume and fluid retention lead to an increased volume of distribution and decreased plasma concentration
- Induction of liver enzyme pathways increases the hepatic metabolism of certain drugs and results in a decreased plasma concentration

The concept of placental transfer is unique to pregnancy. Essentially, every drug (with the exception of heparin) crosses the placenta and has the potential to cause unwanted side-effects, including teratogenic effects in the unborn fetus. Under most circumstances, drugs cross the placenta and will equilibrate between the fetal and maternal compartments. In view of this, drug therapy is best avoided unless absolutely necessary during the period of organogenesis in the first trimester (ie between conception and 12 weeks). If unavoidable, older drugs with established safety data should be the agents of first choice. Specific drugs are discussed in more detail later in this chapter.

12.3 PRE-EXISTING MEDICAL DISORDERS AND PREGNANCY

12.3.1 Diabetes and pregnancy

Before the advent of insulin, women with type 1 diabetes who survived to the age of reproduction and were then able to become pregnant had a less than 50% chance of having a successful pregnancy.

Today maternal mortality is rare, but both fetal and neonatal morbidity and mortality remain higher compared with the general pregnant population.

Terminology and definitions

Pregnancy induces profound metabolic alterations. To maintain stable concentrations of plasma glucose, insulin secretion must double from the end of the first to the third trimester. In pregnancy, glucose concentrations:

- Increase postprandially
- Decrease with fasting
- Decrease with gestation.

Pregnancy is associated with insulin resistance. This is a post-receptor defect, mediated by an increase in pregnancy-associated hormones and cortisol. Changes in insulin also cause accelerated starvation, with an increase in triglyceride breakdown resulting in raised free fatty acids and ketone bodies.

The diagnosis of diabetes in pregnancy is based on a 75-g oral glucose tolerance test (GTT) (Table 12.1).

Women with gestational diabetes mellitus (GDM) are those who are found, during pregnancy, to have a GTT that meets the threshold for diagnosing diabetes (Table 12.1). A small proportion of these women will inevitably have true, previously undiagnosed, diabetes.

With regard to the diagnostic thresholds for GDM, The NICE (National Institute for Health and Care

Excellence) guidelines are not evidence based and never have been. The guidelines are currently being revised by NICE and will be out in the next 2 years.

Table 12.1 Interpreting the oral glucose tolerance test in pregnancy

Diagnosis	Fasting blood glucose (mmol/L)	Two-hour blood glucose (mmol/L)
Diabetes	≥5.1	≥8.5

Impaired glucose tolerance not diagnosed anymore.

Diagnostic thresholds vary significantly around the country.

The IADPSG (International Association of Diabetes in Pregnancy Study Groups) and the WHO (World Health Organization) have recently recommended ≥5.1 mmol/L (fasting) or 8.5 (2-h post 75-g oral glucose load). This is based on an odds ratio (OR) of 1.75 for having a large-for-gestational age (LGA) baby from the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) data. There is enormous debate nationally about the significant resource it would require to treat all these women as GDM.

Risk factors for screening

- BMI >30 kg/m^2
- Previous macrosomic baby weighing ≥4.5 kg
- Previous gestational diabetes
- First-degree relative with diabetes
- Family origin with a high prevalence of diabetes (south Asian, black African–Caribbean and Middle Eastern)

Those with a previous history of gestational diabetes should be offered a GTT between 16 and 18 weeks' gestation, repeated at 28 weeks' gestation if earlier test normal.

Women with an identifiable risk should be offered a GTT between 24 and 28 weeks' gestation.

Effects of diabetes on the fetus

Congenital malformations

- Overall there is a 4- to 10-fold increase in the incidence of congenital abnormalities in infants of diabetic mothers compared with the normal pregnant population
- Cardiac and neural tube defects are among the most common abnormalities
- Caudal regression: an embryological defect that occurs during the third week of intrauterine development and is strongly associated with maternal diabetes, although it is rare compared with cardiac and neural tube defects. Although the syndrome is highly variable in severity, it can result in fusion of the lower limbs and urogenital and anorectal abnormalities

- The exact mechanism underlying the increase in congenital abnormalities is unknown but may reflect an abnormal metabolic environment (high serum glucose) around the time of organogenesis
- Fetal anomaly rates similar to those in the non-diabetic population can be achieved with meticulous preconceptional glycaemic control.

Spontaneous miscarriage

- Poorly controlled diabetes is associated with an increased risk of miscarriage, but women with moderately well-controlled diabetes have only a minimally increased risk
- A rate of miscarriage equivalent to that of the non-diabetic population can be achieved by excellent glycaemic control.

Perinatal mortality

In a multidisciplinary setting, excluding deaths from congenital malformations, perinatal mortality rates are similar between infants of diabetic mothers and those of normal pregnant women.

Unexplained fetal death in utero

Despite improvements in care, death in utero of a normally formed fetus still occurs. Conventional tests of fetal wellbeing have poor sensitivity for predicting such events. The aetiology of these deaths is complex but includes alterations in the following:

- Placental oxygen transfer (reduced red cell oxygen release mediated through 2,3-diphosphoglycerate [2,3-DPG])
- Fetal acid: base balance (tendency towards metabolic acidosis, worsened by increasing maternal glucose concentrations)
- Organomegaly (results in increased metabolic demand)
- Fetal thrombosis (more likely because of fetal polycythaemia).

Effects of diabetes on the neonate

Birthweight

- There is an increased incidence of both small-and large-for-gestational-age (SGA, LGA) fetuses born to diabetic mothers. SGA affects 2% of babies. It is increased in mothers with nephropathy (4.5%) and microalbuminuria (4%)
- Approximately 25–40% of infants of mothers with diabetes have birthweights >90th centile and as many as 35% have birthweights >95th centile. This leads to an increase in intrapartum complications, including an increase in both the caesarean section rate and the incidence of shoulder dystocia
- Increased growth rates may be seen as early as 20–24 weeks' gestation
- Subcutaneous fat deposits correlate with maternal plasma glucose concentrations and glycated haemoglobin (HbA1c) levels, amniotic fluid C-peptide levels and fetal serum insulin/ glucose ratios

- Fetal growth restriction is more frequently seen in diabetic women with long-standing disease and evidence of microvascular complications.

Respiratory dysfunction
Reduced phosphatidylglycerol production results in surfactant deficiency; this in turn predisposes the infant to hyaline membrane disease.

Hypoglycaemia
This arises because of the following:

- Endogenous hyperinsulinaemia developed in utero
- Reduced hepatic phosphorylase activity
- Reduced glucagons and catecholamines resulting in reduced glucose release from the liver.

Polycythaemia and jaundice
Polycythaemia occurs in 29% of infants of diabetic mothers, compared with 6% of infants of normal pregnant women; there is a direct correlation with diabetic control. Polycythaemia results in an increased viscosity, which may cause the following:

- Increased cardiac work
- Microvascular abnormality, leading to respiratory distress, renal vein thrombosis and necrotising enterocolitis
- Jaundice occurs in about 19% of infants due to an increase in red cell destruction as well as liver immaturity and poor handling of bilirubin.

Hypocalcaemia and hypomagnesaemia
Calcium and magnesium levels are lower in infants born to diabetic mothers, predisposing to neonatal seizures; the exact mechanism is unknown.

Hypertrophic cardiomyopathy
As many as 30% of infants may have an enlarged heart, and 10% of these may have associated cardiac dysfunction. This correlates with maternal diabetic control. The heart shows features similar to that of hypertrophic obstructive cardiomyopathy, but the dysfunction tends to resolve in the neonatal period.

Management of pregnancy in the diabetic patient

All patients should be counselled about the risks of pregnancy and the need for vigilant clinical management.

Pregnancy should be planned.

Pre-pregnancy

- Switch to insulin if the patient is on oral hypoglycaemics unless on metformin (± glibenclamide)
- Encourage tight glucose control (eg preprandial levels 3.5–5.9 mmol/L, postprandial <7.8 mmol/L)

- Weight reduction if body mass index (BMI) >27
- HbA1c should be maintained at 48 mmol/mol (previously 6%) (Table 12.2)
- Treat any retinopathy before rapid optimisation of glucose control
- Screen for nephropathy – if creatinine ≥125 μmol/L or estimated glomerular filtration rate (GFR) <45 mL/h refer to nephrologist
- Stop angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and statins
- Start high-dose (5 mg) folic acid.

Table 12.2 Glycated haemoglobin (HbA1c) levels

DCCT: HbA1c (%)	IFCC: HbA1c (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
9.0	75

DCCT, Diabetes Control and Complications Trial; IFCC, International Federation of Clinical Chemistry.

Antenatal care

It is very important to involve the multidisciplinary team in the care of the patient. Patients should be booked in the antenatal clinic at a very early stage with organisation of an ultrasound scan to accurately date the pregnancy (crown–rump length [CRL] at 8–12 weeks gives expected date of delivery (EDD) ± 5 days). Patients should be given dietary advice and baseline renal function should be assessed. Other important aspects of management include:

- Good glycaemic control reduces the risk of miscarriage, congenital malformations, stillbirth and neonatal death. Advise women to test fasting and 1-hour postprandial blood glucose levels after every meal during pregnancy. Maintain tight glucose control (preprandial levels 3.5–5.9 mmol/L); the patient should be warned about the possibility of hypoglycaemic episodes
- Serum screening should be interpreted with care as α-fetoprotein (AFP) and PAPPA (pregnancy-associated plasma protein A) levels are lower in diabetic pregnancies. Nuchal translucency (NT) screening (performed between 11 weeks 6 days and 13 weeks 6 days of gestation) is a more reliable alternative
- A detailed anomaly scan, including fetal echocardiography, should be performed
- Regular review with blood pressure measurement and urinalysis
- Referral to a nephrologist if serum creatinine is abnormal (≥120 μmol/L) or total protein excretion exceeds 2 g/day; thromboprophylaxis if proteinuria is >5 g/day
- Serial fetal growth and liquor volume assessment

- Cardiotocograph (CTG) may be useful after 36 weeks to assess fetal wellbeing, in the light of possible risk of fetal death in utero
- In view of the increased risk of preterm delivery (induced or spontaneous) patients may require high-dose intramuscular fluorinated steroids (eg betamethasone 12 mg, two doses 12–24 h apart) to accelerate fetal lung maturation (by stimulating surfactant secretion). A sliding scale of insulin would be necessary during this treatment. Tocolytics are used to stop uterine activity (ie in the treatment of preterm labour). Avoid ritodrine and salbutamol because these can interfere with glycaemic control. Alternatives are nifedipine and atosiban (an oxytocin receptor antagonist).

The equivalent of the current DCCT HbA1c targets of 6.5% and 7.5% are therefore 48 mmol/mol and 58 mmol/mol in the new units, with the non-diabetic reference range of 4.0–6.0% being 20–42 mmol/mol.

The timing and mode of delivery will be individualised according .to the patient and health of the fetus. Those with a normal size baby do not require induction of labour before term.

Labour

Good diabetic control should be maintained in labour (4–7 mmol/L). This will often necessitate the use of a sliding scale for insulin administration. The following are also important:

- Continuous CTG
- Watch for obstructed labour and be aware of possible shoulder dystocia, both associated with fetal macrosomia
- High caesarean section rate (as high as 60–65%).

Post-partum

- Reduce insulin back to pre-pregnancy levels after delivery of the placenta
- Encourage breastfeeding (safe with insulin, metformin and glibenclamide)
- Discuss contraception (see below).

Gestational diabetes/impaired glucose tolerance in pregnancy

Initially, glycaemic control may be achieved through diet (total calories between 1800 and 2000/ day). Fibre intake should be increased and 50% of energy should be derived from carbohydrates.

- If preprandial blood glucose levels are >6 mmol/L despite lifestyle and dietary changes, then therapy is required
- Regular insulin, the rapid-acting insulin analogues aspart and lispro, and/or the oral hypoglycaemic agents metformin and glibenclamide may be considered
- The fetus is at risk of macrosomia and hence birth trauma
- Insulin requirements cease after delivery of the placenta
- It is vital that a GTT is performed at 6 weeks after delivery and annually thereafter.

The patient should be counselled with regard to her weight, diet and exercise. Without attention to this, more than 50% of women with gestational diabetes will develop true diabetes over the next 20 years.

Contraception for patients with diabetes

The following are important considerations:

- The combined pill (COP): associated with an increased risk of thrombosis, both venous and arterial. Nevertheless this would be suitable for the young woman with well-controlled diabetes and no evidence of vascular disease
- Progesterone-only pill: lower efficacy compared with the COP; greater likelihood of menstrual irregularities
- Intrauterine contraceptive device (IUCD): an effective method of contraception in diabetics. No evidence of reduced efficacy. A Mirena/IUS (intrauterine system) could also be considered
- Sterilisation: this is suitable for diabetic women who have completed their family, or wish to avoid pregnancy because of associated microvascular complications (severe retinopathy or nephropathy).

12.3.2 Cardiac disease and pregnancy

The overall incidence of heart disease in pregnancy is increasing, with a prevalence of 8.8% of pregnancies, due to the development of corrective/palliative surgery over the last 30 years. There is also an increase in ischaemic heart disease. Cardiac disease remains the major cause of direct maternal mortality (Confidential Enquiry into Maternal and Child Health or CEMACH 2006–08). The haemodynamic changes that occur in pregnancy can be dangerous for women with cardiac disease. However, although the prognosis for pregnancy is generally good, in women with cardiac disease the exact level of risk posed by the pregnancy depends upon the underlying pathology:

- In general, regurgitant valvular lesions and mild/ moderate left-to-right shunts are well tolerated due to the decrease in total peripheral vascular resistance which occurs in pregnancy
- Conversely, stenotic valvular lesions, pulmonary hypertension and right-to-left shunts are poorly tolerated.

It is therefore helpful to categorise heart disease in terms of mortality risk, because this will optimise accurate counselling, evaluation and management (Table 12.3).

Table 12.3 Categorisation of heart disease in terms of mortality risk

Risk	Condition
High (mortality rate 25–50%)	Eisenmenger's complex Cyanotic heart disease (tetralogy of Fallot, Ebstein's anomaly, transposition of the great vessels) Pulmonary hypertension Acute myocardial infarction Hypertrophic obstructive cardiomyopathy Heart failure (including peripartum cardiomyopathy)

Moderate to high (mortality rate 5–15%)	Valvular stenosis Coarctation of the aorta History of myocardial infarction Marfan's syndrome Mechanical prosthetic valve
Low (mortality rate 1%)	Acyanotic heart disease Mild-to-moderate valvular regurgitation Mitral valve prolapse Small ventricular septal defect Small atrial septal defect

Symptoms and signs in normal pregnancy

Symptoms of pregnancy may mimic cardiac disease, and dyspnoea, peripheral oedema and palpitations are all common complaints in normal pregnancy. A benign ejection systolic murmur occurs in 96% of pregnant women.

ECG and echocardiographic changes in normal pregnancy

- **ECG changes**
  - Sinus tachycardia
  - Leftward or rightward shift of the QRS axis
  - Premature atrial or ventricular beats
- **Echocardiographic changes**
  - An increase in heart size and left ventricular mass
  - A small pericardial effusion
  - Mild valvular regurgitation

Management of the pregnant woman with cardiac disease

Preconception

Management should take place in a multidisciplinary setting, preferably in a tertiary centre, and this should involve the obstetrician, cardiologist, anaesthetist and, if necessary, the cardiothoracic surgeon.

Preconception evaluation will allow for appropriate counselling about maternal and fetal risks, optimisation of drug therapy and/or pre-pregnancy surgery if indicated.

- Most cardiac drugs are safe, but ACE inhibitors should be avoided because they are associated with fetal and neonatal renal failure and death

  Anticoagulation: due to the hypercoagulable state of pregnancy, there is an increased risk of valve thrombosis and embolism in women with prosthetic valves. Warfarin is teratogenic, particularly in the first trimester, and is also associated with fetal haemorrhage throughout

- pregnancy. Unfractionated heparin (UFH) does not cross the placenta, but is associated with maternal bone demineralisation and thrombocytopenia. In addition, heparin has also been associated with a higher risk of thromboembolic complications. Low-molecular-weight heparin (LMWH: twice daily regimen with close monitoring of anti-factor Xa levels) is the anticoagulant of choice for most women. The risks are less than those for UFH. Anticoagulation in these patients should be determined on an individual risk basis.

Antenatal management

Consideration should be given to the genetic implications of maternal cardiac disease. Congenital heart disease has a multifactorial inheritance. There is a small increase in the risk of congenital heart disease occurring in the fetus (3–5% dependent on the precise condition) but this risk increases sharply if more than one member of the family is affected. Consequently, high-resolution ultrasonography with fetal echocardiography is advised in the second trimester.

- Once pregnant, most women will have no haemodynamic problems. Cardiac decompensation is, however, an indication for termination of pregnancy
- Fetal growth should be assessed regularly, particularly in women with severe heart disease and cyanotic congenital heart conditions
- Indications for cardiac surgery are the same as for the non-pregnant woman
- If surgery is required, it should be performed with the patient in the left decubitus position with provision for caesarean section if the gestation is >24 weeks
- Standard cardiopulmonary bypass may compromise the placenta and fetus due to hypothermia, reduced arterial perfusion and alterations in coagulation and acid–base balance. To avoid these complications, cardiopulmonary support should be high flow, normothermic and initiated without hyperkalaemic arrest.

Intrapartum management

The aim is to minimise cardiac strain. In general, spontaneous vaginal delivery (with limited active second stage (30 min)) is preferred but selected patients with severe heart disease may benefit from elective caesarean section. In labour, care must be taken to avoid supine hypotension due to aortocaval compression by the gravid uterus.

- In most with adequate cardiac reserve, epidural anaesthesia is effective and well tolerated. It should, however, be used with extreme caution in women with restricted cardiac outputs such as in primary pulmonary hypertension or right-to-left shunts. Under these circumstances, general anaesthesia and abdominal delivery may be preferred
- Fluid balance requires special attention and high-risk cases may warrant pulmonary wedge pressure monitoring with a pulmonary catheter
- Under certain circumstances, ergometrine should be avoided during the third stage of labour. The tonic contraction of the uterus caused by this drug will force approximately 500 mL of blood into the circulation, resulting in a rise in left atrial pressure. This would be particularly detrimental in patients with significant mitral stenosis. Alternative option is a slow intravenous infusion of Syntocinon (12 mU/min at 5 IU in 500 mL, rate 7 mL/h for 4 h)
- Delivery is associated with a transient asymptomatic bacteraemia. Therefore, women with structural heart disease may benefit from antibiotic prophylaxis (see guidelines from NICE). This

is mandatory in women with prosthetic valves.

Contraception

Avoid the combined oestrogen/progesterone (COP) pill because of thrombosis risk. Implanon – a small implant that is inserted under the skin in the upper arm – delivers a continuous dose of the hormone etonogestrel. Failure rate is approximately 1 in 1000 per year. Implanon is one of the safest and most effective forms of contraception available.

12.3.3 Renal disease and hypertension in pregnancy

Pregnancy outcome in women with renal disease has improved markedly in recent years. The main risks of pregnancy in a patient with renal disease are of adverse pregnancy outcome and deterioration of renal function accompanying the pregnancy. The risks depend on the following:

- Degree of renal impairment at conception
- Presence of hypertension at conception or in early pregnancy (<20 weeks). Maintain ≤140/ 90 mmHg
- Degree of proteinuria (if >500 µmol/day refer to nephrologist).

Risk is best determined by accurate assessment of renal function.

Mildly impaired renal function

In the presence of mildly impaired renal function (serum creatinine 125 µmol/L or GFR 50–70 mL/min), the live birth rate approaches 95%. There is a slightly increased risk of preterm delivery, preeclampsia and fetal growth restriction (FGR), but pregnancy does not seem to adversely influence renal function. Therefore, women in this category should not be discouraged from becoming pregnant.

Moderately impaired renal function

In the presence of moderately impaired renal function (serum creatinine 125–250 µmol/L or GFR 25–50 mL/min), there is a significantly increased risk (up to 50%) of preterm delivery, pre-eclampsia and FGR. The success of the pregnancy depends upon adequate control of blood pressure.

- Uncontrolled hypertension is associated with significantly increased rates of fetal and neonatal loss
- There is a 25–50% chance of decline in renal function, which may be permanent
- Nevertheless, in a multidisciplinary setting and with rigorous control of blood pressure, the live birth rate approaches 84%.

Severely impaired renal function

In the presence of severely impaired renal function (serum creatinine ≥250 µmol/L or GFR ≤25 mL/min), fertility is reduced. Spontaneous conception may occasionally occur. Again, the key to successful outcome is largely dependent on adequate control of maternal blood pressure. However, the risks to both the fetus and the mother are such that termination of pregnancy may be offered.

- In women who continue with the pregnancy, there is a 90% chance of antenatal complications

- Uncontrolled hypertension is associated with a 10-fold increase in perinatal mortality
- The live birth rate is 50–80% (depending on underlying diagnosis and management).

End-stage renal disease

Patients who are receiving dialysis have very low fertility and, even if conception is successful, there is a high rate of miscarriage. There have only been a handful of reported cases of successful pregnancies in women receiving dialysis.

- In patients with functioning renal transplants, the outcomes are again determined by the level of graft (ie renal) function, as described above. Ideally, pregnancy should be avoided until 12 months post-transplantation, by which stage graft function has stabilised and immunosuppressants are at maintenance levels only
- Most of the commonly used immunosuppressant agents (eg ciclosporin A, tacrolimus, prednisolone and azathioprine) are considered to be safe for administration during pregnancy.
- **Mycophenolate mofetil (MMF)** should be avoided (both during pregnancy and for 3 months preconception), as teratogenic effects, including microtia (one or both ears have hearing loss), cleft lip and palate, have been reported with its use.

Again, optimal blood pressure control is the key to a successful pregnancy.

Specific renal diseases and pregnancy

Specific renal diseases and their effects and outcome in pregnancy are given in Table 12.4.

Management of pregnancy in patients with pre-existing renal disease

The patients with pre-existing renal disease should be managed in a multidisciplinary setting. Where possible, the patients should be referred for preconception evaluation and counselling before embarking on a pregnancy. At this stage, there needs to be a consideration of possible genetic causes of renal impairment (eg polycystic kidney disease or Alport syndrome) which may affect the fetus. Once pregnant, the patient with renal disease should undergo the following management:

- Early referral for antenatal clinic booking with accurate dating ultrasound scan
- False-positive serum screening for T21 when creatinine ≥115 μmmol/L favours NT scanning
- Baseline biochemistry and urinalysis (including urea, creatinine, electrolytes, urate, lactate dehydrogenase and urine protein:creatinine ratio (PCR). These investigations should be repeated at least every 4 weeks
- Preferred antihypertensive drugs include labetalol, methyldopa and long-acting nifedipine
- ACE inhibitors should be discontinued preconceptually or at the earliest opportunity (see earlier – 12.3.2 Cardiac disease in pregnancy)
- The patient should be assessed frequently (fortnightly until 28 weeks, then weekly until delivery)
- Regular fetal surveillance with growth scans, commencing at 24 weeks (particularly if on antihypertensive medication)
- Indications for preterm delivery are deteriorating renal function, the development of superimposed pre-eclampsia and/or severe FGR. Hence, appropriate specialised paediatric

services will be required

- Venous thromboembolism (VTE) risk: assessment particularly for those with proteinuria. Thromboprophylaxis should be given to all with nephrotic syndrome.

Table 12.4 Specific renal diseases and pregnancy

Condition	Possible complications that need monitoring	Key management points
Primary glomerulonephritis	Hypertension; proteinuria; recurrent infection	Treat associated clinical features; outcome relates to control of clinical features and severity of renal impairment
Autosomal dominant polycystic kidney disease	Impaired renal function; hypertension	Make parents aware that the child has a 50% risk of inheriting the condition
Congenital urinary tract obstruction	Increased risk of urinary tract obstruction, even if previously surgically corrected	Perform kidney ultrasound in early pregnancy; serial assessment of renal function, urine culture, and blood pressure; repeat ultrasound if abnormalities in monitored parameters
Vesicoureteric reflux nephropathy	Recurrent urinary tract infections; ureteral obstruction; pre-existing renal impairment; hypertension	Prophylactic antibiotics may be needed; drainage of obstruction may also be necessary
Nephrolithiasis	Renal colic; ureteric obstruction	Magnetic resonance urography can be used in diagnosis to avoid exposure to radiation
Diabetic nephropathy	Declining renal function in women with pre-existing diabetic nephropathy; hypertension and proteinuria	Try to maintain good glycaemic control before, during, and after pregnancy
Nephritis caused by systemic lupus erythematosus	Can present like pre-eclampsia so investigate for distinguishing clinical and immunological features	Drug treatment managed by rheumatologist and obstetrician
	Adjust dialysis to mimic the physiological changes of	Haemodialysis is more effective than peritoneal

Dialysis	pregnancy	dialysis at mimicking physiological change
Renal transplant	Pre-eclampsia; fetal growth restriction; deteriorating graft function	Delay pregnancy until graft function and immunosuppression are stabilised

The table above has been reproduced from Williams D *et al.*, *BMJ*, Jan 26 2008, 336(7637): 211–215), with kind permission of the *BMJ*.

12.3.4 Antiphospholipid syndrome and pregnancy

The antiphospholipid syndrome is defined as a clinical disorder with recurrent arterial and venous thrombotic events and/or pregnancy wastage in the presence of the lupus anticoagulant (LA) and/or a moderate-to-high positive anticardiolipin (ACL) test. The lupus anticoagulant is an inhibitor of the coagulation pathway. Its presence is a good predictor of poor fetal outcome.

- Anticardiolipin antibodies are antibodies active against certain phospholipid components of cell walls. They may be IgG or IgM
- Both a primary form (patients without clinical or serological evidence of autoimmune disorders), and a secondary form (usually in patients with SLE) of the antiphospholipid syndrome are recognised.

Diagnosis of antiphospholipid syndrome requires two positive tests (LA and/or high titres of ACL, ie ≥40 GPL (IgG phospholipid units) or MPL (IgM phospholipid units), or ≥99th centile), at least 12 weeks apart, plus at least one of the following clinical scenarios:

- Vascular thrombosis – arterial, venous or small vessel thrombosis
- Pregnancy morbidity
- Recurrent miscarriage (three or more consecutive losses)
- Fetal loss after 10 weeks' gestation (no fetal heart demonstrated on scan)
- Early onset (≤34 weeks' gestation) preeclampsia and/or FGR (secondary to placental dysfunction)
- Placental abruption
- Fetal death in utero or stillbirth.

The mechanism of pregnancy loss/adverse pregnancy outcome is not clearly elucidated. Current theories include damage to placental vascular endothelium, platelet deposition, imbalance in the thromboxane:prostacyclin (PGI_2) ratio and inhibition of protein C and tissue plasminogen. Inflammatory cytokines may also be implicated.

Treatment

The treatment options include oral therapy with low-dose aspirin (75 mg daily) and/or subcutaneous low-molecular-weight heparin (LMWH). Even with treatment the pregnancies can be complicated by

hypertension and fetal growth restriction (FGR), and hence they require careful monitoring.

- Clinical trials indicate a 'take-home baby rate' of 70% with combined therapy versus 40% with aspirin alone. With no treatment, success is in the region of only 10%
- See also Chapter 9, Haematology.

12.3.5 Thyroid disease and pregnancy

Thyroid disease is relatively common in women of childbearing age. Physiological changes during normal pregnancy include:

- Increased thyroxine-binding globulin (TBG) (twofold)
- Increase in triiodothyronine (T_3) and thyroxine (T_4) secondary to oestrogen
- Relative iodine deficiency, increased renal excretion
- Free T_4/T_3 falls in the third trimester
- Thyroid-stimulating hormone (TSH) falls in first/ second trimester, and increases in third trimester.

Serum screening is less accurate in hypothyroidism. Raised fetal TSH concentrations may falsely elevate both fetal and maternal serum AFP. This results in false-positive screening for neural tube defects and false negatives for trisomy 21 screening.

Beta human chorionic gonadotrophin (βhCG) has weak thyroid-stimulating activity.

Hyperthyroidism

Untreated hyperthyroidism is associated with subfertility and reduced libido. It can also cause miscarriage, FGR/SGA, prematurity and stillbirth. It occurs with an incidence of approximately 1 in 500 pregnancies and is most frequently due to autoimmune thyrotoxicosis (Graves' disease).

Effect of pregnancy on hyperthyroidism

- Flares are seen in both the first trimester, labour and the puerperium
- Typically remits in the second and third trimester, which results in a reduction in medication for many, and cessation of therapy in about 30%
- The change in disease activity reflects the maternal immune state and titres of thyroid hormone receptor-stimulating antibodies

Effect of hyperthyroidism on pregnancy

- If hyperthyroidism is well controlled before and throughout pregnancy, outcomes are good for mother and baby
- Poor control is associated with excess nausea/vomiting, tremors, anxiety, arrhythmias, congestive cardiac failure, preeclampsia, preterm labour, FGR and stillbirth

Treatment

The treatment of choice is propylthiouracil or carbimazole. The dose is titrated against biochemical results (free T_4 at the upper limit of normal, TSH in the normal range) and the maternal condition:

- About 30% of women require dose reduction or discontinuation in the second/third trimester, with possible increase/recommencement in the puerperium
- A blocking/replacement regimen should be avoided in pregnancy.

Fetal and neonatal risks in thyrotoxicosis

In pregnancy the aim of therapy is to reduce the dose of any drugs to the **minimum required** to control maternal disease. However, both propylthiouracil (PTU) and carbimazole cross the placenta, PTU less so. High dosage may be associated with fetal goitre, which usually resolves postnatally.

- Of babies, 10–20% have transient biochemical hypothyroidism which is rarely symptomatic and resolves on days 4–5
- The fetal and neonatal risk of Graves' disease is proportional to the titre of maternal TSH receptor-stimulating antibodies. These should be measured in the first and third trimester in women with active disease, or in those with a history of disease treated with surgery and/or radioactive iodine.

Fetal hyperthyroidism develops between 20 and 24 weeks' gestation.

Complications of fetal hyperthyroidism

- Fetal tachycardia (>160 beats/min)
- Increased fetal movements
- FGR
- Fetal goitre
- Craniosynostosis
- Hydrops
- Polyhydramnios
- Preterm labour

Treatment is dependent on gestation and is either delivery or anti-thyroid agents, titrated against fetal heart rate, movements and growth rate.

Neonatal hyperthyroidism occurs in 1% of cases of maternal thyrotoxicosis. The clinical presentation may be delayed, but treatment with anti-thyroid drugs or β blockers is rarely needed for more than a few months.

Clinical features of neonatal hyperthyroidism

- Jitteriness
- Failure to gain weight
- Poor feeding
- Poor sleeping
- Bossing of frontal bones
- Liver dysfunction
- Jaundice

Hypothyroidism

Hypothyroidism is the most common pre-existing endocrine disorder in pregnancy. The incidence is 9 in 1000 pregnancies. The most common cause is Hashimoto's thyroiditis.

Treatment

Thyroxine is the mainstay treatment, because it is safe in pregnancy and breastfeeding.

- Thyroid function tests should be measured at 8–12 weeks if stable, and every 4–6 weeks if the dosage is being adjusted
- Thyroxine should be altered according to the TSH levels. Maintain TSH <2.5 mU/L preconceptually and in the first trimester, <3.0 mU/L after this time. TSH may remain raised after the correct dosage has been achieved (especially in the third trimester). The dose should be increased by 25–50% at the time of a missed period/positive pregnancy test to cope with the changing demands of pregnancy, which increase at 4–6 weeks until 16/20 weeks, when it plateaus. Suboptimal maternal treatment (ie TSH >2.5 mU/L preconceptually/first trimester) may be associated with miscarriage and/or adverse neurodevelopment in the child
- If the patient is stable pre-pregnancy (TSH <2.5 mU/L), she is likely to remain stable without requiring any dose adjustment (beyond the initial increase) during the pregnancy
- Neonatal hypothyroidism is rare and transient, and caused by TSH receptor-blocking antibodies.

Post-partum thyroiditis

This has an autoimmune aetiology and hence it is associated with other autoimmune diseases. It has a prevalence between 5% and 8%. Thyroid anti-peroxidase antibodies are seen in 90% of women with the condition. The histology of the thyroid gland is typical of autoimmune thyroiditis with focal/diffuse thyroiditis, lymphocytic infiltration, follicular destruction and hyperplasia-destructive thyroiditis.

There are three phases of post-partum thyroiditis:

1. **Thyrotoxicosis**: 1–3 months post-partum. This is associated with low uptake of radioactive iodine (unlike Graves' disease). Treatment is rarely required, but if needed involves only β blockers
2. **Hypothyroidism**: 3–8 months post-partum. This may be associated with symptoms that include lethargy, poor memory and cold intolerance, and treatment with T_4 may be indicated. Treat if

symptomatic of TSH >10 mU/L

3. **Normal thyroid function**: by 1 year post-partum.

The mother may experience one, two or all of these phases. The recurrence risk in another pregnancy is about 70%. Patients will need long-term surveillance as the risk of permanent hypothyroidism is about 3–5% per year (30% after 3 years).

12.3.6 Epilepsy and pregnancy

Epilepsy occurs in 1 in 200 women of childbearing age, and is the most common neurological disorder in pregnancy. In general, the longer a woman has been free of fits before pregnancy the less likely it is that her epilepsy will deteriorate during pregnancy.

Of women with active epilepsy, 1–2% will have a tonic–clonic seizure during labour, and a further 1–2% in the next 24 hours.

Drug monitoring is not routinely recommended because there is no evidence that fit frequency relates directly to drug serum levels.

Indications for monitoring are: detection of non-adherence, suspected toxicity, adjustment of phenytoin dose, management of pharmacokinetic interactions (eg changes in bioavailability), specific clinical conditions (eg status epilepticus), organ failure.

Factors influencing fit frequency in pregnancy

- Disease pattern pre-pregnancy
- Sleep deprivation, especially in the third trimester
- Vomiting in pregnancy
- Altered protein binding, and increased volume of distribution of anticonvulsants
- Altered drug compliance
- Altered metabolism and excretion of anticonvulsant drugs

Effect of maternal epilepsy upon the fetus

The fetus is very tolerant of isolated, short-lived fits. Repeated fits can result in fetal hypoxia and lactic acidosis, which may be associated with fetal bradycardia and adverse effects. In rare instances, fetal intraventricular haemorrhages and death have been attributed to maternal convulsions. The effect may be remote and detected only in developmental delay years later. Status epilepticus doubles the risk of maternal death and is associated with a 50% miscarriage rate.

- **Birth defects**: epilepsy is associated with an increased incidence of certain congenital malformations (3.5–4.5%); the risk is multifactorial and increases with sodium valproate (>800 mg/day) and the number of anticonvulsants used
- **Risk of epilepsy in the newborn**: depends on the type of epilepsy and the family history. For idiopathic epilepsy, it is about 10% if one first-degree relative is affected and 25% if two or

more first-degree relatives are affected

- **Neonatal coagulopathy**: associated with maternal use of phenytoin, phenobarbital and primidone. Maternal coagulation studies are usually normal. Negated by giving infant 1 mg intramuscular vitamin K
- The incidence of stillbirth and perinatal deaths is higher in those exposed to antiepileptics in pregnancy. Recognised increase risk of sudden infant death in women who discontinue antiepileptic drugs.

Management of the epileptic in pregnancy

- Pre-pregnancy counselling should be given to the patient about the risks of pregnancy. Where possible, anticonvulsant monotherapy should be used. Consideration may be given to discontinuing anticonvulsants in women without fits
- Most women will have a healthy pregnancy but there may be an increased risk of complications
- High-dose folic acid (5 mg daily) should be advised preconceptionally and for the first 3 months of pregnancy (particularly for those women on hepatic enzyme-inducing antiepileptics such as phenytoin)
- A detailed fetal anomaly scan should be performed between 18 and 20 weeks
- If fits occur during pregnancy, the anticonvulsant levels should be monitored
- If the patient is receiving phenytoin, then vitamin K should be administered to the mother from 36 weeks' gestation in order to counteract possible neonatal coagulopathy.

12.4 MEDICAL COMPLICATIONS OF PREGNANCY

12.4.1 Hypertensive disorders of pregnancy

Definitions

Hypertension in pregnancy is defined as follows:

- Diastolic BP >110 mmHg on any one occasion

or

- Diastolic BP >90 mmHg on two or more consecutive occasions >4 h apart.

Blood pressure should be measured in the sitting position with a sphygmomanometer cuff size appropriate for the size of the patient's arm.

Phases I and V of Korotkoff's sounds identify the systolic and diastolic limits, respectively, correlating more accurately with outcome than phase IV.

- **Mild hypertension**: diastolic blood pressure 90–99 mmHg, systolic blood pressure 140–149 mmHg
- **Moderate hypertension**: diastolic blood pressure 100–109 mmHg, systolic blood pressure 150–159 mmHg
- **Severe hypertension**: diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥160

- mmHg

Proteinuria in pregnancy is defined as:

- Total protein excretion >300 mg/24 h (with evaluation of the completeness of the sample)

or

- PCR spot test ≥30 mg/mmol.

If an automated reagent device is ≥1+ a PCR should be undertaken in secondary care.

A systematic review published in the *BMJ* in 2008 (Côté *et al*., 2008) concluded that the spot urinary protein:creatinine ratio is a reasonable 'rule-out' test for significant proteinuria of ≥0.3 g/day in pregnancy.

- Hypertension is associated with between 6% and 8% of pregnancies and can have serious repercussions for both fetal and maternal wellbeing. Hypertension can predate the pregnancy (**essential** or **chronic hypertension**) or arise in pregnancy (**pregnancy-induced hypertension** or PIH)
- Most women with PIH have non-proteinuric PIH, a condition associated with minimal maternal or perinatal mortality/morbidity
- Approximately 2% of pregnancies are complicated by proteinuric PIH (**pre-eclampsia**).

Pre-eclampsia is a serious pregnancy complication that causes significant maternal and perinatal morbidity. It is therefore imperative that every effort be made to accurately classify the nature of hypertension occurring in pregnancy because the aetiology and management of the three conditions, chronic hypertension, non-proteinuric PIH and preeclampsia, are very different (Table 12.5).

Pre-eclampsia

Although the primary events leading to preeclampsia are still unclear, it is now thought that the pathophysiology involves a cascade of events which leads to the clinical syndrome.

Table 12.5 The International Society for the Study of Hypertension in Pregnancy classification (modified and abbreviated)

1.	Gestational hypertension and/or proteinuria developing during pregnancy (>20 weeks), labour or the puerperium in a previously normotensive non-proteinuric woman	Gestational hypertension (without proteinuria) Gestational proteinuria (without hypertension) Gestational proteinuric hypertension (preeclampsia)
2.	Chronic hypertension (before the 20th week of pregnancy) and chronic renal disease (proteinuria before the 20th week of pregnancy)	Chronic hypertension (without proteinuria) Chronic renal disease (proteinuria with or without hypertension) Chronic hypertension with superimposed preeclampsia (new-onset proteinuria)

3. Unclassified hypertension and/or proteinuria
4. Eclampsia

Pathophysiology of pre-eclampsia

- Genetic predisposition
- Release of circulating factor(s)
- Endothelial cell alteration
- Faulty interplay between invading trophoblast and decidua
- Decreased blood supply to the fetoplacental unit

Pre-eclampsia is associated with hypertension, proteinuria and FGR.

The maternal mortality rate is about 2% in the UK and, worldwide, 100 000 women die of pre-eclampsia each year. Perinatal mortality is also increased, and this is associated with FGR and iatrogenic preterm delivery. In the most recent CEMACH report (2006–08) hypertensive disorders of pregnancy are the **fifth leading cause** of direct maternal death.

Screening for pre-eclampsia

It is important to take a full history, because several factors can be associated with an increased risk of pre-eclampsia.

Risk factors associated with pre-eclampsia

- **Increased risk**
  - Family history, 4–8 times higher in first-degree relatives
  - Primigravidas 15 times higher than multiparous
  - Longer pregnancy interval
  - Change in partner
  - Teenage pregnancy
  - Donor insemination
  - Medical disorders such as chronic hypertension, renal disease
- **Decreased risk**
  - Previous termination of pregnancy
  - Previous miscarriage
  - Non-barrier contraception
  - Increased duration of sexual cohabitation

Biophysical tests

All currently available tests are of limited clinical value. The uterine artery may appear 'notched' (Figure 12.1).

Doppler waveforms may be of significance but they are only of sufficient sensitivity and specificity when used in a preselected high-risk population.

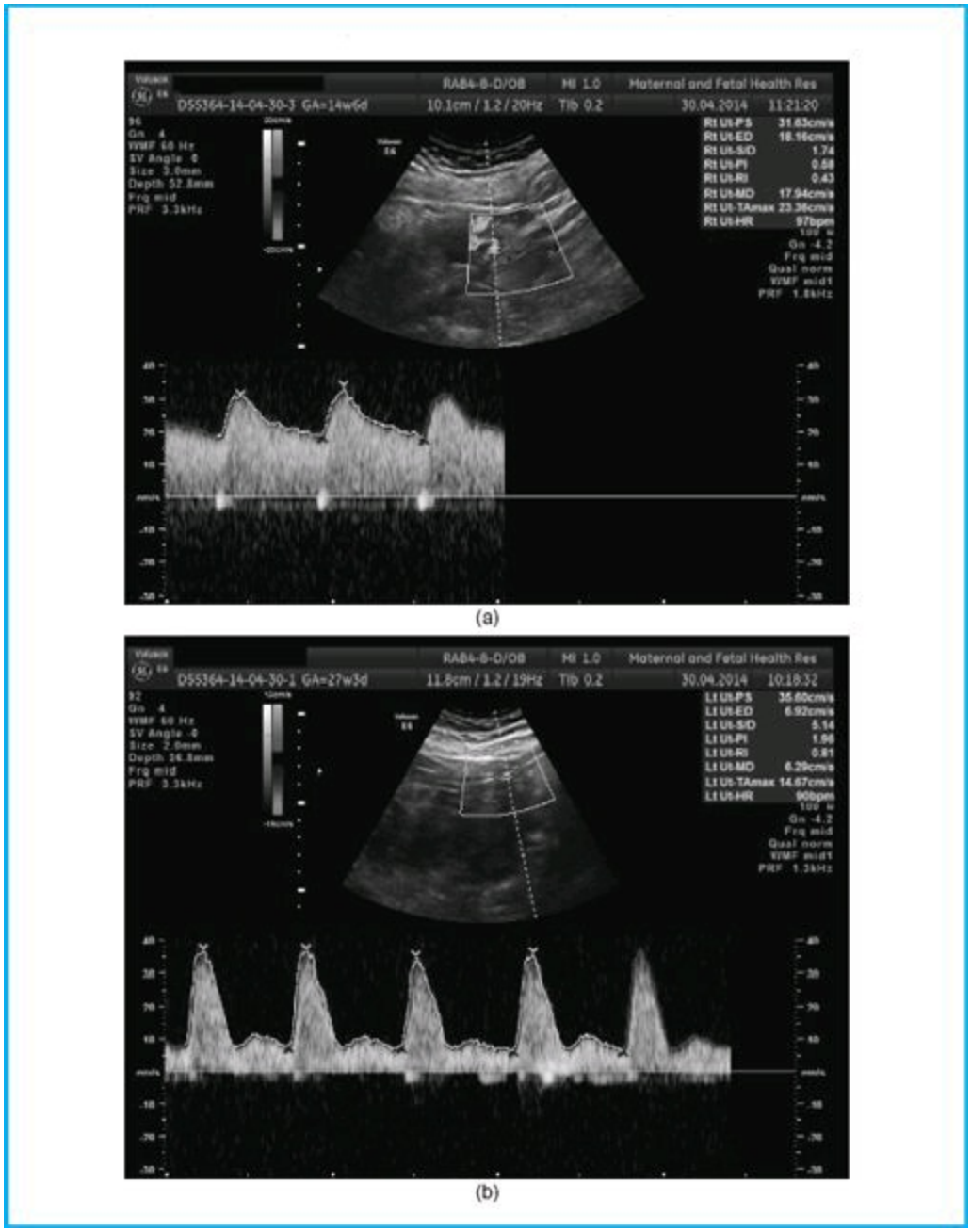
Prophylaxis of pre-eclampsia
Several agents have been investigated:

- Aspirin and a cyclo-oxygenase inhibitor. A Cochrane review of 42 randomised trials demonstrated a 15% relative reduction in the risk of pre-eclampsia with the use of aspirin or other antiplatelet agents
- NICE recommend starting aspirin before 12 weeks' gestation in those who are at high/ moderate risk of developing pre-eclampsia
- Hypertensive disease during a previous pregnancy
- Chronic kidney disease
- Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- Type 1 or 2 diabetes
- Chronic hypertension
- First pregnancy
- Age ≥40 years
- Pregnancy interval of >10 years
- BMI of ≥35 kg/m^2 or more at first visit
- Family history of pre-eclampsia
- Multiple pregnancy
- No evidence for calcium, fish oils containing omega-3 fatty acid or the antioxidant vitamins C and E.

More recently the PELICAN study has been reported.

Pre-eclampsia is a complex disease related to free radical damage and widespread oxidative stress and consequent damage of all blood vessels. Improved understanding of the underlying disease process has meant that a number of tests have been identified that might discriminate between those with preeclampsia and those without. In particular, this study evaluated **placental growth factor** (PlGF) as a marker of subsequent disease and harm, in women with suspected pre-eclampsia.

Figure 12.1 (a) Normal uterine artery waveform; (b) high resistance uterine artery waveform



Results have shown that the PlGF blood test is very good at predicting when women with pre-eclampsia will need to be delivered.

Low PlGF concentration (<5th centile or ≤100 pg/ mL) has high sensitivity and negative predictive value in determining which women presenting with suspected disease at <35 weeks' gestation are likely to need delivery for pre-eclampsia within 14 days.

Time to delivery is markedly different for women with very low, low and normal PlGF values, facilitating stratified management strategies with appropriate surveillance.

A trial comparing management of women with knowledge of PlGF to those for whom this knowledge is not available is now planned to determine whether pre-eclampsia can be diagnosed earlier.

Maternal assessment in pre-eclampsia

Several different organ systems can be affected in the pregnant woman:

- **Platelets**: consumed due to the endothelial activation. Although a platelet count of >50 × 10^9/L will support normal haemostasis, a falling platelet count, particularly to <100 × 10^9/L, may

indicate a need to deliver

- **Hypovolaemia**: results in an increased haematocrit, with an apparent rise in the haemoglobin
- **Clotting disorders**: pre-eclampsia can cause disseminated intravascular coagulation, and clotting disorders must be assessed, particularly in the face of falling platelet numbers
- **Renal tubular function**: uric acid is a measure of 'fine' renal tubular function. It is used to assess the disease severity, although severe disease can still occur with a normal uric acid level. Spuriously high levels of uric acid are associated with acute fatty liver of pregnancy (see below)
- **Renal impairment**: raised urea and creatinine are associated with late renal involvement and hence are not useful as an early indicator of disease severity. However, serial measurements will identify renal disease progression. Proteinuria is a hallmark of pre-eclampsia; protein excretion may increase progressively as the pre-eclamptic process evolves
- **Liver involvement**: pre-eclampsia can cause subcapsular haematoma, liver rupture and hepatic infarction. Aspartate aminotransferase (AST) and other transaminases indicate hepatocellular damage. Elevated levels may again indicate a need to deliver. It should be remembered that the normal range for transaminases is approximately 20% lower than the non-pregnant range. The circulating albumin may fall, especially if urinary protein excretion is high (eg 3 g/24 h); hypoalbuminaemia increases the risk of pulmonary oedema. Note that a raised AST can be associated with either haemolysis or liver involvement; lactate dehydrogenase (LDH) levels are also elevated in the presence of haemolysis (see HELLP syndrome, on page 350).

Fetal assessment in pre-eclampsia

Fetal wellbeing must be carefully assessed in all cases of pre-eclampsia. This involves:

- **Clinical assessment**: the symphyseal–fundal height should be carefully measured and an enquiry as to fetal movements undertaken
- **Investigations**: regular ultrasound assessment of fetal growth and amniotic fluid volume should be performed. Umbilical artery Doppler waveforms may be of use.

Suspected fetal compromise is a frequent indication for delivery in pre-eclampsia.

Management of pre-eclampsia

Pre-eclamptic hypertension can cause direct arterial injury which can, in turn, predispose to possibly fatal cerebral haemorrhage. In order to prevent this injury, severe hypertension should be avoided. Blood pressure >170/110 mmHg (mean arterial pressure [MAP] ≥140 mmHg) requires urgent therapy. The rationale for treating moderate hypertension (BP >140/90 mmHg, but <170/110 mmHg) is less clear. In the most recent CEMACH report, attention was particularly drawn to the importance of treating systolic hypertension (ie SBP >160 mmHg), in line with the recent guidelines from NICE, irrespective of the MAP, because of the risk of maternal cerebral haemorrhage. Consideration should also be given to **initiating treatment at lower** pressures if the overall clinical picture suggests rapid deterioration and/or where the development of severe hypertension can be anticipated. The target systolic blood pressure after treatment is 150 mmHg.

Choice of antihypertensive agents: methyldopa, labetalol and nifedipine are the mainstay in therapy. In practice, the choice of agent probably matters less than the clinician's familiarity with it.

Timing of delivery: in women with established preeclampsia, delivery should be considered once

fetal lung maturity has been achieved. However, in asymptomatic women with pre-eclampsia presenting between 26 and 34 weeks, management can often be expectant in an attempt to achieve improved perinatal survival, without substantial risk to the mother. This does, however, require close inpatient supervision in a unit with adequate numbers of appropriately skilled staff. Trials have confirmed the advantages of this cautiously expectant approach.

Delivery before 37 weeks' gestation is NOT required if BP <160/110 mmHg (NICE).

As stated previously, fetal compromise will indicate the need for delivery.

Indications for delivery in pre-eclampsia

- Refractory severe hypertension
- Deteriorating liver or renal function
- Progressive fall in platelets
- Neurological complications
- Abnormal CTG, abnormal Doppler
- Deteriorating fetal condition

Postnatally: monitor BP daily for 2 days and then at least once between days 3 and 5. Consider reducing antihypertensive treatment if BP falls to <140/ 90 mmHg, and reduce antihypertensive treatment if BP falls to <130/80 mmHg. Maintain therapy for at least 2 weeks and review in secondary care at 6–8 weeks.

HELLP syndrome

HELLP (**h**aemolysis, **e**levated **l**iver enzymes and **l**ow **p**latelets) syndrome is a severe form of pre-eclampsia, associated with:

- Haemolysis
- Elevated liver enzymes (ALT/LDH)
- Low platelets.

It complicates about 10–15% of cases of preeclampsia. Mortality rates vary from 0% to 25%, and mortality is associated with cerebral haemorrhage and disseminated intravascular coagulation (DIC), correlating with the extent of thrombocytopenia. HELLP syndrome and acute fatty liver of pregnancy are two conditions that are very similar and there is a recognised degree of overlap in both aetiology and pathophysiology, such that a definitive diagnosis can be difficult to make.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy typically occurs in obese women or in the third trimester of pregnancy. It is associated with pre-eclampsia (30–100% of cases) and twin pregnancy, and is more common in women with male fetuses.

Symptoms develop acutely and include abdominal pain, nausea/vomiting, headache and jaundice.

Other clinical features that may occur include pruritus, fever, enterocolitis, ascites or pancreatitis.

Investigations in acute fatter liver of pregnancy

- **Laboratory findings**:
  - Neutrophil leukocytosis
  - Increased fibrin degradation products
  - Low platelets
  - Microangiopathic haemolytic anaemia
  - Increased bilirubin
  - Raised AST (3–10 times above normal)
  - Hypoglycaemia
  - Increased uric acid
- **Liver pathology**:
  - The liver is small and yellow
  - Histology reveals microvesicular steatosis with intrahepatic cholestasis and canalicular plugs of bile; distribution is panlobular with sparing of periportal areas
  - Extramedullary haematopoiesis
- **Imaging**:
  - Increased reflectivity of liver on ultrasound scanning and lower attenuation on MRI are both indicative of 'fat' within the liver
  - Infarction appears as multiple non-enhancing lesions of low attenuation, with mottled appearance

Management of acute fatty liver of pregnancy

Early diagnosis is important, followed by transfer of the patient to tertiary care. The patient may need to be transferred to intensive care for correction of hypertension, hypoglycaemia and bleeding diathesis. **The baby needs to be delivered as a matter of urgency**.

The neonate is at risk of fatty infiltration of the liver and this is associated with impaired liver function, hypoglycaemia, thrombocytopenia and neutropenia.

Eclampsia

Eclampsia is defined as convulsions occurring in a woman with pre-eclampsia in the absence of any other neurological cause. The maternal mortality associated with eclampsia in the UK is approximately 1 in 50. It complicates 1 in 2000 pregnancies in the UK. In about 40% of cases it is totally or partially unheralded by prodromal signs or symptoms. In 10% of cases the only warning sign is proteinuria, and in another 20% there is hypertension only. Most cases occur during labour or after delivery. Such cases are usually at term and in hospital. Preterm eclampsia is more likely to be antepartum.

Management of eclampsia

The aim of management is to protect the maternal airway and control the convulsions and extreme hypertension, as well as to expedite delivery.

- **Choice of anticonvulsant**: most fits stop quickly and spontaneously. In the Collaborative Eclampsia Trial (1995) magnesium sulphate was shown to be the anticonvulsant of first choice. A bolus of 4 mg is given intravenously over 10 minutes. About 10% of all fits will not be controlled by magnesium sulphate. A brain scan should be performed if presentation is atypical, if any focal signs develop, or in the case of repeated or prolonged seizures.

Magnesium sulphate treatment in eclampsia

- Toxic side effects: muscular weakness; respiratory paralysis; heart failure and death
- Monitor: check deep tendon reflexes
- Therapeutic levels: 2–3.5 mmol/L
- Antidote: calcium gluconate 1 g over 10 min, intravenously

Prophylactic use of magnesium sulphate may be considered in women with the following:

- Severe hypertension and proteinuria **or**
- Mild or moderate hypertension and proteinuria with one or more of the following:
  - symptoms of severe headache
  - problems with vision, such as blurring or flashing before the eyes
  - severe pain just below the ribs or vomiting
  - papilloedema
  - signs of clonus (≥3 beats)
  - liver tenderness
  - HELLP syndrome
  - platelet count falling to $<100 \times 10^9$/L
  - abnormal liver enzymes (ALT or AST rising to above 70 IU/L).

Long-term risks

- Women with pre-eclampsia are at risk of complications later in life
- These women are also at risk in a subsequent pregnancy
- Risk of gestational hypertension in a future pregnancy ranges from about one in eight (13%) pregnancies to about one in two (53%) pregnancies
- Risk of pre-eclampsia in a future pregnancy is up to about one in six (16%) pregnancies (one in four and one in two, respectively, if severe disease, HELLP and/or eclampsia necessitating delivery <34 or <28 weeks' gestation)

Chronic hypertension

Chronic hypertension (CHT) is detected by either an antecedent medical history or a raised blood pressure in the first half of pregnancy. The physiological decline in the blood pressure in early pregnancy is exaggerated in women with CHT so that they may be normotensive. Conversely, in later pregnancy the normal rise in blood pressure is exaggerated in patients with CHT. Hence a woman with CHT may be normotensive initially, with hypertension only appearing in the third trimester.

- CHT in pregnancy is a major predisposing factor for pre-eclampsia. This risk is about five times greater than in normotensive women
- Women with CHT who do not develop preeclampsia can usually expect a normal, uncomplicated perinatal outcome, although there is some evidence for a modest increase in the incidence of FGR in these women. Perinatal morbidity and mortality is related to treatment and so cautious discontinuation of pharmacological agents may be appropriate (see later)
- Pregnant women with uncomplicated chronic hypertension should be treated with the aim of keeping BP **<150/100 mmHg**
- Pregnant women with target-organ damage secondary to chronic hypertension (eg kidney disease) should be treated with the aim of keeping BP **<140/90 mmHg**
- High BP in pregnancy is associated with risks for mother and baby. However, there is no agreement about whether antihypertensives should be given for **non-severe hypertension** in pregnancy. Some clinicians treat mild-to-moderate hypertension whereas others give medication only once persistent severe hypertension has developed. The CHIPS (Control of Hypertension in Pregnancy Study) randomised women with mild-to-moderate hypertension to 'tight' blood pressure control or 'less tight' control (ongoing – anticipated completion March 2014)
- **Antihypertensive treatment**: ACE inhibitors and ARBs should be avoided, because these classes of drugs are associated with fetal and neonatal renal failure and death. Women with mild-to-moderate hypertension should discontinue treatment before conception because of the risk of FGR. There is no evidence that treating CHT reduces the risk of superimposed pre-eclampsia, nor is there any evidence to support a particular fetal benefit. Long-term use of antihypertensive drugs has been associated with FGR; it is uncertain whether this is a specific drug effect (eg β blockers) or a consequence of a reduction in placental perfusion after a lowering of arterial pressure.

12.4.2 Thrombotic complications in pregnancy

Thromboembolic disease

Pulmonary embolism is one of the leading causes of maternal mortality in the UK. Although that risk is reducing (sixth in the 2006–08 report), pregnancy is a procoagulant state and increases the risk of thromboembolism by about sixfold. The absolute incidence varies widely between 0.1% and 1.2% of all pregnancies. Deep vein thrombosis (DVT) is about twice as common as pulmonary embolism. The risk of thrombosis is as common in the first trimester as in the third.

Aetiology

Pregnancy is a hypercoagulable state due to an increase in factors VII, VIII and X, as well as

fibrinogen and prothrombin. This is exacerbated by venous stasis because the gravid uterus obstructs the inferior vena cava, causing a decrease in venous tone in the lower limbs, which is greater on the left than the right (hence 80% of DVTs occur on the left). Immobility during labour and in the post-partum period, particularly after surgical delivery, further exacerbates the situation. Other factors are listed in Table 12.6.

Obesity remains the most important risk factor for thromboembolism (CEMACH).

Risk assessment in early pregnancy continues to be a key factor in reducing mortality. This should be undertaken repeatedly, assessing for additional risk factors to include admission to hospital, and again intrapartum and post-partum

Women are at risk of thromboembolism from the very beginning of pregnancy until the end of the puerperium, and all health professionals must be aware of this.

Chest symptoms appearing for the first time in pregnancy or the puerperium in at-risk women need careful assessment, and there should be a low threshold for investigation

Thrombophilia

Thrombophilic tendencies may be more significant in women of reproductive age because pregnancy may uncover a hitherto unrecognised condition (Robertson *et al*., 2006). The following are main conditions to consider:

Table 12.6 Other factors increasing the risk of thromboembolism in pregnancy/puerperium

Increased with age (>35 years)
Increased with rising parity (>3)
Multiple pregnancy
OHSS (ovarian hyperstimulation syndrome)
Increased body mass index (three times increased risk if BMI >29)
Smoking, because it causes inhibition of fibrinolysis
Sickle cell disease
Pre-eclampsia
Proteinuria Dehydration – hyperemesis
Sepsis
Varicose veins – symptomatic, above knee, associated phlebitis
Blood group other than O
Thrombophilic conditions (see below)
PPH >1L
Lower segment caesarean section
Protracted labour (>24 h)
Trial of rotational surgical delivery

- Antithrombin deficiency
- Antiphospholipid deficiency/Lupus anticoagulant syndrome
- Protein C deficiency

- Protein S deficiency
- Prothrombin gene variant (see below) (Coulam, 2006)
- Factor V Leiden (see below).

Homocystinuria
Hereditary thrombophilic states may be associated with an adverse pregnancy outcome including: early pregnancy loss (odds ratio [OR] 1.40–6.25); late pregnancy loss (OR 1.3–20.09); pre-eclampsia (OR 1.37–3.49); placental abruption (OR 1.42–7.71); and FGR (OR 1.24–2.92). Low-dose aspirin plus LMWH was the most effective in preventing pregnancy loss in acquired thrombophilias (OR 1.62). With regard to hereditary thrombophilias, despite the increase in relative risk, the absolute risk of venous thromboembolism (VTE) and adverse outcomes remains low. There is also a lack of controlled trials of antithrombotic intervention to prevent pregnancy complications.

The association with recurrent miscarriage is probably limited to those women with acquired rather than hereditary thrombophilias or those with compound thrombophilias.

Similarly there is now evidence to suggest that a single gene variant (to include heterozygosity for factor V Leiden and/or PGV) alone is in itself a relatively weak risk factor for VTE (and/or adverse pregnancy outcome) and is therefore not an indication for antenatal LMWH, with the exception of antithrombin III deficiency. Rather, it should be considered in the light of other risk factors for VTE.

Antithrombin deficiency
Two types of antithrombin deficiency exist:

- Type I – a deficiency of a normal molecule
- Type II – associated with an abnormal molecule.

The risk of thromboembolism is as high as 40–70% and necessitates lifelong warfarin. The risk is greater in type I than type II antithrombin deficiency.

In pregnancy, patients with types I and II antithrombin deficiency (plus additional risk factors; see Table 12.6 for other factors increasing the risk of thromboembolism) should receive therapeutic levels of LMWH. Antithrombin concentrate may be required to cover labour and if thrombosis occurs earlier in pregnancy. Cord blood should be taken to assess neonatal status at birth; tests should be repeated at 6 months.

Antiphospholipid syndrome
Antiphospholipid deficiency/lupus anticoagulant have been considered earlier (see section 12.3.4).

Protein C deficiency

Protein C deficiency may be inherited in autosomal dominant and recessive forms. Patients will often have a history of thrombosis. These patients require thromboprophylaxis with antiembolic stockings and LMWH throughout the antenatal period and for 6 weeks post-partum. In those women without a personal history of thrombosis, additional risk factors need to be considered (eg BMI >30, age >35 years, parity >3, immobility >4 days) in deciding whether to use LMWH – **all** women require antiembolic stockings. Warfarin is avoided because it is associated with skin necrosis (purpura

fulminans in those women with the homozygous form) and both teratogenicity (greatest risk between 6 and 12 weeks' gestation) and fetal intracerebral bleeding (throughout the second and third trimesters). Prenatal diagnosis is achieved by cordocentesis in the second trimester.

Protein S deficiency

Protein S is a cofactor for protein C and levels normally fall in pregnancy, making diagnosis difficult. Deficiency of protein S is associated with a 0–6% risk of thrombosis antenatally and 7–22% postnatally. The usual approach is to treat with prophylactic doses of LMWH in the post-partum period only, unless additional risk factors exist.

Factor V Leiden

Factor V Leiden is caused by a single point mutation. It is resistant to activated protein C, causing thrombosis. Two forms of factor V Leiden exist:

1. Heterozygous: more common; risk of thrombosis 0.25% (Table 12.7)
2. Homozygous: rare; risk of thrombosis 50–80 times greater than in non-carriers.

The risk of thrombosis is low in heterozygotes, particularly in the absence of a personal history of thrombosis and/or additional risk factors. Prophylaxis, in the form of compression stockings, may be offered. LMWH is usually reserved for those women who are homozygous for the gene or have additional risk factors. Recent evidence refutes its association with recurrent miscarriage and/or poor pregnancy outcome (see earlier).

Prothrombin gene variant

Similar to factor V Leiden above. There are heterozygous and homozygous forms. LMWH is considered if additional risk factors and/or postnatally.

Homocystinuria

Homocystinuria is an inborn error of metabolism that is associated with increased risk of both arterial and venous thrombosis. The absolute risk of VTE in pregnancy is low. It should be considered alongside other risk factors. Women should be offered high-dose folic acid. LWMH is not indicated (RCOG).

Table 12.8 gives the prevalence and risk of VTE during pregnancy in relation to inherited thrombophilias.

Diagnosis of thromboembolic disorders in pregnancy

Table 12.9 outlines the diagnosis of thromboembolic disorders in pregnancy.

Treatment of thromboembolic disorders

Warfarin is generally avoided in pregnancy. In the first trimester it is associated with an increased risk of miscarriage and teratogenic side-effects which include chondrodysplasia punctata, asplenia and diaphragmatic hernia. In the second and third trimesters it is associated with retroplacental and intracerebral fetal haemorrhage, as well as fetal microcephaly, optic atrophy and developmental delay. It is safe for breastfeeding.

Table 12.7 Thrombophilic or hereditary hypercoagulable disorders in the general population andinpeoplewith venous thrombosis

Condition	Prevalence in general population (%)	Prevalence in people with venous thrombosis (%)	Increased risk for thrombosis
Factor V Leiden	5–15	20	3.8
Prothrombin 20210A	1–6	2	3.0
Protein C	0.2	3	25–50
Protein S	Unknown	1–2	10–15
Antithrombin III	0.02	1	10

Table 12.8 Prevalence and risk of venous thromboembolism (VTE) associated with pregnancy in relation to inherited thombophilias

Thrombophilia	Prevalence among women with VTE associated with pregnancy (%)	Relative risk of VTE
Factor V Leiden (heterozygous)	8–44	5–10
Factor V Leiden (homozygous)	9–17	10–80
Prothrombin gene mutation (heterozygous)	3–17	2–5
Prothrombin gene mutation (homozygous)	–	–
Compound heterozygote (factor V Leiden and prothrombin gene mutation)	4–9	9–107
Antithrombin deficiency (<80% activity)	12–60 AN; 11–33 PP[a]	10 to unknown
Protein C deficiency (<75% activity)	3–10 AN; 7–19 PP[a]	Unknown[b]
Protein S deficiency (<65% activity)	0–6 AN; 7–22 PP[a]	Unknown[b]

AN, antenatal; PP, post-partum.

[a] For women with protein C or protein S deficiency the risk of VTE is greater post-partum. Conversely, with antithrombin deficiency the risk of VTE is greatest during pregnancy.

[b] Overall annual incidence of VTE in patients with protein S deficiency or protein C deficiency is 3.5% and 2.5%, respectively (Pabinger IPA *et al*. The risk of thromboembolism in asymptomatic patients with protein C and protein S deficiency: a prospective cohort study. *Thromb Haemost* 1994;**71**:441–5.)

LMWH is the mainstay of treatment (but also note use of aspirin in antiphospholipid syndrome). LMWH is preferred to unfractionated heparin because it is less frequently associated with bleeding, thrombocytopenia and osteopenia.

Post-partum thromboprophylaxis

- All women should be encouraged to mobilise both during labour and post-partum, and dehydration should be avoided
- Women with two or more risk factors should be considered for LMWH for 7 days after delivery
- Women with three or more persisting risk factors should be given graduated compression stockings in addition to LMWH
- All women with BMI >40 kg/m^2 should be considered for thromboprophylaxis with LMWH for 7 days after vaginal delivery, 6 weeks after LSCS (lower segment caesarean section).

Women receiving LMWH antenatally should usually continue prophylactic doses of LMWH until 6 weeks post-partum – which can be converted to warfarin soon after delivery

Air travel in pregnancy (RCOG)

A particular concern is the risk of DVT. This risk is likely to be increased (threefold) by air travel owing to immobility, and/or potentially cramped conditions, with an 18% higher risk of VTE for each 2-hour increase in flight duration. Nevertheless, the overall absolute incidence of a symptomatic VTE is low, with a rate of 1 in 4600 flights in the month after a 4-hour flight.

The risk will vary according to the individual's own risk factors for thrombosis.

With regard to minimising the risk of DVT, the following would be the appropriate general advice:

- Have an aisle seat to facilitate ease of movement
- Take regular walks around the cabin and/or carry out in-seat exercises approximately every 30 min on a medium- or long-haul flight
- Maintain a good fluid intake and minimise caffeine and alcohol intake to avoid dehydration
- Make a specific individualised risk assessment for thrombosis in pregnant women who are flying.

Table 12.9 Diagnosis of thromboembolic disorders in pregnancy

Disorder	Diagnostic tool	Description
Deep vein thrombosis	Clinical and laboratory	The clinical diagnosis of deep vein thrombosis (DVT) in pregnant women can be difficult However, **70%** are iliofemoral and therefore clinically obvious, with a tender, swollen painful leg D-dimers are raised in normal pregnancy. They do, however, provide **a useful negative**
	Doppler ultrasonography	Most widely used technique; effective in diagnosis of symptomatic, proximal DVT. If clot is present the vein is incompressible and does not dilate during the Valsalva manoeuvre; sensitivity/specificity about 97%. Insensitive for thrombosis within the calf, or above the inguinal ligament
Pulmonary	Chest radiograph	Confers minimal risk to fetus. Often normal but may

embolism		demonstrate an effusion, decreased vascularity
	ECG	Note that changes can occur within normal pregnancy. In pulmonary embolism (PE) the ECG may be normal, or it may demonstrate a sinus tachycardia, right heart strain or the classic features of a deep S wave in I, Q wave and inverted T wave in III
	Blood gas analysis	May be normal but in the presence of a PE will typically demonstrate hypoxia with ↓ *P*aO2, and normal or ↓ *P*aCO2
	V′/*Q*′ scan	The isotopes used have short half-lives and so exposure of the fetus is minimal. The *V*′/*Q*′ scan can be safely performed in breastfeeding mothers. False negatives are rare and hence a normal scan excludes PE. The typical features are perfusion defect with normal ventilation. Moderate probability scans should be discussed with a respiratory physician. Undertake leg Doppler FIRST
		CTPA (CT pulmonary angiogram) should be considered first line (after leg Doppler) in those patients with additional lung pathology, abnormal chest radiograph, or after a low probability scan when the clinical picture fails to improve or worsens despite thromboprophylaxis, and the underlying diagnosis has not been established

For short-haul journeys: no specific measures are likely to be required.

For medium- to long-haul flights (≥4 hours): all pregnant women are advised to wear properly fitted, graduated, elastic compression stockings.

For women with **additional risk factors for thrombosis** such as morbid obesity, specific prophylaxis with LMWH should be considered for **the day of travel and several days thereafter**, if the woman is not already on LMWH. The appropriate duration of thromboprophylaxis is not yet established and is a matter for clinical judgement.

FURTHER READING

Chappell LC, Duckworth S, Seed PT, *et al*. PELICAN – Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation* 2013;**128**:2121–31.

Côté A-M, Brown MA, Lam E, *et al*. Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. *BMJ* 2008;**336**:1003.

Coulam CB. Multiple thrombophilic gene mutations rather than specific gene mutations are risk factors for recurrent miscarriage. *Am J Reprod Immunol* 2006;**55**:360–8.

National Institute for Health and Care Excellence. *Diabetes and Pregnancy*. Guideline 68. London: NICE, 2008.

National Institute for Health and Care Excellence. *Hypertension in Pregnancy*. Guideline 107. London: NICE, 2011.

Robertson L, Wu O, Langhorne P, *et al*. Thrombophilia in pregnancy: a systematic review. *Br J Haematol* 2006;**132**:171–96.

Royal College of Obstetricians and Gynaecologists. *Thrombosis and Embolism in Pregnancy and the Puerperium – Reducing the* risk. Guideline 37a. London: RCOG, 2009.

Royal College of Obstetricians and Gynaecologists. Cardiac Disease in Pregnancy. RCOG Good Practice. London: RCOG, 2011.

Chapter 13
Metabolic Diseases

CONTENTS

Metabolic Diseases

13.1 DISORDERS OF AMINO-ACID METABOLISM

Most of the inherited metabolic diseases are Mendelian, single-gene defects, transmitted in an autosomal recessive manner. Disease expression requires the affected individual to be homozygous – inheriting a mutant gene from each of their parents, who are both heterozygous for the defect. Although heterozygotes may synthesise equal amounts of normal and defective enzymes they are usually asymptomatic.

- Even the major inborn errors of amino-acid metabolism are rare – phenylketonuria, one of the most common, has an incidence of 1/20 000
- Complete penetrance is common and the onset is frequently early in life
- The consequences of these enzyme deficiencies are varied and frequently multisystem but expression tends to be uniform.

The more common of these conditions are listed in the box below and the major inborn errors of amino-acid metabolism are then discussed.

Inborn errors of amino-acid metabolism

- Albinism

- Alkaptonuria
- Cystinosis
- Cystinuria
- Homocystinuria
- Histidinaemia
- Maple syrup urine disease
- Oxalosis
- Phenylketonuria

13.1.1 Alkaptonuria (ochronosis)

This is a rare autosomal recessive disease with an incidence of 1/100 000. Homogentisic acid accumulates as a result of a deficiency in the enzyme homogentisic acid oxidase.

- The homogentisic acid polymerises to produce the black–brown product alkapton, which becomes deposited in cartilage and other tissues (ochronosis)
- Classic features include pigmentation (dark blue, grey or black) of the sclerae, ears, arthritis, intervertebral disc calcification and dark sweat-stained clothing
- Life expectancy is normal but there is significant morbidity from joint complications. Onset of back pain is around 30 years
- Rarer manifestations include renal stone disease as well as aortic valve and ocular involvement
- The urine darkens on standing because homogentisic acid conversion to alkapton is accelerated in alkaline conditions
- There is a high prevalence of alkaptonuria in Slovakia (1/19 000) due to novel mutations, which have resulted in geographical clustering
- The molecular basis of the disorder is known but there is no specific treatment. Vitamin C is sometimes recommended as a mild antioxidant. Arthritis may require joint replacement.

13.1.2 Cystinosis

Cystinosis is an autosomal recessive lysosomal storage disease which occurs with an approximate frequency of 1/100 000 to 1/200 000 live births. In cystinosis, cystine accumulates in the reticuloendothelial system, kidneys and other tissues.

There is a defect of cystine transport across the lysosomal membrane resulting in widespread intralysosomal accumulation of cystine. The causative gene (*CTNS*), which encodes for an integral membrane protein called cystinosin, has been identified on chromosome 17p13. Unlike cystinuria, stones do not occur in this condition.

Clinical features of cystinosis

- Fanconi syndrome (often with severe hypophosphataemia and consequent vitamin D-resistant rickets)
- Lymphadenopathy
- Severe growth retardation
- Insulin deficiency
- Corneal opacities and photophobia
- Abnormalities of cardiac conduction
- Hypothyroidism
- Bone marrow failure
- Central nervous system (CNS) involvement

Onset is usually in the first year of life and chronic kidney disease (CKD) is progressive, often resulting in end-stage renal disease by the age of 10 years. Corneal or conjunctival crystals usually suggest the diagnosis, which can be confirmed by measuring the cystine content of neutrophils or cultured fibroblasts. Specific therapy with cysteamine bitartrate is effective at reducing cystine accumulation and delaying CKD. Cysteamine eye drops can be used to help with corneal disease. Supportive care, including dialysis and transplantation, is usually needed. Cystinosis does not recur in the transplant but extrarenal disease is progressive. Antenatal testing for cystinosis can be performed by measuring cystine levels in chorionic villi or cultured amniotic fluid cells.

- **Ocular non-nephropathic cystinosis**: this is a variant of the classic disease and is due to different mutations of the cystinosis gene *CTNS*. It is an autosomal recessive lysosomal storage disorder characterised by photophobia due to corneal cystine crystals.

13.1.3 Cystinuria

Cystinuria is an autosomal recessive disorder with a prevalence of about 1/7000. The transport of cystine and the other dibasic amino acids lysine, ornithine and arginine is abnormal in the proximal renal tubule and the jejunum.

- No malnutrition occurs as sufficient dietary amino acids are absorbed as oligopeptides
- Presentation is usually in the second or third decade of life with renal stones
- Cystine accumulates in the urine. It is highly insoluble at acid pH and this results in the formation of radio-opaque calculi (cystine stones account for 1–2% of all urinary tract stones).

A urinary cystine concentration >1 mmol/L (at pH 7.0) is supersaturated and leads to calculi formation.

Diagnosis requires measurement of urinary cystine and/or chromatographic analysis of the stone. Pathognomonic hexagonal crystals can be found on urine microscopy.

Management

Management involves large fluid intake, alkalinisation of urine and D-penicillamine (which chelates cystine and increases its solubility). Tiopronin is an alternative and increasingly first-line cystine

chelator that is better tolerated than D-penicillamine. Captopril is a thiol angiotensin-converting enzyme (ACE) inhibitor and consequently can bind to cystine and increases its solubility.

13.1.4 Homocystinuria

This rare autosomal recessive abnormality results from reduced activity of cystathionine synthase. The resulting homocystine and methionine accumulation interferes with collagen cross-linking. Nearly a quarter of patients die as a result of vascular thrombosis before the age of 30.

Clinical features of homocystinuria

- Downward lens dislocation
- Venous and arterial thromboses
- Spontaneous retinal detachment
- Developmental and learning disability
- Osteoporosis
- Seizures and psychiatric syndromes
- Skeletal abnormalities (eg marfanoid stature, arachnodactyly, chest deformities)

The main differential diagnosis is Marfan syndrome, because patients can have similar skeletal manifestations and ectopia lentis (although this is classically upward lens dislocation in Marfan syndrome). Osteoporosis, learning disability and vascular thrombosis do not occur in patients with Marfan syndrome.

Investigations

Tests show elevated plasma-free methionine and homocystine. Diagnosis is established by the cyanide/nitroprusside test that detects elevated urinary homocystine and reduced cystathionine synthase enzyme activity in tissue (liver or skin biopsy). Heterozygous carriers have elevated serum homocystine but no homocystinuria. Premature cardiovascular risk is also increased in heterozygotes.

Management

- Early detection (of younger siblings)
- Methionine restriction and cystine-supplemented diets
- Pyridoxine supplements (effective in 50%)
- Some variants are responsive to folate or vitamin B_{12} supplements
- Antenatal screening for enzyme deficiency is available.

Other causes of elevated plasma homocystine

Plasma homocystine levels can be elevated in elderly people, postmenopausal women and patients

with advanced CKD and hypothyroidism. Drug treatments such as methotrexate can also increase levels. Elevated homocystine levels have been associated with an increased risk of cardiovascular disease (eg in dialysis populations) and deep vein thrombosis.

13.1.5 Primary hyperoxaluria (oxalosis)

There are two inborn errors of metabolism that cause overproduction of oxalate. Both are autosomal recessive and can lead to hyperoxaluria with stones and tissue deposition of calcium oxalate.

- Type I is due to a deficiency of hepatic peroxisomal alanine:glyoxylate aminotransferase
- Type II is due to a deficiency of D-glyceric acid dehydrogenase.

Clinical features of oxalosis

- Oxalate renal stones
- Severe arterial disease (due to deposition of oxalate crystals in the vessel wall)
- Nephrocalcinosis
- Cardiac disease (conduction delay)
- Bone disease (and bone marrow invasion leading to pancytopenia and fractures)

Diagnosis

Oxalosis should be suspected if there is increased urinary oxalate excretion, but the latter can also occur with pyridoxine deficiency (as this is a necessary coenzyme in oxalate metabolism), ileal disease, ethyl glycol poisoning and excess oxalate ingestion.

Confirmation of diagnosis requires:

- Plasma oxalate
- Liver biopsy to demonstrate enzyme deficiency in type I
- Demonstration of enzyme deficiency in peripheral blood leukocytes in type II
- Genetic testing by mutation and linkage analysis is useful for identifying other affected family members, as well as in prenatal diagnosis and carrier testing.

Treatment of oxalosis

This initially involves high fluid intake, urinary calcium crystallisation inhibitors (eg citrate) and the use of pyridoxine. Only 10–30% of patients respond to pyridoxine. In primary hyperoxaluria type I, early diagnosis and pre-emptive isolated liver transplantation can be curative. In patients who already have advanced CKD (CKD stages 4 and 5), intensive dialysis therapy is appropriate. Concomitant liver and renal transplantation is often performed, but in this situation the renal transplants can be lost due to rapid oxalate crystal deposition (prior liver transplantation is preferable because it would allow clearance of the oxalate load before consideration of renal transplantation).

13.1.6 Phenylketonuria

There are several variants of phenylketonuria (PKU) due to different allelic mutations. For example, mutations of the gene that encodes phenylalanine hydroxylase (and associated enzymes) are found on chromosome 12. Only severe deficiency of the enzyme results in classic PKU with neurological damage. PKU affects between 1/10 000 and 1/14 000 live births.

The biochemical abnormality is an inability to convert phenylalanine into tyrosine due to lack of phenylalanine hydroxylase. This results in hyperphenylalaninaemia and increased excretion of its metabolite, phenylpyruvic acid ('phenylketone') in the urine.

Clinical features of PKU

- Affects children, usually manifesting by 6 months of life
- Irritability
- Decreased pigmentation[a] (pale skin, fair-haired and blue-eyed phenotype)
- Eczema
- Learning disability

[a]This is due to reduced melanin formation.

Diagnosis

The Guthrie screening test is a neonatal blood test taken from a heel prick. Phenylalanine levels are measured by spectrofluorometric methods or using a form of mass spectrometry that has the ability to analyse many amino acids, fatty acids and shortchain organic acid metabolites simultaneously.

Management

A diet low in phenylalanine, with tyrosine supplementation in infancy and childhood, is now also recommended for adults. Commencing the diet as soon as possible after birth can prevent the deleterious consequences, which are irreversible. PKU females should be advised to reinstitute strict dietary control before conception and throughout pregnancy and breastfeeding. Fish oil supplementation can also improve symptoms.

13.2 DISORDERS OF PURINE METABOLISM

Uric acid is the end product of purine metabolism. Purines can be synthesised new or salvaged from the breakdown of nucleic acids of endogenous or exogenous origin. Increased new synthesis of purines is thought to be responsible, at least partly, for primary gout. Deficiency of hypoxanthine–guanine phosphoribosyl transferase (HGPRT), which is involved in the salvage pathway, results in the Lesch–Nyhan syndrome.

Disorders of purine metabolism

- Primary gout
- Lesch–Nyhan syndrome
- Secondary hyperuricaemia

(See also Chapter 20, Rheumatology.)

13.2.1 Gout

More than 10% of the population of the western world has hyperuricaemia, which can be due to a variety of genetic and environmental factors. Gout develops in less than 0.5% of the population. (See also Chapter 20, Rheumatology.)

- Primary hyperuricaemia is more common in males and postmenopausal females than in premenopausal females
- It is rare in childhood
- It is probably polygenic, involving both increased purine synthesis and reduced renal tubular secretion of urate
- Gout can be precipitated by thiazide diuretics, alcohol and high purine (meat) intake
- Treatment is with non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine for acute episodes. NSAIDS or colchicine may be contraindicated or poorly tolerated by some groups of patients (eg CKD); short courses of oral steroids, or a long-acting intramuscular steroid injection, can be prescribed as an alternative. Longer-term lowering of uric acid is achieved with allopurinol. The selective nonpurine xanthine oxidase inhibitor febuxostat has also been shown to effectively lower serum uric acid levels
- Hyperuricaemia is associated with increased cardiovascular risk
- Hyperuricaemia is also a sensitive marker for pre-eclampsia. Elevated levels correlate with maternal and fetal mortality and morbidity.

13.2.2 Lesch–Nyhan syndrome

Lesch–Nyhan syndrome is an uncommon X-linked recessive disease (therefore seen only in males) due to complete lack of hypoxanthine–guanine phosphoribosyl transferase (HaPRT). This results in accumulation of both hypoxanthine and guanine, both of which are metabolised to xanthine and subsequently to uric acid.

Clinical features of Lesch–Nyhan syndrome

- Neurological disability, eg dystonia, choreoathetosis
- Self-injurious behaviour which can be severe
- Learning disability

- Renal calculi
- Gout and gouty arthritis
- CKD due to crystal nephropathy

- Neurological manifestations are usually present in early infancy and consequently patients present with delayed motor development. Patients rarely survive beyond the age of 40. This is usually due to end-stage renal disease or aspiration pneumonia
- Kelley–Seegmiller syndrome is a variant, with mild neurological symptoms, due to a partial deficiency of HaPRT
- Treatment of the uric acid overproduction is with allopurinol or febuxostat. Treatments for the neurological and behavioural symptoms are limited mutation detection and linkage analysis for probands and their families. Biochemical measurement of HaPRT enzyme activity is also possible for at-risk pregnancies.

13.3 DISORDERS OF METALS AND METALLOPROTEINS

Iron and copper play central roles in the function of a number of metalloproteins, including cytochrome oxidase, which is essential in cellular aerobic respiration; haem, based on iron, is the key molecule in oxygen transport. Excessive accumulation can, however, promote free radical injury (eg Wilson's disease and haemochromatosis) and disorders of haem synthesis result in porphyria.

Disorders of metals and metalloproteins

- Wilson's disease
- Secondary iron overload
- Haemochromatosis
- The porphyrias

13.3.1 Wilson's disease

This autosomal recessive disorder has a gene frequency of 1/400 and a disease prevalence of approximately 1/200 000. The responsible defective gene (*ATP 7B*) is on chromosome 13, and this codes for a copper-transporting P-type adenosine triphosphate.

In normal individuals 50% of ingested copper is absorbed and transported to the liver loosely bound to albumin. Here copper is incorporated into an α_2-globulin to form ceruloplasmin, which is the principal transport protein for copper, and necessary for biliary excretion. In Wilson's disease copper absorption is normal but intrahepatic formation of ceruloplasmin is defective. Total body and tissue copper levels rise due to failure of biliary excretion and urinary excretion of copper is increased.

Clinical features of Wilson's disease

- **Onset in childhood or adolescence**
- **Hepatic dysfunction**
  - Acute hepatitis
  - Cirrhosis (most common)
  - Chronic hepatitis
  - Massive hepatic necrosis
- **Hypoparathyroidism**
- **Haemolysis**
- **Neuropsychiatric disturbance** (often presents later than hepatic dysfunction)
  - Slurred speech, ataxia, chorea, seizures
  - Subcortical dementia
  - Frontal lobe impairment resulting in personality change
  - Psychosis, anxiety and depression
- **Kayser–Fleischer corneal rings** (asymptomatic)
  - Due to copper deposition in Descemet's membrane
- **Fanconi syndrome**
- **Musculoskeletal**
  - Degenerative arthropathy resembling premature osteoarthritis
  - Osteopenia (50%)
  - Osteoporosis
  - Chondrocalcinosis

Diagnosis

Wilson's disease should be considered in any patient with unexplained hepatic dysfunction and neurological/neuropsychiatric symptoms. Diagnosis is based on a decrease in serum ceruloplasmin and increases in hepatic copper content and urinary excretion of copper. However, biochemical diagnosis is increasingly recognised to have low sensitivity. Molecular diagnosis is available to identify presymptomatic individuals. Serum copper levels are of no diagnostic value. Liver biopsy is also used to facilitate diagnosis.

Management

Early detection permits lifelong use of medications that can prevent the deleterious effects of copper accumulation. Copper chelators (eg penicillamine and trientine) are used to remove copper in symptomatic patients. In patients who have no symptoms, zinc is used to prevent the build-up of copper. Zinc works by preventing copper absorption in the gut. It is also used in patients who have responded to treatment with chelators as maintenance therapy. Fulminant hepatic failure and end-stage liver disease necessitate liver transplantation, which is curative (but CNS sequelae may persist).

First-degree relatives should be screened for Wilson's disease. (See also Chapter 6, Gastroenterology.)

13.3.2 Haemochromatosis

In the normal adult the iron content of the body is closely regulated. Haemochromatosis is the excessive accumulation of iron. Primary (or idiopathic) haemochromatosis is a common autosomal recessive disorder in which iron accumulates in parenchymal cells, leading to damage and fibrosis.

Haemosiderin is an insoluble iron–protein complex found in macrophages (it is relatively harmless to them) in the bone marrow, liver and spleen. Secondary iron overload, which has many causes, is often referred to as 'haemosiderosis'.

The gene for haemochromatosis (*HFE*) is located on chromosome 6 close to the HLA locus. HFE codes for a transmembrane glycoprotein that modulates iron uptake. Over 85% of white patients are homozygous for the *HFE C282Y* mutation.

The gene frequency is 6% and disease frequency 1/220 people, but the severity of the disease seems to vary. The disease is therefore staged as follows:

- **Stage 1**: genetic disorder with no increase in iron stores in those who have genetic susceptibility
- **Stage 2**: genetic disorder in those who have phenotypic evidence of iron overload but no tissue or organ damage
- **Stage 3**: genetic disorder with iron overload and iron deposition resulting in tissue and organ damage.

Diagnosis

Serum iron is elevated with >45% transferrin saturation. Serum ferritin is >500 µg/L, but it is important to note that the most common causes of elevated ferritin (an acute phase reactant) are inflammation, alcohol and many other conditions. The combination of elevated transferrin saturation and ferritin in a patient with a family history or clinical features of haemochromatosis should prompt molecular genetic diagnosis for an *HFE* mutation. Liver iron concentration >180 µmol/g is also indicative of haemochromatosis.

Management

- Venesection to maintain ferritin between 50 and 100 µg/L
- Chelation therapy with desferrioxamine if unable to undergo venesection
- Avoid vitamin C supplements as they enhance iron absorption
- Screening of first-degree relatives (serum ferritin)
- Screening cirrhotic patients for hepatocellular carcinoma is recommended (6-monthly ultrasound and serum α-fetoprotein)
- Liver transplantation (for end-stage liver disease).

13.3.3 Secondary iron overload

Secondary haemochromatosis is due to iron overload, which can occur in a variety of conditions. The pattern of tissue injury is similar to that in primary haemochromatosis. In the inherited haemolytic anaemias, iron overload can present in adolescence; the features are often modified by the underlying disease. Treatment is with desferrioxamine.

Secondary causes of iron overload

- **Anaemia due to ineffective erythropoiesis**
  - β-Thalassaemia
  - Sideroblastic anaemia
  - Aplastic anaemia
  - Pyruvate kinase deficiency
- **Parenteral iron overload**
  - Blood transfusions
  - Iron transfusions
- **Liver disease**
  - Alcoholic cirrhosis
  - Chronic viral hepatitis
  - Porphyria cutanea tarda
- **Increased oral iron intake** (Bantu siderosis)
- **Congenital transferrinaemia**

13.3.4 The porphyrias

The porphyrias are a rare heterogeneous group of conditions caused by abnormalities of enzymes involved in the biosynthesis of haem, resulting in overproduction of the intermediate compounds called porphyrins. Most porphyrias are hereditary, although some can be acquired. Excess production of porphyrins can occur in the liver or bone marrow and is classified as acute or non-acute.

The haem metabolic pathway and the type of porphyria resulting from different enzyme deficiencies are shown in Figure 13.1. The two most important porphyrias are porphyria cutanea tarda and acute intermittent porphyria – these are described in more detail.

Porphyria cutanea tarda

This is the most common hepatic porphyria. There is a genetic predisposition but the pattern of inheritance is not established. It is more common in men and usually presents after the age of 40. Many sporadic cases are due to chronic liver disease, usually alcohol-related.

- There is reduced uroporphyrinogen decarboxylase activity

- Uroporphyrinogen accumulates in blood and urine
- Manifests as photosensitivity rash with bullae. Porphyrins produce free radicals when exposed to ultraviolet light which results in damage to sun-exposed skin.

Diagnosis

Based on elevated urinary uroporphyrinogen (urine is normal in colour).

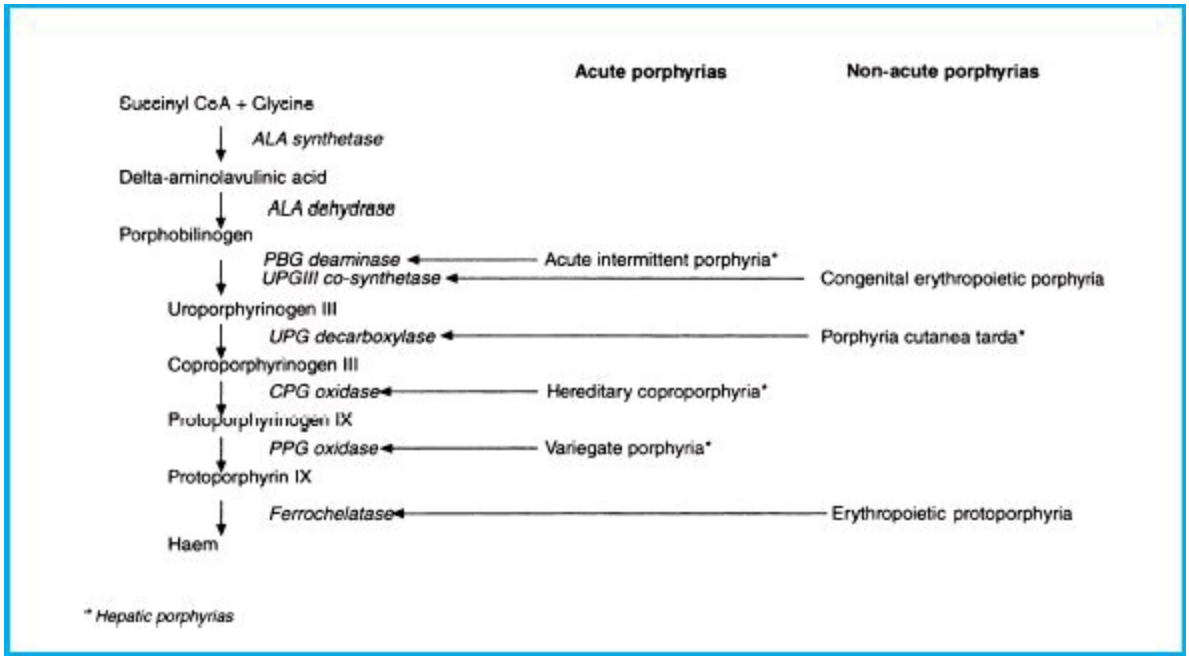
Treatment

- The underlying liver disease
- Venesection
- Low-dose chloroquine – used infrequently to mobilise porphyrins from the liver.

Acute intermittent porphyria

This causes attacks of classic acute porphyria, often presenting with abdominal pain and/or neuropsychiatric disorders. It is an autosomal dominant disorder.

Figure 13.1 Haem synthesis and the porphyrias



- There is reduced hepatic porphobilinogen deaminase activity
- The gene (and disease) frequency is between 1/10 000 and 1/50 000
- Episodes of porphyria are more common in females
- There is no photosensitivity or skin rash
- There is increased urinary porphobilinogen and aminolaevulinic acid, especially during attacks
- Urine turns deep red on standing.

Clinical features of acute intermittent porphyria

- Onset in adolescence
- Abdominal pain occurs in 95% of acute episodes, vomiting, constipation
- Neuropsychiatric disorders
- Episodic attacks
- Polyneuropathy (motor)
- Hypertension and tachycardia
- Tubulointerstitial nephritis

Precipitating drugs:

- Alcohol
- Benzodiazepines
- Rifampicin
- Oral contraceptives
- Phenytoin
- Sulfonamides.

Other precipitating factors:

- Stress
- Pregnancy
- Changes in the menstrual cycle (especially premenstrual)
- Infection
- Fasting.

Management

- Supportive: maintain high carbohydrate intake; avoid precipitating factors
- Early detection of the signs and symptoms of an acute episode
- Acute episodes are treated with daily haem arginate infusions for 3–4 days as well as treatment/withdrawal of any precipitating agents
- Of patients, 10% die as a result of hepatocellular carcinoma.

13.4 DISORDERS OF LIPID METABOLISM

Hyperlipidaemia, especially hypercholesterolaemia, is associated with cardiovascular disease (Table 13.1).

Table 13.1 Cholesterol level and relative risk of myocardial infarct

Total cholesterol (mmol/L)	Relative risk of myocardial infarct

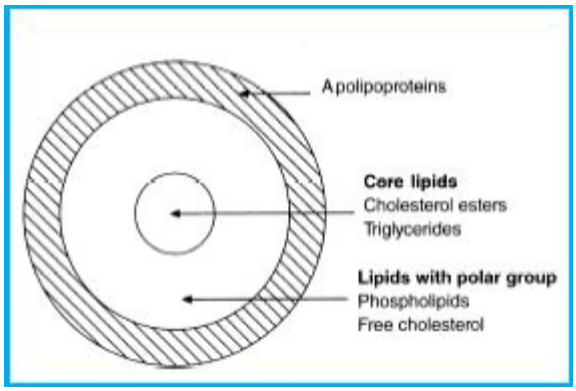
5.2	1
6.5	2
7.8	4

Although lipid metabolism is complex, and many inherited or acquired disorders can disrupt it, the end result is usually elevated cholesterol and/or triglyceride concentrations. These can be managed by dietary and pharmacological means.

13.4.1 Lipid metabolism

Cholesterol and triglycerides are insoluble in plasma and circulate bound to lipoproteins. The lipoproteins consist of lipids, phospholipids and proteins. The protein components of lipoproteins are called apolipoproteins (or apoproteins) and they act as cofactors for enzymes and ligands for receptors. Figure 13.2 is a schema of lipoprotein structure and lipid metabolism is shown in Figure 13.3.

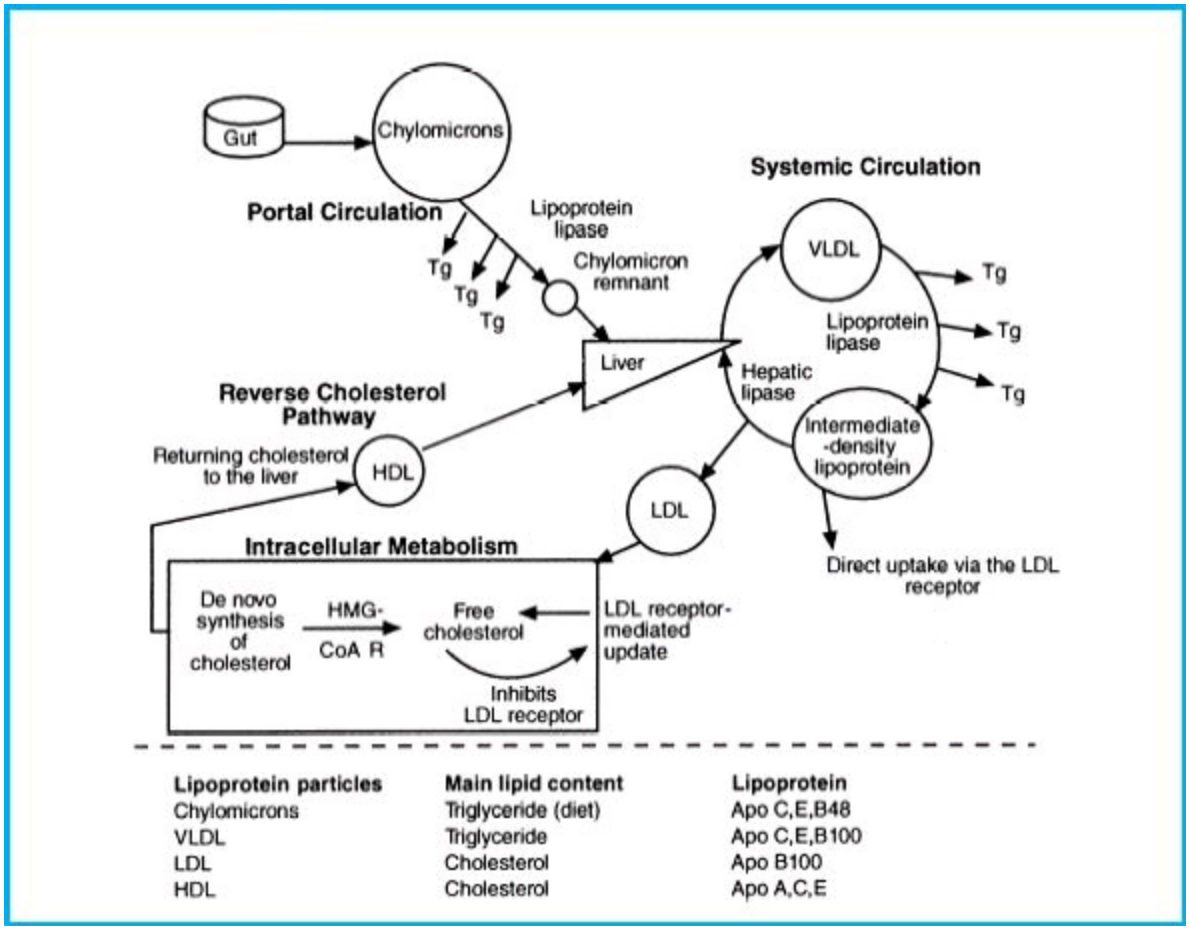
Figure 13.2 Schema of lipoprotein structure



There are four major lipoproteins:

- **Chylomicrons**: large particles that carry dietary lipid (mainly triglycerides) from the gastrointestinal tract to the liver. In the portal circulation, lipoprotein lipase acts on chylomicrons to release free fatty acids for energy metabolism
- **Very-low-density lipoprotein** (VLDL): carries endogenous triglyceride (60%), and to a lesser extent cholesterol (20%), from the liver to the tissues. The triglyceride core of the VLDL is also hydrolysed by lipoprotein lipase to release free fatty acids. The VLDL remnants are called intermediate-density lipoprotein (IDL)

Figure 13.3 Lipid metabolism



- **Low-density lipoprotein** (LDL): formed from the IDLs by hepatic lipase. LDL contains a cholesterol core (50%) and lesser amounts of triglyceride (10%). LDL metabolism is regulated by cellular cholesterol requirements via negative feedback control of the LDL receptor
- **High-density lipoprotein** (HDL): carries cholesterol from the tissues back to the liver. HDL is formed in the liver and gut and acquires free cholesterol from the intracellular pools. Within the HDL, cholesterol is esterified by lecithin cholesterol acyltransferase (LCAT). HDL is inversely associated with ischaemic heart disease.

The LDL receptor

Circulating LDL is taken up by the LDL receptor. Cells replete in cholesterol reduce LDL-receptor expression. In contrast, inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that controls the rate of new cholesterol synthesis, leads to a fall in cellular cholesterol and an increase in LDL-receptor expression.

Lipoprotein (a)

Lp(a) is a specialised form of LDL. Lp(a) inhibits fibrinolysis and promotes atherosclerotic plaque formation. It is an independent risk factor for ischaemic heart disease.

13.4.2 The hyperlipidaemias

Population studies have consistently demonstrated a strong relationship between both total and LDL-cholesterol and coronary heart disease. HDL is protective. A total cholesterol:HDL ratio >4.5 is

associated with an increased risk. Intervention trials (eg the Cholesterol Treatment Trialists' [CTT] Collaborators) have shown that a reduction of LDL cholesterol of 1 mmol reduces cardiovascular events by 21% and reduces the mortality rate by 12%.

Triglycerides are also associated with cardiovascular risk; very high triglyceride levels are also associated with pancreatitis, lipaemic serum and eruptive xanthomas. Triglycerides must be measured fasting.

A genetic classification of lipid disorders has now replaced the Fredrickson (WHO) classification, which was based on lipoprotein patterns. The primary hyperlipidaemias can be grouped according to the simple lipid profile. Secondary causes of hyperlipidaemia need to be excluded and are discussed below.

Primary hypercholesterolaemia (without hypertriglyceridaemia)

Familial hypercholesterolaemia (FH) is a monogenic disorder resulting from LDL-receptor dysfunction. A definitive diagnosis of FH is made using the Simon Broome criteria:

1. Tendon xanthomas in a patient or a first-degree relative (parent, sibling, child), or in a second-degree relative (grandparent, uncle, aunt), and elevated cholesterol concentrations as defined below:

	Total cholesterol (mmol/L)	LDL-C (mmol/L)
Child/young person	>6.7	>4.0
Adult	>7.5	>4.9

2. DNA-based evidence of an LDL-receptor mutation, familial defective Apo B100, or a *PCSK9* mutation

- There are many different mutations in different families, all resulting in LDL-receptor deficiency/dysfunction and producing isolated hypercholesterolaemia
- Heterozygote prevalence is 1/500; homozygous FH is rare
- Other typical clinical features are Achilles tendon xanthomas (can also occur in other extensor tendons) and xanthelasma
- All patients with FH should have lipid-lowering therapy titrated upwards until there has been at least a 50% reduction in LDL-cholesterol
- Untreated FH results in coronary heart disease in 50% of men by the age of 50 and 30% of women by the age of 60.

LDL-lowering apheresis (plasma exchange)

LDL apheresis can lower plasma LDL by up to 65% after each treatment. This procedure involves the extracorporeal removal of LDL in a process similar to dialysis. The treatment is lifelong and performed weekly to fortnightly. It can be used to lower LDL-cholesterol in homozygous FH patients who have not responded to drug treatment or have evidence of coronary heart disease. It can also be used in exceptional cases for patients with heterozygous FH, ie progressive coronary heart disease despite maximal medical and surgical intervention. ACE inhibitors should not be used in patients

undergoing LDL apheresis due to the increased risk of anaphylaxis.

Liver transplantation

Patients who have had maximal medical treatment and LDL apheresis can be considered for liver transplantation. The new liver provides functionally normal LDL receptors, thereby reducing plasma cholesterol levels

In **polygenic hypercholesterolaemia**, the precise nature of the metabolic defect(s) is unknown.

These individuals represent the right-hand tail of the normal cholesterol distribution. They are at risk of premature atherosclerosis. Depressed HDL levels are a risk factor for vascular disease.

Factors modifying HDL levels

- **Decreasing**
  - Familial deficiency of HDL
  - Hyperandrogenic state
  - Post-pubertal males
  - Obesity
  - Hypertriglyceridaemia
  - Diabetes mellitus
  - Sedentary states
  - Cigarette smoking
- **Increasing**
  - Familial hyper-α-lipoproteinaemia
  - Low triglyceride levels
  - Thin habitus
  - Exercise
  - Oestrogens
  - Alcohol

Primary hypertriglyceridaemia (without hypercholesterolaemia)

- Polygenic hypertriglyceridaemia is analogous to polygenic hypercholesterolaemia. Some cases are familial but the precise defect is not known. There is elevated VLDL
- Lipoprotein lipase deficiency and apoprotein CII deficiency are both rare. They result in elevated triglycerides due to a failure to metabolise chylomicrons
- These patients present in childhood with eruptive xanthomas, lipaemia retinalis, retinal vein thrombosis, pancreatitis and hepatosplenomegaly
- Chylomicrons can be detected in fasting plasma.

Primary mixed (or combined) hyperlipidaemia

- Familial polygenic combined hyperlipidaemia results in elevated cholesterol and triglycerides
- The prevalence is 1/200
- There is premature atherosclerosis
- Remnant hyperlipidaemia is a rare cause of mixed hyperlipidaemia (palmar xanthomas and tuberous xanthomas over the knees and elbows are characteristic). It is associated with apoprotein E_2: There is a high cardiovascular risk.

Secondary hyperlipidaemias are usually mixed, but either elevated cholesterol or triglycerides may predominate.

Causes of secondary hyperlipidaemias

- **Predominantly increased triglycerides**
  - Alcoholism
  - Obesity
  - CKD
  - Diabetes mellitus
  - Liver disease
  - High-dose oestrogens
- **Predominantly increased cholesterol**
  - Hypothyroidism
  - Renal transplant
  - Cigarette smoking[a]
  - Nephrotic syndrome
  - Cholestasis

[a]Cigarette smoking reduces HDL.

13.4.3 Lipid-lowering drugs

Cholesterol and triglyceride levels should be considered in combination with other risk factors (also see Chapter 1, Cardiology). Potential secondary causes of hyperlipidaemia should be corrected.

Dietary intervention can be expected to reduce serum cholesterol by a maximum of 30%. Dietary measures should be continued with pharmacological therapy. Table 13.2 shows the impact that can be expected with the various agents.

The side-effect profile of the older agents made them unpopular and reduced compliance. In most cases, hypercholesterolaemia will respond to dietary intervention and statin therapy; and mixed or isolated hypertriglyceridaemia, to diet and a fibrate. Treatment of hyperlipidaemia can reduce the risk

of coronary heart disease by 30%. The side-effects and interactions of lipid-lowering drugs are given in Table 13.3.

HMG-CoA reductase inhibitors (statins)

Statins are widely used to lower cholesterol and have been shown to reduce cardiovascular events. Simvastatin is now available in a generic formulation; consequently many patients are having their current statin treatment 'switched' to simvastatin on the assumption that all statins are the same, which they are not. While switching patients to generic simvastatin is more often than not complication free, care should be taken to avoid potential drug interactions, eg protease inhibitors used in antiretroviral regimens inhibit the metabolism of simvastatin and are contraindicated. However, protease inhibitors do not interact with atorvastatin or pravastatin.

Table 13.2 Impact of lipid-lowering drugs

Drug class	↓LDL (%)	↑HDL (%)	↓TGs (%)
HMG-CoA reductase inhibitors	20–40	5–10	10–20
Fibrates	10–15	15–25	35–50
Ezetimibe	15–20	No change	No change
Sterols and stanols	10–20	No change	No change
Anion-exchange resins	15–30	No change	No change
Nicotinic acid	10–25	15–35	25–30
Probucol	10–15	↓20–25	No change
Neomycin	20–25	No change	No change
Fish oil	5–10	No change	30–50

HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein; TGs, triglycerides.

Table 13.3 Side-effects and drug interactions of lipid-lowering drugs

Drug class	Side effects/interactions
HMG-CoA reductase inhibitors	Simvastatin (but not pravastatin) potentiates warfarin and digoxin Increased risk of myopathy with a number of drugs including amlodipine and diltiazem
Fibrates	
Gemfibrozil Bezafibrate	Potentiates warfarin. Gemfibrozil absorption is impaired by anion-exchange resins
Ezetimibe	Headache, abdominal discomfort. Rarely, hypersensitivity, thrombocytopenia, myositis, pancreatitis and abnormal LFTs
Sterols and stanols	Well tolerated as naturally occurring substances but may cause lower

	GI symptoms: diarrhoea, constipation
Anion-exchange resins (aka bile acid sequestrants)	
Cholestyramine	GI side-effects: nausea, cramping, abnormal LFTs
Cholestipol	Impaired absorption of digoxin, warfarin, thyroxine and fat-soluble vitamins
Nicotinic acid	Flushing, headaches, upper GI symptoms, acanthosis nigricans and myositis
Probucol	Diarrhoea, eosinophilia, long QT syndrome, angioneurotic oedema
Neomycin	Ototoxicity, nephrotoxicity
Fish oil	Halitosis, bloating, nausea Impaired glycaemic control in type 2 diabetes mellitus

GI, gastrointestinal; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LFTs, liver function tests.

Current UK guidelines recommend that cardiovascular risk should be estimated using the Framingham 1991 10-year risk equation. However the Framingham risk equation was developed from North American patients and consequently they have been shown to overestimate cardiovascular risk in northern European populations by up to 50% and underestimate cardiovascular risk in patients who are socially deprived. Alternative risk equations are available, eg QRISK (UK), ASSIGN (Scotland). The QRISK equations have been developed using data from the UK population. Published data suggest QRISK equations may be better predictors of cardiovascular events than the Framingham equation in the UK. The QRISK equations take family history and social deprivation into consideration. These equations are currently in evolution and it is likely that future guidelines will use QRISK or similar equations to calculate cardiovascular risk in England and Wales.

Ezetimibe

Ezetimibe selectively inhibits intestinal absorption of cholesterol. It is indicated for patients with primary hypercholesterolaemia who are intolerant of statins or when there is a contraindication to statin use.

Sterols and stanols, eg Flora Pro-active Benecol

These substances inhibit cholesterol absorption in the gut and thereby lower LDL-cholesterol. They are found naturally in a number of foods including extra virgin olive oil. They have no effect on HDL-cholesterol or triglycerides. Sterols and stanols are being increasingly used commercially as an additive to margarines. Although studies have shown a reduction in LDL-cholesterol, further research is required to show whether this translates into a reduction in cardiovascular events.

Secondary prevention

- It is recommended that all patients with established cardiovascular disease should be treated with a statin as first-line agent
- If total cholesterol is >4 mmol/L or LDL remains >2 mmol/L, statin treatment should be titrated upwards.

13.4.4 Rare lipid disorders

A multitude of rare inborn errors of lipid metabolism can lead to multisystem diseases. The most common (all very rare) are shown in Table 13.4.

Table 13.4 Rare inborn errors of lipid metabolism

Disorder	Serum lipid abnormality	Clinical features
Abetalipoproteinaemia	Low cholesterol Low triglycerides	Onset in childhood Fat malabsorption Acanthocytosis (of RBCs) Retinitis pigmentosa Ataxia and peripheral neuropathy
Tangier's disease	Low cholesterol	Onset in childhood Large orange tonsils Polyneuropathy No increased IHD risk
LCAT deficiency	↑Triglycerides Variable cholesterol	Affects young adults CKD
Cerebrotendinous xanthomatosis	None	Affects young adults Cerebellar ataxia Dementia, cataracts Tendon xanthomas
β-Sitosterolaemia	None	Affects adults
Fabry's disease	None	Affects young male adults (mild disease in females) Angiokeratomas Periodic crises Thrombotic events CKD
Adrenoleukodystrophy (ALD)	None	Children >2 years Addison's disease and progressive brain damage
Adrenomyeloneuropathy	A milder form of ALD that can be seen in men in their 20s and 30s. Presentation is similar to multiple sclerosis	

Disorder	Pathogenesis	Treatment
Abetalipoproteinaemia	Defective apoB synthesis	Vitamin E

Tangier's disease	Increased apoA catabolism	None
LCAT deficiency	Reduced LCAT activity	Low-fat diet
Cerebrotendinous xanthomatosis	Not known	None
β-Sitosterolaemia	Increased sitosterol absorption	Low plant-fat diet
Fabry's disease	Deficiency of α-galactosidase A	Human recombinant α-galactosidase A therapy
	X-linked recessive	Renal replacement therapy if end-stage renal failure develops
Adrenoleukodystrophy (ALD)	X-linked	Lorenzo's oil (a combination of oleic acid and euric acid) can reduce or delay symptoms
	Accumulation of very long-chain fatty acids (VLCFAs) in the brain and adrenal cortex	
Adrenomyeloneuropathy		Restrict dietary VLCFA intake Hormone replacement for adrenal insufficiency

CKD, chronic kidney disease; LCAT, lecithin–cholesterol acyltransferase; RBCs, red blood cells.
IHD, ischaemic heart disease.

13.5 DISORDERS OF BONE, MINERAL METABOLISM AND INORGANIC IONS

Bone is a unique type of connective tissue that mineralises. Biochemically it is composed of matrix (35%) and inorganic calcium hydroxyapatite (65%). Bone and mineral homeostasis are tightly regulated by numerous factors, so as to maintain skeletal integrity and control plasma levels.

13.5.1 Calcium homeostasis

Calcium homeostasis is linked to phosphate homeostasis to maintain a balanced calcium phosphate product.

- Hypocalcaemia activates parathyroid hormone (PTH) release to restore serum ionised calcium; other stimuli to PTH release include hyperphosphataemia and decreased vitamin D levels
- Hypercalcaemia switches off PTH release
- Vitamin D promotes calcium and phosphate absorption from the gastrointestinal (GI) tract

- Bone stores of calcium buffer the serum changes.

The metabolism and effects of vitamin D, and the actions of PTH, are shown schematically in Figures 13.4 and 13.5.

13.5.2 Hypercalcaemia

In over 90% of cases hypercalcaemia is due to either hyperparathyroidism or malignancy. Hypercalcaemia normally suppresses PTH and so PTH is therefore the best first test to identity the cause of hypercalcaemia – if it is detectable (in or above the normal range) the patient must have hyperparathyroidism.

- Primary hyperparathyroidism is common, especially in women aged 40–60 years. It is usually due to an adenoma of one of the four parathyroid glands

Figure 13.4 Metabolism and the actions of vitamin D

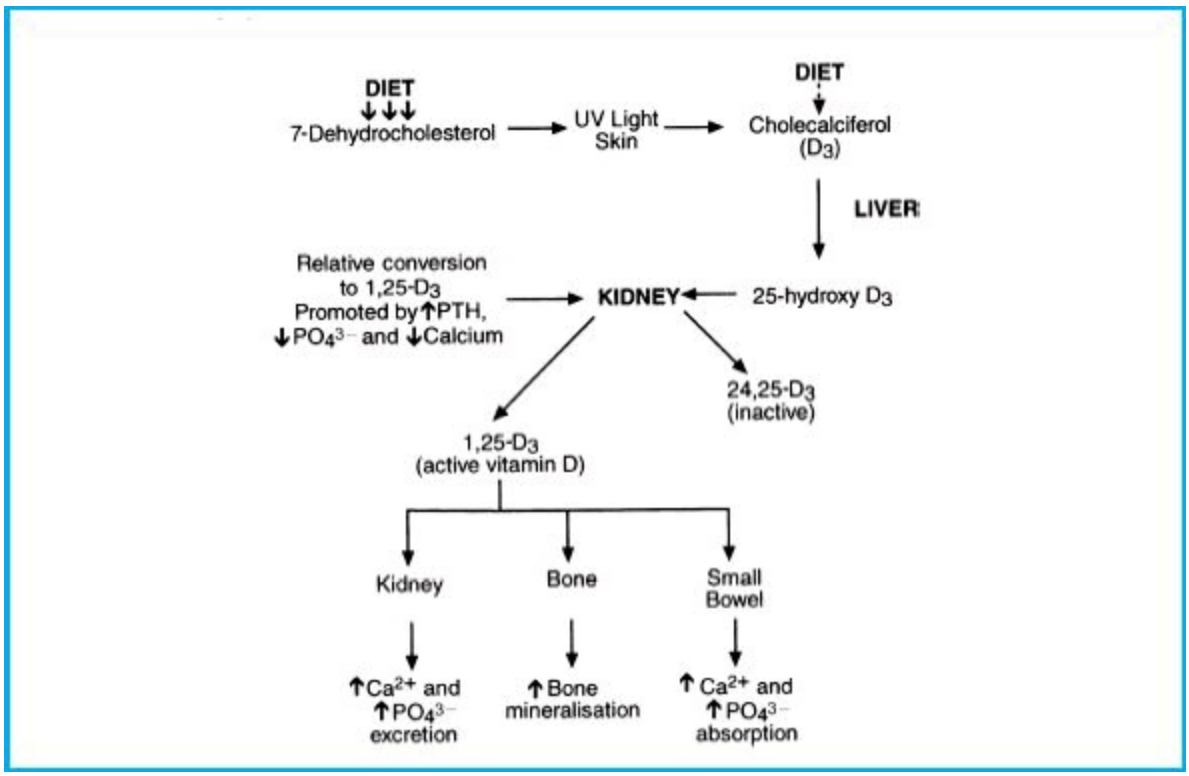
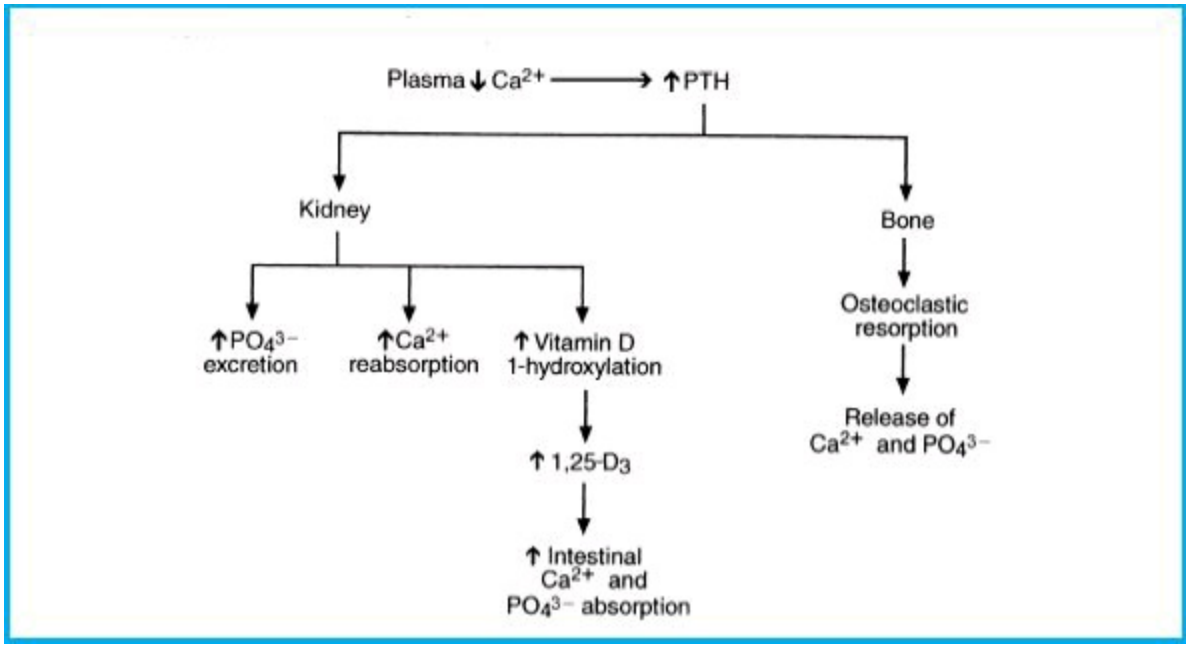


Figure 13.5 Control and actions of parathyroid hormone (PTH)



- PTH-related protein (PTH-rP) is responsible for up to 80% of hypercalcaemia in malignancy
- PTH-rP acts on the same receptors as PTH and shares the first (N-terminal) 13 amino acids with PTH; however, they are coded from two separate genes
- Common malignancies secreting PTH-rP are squamous cell tumours, breast and kidney.

Causes of hypercalcaemia

- **Increased calcium absorption**
  - Increased calcium intake
  - Increased vitamin D
- **Increased bone reabsorption**
  - Primary and tertiary hyperparathyroidism
  - Malignancy
  - Hyperthyroidism
- **Miscellaneous unusual causes**
  - Lithium
  - Thiazide diuretics
  - Addison's disease
  - Sarcoidosis[a]
  - Phaeochromocytoma
  - Familial hypocalciuric hypocalcaemia[b]
  - Theophylline toxicity
  - Milk-alkali syndrome[c]
  - Vitamin A toxicity (rarely)

[a]Sarcoidosis causes hypercalcaemia due to excess production of 1,25-vitamin D_3 by macrophages in the sarcoid lesions.

[b]Familial hypocalciuric hypercalcaemia (FHH) is an autosomal dominant condition. Most cases of FHH are a result of mutations in the calcium-sensing receptor. Patients are often incorrectly diagnosed with primary hyperparathyroidism. In contrast to primary hyperparathyroidism, FHH does not require any treatment.

[c]Hypercalcaemia can be seen in patients who consume excess quantities of Rennies bought over the counter.

The symptoms of hypercalcaemia are often mild but a range of manifestations can occur. The mnemonic 'stones, bones, abdominal groans and psychic moans' can be used to describe these symptoms.

Clinical manifestations of hypercalcaemia

- Malaise/depression
- Lethargy
- Muscle weakness
- Confusion
- Peptic ulceration[a]
- Pancreatitis
- Constipation
- Nephrolithiasis
- Nephrogenic diabetes insipidus
- Distal renal tubular acidosis (RTA)
- CKD[b]
- Short QT syndrome
- Band keratopathy
- Diabetes insipidus

[a]Peptic ulceration is due to excess gastrin secretion.

[b]CKD is due to chronic tubulointerstitial calcification and fibrosis.

The management of acute hypercalcaemia (serum calcium >3 mmol/L) involves:

- Adequate rehydration – 3–4 L saline/day
- Intravenous bisphosphonates (eg pamidronate disodium)
- Identification of the cause, and its subsequent specific treatment (eg corticosteroids for sarcoid) if indicated.

13.5.3 Hyperparathyroid bone disease

Hyperparathyroidism has a prevalence of about 1/1000. It results in bone reabsorption due to excess PTH action.

Primary hyperparathyroidism is caused by a single (80+%) or multiple (5%) parathyroid adenomas or by hyperplasia (10%). Parathyroid carcinoma is rare (<2%). It results from abnormal regulation of PTH by calcium because of an increase in the calcium set point. Familial cases (as seen in multiple endocrine neoplasia [MEN] type 1) have a higher incidence of hyperplasia and, similar to parathyroid carcinoma, can be associated with abnormalities of chromosome 11 (usually deletions in the little q13 region).

Biochemically there is increased PTH, serum and urinary calcium, reduced serum phosphate and increased alkaline phosphatase. Histologically there is an increase of both osteoblasts and osteoclasts resulting in 'woven' osteoid, increased resorption cavities ('osteitis fibrosa cystica') and marrow fibrosis. The definitive treatment of primary hyperparathyroidism is by surgical parathyroidectomy.

Secondary hyperparathyroidism is physiological compensatory hypertrophy of all four glands due to hypocalcaemia (eg CKD, malabsorption). PTH levels are raised; calcium is low or normal. The secondary hyperparathyroidism in CKD is controlled by phosphate restriction, phosphate binders and with use of 1α-hydroxylated vitamin D preparations (see also Chapter 15, Nephrology). Cinacalcet is a calcimimetic that acts on calcium-sensing receptors to increase receptor sensitivity to calcium, which in turn results in a decrease in PTH. Cinacalcet is licensed for the treatment of advanced secondary hyperparathyroidism.[a]

Tertiary hyperparathyroidism is the development of autonomous parathyroid hyperplasia in the setting of long-standing secondary hyperparathyroidism – usually in CKD. Calcium levels are raised. Treatment is in the form of parathyroidectomy or cinacalcet.[a]

13.5.4 Hypocalcaemia

Hypocalcaemia is usually secondary to CKD (increased serum phosphate), hypoparathyroidism or vitamin D deficiency.

Causes of hypocalcaemia

- **Decreased calcium absorption**
  - Hypoparathyroidism
  - Hypovitaminosis D
  - Malabsorption
  - Sepsis
  - Fluoride poisoning
  - Hypomagnesaemia[a]
- **Acute respiratory alkalosis**
- **Hyperphosphataemia (by reduction in ionised calcium)**
  - CKD
  - Phosphate administration
  - Rhabdomyolysis

- Tumour lysis syndrome
- **Deposition of calcium**
  - Pancreatitis
  - Hungry bone syndrome
  - EDTA infusion
  - Rapidly growing osteoblastic metastases

[a]Cause of functional hypoparathyroidism.

Hypoparathyroidism can be spontaneous (autoimmune), post-surgical or due to a receptor defect (pseudohypoparathyroidism). Autoimmune hypoparathyroidism may be part of autoimmune polyglandular failure type I (mucocutaneous candidiasis, with adrenal, gonadal and thyroid failure). Treatment is with calcium and vitamin D supplements.

Recombinant human 1–34-PTH (teriparatide) is available but is not used in clinical practice for hypoparathyroidism because of its cost, need for parenteral administration and short half-life. It has been used for post-surgical hypoparathyroidism over a short-term period, but it is more routinely used in the management of osteoporosis.

In **pseudohypoparathyroidism** there is a characteristic phenotype with short stature, short metacarpals and intellectual impairment. The disorder is due to a G-protein abnormality (see Chapter 14, Molecular medicine).

Vitamin D deficiency can occur in several settings, including:

- Dietary deficiency/lack of sunlight
- Malabsorption
- CKD (failure of 1α-hydroxylation)
- 1α-hydroxylase deficiency (vitamin D-dependent rickets type I)
- Vitamin D-receptor defect (vitamin D-dependent rickets type II).

Rickets without vitamin D deficiency and with normal calcium may be due to hypophosphataemia, as in X-linked dominant, hypophosphataemic, vitamin D-resistant rickets.

The symptoms of hypocalcaemia are mainly those of neuromuscular irritability and neuropsychiatric manifestations. Signs include Chvostek's sign (tapping the facial nerve causes twitching) and Trousseau's sign (precipitation of tetanic [carpopedal] spasm in the hand by sphygmomanometer-induced ischaemia). Trousseau's sign is a more specific test for hypocalcaemia. The development of symptoms depends on how quickly the level of calcium falls as well as the serum concentration.

Clinical manifestations of hypocalcaemia

- **Neuromuscular**
  - Tetany
  - Seizures

    - Confusion
    - Extrapyramidal signs
    - Papilloedema
    - Psychiatric
    - Myopathy
    - Prolonged QT syndrome
- **Ectodermal**
    - Alopecia
    - Brittle nails
    - Dry skin
- **Cataracts**
- **Dental hypoplasia**

Table 13.5 lists the causes of hypocalcaemia and the related biochemical findings.

The **management** of hypocalcaemia involves:

- Intravenous calcium gluconate if severe (tetany/seizures)

Table 13.5 Causes of hypocalcaemia – biochemical findings

Cause	Serum PTH	Vitamin D levels	Phosphate	Alkaline phosphatase
Hypoparathyroidism	Low	Normal	High	Normal
Vitamin D deficiency	High	Low	Low	High
Pseudohypoparathyroidism	High	Normal	High	Normal
CKD	High	Low	High	High

CKD, chronic kidney disease; PTH, parathyroid hormone.

- Oral calcium supplements
- Vitamin D (for hypoparathyroidism, vitamin D deficiency and CKD)
- Normalise serum magnesium levels Hypocalcaemia is difficult to correct if serum magnesium levels are low
- Thiazide diuretic and low-sodium diet.

13.5.5 Hypercalciuria

Hypercalciuria is the most common cause of kidney stones and contributes to the development of osteoporosis. Hypercalciuria occurs as a result of excessive duodenal calcium absorption (normally the duodenum absorbs only 20% of ingested calcium), renal calcium leak or excessive bone

absorption (eg hyperparathyroidism), resulting in excess serum calcium and subsequent hypercalciuria. Excessive calcium absorption is the most common cause of hypercalciuria, although the causes often overlap.

Causes of hypercalciuria

- **Absorptive**
  - Excess calcium ingestion
  - Milk-alkali syndrome
  - Vitamin D excess
  - Sarcoidosis[a]
- **Renal hypercalciuria (renal leak)**
  - Medullary sponge kidney (30–50%)
  - Bartter syndrome[b]
  - Dent's disease[c]
  - Autosomal-dominant hypercalciuric hypocalcaemia[d]
- **Resorptive**
  - Hyperparathyroidism
  - MEN-1 (with hyperparathyroidism)
- **Miscellaneous**
  - Hyperthyroidism
  - Renal tubular acidosis
  - Prolonged immobilisation
  - Paget's disease
  - Pregnancy

[a]Excess 1,25-vitamin D_3 production results in hypercalcaemia and hypercalciuria.

[b]Rare autosomal recessive condition caused by mutations in the genes involved in the active absorption of chloride in the loop of Henle. This results in excess sodium and potassium loss in the urine. Secondary hyperaldosteronism occurs with hypokalaemic alkalosis. Blood pressure is usually normal.

[c]Also known as X-linked recessive hypophosphataemic rickets.

[d]Mutation in the calcium-sensing receptor.

Investigations

- 24-hour urinary calcium
- Serum calcium, phosphate, creatinine and PTH

  Calcium loading test in patients who have not responded to dietary calcium restriction. Patients are fasted and then administered a calcium load. Urine calcium is checked at intermittent periods

- to distinguish the cause of hypercalciuria, eg patients with renal leak hypercalciuria will not change the amount of calcium excreted, whereas patients with absorptive hypercalciuria will increase calcium excretion in response to the calcium load.

Treatments

- Most hypercalciuria can be managed with dietary calcium restrictions
- Reduce sodium intake (elevated sodium intake increases calcium excretion, raises urinary pH and reduces urinary citrate excretion, thereby increasing stone formation)
- Thiazide diuretics are used in patients with renal leak or who have not responded to dietary restriction alone. Thiazide diuretics reabsorb calcium in the renal tubule
- Bisphosphonate can be used in patients who have hypercalciuria as a result of excessive bone resorption (especially patients with osteoporosis)
- Orthophosphates reduce hypercalciuria by reducing vitamin D_3 levels and increasing tubular reabsorption of calcium. Side-effects include GI disturbance.

13.5.6 Osteomalacia

Osteomalacia (adults) or rickets (children) result from inadequate mineralisation of osteoid. The biochemical features are: elevated alkaline phosphatase (95%), hypocalcaemia (50%) and hypophosphataemia (25%). It is usually caused by a defect of vitamin D availability or metabolism. Approximately 1 billion people have osteomalacia worldwide. In the UK the prevalence increases with age, with a prevalence of 30% in the over-65s.

Causes of osteomalacia

- **Vitamin D deficiency**
  - Dietary[a]
  - Sun exposure[b]
  - Malabsorption
  - Gastrectomy
  - Small-bowel disease
  - Pancreatic insufficiency
- **Defective 25-hydroxylation**
  - Liver disease
  - Anticonvulsant treatment[c]
- **Loss of vitamin D-binding protein**
  - Nephrotic syndrome
- **Defective 1α-hydroxylation**
  - Hypoparathyroidism

    - CKD[d]
- **Defective target organ response**
    - Vitamin D-dependent rickets (type II)
- **Mineralisation defects**
    - Abnormal matrix
    - Osteogenesis imperfecta
    - CKD[d]
    - Enzyme deficiencies
    - Hypophosphatasia
- **Inhibitors of mineralisation**
    - Fluoride
    - Aluminium
    - Bisphosphonates
- **Phosphate deficiency**
    - Decreased GI intake
        - Antacids (reduce absorption)
    - Impaired renal reabsorption
        - Fanconi syndrome
        - X-linked hypophosphataemic rickets (vitamin D-resistant rickets)

[a]Vegans in particular may not benefit from dietary vitamin D.

[b]Asian immigrants in western countries are at increased risk because melanin in skin decreases D_3 formation and certain foods (eg chapattis) bind calcium, unmasking vitamin D deficiency.

[c]Especially phenytoin.

[d]Patients with CKD can have mixed bone disease where there is hyperparathyroid bone disease in combination with osteomalacia.

The **management** of osteomalacia involves:

- Diagnosis and treatment of the underlying disorder
- Vitamin D therapy to correct hypocalcaemia and hypophosphataemia
- Beware iatrogenic hypercalcaemia when alkaline phosphatase begins to fall at the time of bone healing.

Oncogenic osteomalacia

This is a paraneoplastic syndrome usually caused by benign tumours of mesenchymal origin. Patients have osteomalacia, bone pain, phosphaturia and hypophosphataemia.

13.5.7 Paget's disease

Paget's disease is a focal (or multifocal) bone disorder characterised by accelerated and disorganised bone turnover resulting from increased numbers and activity of both osteoblasts and osteoclasts. A viral aetiology has not been confirmed.

- Rare in patients aged <40 years
- Prevalence of 1–2% in white people aged >55 years. The UK has the highest prevalence (4.6%) in Europe
- Familial clustering and HLA linkages (15% have a positive family history)
- Biochemically characterised by raised alkaline phosphatase, osteocalcin and urinary hydroxyproline excretion. Radiographs and radionuclide bone scans aid diagnosis
- There is an increased risk of malignant transformation.

Paget's disease is usually diagnosed because of asymptomatic sclerotic changes (which can mimic sclerotic bone metastases) but a number of complications can arise.

Clinical manifestations of Paget's disease

- Bone pain
- Fractures (and pseudofractures)
- Secondary arthritis
- Neurological compression syndromes[a]
- Osteosarcoma (rare)
- High-output congestive cardiac failure
- Hypercalcaemia (only with immobilisation)
- Skeletal deformity

[a]Including deafness, other cranial nerve palsies and spinal stenosis.

Treatment is indicated for bone pain, nerve compression, disease impinging on joints and immobilisation hypercalcaemia. Options include:

- Bisphosphonates
- Calcitonin
- Surgery.

Causes of a raised bone alkaline phosphatase

- **With high calcium**
  - Hyperparathyroidism
- **With high or normal calcium**
  - Malignancy
  - Paget's disease

- **With normal calcium**
  - Puberty
  - Fracture
  - Osteogenic sarcoma
- **With low calcium**
  - Osteomalacia

13.5.8 Osteoporosis

A very common disorder characterised by reduced bone density and increased risk of fracture. The most common form is postmenopausal osteoporosis, which affects 50% of women aged 70. Common sites of fracture are the vertebrae, neck of femur (trabecular bone), and distal radius and humerus (cortical bone); these fractures can occur with minimal trauma.

Diagnosis is by bone mineral densitometry, measured by dual-energy X-ray absorptiometry (DXA), single-photon absorptiometry (SPA) or quantitative computed tomography (QCT) (Table 13.6).

The measured bone density is compared with the mean population peak bone density (ie that of young adults of the same sex) and expressed as the number of standard deviations from that mean, the *T* score. The bone mineralisation and serum biochemistry are normal.

- *T* scores down to −1 are regarded as normal
- *T* scores between −1 and −2.5 represent osteopenia
- *T* scores below −2.5 are osteoporotic.

Table 13.6 Comparison of DXA, SPA and QCT

Method	Measurements	Pros and cons	Cost
DXA	Spine, hip, radius	Most widely available	££
QCT	Spine, hip, radius	Most accurate	£££
		Better for patients with extensive osteoarthritis	
		Increased radiation	
E		Expensive	
SPA	Radius, calcaneum	Not as accurate as DXA and QCT	£

DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; SPA, single-photon absorptiometry.

Fracture risk

The risk of future fractures is dependent on both bone quality (strength and resilience) and the risk of falling. Fractures increase twofold with each standard deviation of the *T* score and independently with age by 1.5-fold per decade.

Aetiology

From the age of 30, bone loss occurs at about 1% per year. This is accelerated to about 5% per year in the 5 years after the menopause. Persistent elevations of PTH will accelerate bone loss further. This occurs both in primary hyperparathyroidism but also in secondary hyperparathyroidism arising in vitamin D deficiency, or in negative calcium balance (eg hypocalcaemia, hypercalciuria).

Aetiology of osteoporosis

- **Primary**
  - Type 1: postmenopausal
  - Type 2: age-related or involutional
  - Osteoporosis of pregnancy
- **Secondary**
  - *Endocrine*: premature menopause, Cushing syndrome, hypopituitarism, hyperparathyroidism, prolactinomas, hypogonadism, hyperthyroidism
  - *Drugs*: steroids, heparin, ciclosporin, anticonvulsants
  - *Malignancy*: multiple myeloma, leukaemia
  - *Inflammatory*: rheumatoid arthritis, ulcerative colitis
  - *GI*: gastrectomy, malabsorption, primary biliary cirrhosis
  - *CKD*
  - *Immobilisation*, eg space flight
  - *Other*: osteogenesis imperfecta, homocystinuria, Turner syndrome (oestrogen deficiency), rheumatoid arthritis,[a] scurvy
- **Additional risk factors for osteoporosis**
  - Race: White/Asian
  - Short stature and low body mass index
  - Positive family history
  - Multiparity
  - Amenorrhoea >6 months (other than pregnancy)
  - Poor calcium and vitamin D intake
  - Excess alcohol and smoking

[a] In rheumatoid arthritis, osteoporosis is multifactorial but corticosteroids and immobility are major contributors.

In the absence of a recent fracture or secondary cause of osteoporosis, bone biochemistry should be normal.

Treatment of osteoporosis

- **General measures**
  - Correct any secondary cause
  - Weight-bearing exercise
  - Adequate dietary calcium and vitamin D intake
- **Specific drug treatments**

  (These may reduce fractures by approximately 50%)
  - Bisphosphonates[a]
  - Denosumab (novel human monoclonal antibody)[b]
  - Oestrogens (hormone replacement therapy [HRT])
  - Calcium and vitamin D combination therapy
  - Testosterone (in males)
  - Selective oestrogen receptor modulators (SERMs), eg raloxifene
  - Teriparatide (1–34-PTH)
  - Strontium ranelate
- **Other**
  - Fluoride (increases bone density, but reduces bone microstructure quality). Fluoride accumulates in peripheral bone and increases the risk of microfractures (stress fractures) and fracture in peripheral weight-bearing bones
  - Calcitonin

[a]Prophylaxis with bisphosphonates is now recommended for patients receiving high-dose (eg relapsing nephrotic syndrome) or long-term (eg asthma) steroids.

[b]Denosumab is a human monoclonal antibody against RANKL (receptor activator of nuclear factor *k*B ligand). RANKL is involved in bone resorption.

13.5.9 Disorders of magnesium

Magnesium is principally found in bone (50–60%) as an intracellular cation and plasma levels are maintained within the range 0.7–1.1 mmol/L. It plays an important role in many metabolic pathways. Disorders of magnesium balance usually occur in association with other fluid and electrolyte disturbances, in particular calcium and potassium.

Hypomagnesaemia

Hypomagnesaemia is frequently accompanied by hypocalcaemia, hypophosphataemia and hypokalaemia. Patients are often asymptomatic but may complain of weakness or anorexia, and features of neuromuscular irritability have been described. Hypomagnesaemia is an important risk factor for ventricular arrhythmias.

Causes of hypomagnesaemia

- **Gastrointestinal losses**
  - Diarrhoea
  - Malabsorption
  - Small-bowel disease
  - Acute pancreatitis[a]
- **Loop of Henle dysfunction**
  - Acute tubular necrosis[b]
  - Renal transplantation
  - Post-obstructive diuresis
  - Bartter syndrome
  - Gitelman syndrome
- **Renal losses**
  - Loop and thiazide diuretics
  - Volume expansion
  - Alcohol[c]
  - Diabetic ketoacidosis
  - Hypercalcaemia[d]
- **Nephrotoxins**
  - Aminoglycosides
  - Amphotericin B
  - Cisplatin
  - Pentamidine
  - Ciclosporin
- **Primary renal magnesium wasting**[e]

[a]Due to the formation of magnesium soaps in the areas of fat necrosis.

[b]Diuretic phase.

[c]Alcohol acutely increases urinary magnesium excretion; in chronic alcoholism this is compounded by ketoacidosis and phosphate depletion.

[d]Hypercalciuria increases magnesium excretion; if saline and diuretics are given to treat hypercalcaemia then the three stimuli together predispose to hypomagnesaemia.

[e]Primary magnesium wasting is a rare familial disorder.

Hypermagnesaemia

Hypermagnesaemia is rare. It is usually due to magnesium ingestion or infusion in the setting of CKD (ie when the kidney cannot excrete a magnesium load).

- At concentrations >4 mmol/L symptoms develop, including lethargy, drowsiness, areflexia, paralysis, hypotension, heart block and finally cardiac arrest

- Toxic effects can be temporarily reversed by intravenous calcium (antagonises the neuromuscular and cardiac effects of hypomagnesaemia). In patients with normal renal function, intravenous physiological saline with forced diuresis using loop diuretics can increase renal magnesium loss. Dialysis can also be used in patients with CKD or in severe hypermagnesaemia.

Causes of hypermagnesaemia

- CKD
- Adrenal insufficiency
- Magnesium infusion
- Milk-alkali syndrome
- Oral ingestion
- Lithium
- Magnesium enemas
- Theophylline intoxication
- Familial hypocalciuric hypercalcaemia
- Tumour lysis syndrome (release of intracellular magnesium)
- Rhabdomyolysis

13.5.10 Disorders of phosphate

Serum phosphate is maintained between 0.8 and 1.4 mmol/L largely by renal regulation of excretion. Bone accommodates 85% of body stores; the rest is found extracellularly as inorganic phosphate and intracellularly as phosphate esters, eg phospholipids, nucleic acids and high-energy compounds such as adenosine triphosphate (ATP).

Hypophosphataemia

Hypophosphataemia can occur in a variety of settings, due to redistribution, renal losses or decreased intake.

- Symptoms rarely develop unless phosphate <0.6 mmol/L; <0.3 mmol/L rhabdomyolysis likely
- Hypophosphataemia leads to reduced oxygen delivery (via reduced levels of 2,3-diphosphoglycerate [2,3-DPG]) and also impairs intracellular metabolism (by depleting ATP)
- Symptoms include weakness (especially respiratory muscles – a particular problem when weaning certain ICU patients from respiratory support), confusion, coma, heart failure and rhabdomyolysis
- Fibroblast growth factor 23 (FGF-23) is phosphaturia. Patients with X-linked hypophosphataemic rickets have very high levels of FGF-23 and marked phosphaturia. There is increasing research into the wider role of FGF-23 and phosphate metabolism.

Causes of hypophosphataemia

- **Internal redistribution**
  - Acute respiratory alkalosis
  - Hyperinsulinaemia
  - Post renal transplantation
- **Decreased intestinal absorption**
  - Inadequate intake (especially alcoholism, persistent vomiting)
  - Antacids containing aluminium or magnesium
  - Steatorrhoea and chronic diarrhoea
- **Increased urinary excretion (phosphate wasting)**
  - Primary and non-renal secondary hyperparathyroidism
  - Vitamin D deficiency/resistance
  - Fanconi syndrome
  - X-linked hypophosphataemic rickets
  - Miscellaneous – osmotic diuretics, thiazide diuretics
  - Acute volume expansion
  - Heavy metal poisoning
  - Oncogenic osteomalacia

Treatment depends on the underlying condition and phosphate supplementation is commonly used. Vitamin D levels should be corrected.

Hyperphosphataemia

Hyperphosphataemia is common in acute and advanced CKD. It can also occur in massive tissue breakdown (eg rhabdomyolysis) and if there is increased tubular reabsorption of phosphate.

- It is usually asymptomatic. If symptoms do occur, they are secondary to a reduction in ionised calcium
- In acute hyperphosphataemia (with normal renal function), saline infusion to volume replete with forced diuresis using a loop diuretic can be used to increase phosphate excretion
- In CKD a low-phosphate diet, phosphate binders and dialysis may be required. The high serum phosphate in CKD is a major vascular risk factor in this population.

Causes of hyperphosphataemia

- **Massive acute phosphate load**
  - Tumour lysis syndrome[a]
  - Rhabdomyolysis

- Lactic and ketoacidosis
- Exogenous phosphate
- Vitamin D intoxication

- **CKD**
- **Increased tubular reabsorption of phosphate**
  - Hypoparathyroidism
  - Pseudohypoparathyroidism
  - Severe hypomagnesaemia (results in PTH resistance)
  - Acromegaly
  - Thyrotoxicosis
  - Bisphosphonates

[a]The tumour lysis syndrome results in release of phosphate, potassium, purines (metabolised to uric acid) and proteins (metabolised to urea). It can result in acute kidney injury due to uric acid crystal deposition.

13.6 NUTRITIONAL AND VITAMIN DISORDERS

In the developed countries, the most common nutritional problem is obesity (see also Chapter 4, Endocrinology). In contrast, in the developing countries, protein–energy malnutrition is common.

In developed countries, the long-term sequelae of fetal and childhood undernutrition are increased cardiovascular disease in adult life.

13.6.1 The obesity and diabetes epidemic

The World Health Organization (WHO) has also projected that the number of deaths attributable to diabetes will increase by 50% between 2005 and 2015.

The increasing prevalence of obesity and its medical sequelae has become an increasing public health concern. Strategies to stem the epidemic are multifactorial and include:

- Increase general population awareness of the impact of obesity
- Engage patients, local schools, workplaces and organisations in promoting healthier diets and physical activity
- Consider referral to weight management programmes, and behavioural change strategies to encourage physical activity and healthier diet choices
- Drug treatments
- Bariatric surgery.

Clinical judgement should be used when interpreting body mass index (BMI), eg high muscle mass (Table 13.7). Asian patients may have increased risk factors at lower BMI. Waist circumference should also be used in patients with a BMI <35 kg/m^2:

Table 13.7 Classification of overweight and obesity

Classification	BMI (kg/m^2)
Healthy weight	18.5–24.9
Overweight	25–29.9
Obesity I	30–34.9
Obesity II	35–39.9
Obesity III	≥40

Treatment

Drug treatment is recommended after dietary, exercise and behavioural strategies have been undertaken and assessed. Patients who have failed to reach their target weight or reached a plateau may benefit from drug treatment. There has been considerable interest in the development of anti-obesity medication but at the time of writing, Orlistat remains the only drug recommended by the National Institute for Health and Care Excellence (NICE).

Orlistat is an inhibitor of gastrointestinal and pancreatic lipase. It can reduce absorption of some fat-soluble vitamins and some medications. Side-effects include GI disturbance such as flatulence, diarrhoea and oily stools. Alternative short-term anti-obesity medications include CNS stimulants and appetite suppressants.

Surgery is recommended in certain groups of patients and there are a number of different techniques available. A multidisciplinary team including the patient determines the choice of surgical technique. The box gives the NICE criteria for bariatric surgery.

NICE criteria for bariatric surgery

- BMI ≥40 kg/m^2
- BMI between 35 kg/m^2 and 40 kg/m^2 and other significant disease (eg type 2 diabetes or high blood pressure) that could be improved if they lost weight
- All appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months
- The person has been receiving or will receive intensive management in a specialist obesity service
- Medically fit for anaesthesia and surgery, and commits to the need for long-term follow-up
- Bariatric surgery is also recommended as a first-line option (instead of lifestyle interventions or drug treatment) for adults with a BMI ≥50 kg/m^2 in whom surgical intervention is considered appropriate

Certain countries will also face a ‘double burden’ of disease. Middle-income countries (eg India) are seeing an increase in obesity in urban settings while still having to manage problems associated with

undernutrition.

13.6.2 Protein–energy malnutrition

Starvation is common in the developing world. In the developed countries, PEM frequently complicates severe sepsis, cachexia, liver cirrhosis, advanced CKD and malabsorption. In these circumstances undernutrition is a risk factor for death.

Elderly people and in particular institutionalised individuals are at a markedly increased risk of malnutrition. Protein–energy malnutrition in both adults and children can be divided into undernutrition, kwashiorkor and marasmus (Table 13.8).

Table 13.8 Wellcome Trust classification of protein–energy malnutrition

Weight (% of standard for age)	Oedema present	Oedema absent
60–80	Kwashiorkor*	Undernutrition
<60	Marasmic kwashiorkor	Marasmus

*Kwashiorkor literally means 'disease of the displaced child'.

- **Marasmus** results from severe deficiency of both protein and calories
- **Kwashiorkor** results primarily from protein deficiency (ie diet entirely of carbohydrate)
- **Oedema** is the cardinal sign separating marasmus from kwashiorkor; fatty liver also develops in kwashiorkor
- **Growth failure** is more severe in marasmus.

13.6.3 Vitamin deficiencies

Multiple vitamin deficiencies frequently accompany PEM. Isolated or grouped vitamin deficiencies (for example, of fat-soluble (Table 13.9) or water-soluble (Table 13.10) vitamins) can also occur in specific circumstances.

13.7 METABOLIC ACID–BASE DISTURBANCES (NON-RENAL)

The kidneys and the lungs are intimately involved in the regulation of hydrogen ion concentration. Metabolic acid–base disturbances arise from abnormalities in the regulation of bicarbonate and other buffers in the blood. Acidosis results from an increase in H^+ concentration and alkalosis from a fall in H^+: The pH is the negative logarithm of H^+ – a small change in pH represents a large change in H^+ concentration; this is often poorly appreciated in clinical practice.

13.7.1 Metabolic acidosis

The metabolic acidoses are conveniently divided on the basis of the anion gap.

$$\text{Anion gap} = Na^+K^+(Cl^- + HCO_3^-)$$

The normal anion gap is 10–18 mmol/L and represents the excess of negative charge (unmeasured anions) present on albumin, phosphate, sulphate and other organic acids, eg lactic acid

Relationship of metabolic acid to anion gap

- **Normal anion gap**
  - Diarrhoea (or other GI loss)
  - Renal tubular acidosis
  - Hypoaldosteronism
  - Treatment of ketoacidosis
- **Increased anion gap**
  - Lactic acidosis
  - Ketoacidosis
  - Acute kidney injury and advanced CKD
  - Hepatic failure
  - Toluene ingestion
  - Intoxications, eg methanol, aspirin, ethylene glycol

Table 13.9 Deficiencies of fat-soluble vitamins

Vitamin	Causes of deficiency syndromes	Roles of vitamin	Deficiency
Vitamin A	Severe PEM[a]	Component of visual pigment Maintenance of specialised epithelia Bitot's spots[b]	Night blindness Xerophthalmia[c] Follicular hyperkeratosis[d] Keratomalacia
Vitamin D	Vegans[e] Elderly with poor diet CKD	Absorption of calcium and phosphate Bone mineralisation	Rickets Osteomalacia
Vitamin E	Severe (near-total) fat malabsorption[f] Abetalipoproteinaemia	Antioxidant Scavenger of free radicals Cofactor in carboxylation of	Spinocerebellar degeneration

Vitamin K	Oral antibiotics[g] Biliary obstruction	coagulation cascade factors	Bleeding tendency

PEM, protein–energy malnutrition.

[a]Although vitamin A is fat-soluble and deficiency can occur in any chronic malabsorptive state, this is rare unless there is severe protein–energy malnutrition.

[b]Conjunctival foamy patches are an early sign of vitamin A deficiency.

[c]Xerophthalmia – dryness of the cornea.

[d]Keratomalacia – corneal ulceration and dissolution.

[e]Vitamin D_3 is produced in the skin by photoactivation of 7-dehydrocholesterol. If sun exposure is sufficient, dietary vitamin D is not essential.

[f]Vitamin E deficiency is rare. It can complicate biliary atresia. In abetalipoproteinaemia (see earlier section), chylomicrons cannot be formed.

[g]Antibacterial drugs interfere with the bacterial synthesis of vitamin K.

Table 13.10 Deficiencies of water-soluble vitamins

Vitamin	Causes of deficiency	Roles of vitamin	Deficiency syndromes
Vitamin B_1 (thiamine)[a]	Alcoholism	Nerve conduction	Dry beri-beri – symmetrical Polyneuropathy Wernicke–Korsakoff syndrome
	Dietary Bariatric surgery	Coenzyme in decarboxylation	Wet beri-beri[b] – peripheral vasodilatation, heart failure
Vitamin B_2 (riboflavin)	Severe PEM[c]	Enzyme cofactor	Angular stomatitis Glossitis Corneal vascularisation
Niacin (nicotinic acid)	Carcinoid syndrome[d] Alcoholism Low-protein diets Isoniazid[e]	Incorporated into NAD and NADP	Pellagra – dementia, dermatitis and diarrhoea (the three Ds)
Vitamin B_6 (pyridoxine)[f]	Isoniazid Hydralazine	Enzyme cofactor	Peripheral neuropathy Dermatitis Glossitis
Vitamin B_{12} (cyanocobalamin)	Pernicious anaemia Post-gastrectomy Vegan diet Terminal ileal	Coenzyme for DNA synthesis; coenzyme in myelin metabolism	Pernicious anaemia Subacute combined degeneration of the

	disease Blind loops		spinal cord
Vitamin C[g]	Dietary	Redox reactions Collagen formation	Scurvy – bleeding, joint swelling, hyperkeratotic hair follicles, gingivitis

[a]Thiamine deficiency is confirmed by reduced red-cell transketolase activity.

[b]In people with alcohol problems, wet beri-beri must be distinguished from alcoholic cardiomyopathy.

[c]Riboflavin deficiency usually occurs with multiple deficiencies.

[d]In the carcinoid syndrome (and to a lesser extent in phaeochromocytoma) tryptophan metabolism is diverted from nicotinamide to form amines.

[e]Isoniazid can lead to deficiency of pyridoxine, which is needed for the synthesis of nicotinamide from tryptophan.

[f]Dietary deficiency of pyridoxine is extremely rare.

[g]Deficiency of vitamin C is confirmed by low white-cell (buffy coat) ascorbic acid levels.

Specific metabolic acidoses

Metabolic acidosis with diarrhoea

The GI secretions (below the stomach) are relatively alkaline and have a high potassium concentration. There is usually hypokalaemia, low urinary potassium loss (<25 mmol/L) and low urine pH (<5.5). Causes include:

- Villous adenoma
- Enteric fistula
- Obstruction
- Laxative abuse.

Renal tubular acidosis

RTA describes diseases/conditions in which there is a net urinary reduction in acid excretion, resulting in metabolic acidosis. This can be due to reduced acid excretion (reduced H^+ secretion in type 1), increased bicarbonate excretion (as a result of loss of bicarbonate reabsorption in type 2 RTA) or reduced ammonia production (type 4 RTA). In type 4 RTA the kidney is either resistant to aldosterone or plasma aldosterone levels are low. This results in hyperkalaemia, reduced ammonia production and acidosis. It is the most common RTA and occurs in patients with tubulointerstitial disease such as diabetes. The RTAs are covered in more detail in Chapter 15, Nephrology.

Metabolic acidosis with ureteric diversion and ileal loop diversion

This results in hyperchloraemic acidosis in 80% of ureterosigmoid diversions. The mechanism is due to urinary chloride exchange for plasma bicarbonate, which is then lost in the urine. Urinary ammonia is also absorbed across the sigmoid epithelium. Ileal loop diversions also result in significant hyperchloraemic acidosis but less so than ureterosigmoid diversions.

Metabolic acidosis accompanying poisoning

Metabolic acidosis often accompanies poisoning (eg toluene, ethylene glycol, salicylates,

paracetamol). (See also Chapter 2, Clinical pharmacology, toxicology and poisoning.)

13.7.2 Metabolic alkalosis

Metabolic alkalosis is less common than metabolic acidosis because metabolic processes produce acids as by-products, and also because renal excretion of excess bicarbonate is very efficient. Many causes of metabolic alkalosis are associated with hypokalaemia.

Metabolic alkaloses

- **Gastrointestinal hydrogen ion loss**
  - Vomiting/pyloric stenosis
  - Nasogastric suction
  - Antacids (in CKD)
- **Intracellular shift of hydrogen ion**
  - Hypokalaemia
- **Alkali administration**
- **Renal hydrogen ion loss**
  - Mineralocorticoid excess, eg Cushing syndrome
  - Loop or thiazide diuretics
  - Post-hypercapnic alkalosis
  - Hypercalcaemia and the milk-alkali syndrome
- **Contractional alkalosis**
  - Volume depletion

Specific metabolic alkaloses

Gastric loss of hydrogen ions

In protracted vomiting (eg pyloric stenosis) or nasogastric suction there can be complete loss of up to 3 L of gastric secretions per day. The gastric secretions contain:

- Hydrogen ions: 100 mmol/L
- Potassium: 15 mmol/L
- Chloride: 140 mmol/L.

Alkalosis will result but, paradoxically, acid urine is produced due to renal tubular sodium bicarbonate reabsorption to maintain plasma volume. Patients respond to volume expansion with physiological saline and correction of hypokalaemia.

Milk-alkali syndrome

This is defined as the triad of hypercalcaemia, metabolic alkalosis and ingestion of large amounts of

calcium with absorbable alkali (traditionally for peptic ulcer pain). The hypercalcaemia increases renal bicarbonate reabsorption, exacerbating the alkalosis. Clinical presentation is with symptoms of hypercalcaemia or metastatic calcification.

Post-hypercapnic alkalosis

Chronic respiratory acidosis leads to a compensatory increase in urinary hydrogen ion secretion, resulting in a rise in plasma bicarbonate concentration. Rapid lowering of a raised *P*CO2 (usually by mechanical ventilation) is not immediately accompanied by a fall in plasma bicarbonate. There is often an accompanying chloride loss that must be replaced before bicarbonate can fall to normal.

13.8 HYPOTHERMIA

Hypothermia is defined as a fall in core temperature to <35°C. It is frequently fatal if the core temperature falls to <32°C. Hypothermia must be classified by the duration of hypothermia:

- **Acute (immersion) hypothermia**: rapid loss of heat, eg fall into cold water
- **Subacute (exhaustion) hypothermia**: patients are unable to generate heat due to exhaustion
- **Chronic hypothermia**: a gradual loss of heat often seen in elderly patients with inadequate heating and homeless people.

Causes of hypothermia

- **Exposure to low external temperatures**
  - Elderly and very young people with inadequate heating
  - Immersion in cold water
  - Mountaineers
- **Medical conditions**
  - Hypothyroidism
  - Hypoglycaemia
  - CNS disorders, eg stroke, hypopituitarism
  - Post-cardiac arrest and unconscious patients
- **Drugs**
  - General anaesthetics resulting in perioperative hypothermia
  - Alcohol
  - Sedative drugs, eg benzodiazepines and narcotics

Mild hypothermia (32–35°C) causes shivering and intense feeling of cold, altered judgement and ataxia.

Moderate hypothermia (28–32°C) can cause confusion and drowsiness; patients are often

unconscious and lose the ability to shiver. The risk of arrhythmias increases.

Severe hypothermia (<28°C) increases the risk of asystole, coma, apnoea, fixed pupils, pulmonary oedema and death.

- **Clinical features of hypothermia** include bradycardia, hypoventilation, muscle stiffness, cold diuresis, hypotension and loss of reflexes. The pupils can be fixed and dilated in recoverable hypothermia
- **Metabolic acidosis** due to lactate accumulation is common; pancreatitis can complicate hypothermia
- **Electrocardiograph changes** include J waves, prolonged P–R interval, prolonged QT and QRS complexes. Death results from ventricular arrhythmias or asystole.

In certain medical situations therapeutic hypothermia (cooling to 32–34°C) can be induced (eg after cardiac arrest, complex cardiac surgery). This reduces tissue oxygen requirements and can improve patient outcomes.

13.8.1 Treatment of hypothermia

Hypothermia >30°C: surface rewarming is usually adequate with removal of wet clothes, and provision of warm blankets and heaters.

Hypothermia <30°C: active internal warming until core temperature is at least 32°C using warm intravenous fluids and warm humidified oxygen. If necessary, peritoneal lavage, pleural lavage and haemodialysis can also be helpful. Cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO) can be used in patients who are in ventricular fibrillation or have profound hypothermia and are deteriorating.

Cardiac arrest in the hypothermic patient

Severe hypothermia can mimic death. Consequently cardiopulmonary resuscitation should be continued in hypothermic patients until the patient has been rewarmed or until all attempts have failed to improve core temperature. The hypothermic heart has reduced responsiveness to cardiac drugs, pacemakers and defibrillation. Cardioactive drugs can also accumulate as drug metabolism is decreased. Therefore, intravenous drugs are often withheld until core temperature is >30°C. Hypothermia protects the brain during cardiac arrest, so patients can have a full neurological recovery despite prolonged cardiac arrest.

---

[a] UK NICE guidelines do not recommend cinacalcet for the routine treatment of secondary hyperparathyroidism because it has not been shown to be cost-effective. It can be used in patients who have failed to respond to other treatments or in patients with tertiary hyperparathyroidism who are unsuitable for parathyroidectomy.

Chapter 14
Molecular Medicine

CONTENTS

Molecular Medicine

14.1 MOLECULAR DIAGNOSTICS

The diagnostic process in medicine has entered a new and important historical phase. Increasingly, diagnostic entities are being reclassified according to the molecules that are central to the disease process and also according to changes in the expression of genes that code for these molecules. With the advent of the complete human gene sequence we now have the tools for a complete understanding of how cells develop and how they function in health and disease.

14.1.1 Genomes, transcriptomes, proteomes and metabolomes

The genome of an organism is its complete complement of coding genes. Comparison of the organisms in Table 14.1 reveals that the level of complexity of an organism is not explained by the number of genes predicted to code for protein. Fruit flies (*Drosophila melanogaster*, a favourite organism for geneticists) have more complex behaviours than nematode worms (*Caenorhabditis elegans*) but fewer genes. One reason for this is that flies process genes in a more complex way. Humans and mice have the same number of predicted genes and 98% of these are **orthologues** (have a common ancestral gene and code for equivalent proteins). Biological complexity is explained by:

- **The transcriptome**: this is the name given to the total complement of expressed mRNA sequences in an organism. In lower organisms, this will be the same as the number of genes. In mammals, genes are transcribed in a more complex way, with transcription being initiated from different exons in different tissues and alternative splicing (post-transcriptional processing). The temporal (when in development) and spatial (in which cells) expression of genes allows significant diversity which is not evident just from looking at gene number. It is likely therefore that the transcriptomes of mice and humans contain significant differences
- Processed mRNA is translated into protein. Similarly, differences in mRNA transport, localisation and stability mean that the **proteome** cannot be inferred directly from the transcriptome
- **Post-translational processing**: proteins can be modified by glycosylation, sialylation, etc. Protein stability and turnover may be very different in different cell types and between similar cells in different organisms
- Finally, the progressive diversity of the proteome with evolution leads to an exponential amplification of combinatorial possibilities between proteins. Therefore, although the human genome may have 30 000 information units (genes), the final number of information units needed to explain human biological complex is theoretically several orders of magnitude greater.

Table 14.1 The genomes of various organisms

Organism	Number of proteins	Approx. genome size	Introns	Splicing
Human	30 000	3×10^9 (3 Gb)	Yes	Highly complex
Mouse	30 000	3 Gb	Yes	Complex
Fruit fly	13 500	40×10^6 (40 Mb)	Yes	Yes
Nematode	19 000	96 Mb	Very few	Very little
Fission yeast	6000	12 Mb	Rare	Absent
Bacterium	2000–6000	2–6 Mb	Absent	Absent

The Human Genome Project

The Human Genome Project (HGP) was possibly the greatest scientific undertaking in recent history. The project began in 1990 and sequencing was completed in 2003. Analysis of the vast amounts of data generated by the project is still ongoing, but medical science has already profited from the results. As a direct consequence of the HGP, genetic tests are now available that show predisposition to a range of diseases, including breast cancer, cystic fibrosis and liver diseases.

The main goals of the HGP were as follows:

- Identify all the approximately 20 000–25 000 genes in human DNA
- Determine the sequences of the 3 billion chemical base pairs that make up human DNA
- Store this information in databases
- Improve tools for data analysis
- Transfer related technologies to the private sector
- Address the ethical, legal and social issues (ELSIs) that may arise from the project.

Ten years after the completion of the HGP, there is still no definitive number of genes in the human genome, and is a topic of much conjecture. The most recent study in 2012 found 20 687 protein-coding genes.

The HGP created the field of genomics, that of understanding genetic material on a large scale. The field of medicine is profiting from the HGP as we learn more about the genetic contribution to disease.

Epigenetics

Epigenetics (meaning above genetics) is the study of modifications to DNA that do not affect the sequence, but can alter levels of gene activation. Epigenetic modifications alter the physical structure of DNA, which in turn alters the ability for transcription factors and the transcriptional apparatus to access particular genes. The epigenetic status of any particular gene can vary across cell types, whilst the DNA sequence does not. This confers a mechanism by which we can get different cell-specific gene activation states.

Chromatin structure and epigenetics

A good understanding of chromatin structure is important in understanding epigenetics. The DNA contained in a chromosome, if it were not compacted in some way, would take up too great a volume to be contained in a cell. The DNA is therefore condensed by tightly packing it into a smaller structure, a chromosome. A chromosome is actually a complex of DNA, protein and RNA. The smallest unit in a chromosome is a nucleosome. A nucleosome consists of 147 base pairs (bp) of double-stranded DNA wrapped around an octamer of proteins called histones. This octamer is made up of two copies of a heterotetramer that consists of histones H2A, H2B, H3 and H4 (Figure 14.1). The DNA wraps around this 'core octamer' of histones twice and then binds to a single H1 histone.

The appearance of DNA wrapped around an octamer of histones has led to it being referred to as 'beads on a string'. The H1 histone does not form part of the 'bead' but binds to the top of the structure, stabilising the 'linker DNA' region (a 20-to 28-bp length of DNA in-between nucleosomes) and keeping in place the DNA that is wrapped around the core octamer of histones (Figure 14.2).

The nucleosome 'beads on a string' then tightly pack to form chromatin, and the chromatin coils and packs into the chromosome (Figure 14.3). In mammalian cells most chromatin is found in the form of heterochromatin. Heterochromatin is a highly condensed, transcriptionally silent form of chromatin. In regions of DNA that contain transcriptionally active genes, the chromatin is termed 'euchromatin'. Euchromatin is less condensed than heterochromatin and allows transcription factors and the transcription apparatus access to the DNA.

Figure 14.1 Chromatin consists of DNA spooled around a complex of histone proteins

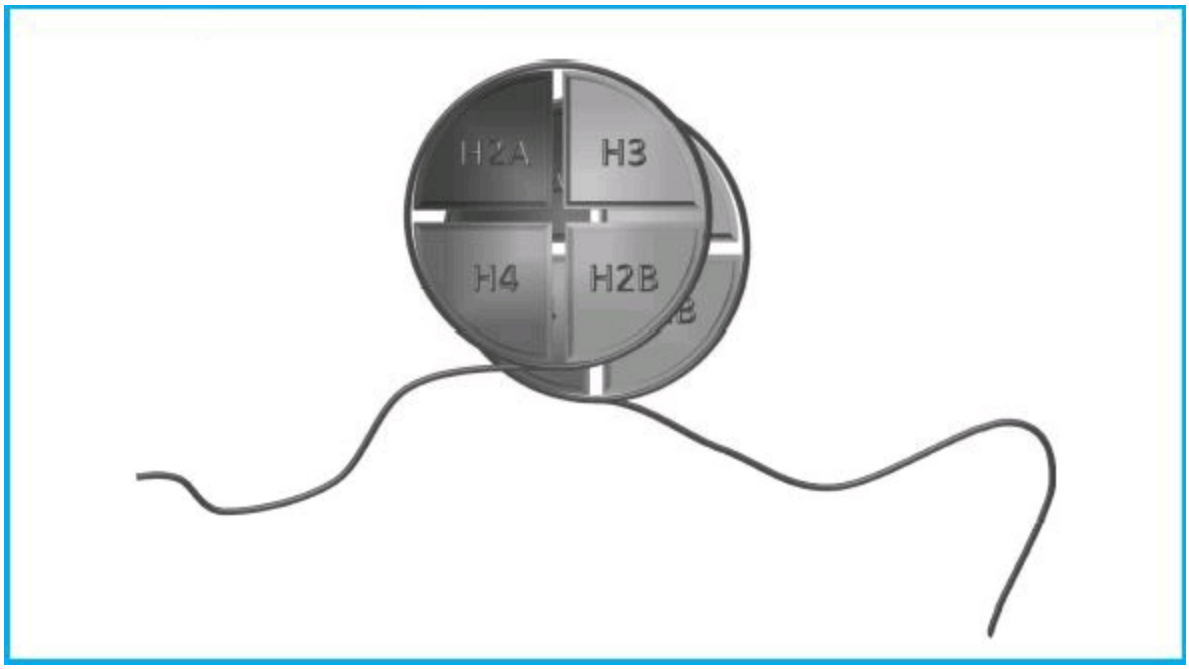


Figure 14.2 The H1 histone binds outside the nucleosome and stabilises the linker DNA

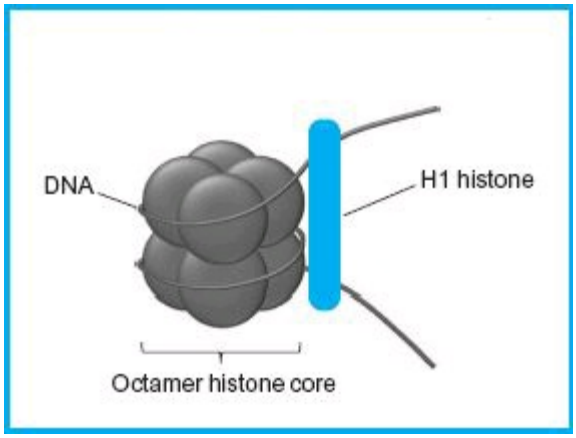
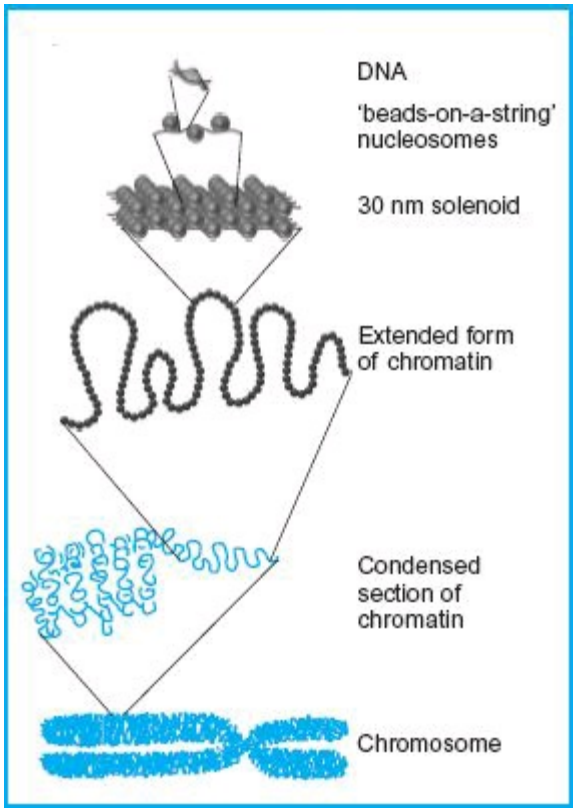


Figure 14.3 From DNA to chromosome



Epigenetic markers

Epigenetic markers are chemical modifications to histones and DNA that can affect chromatin structure, making it either easier or harder for transcription factors and the transcriptional apparatus to access regions of DNA. They do this by altering the electrostatic nature of the chromatin or by altering the affinity of chromatin-binding proteins.

DNA methylation

DNA methylation is vital for normal development and is associated with a number of key cellular processes including cell differentiation, carcinogenesis, genomic imprinting, X-chromosome inactivation and suppression of repetitive elements. DNA methylation is the addition of a methyl group to the 5′ position of the cytosine pyrimidine ring by a methyltransferase enzyme. DNA methylation is not irreversible. As there is a family of DNA methylase enzymes, so there are mechanisms of removing methylated cytosines (not thought to be through direct removal of the methyl group, but by replacement of the methylated cytosine with an unmethylated one).

The vast majority of cytosine methylation occurs in cytosines immediately followed by a guanine base (5′-CG-3′). This sequence is termed a CpG site.

In mammalian cells between 60% and 90% of all CpGs are methylated. The variably methylated CpG sites are the important ones and these tend to be found in 'CpG islands' located in the 5′-regulatory regions of genes.

DNA methylation leads to a decrease in the transcriptional activity of genes and may lead to 'transcriptional silencing'. DNA methylation can affect the transcription of genes in two ways:

1. The methyl groups added during DNA methylation may cause steric hindrances and prevent the binding of transcription factors
2. More importantly, methylated CpG sites attract and bind a series of proteins called methyl-CpG-binding domain proteins (MDBs).

MDB proteins, once bound, can further recruit other proteins capable of remodelling chromatin, such as histone deacetylases. These proteins convert transcriptionally active euchromatin into transcriptionally silent heterochromatin. In medicine the loss of MDB activity can be crucial. Loss of methyl-CpG-binding protein 2 (MeCP2) has been implicated in Rett syndrome (a neurodevelopmental disorder) and loss of methyl-CpG-binding domain protein 2 (MDB2) mediates the transcriptional silencing of hypermethylated genes in cancer.

DNA methylation in cancer

Abnormal DNA methylation has been associated with a large number of human cancers and is brought about by both hypermethylation and hypomethylation. Incidences of hyperermethylation in cancer far outnumber those of hypomethylation. The way in which hypermethylation brings about cancer is through the methylation of CpG sites in the 5′-promoter regions of tumour-suppressor genes. This hypermethylation leads to repression of transcription and gene silencing. Genome hypomethylation can result in the activation of germline-specific genes that are normally repressed, primarily, by DNA methylation. This group of genes has been termed 'cancer-germline genes'. Table 14.2 lists the genes commonly methylated in human cancer.

Histone acetylation

The association of histones with DNA is vital for the organisation of the billions of base pairs that make up the human genome. The organisation of DNA into chromatin has implications on all DNA-dependent events, such as transcription, recombination, replication and repair. The chromatin in a chromosome is not a static structure but rather a dynamic molecule in which changes in the level of organisation can occur in response to the myriad of different signalling pathways found in a cell. There are several mechanisms by which the organisation of chromatin may be dynamically changed. Transcriptional silencing through DNA methylation is not a dynamic process, although methylation can be reversed it cannot be done in a timely manner that would allow for rapid response to acute signalling pathways. The most notable mechanism of dynamic chromatin regulation is brought about through post-translational changes to histones. The most widely understood histone modification is acetylation.

Histones are proteins that are rich in positively charged lysine residues. These positive charges form a strong association with the negatively charged DNA. By the addition of an acetyl group to the lysine

rich amino-terminal tails of histones by dedicated histone acetlytransferases (HATs), these positive charges are removed and the histone's association with DNA is weakened. With a decreased affinity for DNA there is a 'relaxation' in the chromatin structure which can increase the access of transcription factors to the upstream regulatory region of genes.

Table 14.2 Genes commonly methylated in human cancer and their role in tumour development

Gene	Role in tumour development	Site of tumour
APC	Deranged regulation of cell proliferation, cell migration, cell adhesion, cytoskeletal reorganisation and chromosomal stability	Breast Lung Oesophageal
BRCA1	Implicated in DNA repair and transcription activation	Breast Ovarian
CDKN2A/p16	Cyclin-dependent kinase inhibitor	GIT Head and neck NHL Lung
DAPK1	Calcium/calmodulin-dependent enzyme that phosphorylates serine/threonine residues on proteins; suppression of apoptosis	Lung
E-cadherin	Increasing proliferation, invasion and/or metastasis	Breast Thyroid Gastric
ER	Hormone resistance	Breast Prostate
GSTP1	Loss of detoxification of active metabolites of several carcinogens	Prostate Breast Renal
hMLH1	Defective DNA mismatch repair and gene mutations	Colon Gastric Endometrium Ovarian
MGMT	p53-related gene involved in DNA repair and drug resistance	Lung Brain
p15	Unrestrained entry of cells into activation and proliferation	Leukaemia Lymphoma Squamous cell carcinoma, Lung
RASSF1A	Loss of negative regulator control of cell proliferation through inhibition of G_1/S-phase progression	Lung Breast Ovarian Kidney

		Nasopharyngeal
Rb	Failure to repress the transcription of cellular genes required for DNA replication and cell division	Retinoblastoma Oligodendroglioma
VHL	Altered RNA stability through and erroneous degradation of RNA-bound proteins	Renal cell cancer

GIT, gastrointestinal tract; NHL, non-Hodgkin's lymphoma.

The acetylation of histones, and hence all effects on chromatin structure, can be reversed by the removal of the acetyl groups by dedicated histone deacetylases (HDACs). The interplay of HATs and HDACs results in dynamic changes in chromatin structure which in turn leads to changes in the activation state of genes.

Disregulation of HATs and HDACs has been linked to the progression of cancers as well as various syndromes such as Rubinstein–Tabi and fragile X syndromes. Histone deacetylase inhibitors (HDIs) are an established group of drugs used as mood stabilisers and antiepileptics. They are showing increasing promise in the treatment of cancer where they have been shown to induce differentiation, cell-cycle arrest and apoptosis, and to inhibit migration, invasion and angiogenesis.

Inheritance of epigenetic markers

It used to be thought that all epigenetic marks were removed in the genetic material included in gamete cells. It was thought that epigenetic tags were not inherited and that an embryo had a clean epigenome that was rebuilt from scratch. We now know this not to be the case. Most, but not all, epigenetic information is removed, but some tags remain in place and are passed from generation to generation in 'epigenetic inheritance'.

Epigenetic inheritance has profound implications. It means that as well as information from our genetic code being passed on, so can information from our experiences in life, in the form of epigenetic marks. Epigenetic inheritance has been shown through the altered traits of offspring in response to their parents' experiences. Periods of famine have resulted in health effects in the children and grandchildren of individuals that had severely restricted diets. Their genetic code had not changed, but epigenetic tags caused by the restricted diet have been inherited and have then affected gene expression profiles of subsequent generations.

Normally epigenetic marks are erased in sperm and egg precursor cells (primordial gene cells, PGC). Methylation marks are converted to hydroxymethylation which is progressively diluted out as cells divide. However, some rare methylation can 'escape' the reprogramming process and therefore may be inherited by subsequent progeny.

Fluorescent in situ hybridisation

Fluorescent in situ hybridisation (FISH) is a technique that, using fluorescently labelled DNA probes (often derived from fragments of DNA that were isolated during the HGP), can detect and confirm gene and chromosome abnormalities beyond the resolution of routine cytogenetics.

Sample DNA is first denatured, converting double-stranded to single-stranded DNA. The fluorescently labelled probe (complementary to the DNA sequence of interest) is then added to the single-stranded DNA. If the DNA sequence of interest is present in the sample, the probe hybridises

with the complementary bases as the DNA re-forms back into a double helix.

The probe signal can then be detected through a fluorescence microscope and the sample DNA scored for the presence or absence of the signal.

FISH can be performed using two sample types: metaphase chromosomes and interphase nuclei.

Metaphase FISH

FISH can be performed on metaphase chromosomes to detect specific microdeletions undetectable by routine cytogenetics, or to identify chromosome translocations or extra material of unknown origin.

Microdeletion syndromes currently detectable using FISH

- **Cri-du-chat syndrome**
  - A syndrome that results from the deletion of part of the short arm of chromosome 5. The main clinical feature is the presence of a high-pitched 'cat-like' cry present in the newborn that may disappear with age. Other features include a round, full face, widely spread eyes (hypertelorism), an extra fold of skin at the inner corners of the eyes (epicanthal folds), a flattened and widened nasal bridge and ears that are positioned low on the head, severe cognitive, speech and motor delays, and feeding problems from birth which may lead to poor growth
- **Miller–Dieker syndrome**
  - A congenital malformation syndrome that results from the deletion of several adjacent genes in the short arm of chromosome 17 (17p). Clinical features include lissencephaly and a characteristic facial appearance (prominent forehead with bitemporal hollowing, short nose with upturned nares, thickened upper lip with a thin vermilion upper border, widely spaced eyes, low ears, and small jaw). The syndrome may result in mental retardation, epilepsy, pre- and postnatal growth retardation, and reduced lifespan. There may also be multiple abnormalities of the brain, kidneys, heart, and gastrointestinal tract
- **Smith–Magenis syndrome**
  - Results from a microdeletion in the short arm of chromosome 17 [del(17)(p11.2 p11.2)]. As well as characteristic facial abnormalities (short flat head, prominent forehead, broad square face, upslanting eyeslits, deep-set eyes, underdeveloped midface, broad nasal bridge, short nose and tented upper lip), the syndrome may also cause mild-to-moderate mental retardation
- **Steroid sulphatase deficiency**
  - Also known as X-linked ichthyosis, it is a genetic disorder of the skin that occurs only in males. The condition develops in infancy and manifests as tan or grey scales on the skin that are a result of a deficiency in the enzyme steroid sulphatase due to genetic mutations of the gene
- **DiGeorge syndrome** (also known as velocardiofacial/CATCH-22/Shprintzen syndrome) (see Chapter 7, Section 7.1.3 and Chapter 10, section 10.9.4)
- **Kallman syndrome** (see Chapter 4, section 4.8.3)
- **Williams syndrome** (see Chapter 1, section 1.3.5 and Chapter 7, section 7.1.3)

- **Wolf–Hirschhorn syndrome**
  - Results from a partial deletion of the short arm of chromosome 4. Many parts of the body are affected by this syndrome as the deletion affects fetal growth and development. Common features include profound learning disability, microcephaly, seizures, low muscle tone and poor muscle development, heart defects, and cleft lip and/or palate

Interphase FISH

FISH can be used in interphase cells to determine the chromosome number of one or more chromosomes as well as to detect some specific chromosome rearrangements characteristic of certain cancers. The advantage of interphase FISH is that it can be performed very rapidly as cell growth is not required.

An example of interphase FISH is the aneuploid screen test performed on amniotic fluid cells to determine the presence of the common trisomies. Sample nuclei are denatured and incubated with probes for chromosomes 13, 18, 21, X and Y.

Transcriptomics

The gene expression profile (transcriptome) of a particular tissue is the key to understanding the cell phenotype in health and disease. An average cell expresses about 16 000 genes throughout its lifetime, but clearly the range of genes expressed in the lifetime of an individual cell will vary during development, maintenance and ultimately cell death. Inevitably the genes expressed by a neuron in the cerebellum will be very different from those expressed by a lymphocyte, though housekeeping genes are common to many cells and encode constitutive cellular processes.

The transcriptome of a cell can be captured using a technique known as microarray analysis. This depends on the same hybridisation reaction as other nucleic acid techniques but represents dramatic scaling up of the procedure, such that many thousands of hybridisation reactions occur on a single medium and changes in transcription in many genes can be assessed simultaneously. RNA is prepared from the tissue of interest (eg a tumour biopsy specimen) and from a control sample (eg normal tissue from the same organ from which the biopsy was obtained). The RNA is hybridised to a ‘DNA chip’. This consists of a silicon slide 1–2 cm in size onto which have been spotted oligonucleotides, 20–30 bp long. Each oligonucleotide represents a particular gene. The RNAs from the abnormal and control tissues are labelled with different colour fluorescent dyes (eg red and green) and the level of expression of many thousands of genes can then be analysed by computer software, which compares the differences in intensity generated by the hybridisation reaction.

- The power of this technology is such that it is not necessary to know anything about the function of the particular gene spotted onto the chip
- As the sequence of every gene is now known, DNA chips with a representative coverage of the whole human genome can be produced commercially
- It is also possible to produce tissue-specific chips (eg human CNS) or chips with a limited number of genes of interest for use in diagnostics, when a specific question is being asked
- DNA microarrays can in principle identify a whole array of downstream genetic consequences of a particular gene mutation and provide a molecular profile of a disease state that can act as a

marker of therapeutic effect.

Practical applications

- Rapid sequencing for many genetic mutations can be performed simultaneously in a high-throughput approach, eg specific oligonucleotides that recognise all of the mutations responsible for a particular disease can be spotted onto a chip and DNA from an affected individual analysed
- Tumours or other abnormal tissue can undergo molecular profiling in order to identify patterns of gene expression, eg it is now possible in clinical practice to use microarrays to analyse the expression of panels of key genes that determine the clinical response to chemotherapeutic agents in lymphoma. Also, tissue or fluid from infections can be analysed for the expression of genes conferring antibiotic resistance before organisms have even been cultured
- Though still a research tool, it is likely that microarrays will be routinely used in the near future in genotyping large numbers of genes simultaneously to look at specific disease risk (eg cardiovascular) associated with single nucleotide polymorphisms (SNPs) or other genetic variants
- Individual responses to common drug treatments (eg antihypertensive agents) are likely to have a basis in genetic variation. The application of knowledge acquired through genetic profiling such as with microarrays is known as pharmacogenomics.

Proteomics

As discussed above, the total protein content of a cell or tissue may be a more meaningful target for analysis in certain situations than either the genome or transcriptome.

Protein from whole tissue or from subcellular fractions (eg membrane, nuclear, mitochondrial) can be separated by physical methods, such as on a two-dimensional gel, in which proteins are resolved by charge and mass to produce individual spots on a polyacrylamide gel which can then be silver stained. Individual spots of interest can be removed and eluted from the gel. The protein within can then be identified using tandem mass spectrometry which can sequence short peptides. A known protein can then be identified by reference to protein sequence databases.

Where the oligopeptide does not produce a match, a search can be made of the human genome sequence databases – computer programs have been used to predict genes and therefore protein sequences from the primary data (an example of what is known as bioinformatics). Currently, proteomics is largely a research tool, but with time and improved technology it will inevitably be used in clinical practice.

Potential applications

- The identification of all of the proteins expressed in a particular cell, groups of cells or whole tissues throughout the whole development of an organism from conception to death. Ultimately a complete description of the ontogeny of the cell will be possible allowing virtual modelling and computer-based drug design
- Comparisons can be made between healthy and diseased tissue in the same way as for mRNA with microarrays. However, the advantage with proteomics is that it may be possible to detect differences at the protein level that are not reflected at the transcriptional level due to changes in

turnover or post-translational processing. As with RNA techniques, protein from different sources can be differentially labelled with fluorescent dyes to aid the detection of differences

- Protein chips contain antibodies spotted onto silicon-based media similar to microarrays. Several hundred targeted proteins can be analysed in this way.

Metabolomics

Metabolomics is the study of the specific and unique metabolite profile left behind by cellular processes. In different disease states it is thought that this profiles small metabolite changes. If characteristic profiles for specific diseases can be determined, it may be used as a diagnostic tool.

The metabolome is the complete set of smallmolecule metabolites found in an organism. Similar to the transcriptome and proteome, the metabolome is constantly changing. At present the Human Metabolome Project (http://metabolomics.ca) has identified and quantified over 300 metabolites in cerebrospinal fluid, over 1000 metabolites in serum, over 400 metabolites in urine and approximately 300 metabolites in other tissues and biofluids, but the major limiting factor in the application of this technology is the incomplete characterisation of the human metabolome. With many of the molecules being small and difficult to extract, further work is required so that we can use the 'whole' metabolome in disease diagnosis. The metabolome of an organism is related to both its genotype and its physiology, and can also be affected by its environment (what it eats and breathes). This complex interaction therefore allows us to look at genotype–phenotype as well as phenotype–environment relationships.

Metabolomics technology is increasingly used in a variety of health applications, including pharmacology, preclinical drug trials, toxicology, transplant monitoring, newborn screening and clinical chemistry.

There are four key steps:

1. Efficient and unbiased extraction of the metabolites from biological samples
2. Separation of the analytes (typically by chromatography, either gas or high-performance liquid chromatography)
3. Detection of the metabolites after separation (usually by either mass spectrometry [MS] or nuclear magnetic resonance [NMR])
4. Identification and quantification of detected metabolites.

Physicians are now coming to understand that metabolic profiling can be used in the diagnosis, prediction, prevention and monitoring of many genetic, infectious and environmental diseases. In practice, complex computer software looks for patterns and changes in the metabolic profile from samples taken from patients with a particular disease compared with healthy controls. Having been 'taught' that a particular pattern is characteristic of a disease, samples from patients with unknown disease status can then be screened comparatively.

14.1.2 The polymerase chain reaction

The polymerase chain reaction (PCR) is an amplification reaction in which a small amount of target DNA (the template) is amplified to produce enough to perform analysis. This might be the detection

of a particular DNA sequence, such as that belonging to a pathogenic microorganism or an oncogene, or the detection of differences in genes, such as mutations causing inherited disease. Therefore, the template DNA might consist of total human genomic DNA derived from peripheral blood lymphocytes, amniocentesis or chorionic villous sampling; alternatively, it might consist of a tumour biopsy or a biological fluid from a patient with an infection.

- Two unique oligonucleotide sequences, known as **primers**, are mixed with a DNA template and a thermostable DNA polymerase (*Taq* polymerase, derived from an organism that inhabits thermal springs). Sometimes more than two primers can be used if more than one gene is to be amplified (multiplex PCR) or the region of DNA to be amplified needs special definition ('nested' PCR), eg if it is similar to other sequences in the genome which may give spurious reaction products
- In the initial stage of the reaction, the DNA template is heated (typically for about 30 seconds) to make it single-stranded and then as the reaction cools, the primers will anneal to the template if the appropriate sequence is present
- Then the reaction is heated to 72°C (for about a minute) and the DNA polymerase synthesises new DNA between the two primer sequences. During 30 or so cycles (each typically lasting a few minutes) the target sequence will have been amplified exponentially.

The crucial feature of PCR is that to detect a given sequence of DNA, it needs to be present only in one copy (ie one molecule of DNA); this makes it extremely powerful.

Clinical applications of PCR

- Mutation detection
- Detection of viral and bacterial sequences in tissue (herpes simplex virus in CSF, hepatitis C, HIV in peripheral blood, meningococcal strains)
- Single-cell PCR of in vitro fertilised embryo to diagnose genetic disease before implantation

In the example in Figure 14.4, some CSF from a patient suspected of having herpes simplex encephalitis is used in a PCR reaction in an effort to detect the presence of the virus directly.

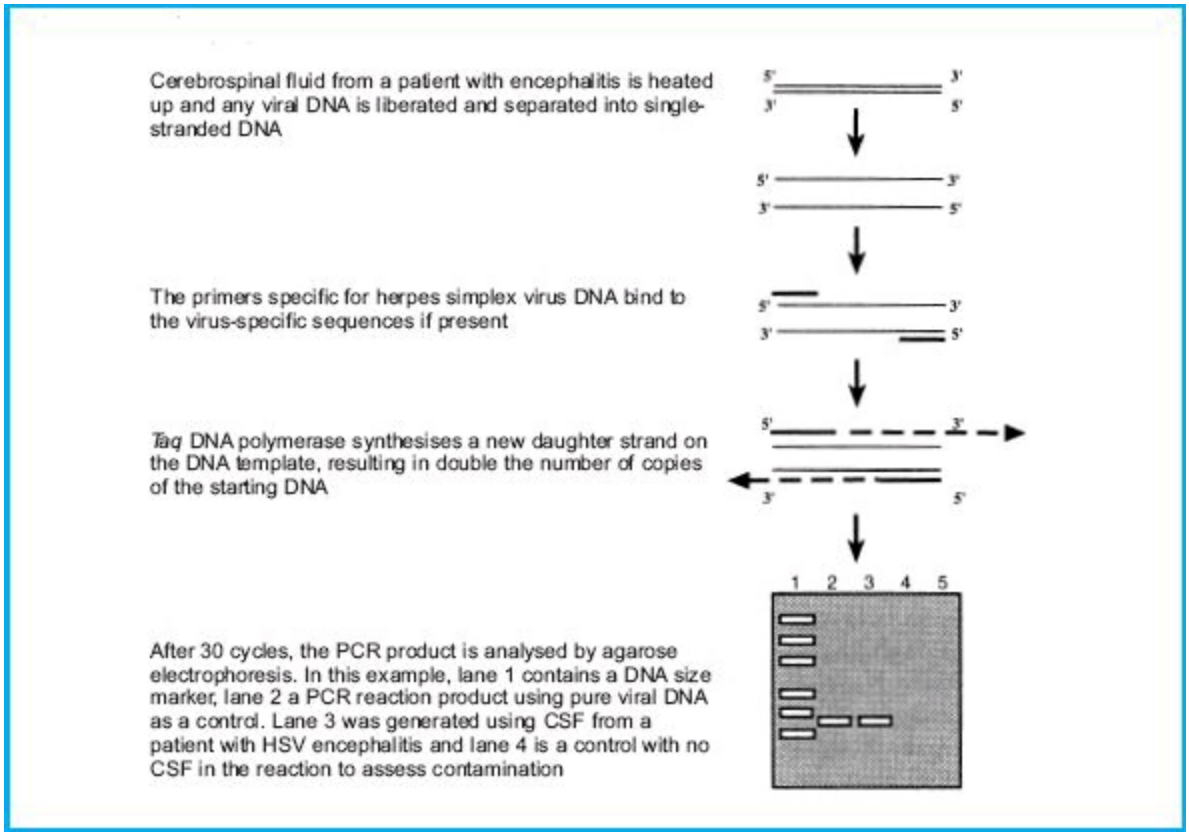
Small amounts of target DNA are amplified with a thermostable DNA polymerase.

14.1.3 Reverse transcription PCR

Conventional PCR looks at genomic DNA. Every cell in our body contains our total genome in two copies. However, the phenotype of a cell (what makes a hepatocyte different from a Purkinje cell) depends on which genes are being expressed at any one time. To look at the expression of genes we must therefore analyse only those genes that are being transcribed into mRNA.

- RNA is too unstable to be used in PCR so it must first be converted to complementary DNA (cDNA) using **reverse transcriptase**, a retroviral enzyme that makes a precise copy of the mRNA
- PCR is then performed in the normal way but, as the template reflects the mRNA of the starting material, this technique can look at **gene expression** in individual tissues.

Figure 14.4 The polymerase chain reaction (PCR)



Clinical applications of reverse transcription PCR (rtPCR)

- Detection of the expression of particular genes in tumour tissue carries important prognostic information
- Basic scientific research into normal function of disease genes by understanding their spatial and temporal expression

14.1.4 Monoclonal antibodies

The detection of specific proteins in molecular diagnosis relies on the fact that the antibody used has a high specificity for the target protein. An immune response to an antigen consists of a polyclonal proliferation of cells giving rise to antibodies with a spectrum of specificity for the target. Therefore, useful diagnostic and therapeutic antibodies must be selected from this complex immune response before they can be used.

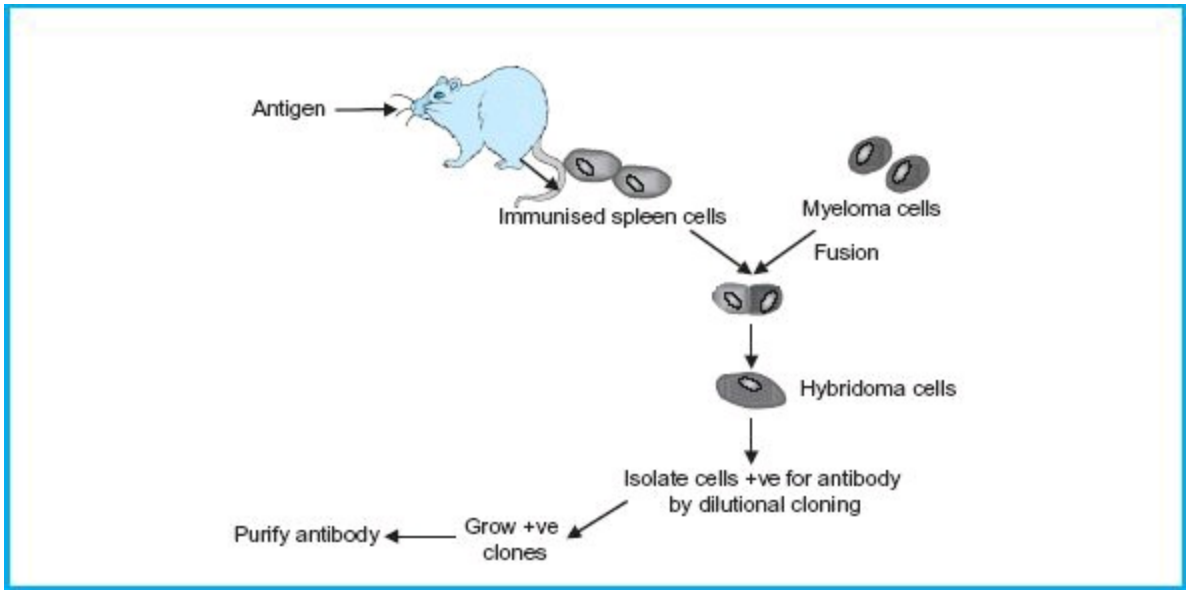
Myeloma is a malignantly transformed B-cell lineage that secretes a specific antibody. This fact is used to produce unlimited amounts of specific antibodies directed towards an antigen of choice.

- A laboratory animal is injected with the antigen of choice (Figure 14.5); it mounts an immune response and its spleen, which contains B-cell precursors with a range of specificity for the antigen, is harvested
- The spleen cells are fused en masse to a specialised myeloma cell line that no longer produces

its own antibody

- The resulting fused cells, or **hybridomas**, grow in individual colonies, are immortal and produce antibodies specified by the lymphocytes of the immunised animal. These cells can be screened to select for the antibody of interest which can then be produced in limitless amounts.

Figure 14.5 Monoclonal antibody production



Clinical applications of monoclonal antibodies

- Diagnosis of cancer and infections
- Imaging of tumours, radiotherapy
- As a 'magic bullet' to direct drugs to target
- Transplantation and other immune modulations (eg OKT3)

Limitations of monoclonal antibody therapies

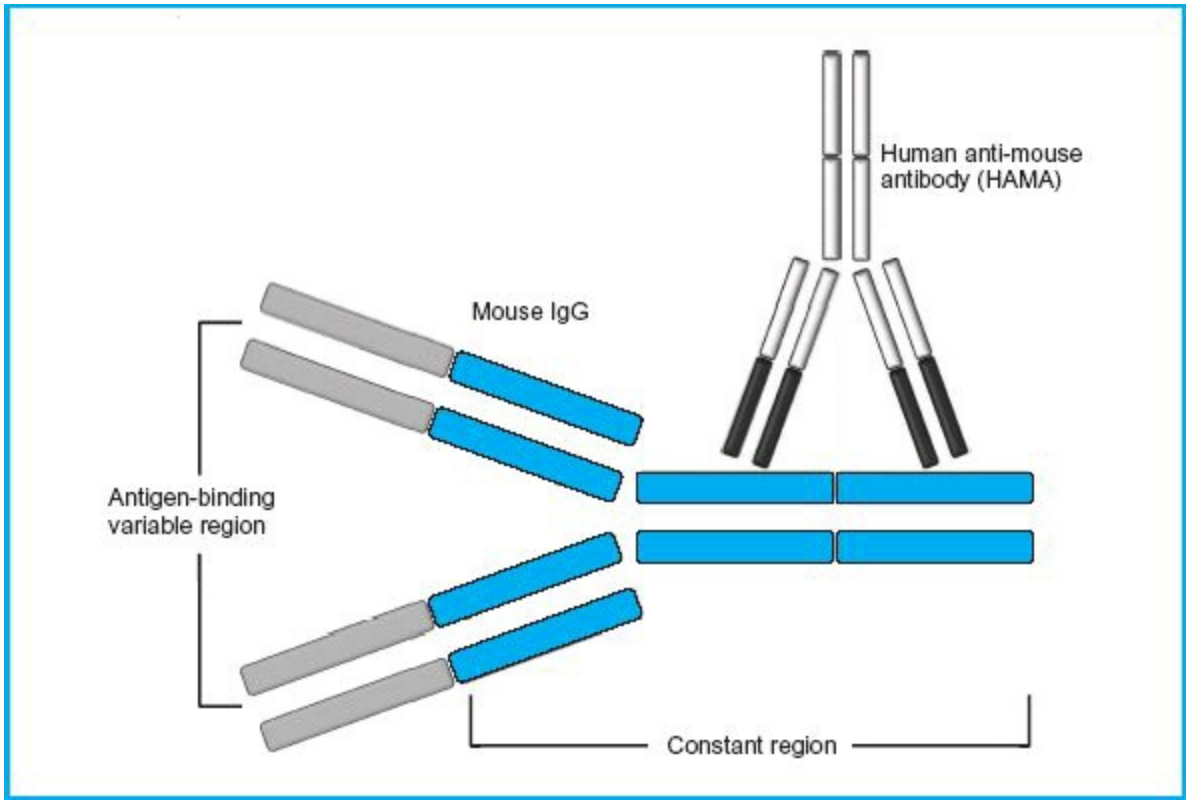
The specificity of binding of monoclonal antibodies makes them excellent therapies where specific disease-related antigens are present. There are, however, limitations to using murine/rabbit monoclonal antibodies. As the antibody was produced in a foreign species, the human body recognises it as foreign and mounts an immune response against it. A mouse/rabbit IgG antibody is made of two main domains: the variable region, which confers the specificity of binding, and the constant region, an area that is not involved in binding so can remain the same between different IgGs. If the human anti-mouse/rabbit antibodies are raised against the variable region, then any further treatments with that therapy will be rapidly cleared by the immune system before it can reach its therapeutic target. Treatment with other antibody therapies will be unaffected. If the human anti-mouse/rabbit antibodies are raised against the constant region of the IgG, because these regions are shared in all mouse/rabbit IgGs, not only that drug, but any subsequent IgG therapy, will be rapidly cleared (Figure 14.6).

Humanisation of monoclonal antibodies

In response to the limitations of use of monoclonal antibodies as a therapy, scientists have tried to decrease the immunogenicity of the murine/rabbit IgGs. Initially this was brought about through the creation of chimeric and humanised antibodies.

A chimeric antibody is one that still has the murine/rabbit variable region, but fused to human constant regions. Overall this results in a protein that is made up of 65% human regions. This may trick the human immune system into thinking that the protein is native so as to alleviate an immune response against it. The 35% murine/rabbit regions do still mean that there is a chance that the antibody will be recognised as foreign, however.

Figure 14.6 The immunogenicity of monoclonal antibodies



A humanised antibody goes one step further and uses only a small portion of the mouse/rabbit variable region, the hypervariable region that is most responsible for antigen binding, and fusing it into human domains. This can result in a protein that is up to 95% human, which results in a much reduced immunogenicity, but as the whole mouse/rabbit variable region is not used there is usually a drop in antibody-binding affinity.

Recently scientists have been creating human monoclonal antibodies. These antibodies are still created in a mouse/rabbit using the same method as described, but the mouse/rabbit is transgenic. The mouse/rabbit IgG genes have been replaced with human copies. When the mouse/rabbit is immunised with a new antigen, the IgG produced will use human sequences and will therefore have no immunogenicity when used as a therapy.

14.1.5 Antibody-based assays

An assay is defined as a procedure where a property or concentration of an analyte is measured. In medicine the specific binding of labelled antibodies is used to assay for a huge range of analytes that

may aid in the diagnosis of disease. Assays are available for numerous serum proteins (growth factors, cytokines, clotting factors, etc) as well as for proteins found on infectious organisms (bacterial and viral). Previous radioactive methodology (radioimmunoassay [RIA] and immunoradiometric assay [IRMA]) is being replaced by enzyme immunoassays, the most common of which is the enzyme-linked immunosorbent assay (ELISA).

1. A plate is coated with capture antibody specific to the analyte of interest (Figure 14.7)
2. Sample is added and incubated for sufficient time to allow any analyte present to bind to the capture antibody; non-specific, unbound proteins are washed off
3. Secondary antibody is added that also recognises the antigen, but which has been raised against a different part of the protein – so both antibodies can bind at the same time. Excess secondary antibody is washed off
4. Enzyme-linked tertiary antibody is added that recognises the secondary antibody; excess tertiary antibody is washed off
5. Substrate is added and is converted by the linked enzyme to a detectable form (fluorescent or colorimetric). The intensity of signal is directly proportional to the amount of analyte present. Concentration is calculated by constructing a standard curve with known amounts of analyte.

14.2 CELL SIGNALLING

Central to all cellular processes is the conversion of external signals (first messengers) via intermediates (second messengers) into changes that alter the state of that cell. This often involves adjustment in the expression of genes in the cell nucleus and new protein synthesis. In the following example (Figure 14.8), a photon of light is the external stimulus that produces, via second messengers, a change in the resting state of the rod cell, leading it to transmit a signal to the visual cortex.

Figure 14.7 The ELISA (enzyme-linked immunosorbent assay) process

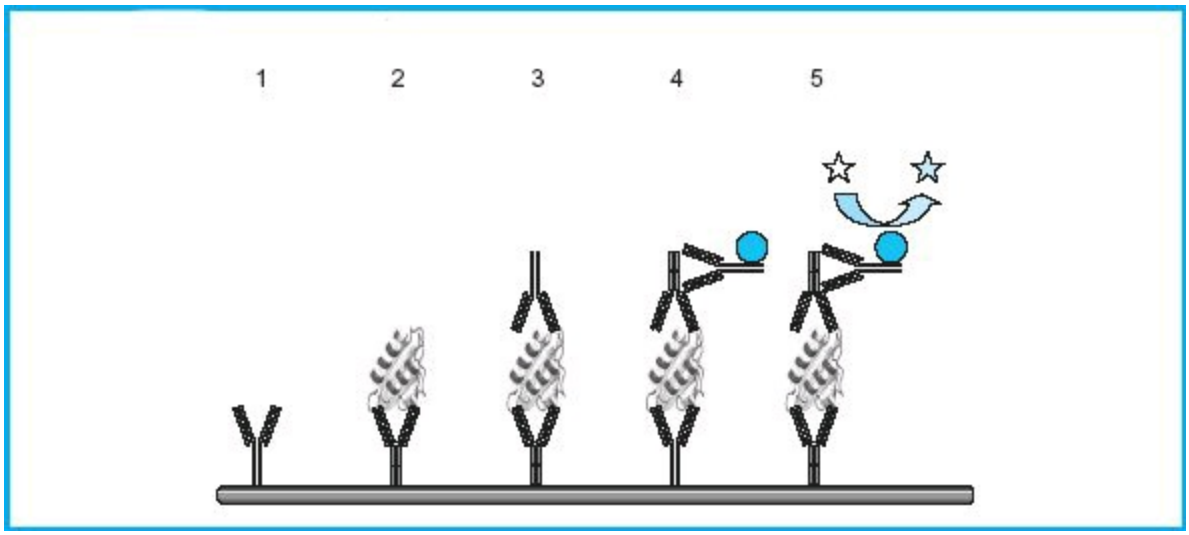
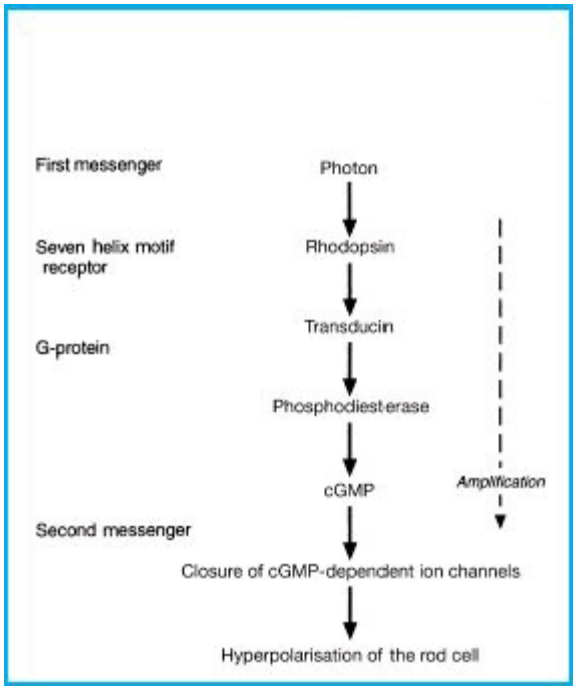


Figure 14.8 A typical signalling pathway (the rod receptor). This involves a G-protein-coupled membrane receptor that activates a second messenger pathway



14.2.1 Types of receptor

The chief function of the cell membrane is to provide a barrier to ion flux and therefore to maintain the internal milieu of the cell. There are, as described below, certain lipophilic modules that travel freely into the cell. However, most external signals can effect changes only inside the cell by interaction with membrane-bound receptor modules. This biologically ubiquitous system of signal transduction by receptors underlies the action of many hormones, growth factors and drugs.

Ligand-gated ion channel

For example, **acetylcholine receptor** (nicotinic):

- Five non-covalently assembled subunits ($\alpha_2\beta\gamma\delta$) are located at the postsynaptic neuromuscular junction
- Each subunit is coded for by a different gene, which enables mixing and matching of subunits between different tissues and in embryological development to generate a repertoire of responses
- On binding of acetylcholine to the α subunits the whole complex undergoes a conformational change leading to the passage of sodium ions into the cell and cellular depolarisation.

Other examples include some **glutamate** receptors (excitatory), γ-aminobutyric acid (GABA) and **glycine** (inhibitory: the passage of chloride ions into the cell renders it more resistant to depolarisation).

Receptors that contain cytoplasmic domains with protein tyrosine kinase activity

- **Insulin** binds to its receptor, which then undergoes dimerisation and autophosphorylation at a tyrosine residue
- The tyrosine kinase activity intrinsic to the receptor is then activated and the result is the

phosphorylation of cytoplasmic proteins and initiation of an intracellular cascade
- This ultimately leads to the action of insulin on glucose uptake, etc.

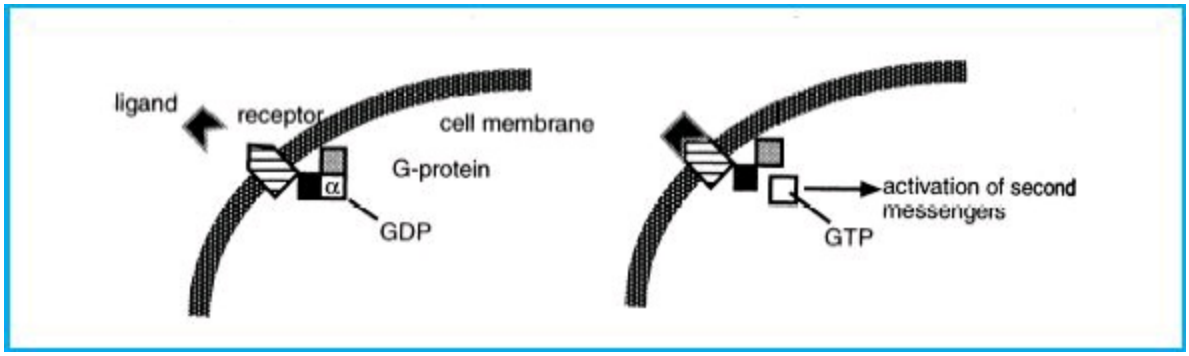
Other examples include platelet-derived growth factor, insulin-like growth factor 1 (IGF-1), macrophage colony-stimulating factor and nerve growth factor.

G-protein-coupled receptors

Guanine nucleotide-binding proteins are a ubiquitous cellular mechanism for coupling an extracellular signal to a second messenger, such as cAMP (Figure 14.9).

- G-proteins have three non-covalently associated subunits: α, β, γ. In the inactive state GDP is bound to the α subunit of the G-protein
- When the receptor is activated by ligand binding, the G-protein is activated by the hydrolysis of GTP to GDP
- In this active state the α subunit dissociates from the β and γ subunits. Either of these two complexes (the GTP-α or the -γ) can then interact with second messengers
- The α subunit is rapidly inactivated by hydrolysis of GDP to GTP (this is an intrinsic property of the α subunit, which is therefore known as α-GTPase) and then re-associates with the β and γ subunits, resetting the whole system to the inactive state.

Figure 14.9 G-proteins are activated by ligand binding to a transmembrane receptor



G-proteins can be inhibitory (Gi) or stimulatory (Gs) and the overall activity of a second messenger such as adenylyl cyclase is likely to be regulated by the differential activation of these different forms. The **muscarinic acetylcholine receptor**, the α- and β **-adrenergic receptors** and the retinal photoreceptor **rhodopsin** are all G-protein-coupled receptors. These can be linked to a variety of second messenger systems or sometimes directly to ion channels.

Diseases associated with G-protein abnormalities

- **Cholera**: *Vibrio cholerae* secretes an exotoxin that catalyses ADP-ribosylation of an arginine residue on Gsα. This makes the subunit resistant to hydrolysis and the second messenger (in this case cAMP) remains activated, and this ultimately leads to the fluid and electrolyte loss characteristic of the disease
- Pituitary adenomas[a]
- McCune–Albright syndrome[a]

- Albright's hereditary osteodystrophy[a] (or pseudohypoparathyroidism)

[a] See Chapter 4, Endocrinology.

14.2.2 Protein kinases and phosphatases

Protein kinases catalyse the transfer of a phosphate group from ATP to a serine, threonine or tyrosine residue on a target protein (the substrate). Phosphorylation of this amino-acid residue results in an alteration in the conformation of the target protein and thus leads to its activation or inactivation. Many **growth factor receptors** are protein tyrosine kinases (see above). Many of the 'downstream' intracellular pathways that are initiated by the activation of a second messenger system involve protein kinases (usually serine kinases in the cytoplasm). In this way an external signal can, through the activation of one receptor, influence a vast array of cellular processes due to a cascade of protein interactions.

14.2.3 Nuclear hormones

Not all extracellular signals use second messenger systems to effect changes to the cell. Important exceptions are **steroid hormones** that bind to an intracellular receptor, allowing the receptor to be freed from its cytosolic membrane-bound anchor (Figure 14.10). The receptor–hormone complex then travels to the nucleus where it binds to specific regions of DNA called **hormone-responsive elements** (HRE), thereby effecting alterations in the transcription of DNA.

Examples of nuclear hormones

- Corticosteroids
- Vitamin D
- Retinoic acid
- Sex steroids.

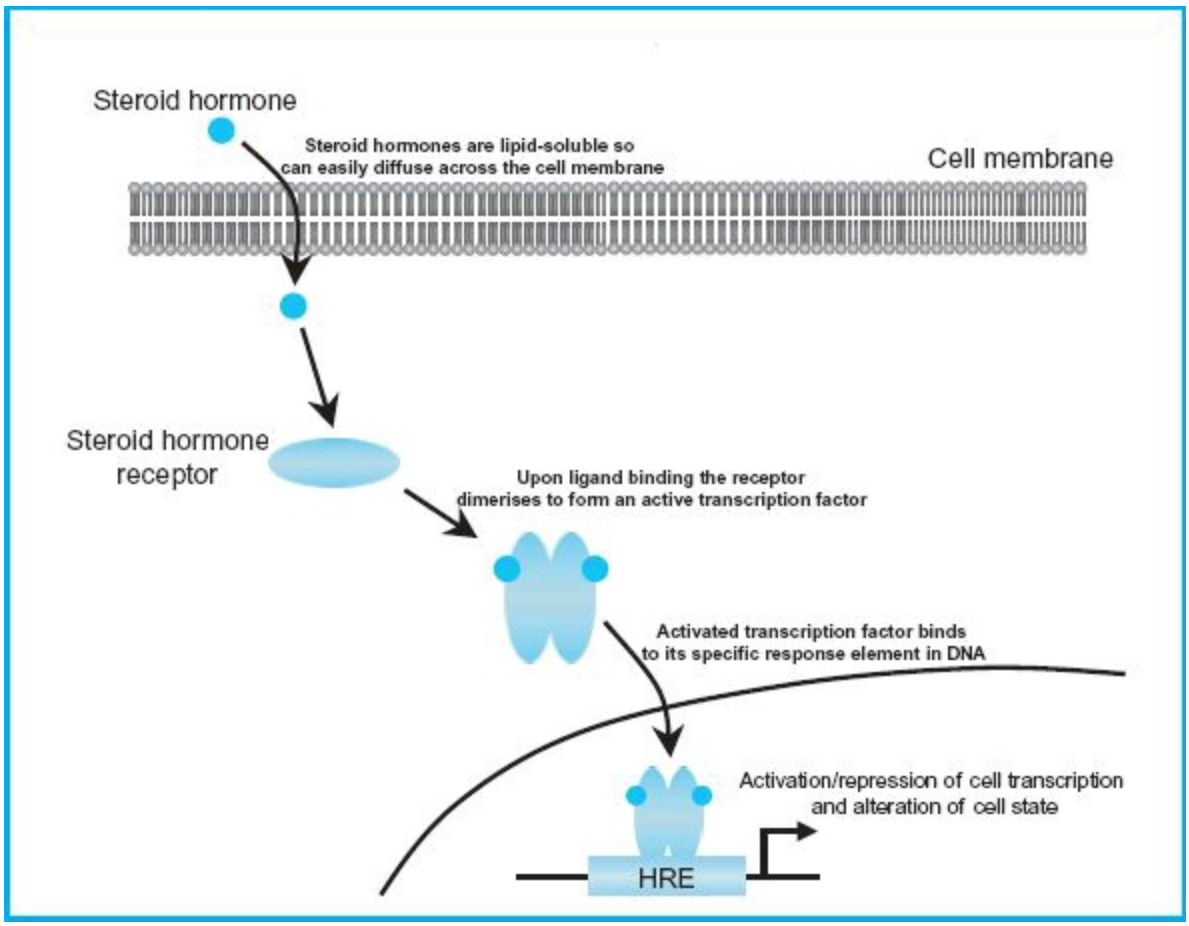
14.2.4 Transcription factors and the regulation of gene expression

The human genome is present in two copies in every cell in the body, and is estimated to consist of around 30 000 genes. The spatial and temporal expression of a proportion of these genes (typically 10 000–15 000 genes are expressed in any one cell at any time) determines the differentiation, morphology and functional characteristics of each cell type (the **cellular phenotype**). Clearly, for cells to maintain a specific identity, this process must be very tightly regulated.

Eukaryotic genes consist of **exons** that are transcribed into the mRNA template, which is translated into protein (Figure 14.11). Exons are separated by **introns**, which do not code for protein, but have a role in mRNA stability and are spliced out of the pre-mRNA before translation. Sometimes exons are also spliced out to produce variant forms of the protein with tissue-specific functional elements (splice variants).

Clearly some genes have a fundamental biological role and will be expressed in all cells at all times ('housekeeping genes'). However, the transcription of most genes proceeds only when a macromolecular complex (the initiation complex) binds to a region of the 5′ end of genes called the **promoter**. The assembly of this complex is directed by the presence of transcription factors and facilitates the binding of RNA polymerase, which leads to transcription. Muscle, for example, will contain specific transcription factors that lead to the expression of muscle-specific genes which determine the muscle phenotype.

Figure 14.10 The nuclear hormone superfamily of receptors act by controlling gene transcription in the nucleus



The promoter

- A modular arrangement of different elements that act as a binding site for RNA polymerase II and the initiation of transcription
- The initiation of transcription involves a large complex of multimeric proteins (RNA polymerase II plus the general transcription factors (GTFs): TFII A–H)
- The GTFs can activate transcription of any gene that has a TATA box (see below).

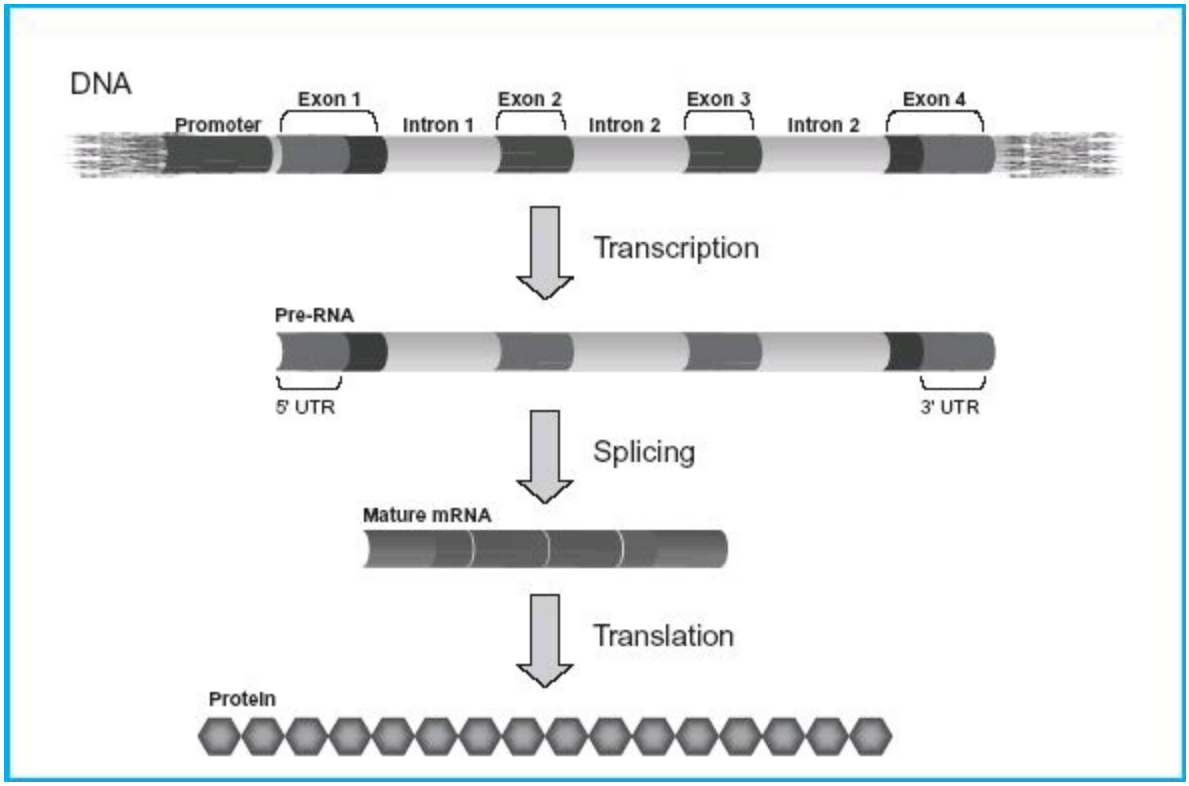
Enhancers

- Elements that can be at the 5′ or the 3′ end of genes and can vary in distance from the coding sequence itself
- Enhancers are not obligatory for the initiation of transcription but alter its efficiency in such a way as to lead to an increase in gene expression.

5′-Untranslated region

The five prime untranslated region (5′-untranslated region or 5′-UTR) is a section of mRNA and the DNA that codes for it. It starts at the transcription start site and ends just before the transcription start codon (usually AUG). The region can contain several regulatory sequences:

Figure 14.11 Structure of a typical gene



- A ribosome-binding site
- Binding sites for proteins that may affect the stability or translation rate of the mRNA
- Sequences that promote the initiation of translation.

3′-Untranslated region

The three prime untranslated region (3′-UTR), similar to the 5′-UTR, is a section of mRNA and the DNA that codes for it. It starts after the stop codon (usually UAG, UAA or UGA) and may contain several regulatory sequences:

- **A polyadenylation signal**: this initiates the cleavage of the transcript, which usually happens about 30 base pairs downstream. This is then followed by the addition of several hundred adenine residues (poly-A tail)
- **Binding sites for regulatory proteins**: these proteins may affect the stability or cellular localisation of the mRNA. AU-rich elements (AREs) are sequences in the 3′-UTR rich in adenine and uridine nucleotides which can stabilise or destabilise the mRNA depending on the protein bound.

Poly-A tail

The addition of a stretch of adenine residues (typically 50–200) at the 3′ end of mRNAs protects them

from degradation by exonucleases present in the cytoplasm, and aids in transcription termination, export from the nucleus and translation. The length of the adenine repeat may also have an effect on stability; when the tail is shortened the mRNA is enzymatically degraded.

Transcription factors

Transcription factors are proteins that bind to sequence-specific regions of DNA at the 5′ end of genes called **response elements** to regulate gene expression. These elements can form part of promoters or enhancers. They can be divided into:

- Basal transcription factors – involved in the constitutive activation of so-called 'housekeeping genes'
- Inducible transcription factors – involved in the temporal and spatial expression of genes that underlie tissue phenotype and developmental regulation.

They fall into a number of groups based on their structure:

- Helix–loop–helix
- Helix–turn–helix
- Zinc finger
- Leucine zipper.

The **TATA box** is a promoter element that is always located 25–30 base pairs from the start of transcription and serves to anchor RNA polymerase II.

Clinical applications of transcription factors

- An increasing number of diseases are being described where an inherited mutation in transcription factors leads to a developmental disorder. These are usually complex congenital malformations
- Transcription factors can be oncogenes, eg c-*myc*, *TP53* (see section 14.3.2)
- Many future drugs will be developed to alter gene transcription by acting directly or indirectly on gene transcription in the manner described above for steroids

14.3 THE MOLECULAR PATHOGENESIS OF CANCER

14.3.1 Somatic evolution of cancer

Cancer cells are a clonal population. The accumulation of mutations in multiple genes results in escape from the strictly regulated mechanisms that control the growth and differentiation of somatic cells. It will be evident that some of these genetic 'errors' will be inherited and form the basis of a familial tendency to cancer. For cancer to develop, in most cases, an environmentally driven genetic mutation is necessary. Genotoxic damage from ionising radiation and some of the constituents of tobacco smoke fall into this category.

In addition, all somatic cell division requires the copying of DNA and this can result in the spontaneous mutations of genes. It is a combination of these three types of genetic mutation (inherited, spontaneous and environmentally determined) that leads to cancer. Therefore, cancer evolution is a complex, multifactorial process.

Most tumours show visible abnormalities of chromosome banding on light microscopy, suggesting that as tumours develop they become more bizarre and more prone to genetic error. Although there are some cancer genes that lead to Mendelian (ie monogenic) inheritance of specific tumours, most cancers result from a complex mixture of polygenetic and environmental influences.

14.3.2 Oncogenes

Originally identified as genes carried by cancer-causing viruses that are integrated into the host genome and, when expressed, lead to loss of growth control (viral oncogenes are denoted *v-onc*). They have cellular homologues, **proto-oncogenes** (denoted *c-onc*), found in the normal human genome and expressed in normal tissue, that are usually highly conserved in evolution and have central roles in the signal-transduction pathways that control cell growth and differentiation. They can be thought of as exerting a dominant effect in that they cause cancer in the presence of the normal gene product because, in mutating, they have gained a new function.

- **Ras** is a small, monomeric G-protein and is likely to be involved in the transduction of growth-promoting signals. The relative abundance of the active and inactive forms of Ras is controlled by positive and negative regulators of GTP–GDP exchange (GAP and GNRF) (Figure 14.12). Mutations affecting the GTP-binding site prevent GTP hydrolysis and prolong Ras activation. At least a third of sporadic tumours contain acquired somatic mutations in the *ras* gene
- Further downstream, after a number of protein kinase steps have been activated, the transduction of growth signals culminates in the activation of the transcription factors Fos and Jun, which in turn induce the transcription of the proto-oncogene *myc*; this commits the cell to a round of DNA replication and cell division. Mutant forms of these proteins can induce tumour growth
- The 9:22 balanced translocation (Philadelphia chromosome) found in chronic myeloid leukaemia (CML) generates a composite gene comprising exons from the *bcr* locus on chromosome 22 and the *c-abl* locus on chromosome 9, generating a fusion protein with distinct biochemical properties which presumably promote tumour growth
- In Burkitt's lymphoma the *c-myc* gene is transposed from its normal position into the immunoglobulin heavy-chain locus on chromosome 14, resulting in a gross increase in its expression and a potent molecular signal for cells to undergo mitosis (Figure 14.13).

14.3.3 Tumour suppressor genes

- In contrast to oncogenes these exert a recessive effect, in that both copies must be mutated before tumorigenesis occurs
- Mutation results in loss of function
- These genes normally function to inhibit the cell cycle and therefore, when inactivated, lead to loss of growth control.

A pivotal role in the cell cycle is played by protein p53, and its gene is the most commonly mutated gene in tumours (breast, colon, etc). It encodes a transcription factor, the normal function of which is to downregulate the cell cycle. Inactivation of p53 is the primary defect in the Li–Fraumeni syndrome (a dominantly inherited monogenic cancer syndrome characterised by breast carcinoma, sarcomas, brain and other tumours), and is a central regulator of apoptosis (see Section 14.4, Apoptosis and disease).

Figure 14.12 Activation of the oncoprotein Ras is under reciprocal control by GNRF and GAP

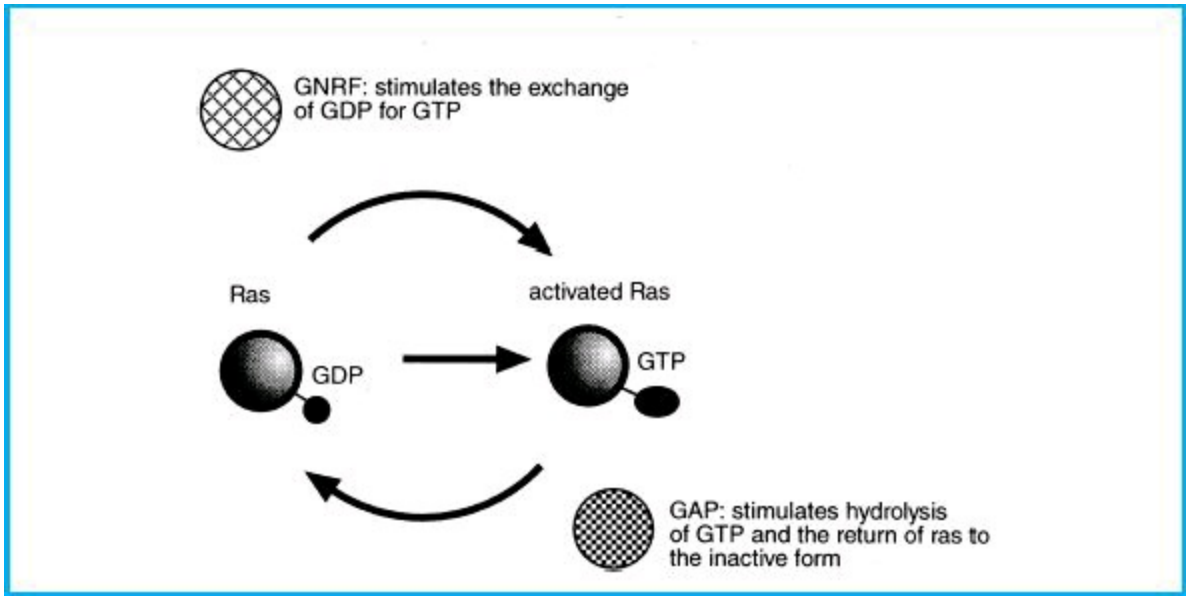
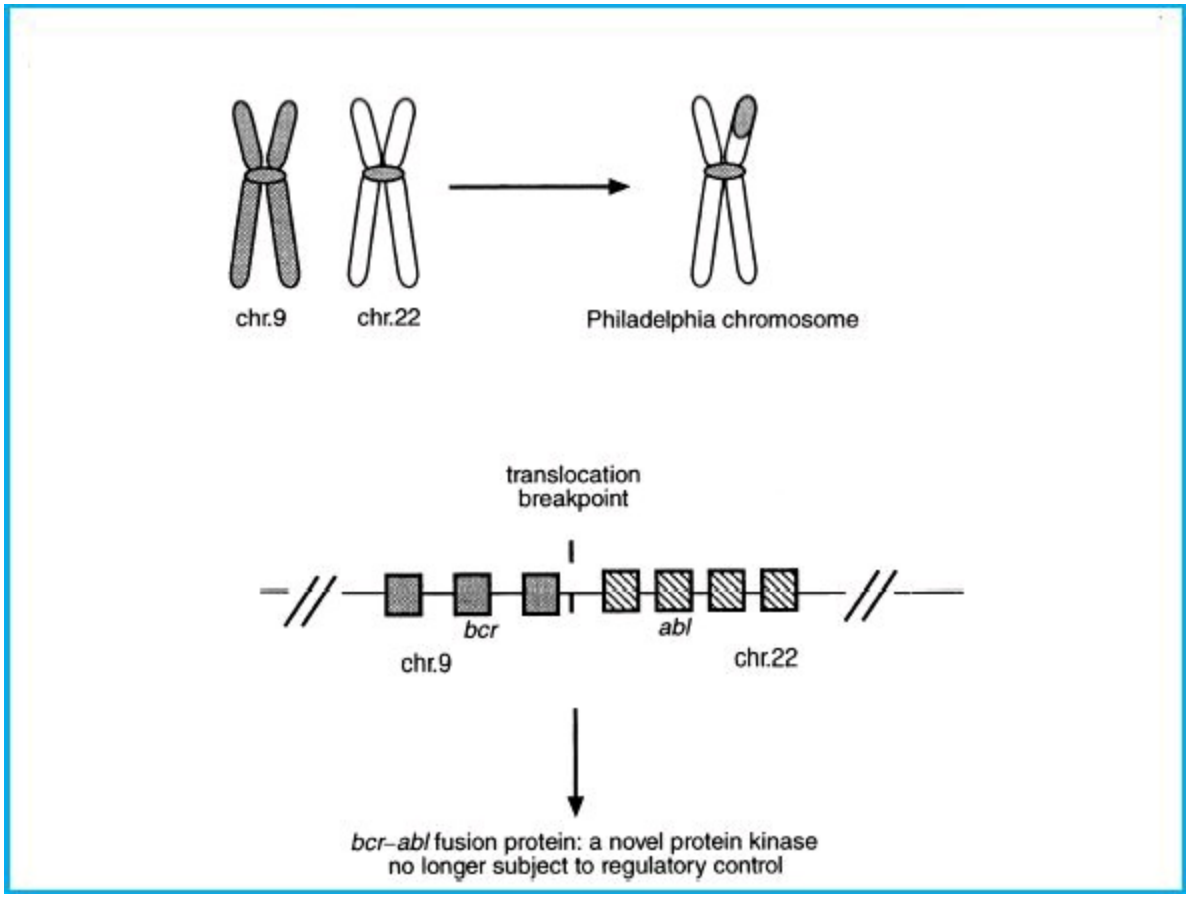


Figure 14.13 In chronic myeloid leukaemia the Philadelphia chromosome leads to the production of an oncoprotein



14.4 APOPTOSIS AND DISEASE

It has only recently been fully appreciated that widespread cell death occurs in human development and in the normal regulation of cell number in the adult organism. In embryonic development, cells are lost, eg as finger webbing disappears or as neurons are 'selected' for survival, by making the appropriate synaptic contact. In postnatal life, the expansion of lymphocyte numbers in response to antigen stimulation must be regulated by the subsequent death of these cells or clonal proliferation would continue unabated. It turns out that this process of naturally occurring cell death is regulated by the activation of a specific set of genes in response to external signals in a process referred to as **programmed cell death**. The morphological change that accompanies this process is called **apoptosis**.

- Cells undergo shrinkage, compaction of chromatin, nuclear and cytoplasmic budding to form membrane-bound apoptotic bodies and finally phagocytosis by surrounding macrophages
- The activation of intracellular nucleases can be detected by the 'laddering' of DNA on electrophoresis gels, which serves as a marker for apoptosis.

In contrast to necrosis, apoptosis does not induce the release of destructive proteolytic enzymes and free radicals and is thus a non-inflammatory process. Therefore, collateral damage to neighbouring cells is not seen. Most cells seem to rely on a constant supply of survival signals without which they will undergo apoptosis. These are provided by neighbouring cells and the extracellular matrix. The absence or withdrawal of these molecular signals is a trigger to apoptosis.

The 'cell death programme' is genetically regulated and there are specific proteins that promote or inhibit apoptosis.

- A family of proteases called caspases (ICE, or interleukin-1-converting enzyme, is the best-studied example) is central to apoptosis in mammals and is responsible for driving all the structural changes in the nucleus that accompany apoptosis. Caspases have been shown to be present in all cells and thus to prevent apoptosis there must be specific inhibitors of these proteases
- The Bcl-2 family of molecules inhibit apoptosis by a variety of mechanisms and are thus cytoprotective survival signals. Over-expression of Bcl-2 specifically prevents cells from entering apoptosis and its high expression has been correlated with poor survival from cancer
- Fas, or CD95, is a transmembrane receptor that belongs to the tumour necrosis factor (TNF) receptor family. The binding of TNF-like ligands to Fas is coupled to the activation of intracellular caspases. Some tumours express the Fas ligand on their surface, thus activating Fas on cytotoxic T lymphocytes, leading to their death (a way of evading immune surveillance)
- p53 is required for the apoptosis of cells in which DNA has been damaged. The failure of tumour cells to die in the face of genotoxic damage may be due to the accumulation of p53 gene mutations.

Programmed cell death can be stimulated by a variety of triggers and leads to the activation of proteases such as ICE that initiate a cascade of morphological changes (collectively known as apoptosis) which result in inevitable phagocytosis.

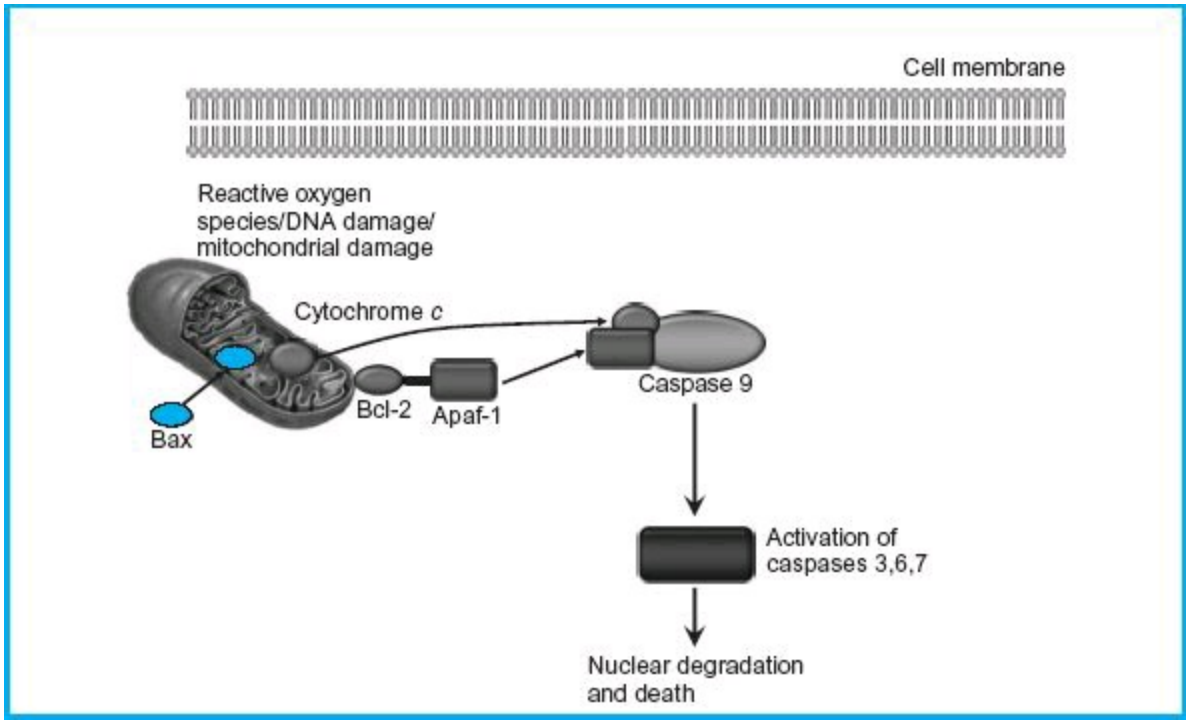
Certain disorders (cancer, autoimmunity and some viral illnesses) are associated with increased

- cell survival (and therefore a failure of programmed cell death). Metastatic tumour cells have circumvented the normal environmental cues for survival and can survive in foreign environments
- Physiological cell death is necessary for the removal of potentially autoreactive T cells during development and for the removal of excess cells after the completion of the immune response. Animal models of systemic lupus erythematosus (CD95/Fas knockout mice) have implicated apoptosis genes in the pathogenesis of autoimmunity
- Death by apoptosis can be seen as an evolutionary adaptation to prevent the survival of virally infected cells. Therefore, viruses have developed strategies for circumventing this. Pox viruses appear to inhibit apoptosis by producing an inhibitor of ICE
- Excessive cell death due to an excess of signals promoting apoptosis has been hypothesised to occur in many degenerative disorders where cells have been observed to die by apoptosis. Direct evidence that this actually occurs has yet to be found.

Apoptosis may be initiated by two main mechanisms termed the ‘intrinsic’ and ‘extrinsic pathways’. In the intrinsic pathway the cell makes its own decision that the cell is no longer viable and that it should undergo apoptosis. It does this in response to internal damage due to such things as reactive oxygen species, DNA or mitochondrial damage. The damage caused is determined to be significant enough that the cell is no longer viable or if allowed to live would become tumorigenic. The pathway can be seen in Figure 14.14 in which the caspase cascade is activated by a complex of caspase 9 in combination with cytochrome *c* and Apaf-1.

The extrinsic pathway is when an external stimulus leads to the activation of transmembrane death receptors, resulting in a healthy cell committing suicide. The death receptors are members of the TNF-receptor gene superfamily and the main ligands are FasL, TNF-α, Apo3L and Apo2L. The extrinsic pathway is used in tissue remodelling, limiting the clonal expansion of immune cells and maintaining tissue homeostasis by maintain equilibrium between cell proliferation and cell death. The main differences between the intrinsic and extrinsic pathways are that the extrinsic pathway is not mitochrondrially mediated, but rather activated by a death receptor, and that the upstream caspases in the caspase cascade are caspases 8 or 10 in the extrinsic pathway rather than caspase 9 in the intrinsic pathway (Figure 14.15).

Figure 14.14 Apoptosis, the intrinsic pathway



14.5 MOLECULAR REGULATION OF VASCULAR TONE

Both the regulation of systemic arterial blood pressure and the local control of the microcirculation in organs such as the kidney and the brain are vital for the maintenance of homeostasis. In recent years there has been an explosion of knowledge about the molecular mediators of blood flow and this is already having an impact in the therapy of some common disorders.

Two important principles should be kept in mind:

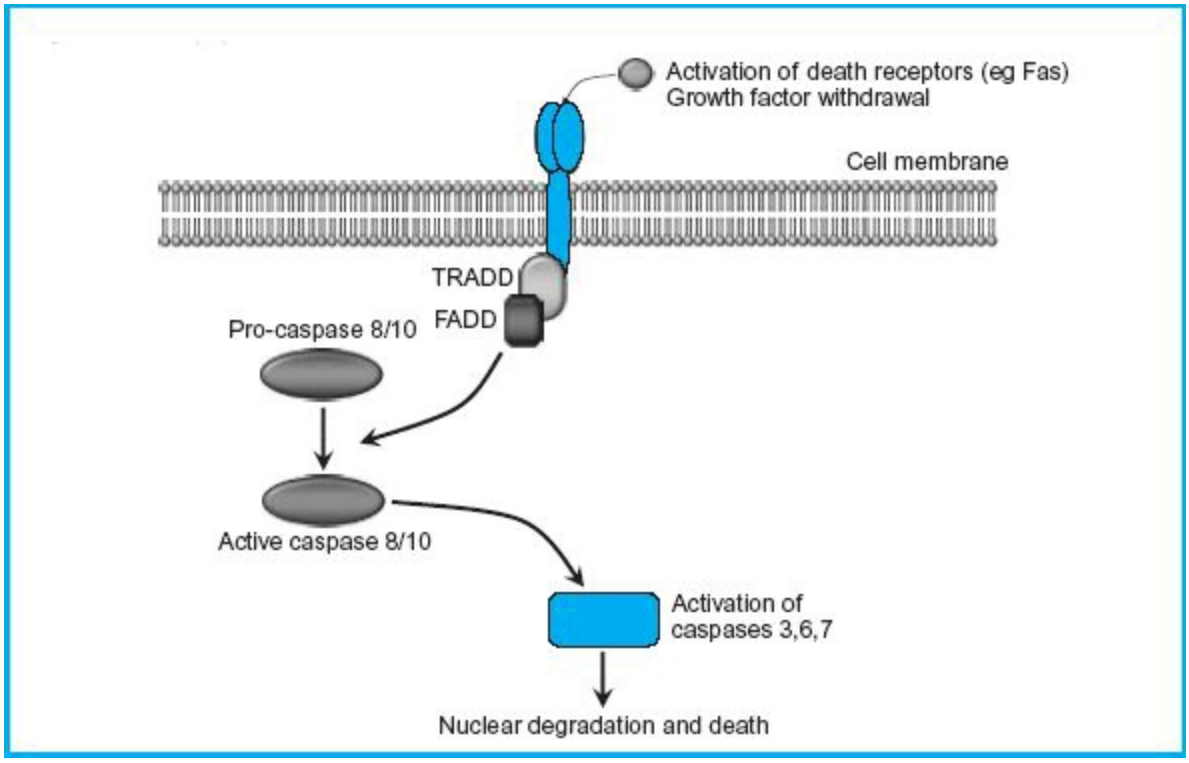
1. The regulation of vascular tone is predominantly a **paracrine** process, where molecules are released to act in adjacent cells
2. Vascular control is often a balance between competing vasodilators and vasoconstrictors.

14.5.1 Nitric oxide

Previously called endothelium-derived relaxant factor (EDRF), nitric oxide (NO) is an important transcellular messenger molecule that is involved in a diverse range of processes.

NO is synthesised from the oxidation of nitrogen atoms in the amino acid L-arginine by the action of NO synthase (NOS) (Figure 14.16).

Figure 14.15 Apoptosis, the extrinsic pathway



Cell types that synthesise nitric oxide

Vascular endothelium

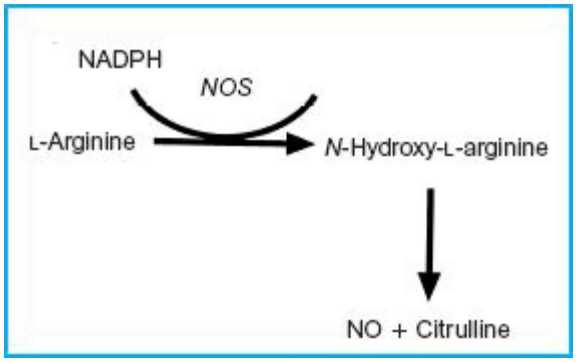
- Platelets
- Macrophages
- Vascular smooth muscle
- Neutrophils
- Hepatocytes
- Central and peripheral nerve cells

NO acts on target cells close to its site of synthesis where it activates guanylyl cyclase, leading to a rise in intracellular cGMP, which acts as a second messenger to modulate a variety of cellular processes. It has a very short half-life.

There are at least three distinct **isoforms** of NOS:

1. Neuronal (constitutive)
2. Endothelial (constitutive)
3. Macrophage (inducible).

Figure 14.16 Formation of nitric oxide



Constitutive NO production is involved in regulation of vascular tone and neurotransmission and is calcium/calmodulin-dependent. **Inducible NO production** is mainly involved in cell-mediated immunity and is activated by cytokines.

Synthetic nitrates, such as GTN and sodium nitroprusside, act after their conversion into NO.

Functions of nitric oxide

- Vasodilator tone modulation in the regulation of systemic blood pressure
- CNS neurotransmission, including the formation of new memories
- Inhibition of platelet aggregation
- Cytotoxic action utilised in the generation of the host immune response in activated macrophages
- Organ-specific microregulatory control (eg kidney)
- Peripheral nervous system 'non-adrenergic, non-cholinergic neurotransmission' (NANC), mediating neurogenic vasodilatation

Diseases related to abnormalities in the generation or regulation of NO

- **Septic shock**: NO is released in massive amounts and correlates with low blood pressure
- **Atherosclerosis**: NO synthesis may be impaired more than endothelin synthesis, leading to tonic vasoconstriction and vasospasm
- **Primary and secondary pulmonary hypertension**: inhaled NO reverses pulmonary hypertension
- **Hepatorenal syndrome** and the **hypertension of chronic renal failure**: failure of breakdown and secretion of endogenous antagonists of NO leads to a microcirculatory imbalance between NO and endothelin (see Section 14.5.2, Endothelin-1)
- **Excitotoxic cell death in the CNS**: glutamate is the principal excitatory neurotransmitter in the CNS. NO is the transduction mechanism when glutamate binds to NMDA (*N*-methyl-Daspartate) receptors on neurons. The final event in the presence of excess glutamate is a rise in intracellular calcium and the cell becomes vulnerable to dying. This process, in which NO is now implicated, is thought to be important in neuronal loss in many neurodegenerative conditions such as Alzheimer's disease and also in acute brain injury such as stroke
- **Tissue damage in acute and chronic inflammation** (probably by interacting with oxygen-derived free radicals)
- **Adult respiratory distress syndrome** (ARDS).

14.5.2 Endothelin-1

This is the most potent vasoconstrictor substance yet described. It is manufactured after vascular endothelial 'stress' (shear, hypoxia, growth factors, expansion of plasma volume). It is produced from preproendothelin (ET) by the action of endothelin-converting enzyme (ETCE). Very little endothelin reaches the circulation and serum levels do not generally carry any diagnostic significance.

There are endothelin receptors:

- On the vascular endothelium and on some smooth muscle cells (gut and heart), including coronary arteries where they cause constriction
- On capillary endothelium where they cause vasodilatation.

When ET-1 is infused intravenously it causes a transient vasodilatation followed by a long period of intense vasoconstriction lasting up to 2 hours. The normal function of endothelin is in the regulation of vascular tone. The endothelin-receptor blockers sitaxsentan and bosentan have been developed to counter pulmonary hypertension. Bosentan is a non-selective endothelin-receptor blocker whereas sitaxsentan is selective for the endothelin-A receptor. As endothelin receptor-B activation is believed to be beneficial, it is believed that sitaxsentan could be a more effective treatment. More diverse functions of endothelin are indicated by the recent finding of mutations in the endothelin-B receptor in some patients with Hirschsprung's disease.

Disorders with pathogenesis possibly related to endothelin

- Essential hypertension
- Primary pulmonary hypertension
- Renovascular hypertension
- Hepatorenal syndrome
- Acute renal failure
- Chronic heart failure
- Raynaud's phenomenon
- Vasospasm after subarachnoid haemorrhage

14.6 MOLECULAR MEDIATORS OF INFLAMMATION, DAMAGE AND REPAIR

The process of tissue injury, inflammation and subsequent repair is highly conserved in evolution and represents part of the 'primitive' repertoire of protective mechanisms against invasion by foreign organisms and other insults. This is in contrast to the more sophisticated mechanisms of defence mediated by the immune system. Some of the same molecules are involved in both processes but they are considered here to emphasise the enormous importance of inflammation as a pathological process

central to many diseases. These molecular interactions are to a certain extent therefore independent of the immune system.

The principal molecules involved are termed ‘cytokines’, because they function in the immune system as products secreted by one cell to act on another cell to direct its movement (‘kinesis’). In the context of inflammation it is the **proinflammatory cytokines** that are relevant. (See also Chapter 10, Immunology.)

14.6.1 Interleukin-1

This molecule has a broad spectrum of both beneficial and harmful biological actions and, as a central regulator of the inflammatory response, has been implicated in many diseases.

There are three structurally related polypeptides in the interleukin-1 family:

- IL-1α
- IL-1β
- IL-1-receptor antagonist.

IL-1α and IL-1β are synthesised by mononuclear phagocytes that have been activated by microbial products or inflammation:

- IL-1α stays in the cell to act in an autocrine or paracrine fashion
- IL-1 is secreted into the circulation and cleaved by interleukin-1-converting enzyme (ICE).

IL-1 levels in the circulation are undetectable except:

- After strenuous exercise
- With sepsis
- With acute exacerbation of rheumatoid arthritis
- In ovulating women
- With acute organ rejection.

IL-1 in disease

- **Rheumatoid arthritis**: IL-1 is present in the synovial lining and fluid of patients with rheumatoid arthritis and it is thought to activate gene expression for collagenases, phospholipases and cyclo-oxygenases. It is thus acting as a molecular facilitator of inflammatory damage in the joint but is not an initiator
- **Atherosclerosis**: the uptake of oxidised LDL by vascular endothelial cells results in IL-1 expression, which stimulates the production of platelet-derived growth factor. IL-1 is thus likely to play a role in the formation of the atherosclerotic plaque
- **Infection**: IL-1 has some host defence properties, inducing T and B lymphocytes, and reduces mortality from bacterial and fungal infection in animal models
- **Septic shock**: IL-1 acts by increasing the concentration of small mediator molecules such as platelet-activating factor (PAF), prostaglandins and NO, which are potent vasodilators.

14.6.2 Tumour necrosis factor

This is a proinflammatory cytokine that has a wide spectrum of actions. Either through neutralising antibodies (anti-TNF-α) or inhibitor drugs, it is the target of therapy in disorders such as rheumatoid arthritis and multiple sclerosis.

Two non-allelic forms of TNF, α and β, are expressed in different cells.

- TNF-α is produced by macrophages, eosinophils and NK cells
- TNF-β is made by activated T lymphocytes.

Its name is derived from the early observation that it can have a cytotoxic effect on tumour cells in vitro. Trials with TNF-α as a therapeutic agent were soon stopped due to the severe toxicity of the substance. In fact in certain situations it can promote tumour growth.

Its action in diseases such as **rheumatoid arthritis** depends on a synergistic effect with IL-1. Both are found in the synovial membrane of patients with the disease. TNF-α strongly induces monocytes to produce IL-1 at a level comparable to that stimulated by bacterial lipopolysaccharide (LPS).

Actions of TNF

- TNF-α is a potent stimulator of prostaglandin production
- TNF is a key cytokine in the pathogenesis of multiorgan failure
- It induces granulocyte–macrophage colony-stimulating factor (GM-CSF) and thus is an activator of monocytes and macrophages in diseased tissue

14.6.3 Transforming growth factor β

A key cytokine that initiates and terminates tissue repair, and the sustained production of which underlies the development of tissue fibrosis.

Transforming growth factor β (TGF-β) is released by platelets at the site of tissue injury and is strongly chemotactic for monocytes, neutrophils, T cells and fibroblasts. It induces monocytes to begin secreting fibroblast growth factor (FGF), TNF and IL-1, but inhibits the functioning of T and B cells and their production of TNF and IL-1. It also induces its own secretion. This **autoinduction** may be important in the pathogenesis of fibrosis.

TGF-β in disease

- TGF-β-deficient (knockout) mice die of an autoimmune disease in which levels of TNF and IL-1 are very high
- It has a potent effect on cells to induce the production of extracellular matrix (a dynamic superstructure of self-aggregating macromolecules including fibronectin, collagen and proteoglycans to which cells attach by means of surface receptors called **integrins**). Extracellular matrix is continually being degraded by proteases that are inhibited by TGF-β

- In **mesangioproliferative glomerulonephritis**, glomerular immunostaining for TGF-β correlates well with the amount of mesangial deposition
- In **diabetic nephropathy**, increased TGF-β is found in the glomeruli, and TGF-β may be central to the pathogenesis of progression of many chronic renal diseases
- Elevated plasma levels of TGF-β are highly predictive of **hepatic fibrosis** in bone marrow transplant recipients. Messenger RNA for TGF-βis found in areas of active disease in liver biopsy samples of patients with chronic liver disease
- In patients with **idiopathic pulmonary fibrosis**, TGF-β is increased in the alveolar walls. It is also implicated in **bleomycin lung**.

14.6.4 Heat shock proteins

The **heat shock response** is a highly conserved and phylogenetically ancient response to tissue stress that is mediated by activation of specific genes, leading to the production of specific heat shock proteins (HSPs) that alter the phenotype of the cell, and enhance its resistance to stresses.

Some HSPs are extremely similar to constitutively activated proteins that have essential roles in unstressed cells. Their diverse functions include:

- Export of proteins in and out of specific cell organelles (acting as **molecular chaperones**)
- Catalysis of protein folding and unfolding
- Degradation of proteins (often by the pathway of ubiquitination).

As well as heat, HSP expression can be triggered by cytotoxic chemicals, free radicals and other stimuli. The unifying feature that leads to the activation of HSPs in these situations is thought to be the accumulation of damaged intracellular protein.

Clinical relevance

- Tumours have an abnormal thermotolerance, which is the basis for the observation of the enhanced cytotoxic effect of chemotherapeutic agents in hyperthermic individuals
- Stress proteins are prominent among the bacterial antigens recognised by the immune response of humans to bacterial and parasitic infections and are thought to be involved in some autoimmune diseases
- Mutations in small heat shock proteins (sHSPs) have been associated with diseases as diverse as cataract (α-crystallin) and forms of motor neuron degeneration (sHSPs 22 and 27).

14.6.5 Free radicals and human disease

Free radicals have been implicated in a large number of human diseases and are currently the subject of much interest. Therapeutic trials have been undertaken with putative free-radical scavengers such as vitamin E. A free radical is literally any atom or molecule that contains one or more unpaired electrons, making it more reactive than the native species.

Free radical species produced in the human body

- –HOO· (peroxide radical)
- $O^{\cdot}_2$ (superoxide radical)
- –HO· (hydroxyl radical)
- –NO· (nitric oxide)

The hydroxyl radical is by far the most reactive species but the others can generate more reactive species as breakdown products.

When a free radical reacts with a non-radical a chain reaction ensues, which results in the formation of further free radicals and direct tissue damage by lipid peroxidation of membranes. This is particularly implicated in **atherosclerosis**, and **ischaemia–reperfusion injury** (eg acute tubular necrosis within the kidney) within tissues. Hydroxyl radicals can cause mutations by attacking purines and pyrimidines. Also:

- **Activated phagocytes** generate large amounts of superoxide within lysosomes as part of the mechanism whereby foreign organisms are killed. During chronic inflammation this protective mechanism may become harmful
- **Superoxide dismutases** (SODs) convert superoxide to hydrogen peroxide and are thus part of an inherent protective antioxidant strategy. Catalases remove hydrogen peroxide. **Glutathione peroxidases** are major enzymes that remove hydrogen peroxide generated by SODs in cytosol and mitochondria
- **Free-radical scavengers** bind reactive oxygen species. α-Tocopherol, urate, ascorbate and glutathione remove free radicals by reacting directly and non-catalytically. Severe deficiency of α-tocopherol (vitamin E deficiency) causes neurodegeneration.

Clinical relevance

There is growing evidence that cardiovascular disease and cancer can be prevented by a diet rich in substances that diminish oxidative damage.

Principal dietary antioxidants

- Vitamin E
- Vitamin C
- β-Carotene
- Flavonoids

Epidemiological studies have demonstrated an association between increased intake of vitamins C and E and morbidity and mortality from coronary artery disease. This supports models where atherogenesis is initiated by lipid peroxidation of LDL.

Patients with dominant familial forms of amyotrophic lateral sclerosis (motor neuron disease) have mutations in the gene for Cu/Zn SOD-1, suggesting a link between failure of oxidative damage and neurodegeneration.

14.7 TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

The transmissible spongiform encephalopathies (TSEs) are a group of diseases that are characterised by progressive spongiform degeneration in the brain and neuronal loss. Although these conditions are rare, they are the subject of intense interest because of an epidemic of human infection that is linked to the cattle disease bovine spongiform encephalopathy (BSE). The biologically unique features of these diseases are, first, that they can be simultaneously inherited and also infectious, and, second, that the agent of transmission is thought to be a protein only rather than an 'organism' containing DNA or RNA. This protein has been called a prion; it is encoded by the host genome and cannot replicate.

Diseases caused by TSEs

- **Sporadic Creutzfeldt–Jakob disease (CJD)**: rare ($1/10^6$), causes rapid dementia with myoclonus and characteristic EEG
- **Variant CJD (vCJD):** 167 cases had occurred in the UK up to 1 September 2008, with 164 deaths and 3 additional probable cases reported. This affects young people and has a slower course than sporadic CJD; it has characteristic pathological features
- **Autosomal dominant CJD**: familial form of classic CJD
- **Gerstmann–Straussler–Scheinker syndrome (GSS):** familial spongiform encephalopathy with prominent ataxia
- **Fatal familial insomnia**
- **Kuru**: previously endemic in New Guinea highlanders who performed ritual cannibalism. This condition is now disappearing.

Molecular features of TSEs

The accidental or deliberate inoculation of affected brain tissue from a case of inherited or sporadic TSE results in the passage of the disease to the recipient. Procedures that destroy nucleic acid do not prevent this passage, which has led to the proposition that the prion protein itself causes the disease by interacting with the host-encoded protein, leading to its conversion to the mutant form of the protein. Other important considerations for the TSEs are:

- **Prion protein**: this is encoded by a gene on chromosome 20, exact function unknown. Curiously, mice lacking this gene have only subtle neurological defects. Prion proteins are not destroyed by boiling, UV irradiation or formaldehyde, nor do they elicit an immune response of any recognisable kind
- **Species barrier**: This means that the diseases are, to some extent, species-specific, eg scrapie in sheep has never been passed on to humans as far as is known. Similarly, the transmission of a spongiform encephalopathy from one species to another is very difficult. If CJD brain tissue is injected into the brain of a monkey then there is very little cell death, but if brain tissue from that

same monkey is injected into another monkey (second passage) then there is severe neuronal loss. This suggests that the pathological process leading to spongiform change depends on the host protein

- **Susceptibility polymorphism**: at codon 129 of the prion protein the amino acid can be either a valine or a glycine residue. Given that there is one copy of the gene on each chromosome, we can be either heterozygous (valine/glycine) or homozygous (valine/valine or glycine/glycine). It turns out that homozygosity at this residue is vastly over-represented in affected individuals in sporadic CJD and in variant CJD. It would appear that the one amino acid can confer susceptibility to the disease
- **Strain type**: when the protein from affected brains is electrophoretically separated and blotted onto a membrane (western blotting) and then incubated with anti-prion protein antibody, different patterns can be seen. This is what is referred to as the 'strain' of the infective agent but is really a surrogate marker. It is the fact that the observed pattern with variant CJD is identical to that observed with BSE, and different from sporadic CJD, that provides the strongest evidence of a link between the two.

14.8 ADHESION MOLECULES

The way in which cells communicate with each other is fundamental to the maintenance of homeostasis in the developing and adult organism. In particular, the molecular basis of neural connectivity, the immune response and the prevention of cancer are all dependent on **adhesion molecules**. Adhesion involves the interaction of one molecule, eg a cell surface molecule, with a specific ligand which may be on another cell or a part of the extracellular matrix. These can be divided into four groups on the basis of structure and function:

1. The immunoglobulin superfamily
2. The cadherin superfamily
3. Integrins
4. Selectins.

The **immunoglobulin superfamily** is so called because at the genetic level it has a sequence similarity that suggests that it arose from the same set of ancestral genes by duplication. These molecules are involved as cofactors in antigen presentation and are present as cell surface receptors on leukocytes (eg CD2, CD3, T-cell receptor), and some function as **integrin ligands** (eg ICAM, NCA: intercellular and neural-cell adhesion molecule, respectively).

Cadherins are involved in the interaction between muscle and nerve in the developing embryo.

Integrins are heterodimeric (two subunits, different from each other) transmembrane glycoproteins which are widely distributed in different tissues and serve to interact with molecules of the extracellular matrix (laminin, fibronectin, collagen).

Selectins are expressed on leukocytes and are thought to be involved in leukocyte adherence to endothelium during acute inflammation and coagulation.

Expression of adhesion molecules is dynamic and can be upregulated by proinflammatory cytokines

(IL-1, TNF), viral infection, T-cell activation and many other stimuli.

Clinical relevance of adhesion molecules

Adhesion molecule expression is upregulated in many forms of solid organ inflammation (eg autoimmune and viral hepatitis, and also in organ rejection after transplantation). The adhesion molecule intercellular adhesion molecule-1 (ICAM-1) is a receptor for the integrin lymphocyte function-associated molecule-1 (LFA-1) and may be involved in the recruitment and maintenance of activated lymphocytes in tissue inflammation.

- It is theoretically possible to block these molecules to treat inflammation (eg in acute renal failure and in transplant rejection)
- The integrin $\alpha_{IIb}\beta$ is the platelet receptor for fibrinogen
- Mutations in its gene lead to the congenital bleeding disorder **Glanzmann's thrombasthenia**
- In another genetic disease, **leukocyte adhesion deficiency** (LAD), lack of β_2-integrins leads to failure of leukocyte migration to sites of infection and hence to recurrent bacterial sepsis
- Conversely, antibodies against α_{IIb} are routinely used in clinical practice (ie abciximab) as antithrombotic agents in coronary artery disease.

14.9 STEM CELLS

A number of tissues in the body contain progenitor cells, which are capable of producing progeny, or daughter cells, to replenish cell populations. The most obvious example is the bone marrow where red and white cells are constantly being replaced to match turnover in the peripheral blood. It is now known that a number of other tissues contain stem cells:

- Embryonic stem cells are totipotential and hence can give rise to any tissue type. There are ethical difficulties in the acquisition and use of these cells that may limit their therapeutic use. Embryonic stem cells from mice are a powerful investigative tool in basic science
- Bone marrow stem cells can be easily accessed and purified by antigen sorting with CD34 antibodies. If these cells undergo transdifferentiation they can then function as a replacement for degenerating cells of nonhaematological origin (eg neurons).

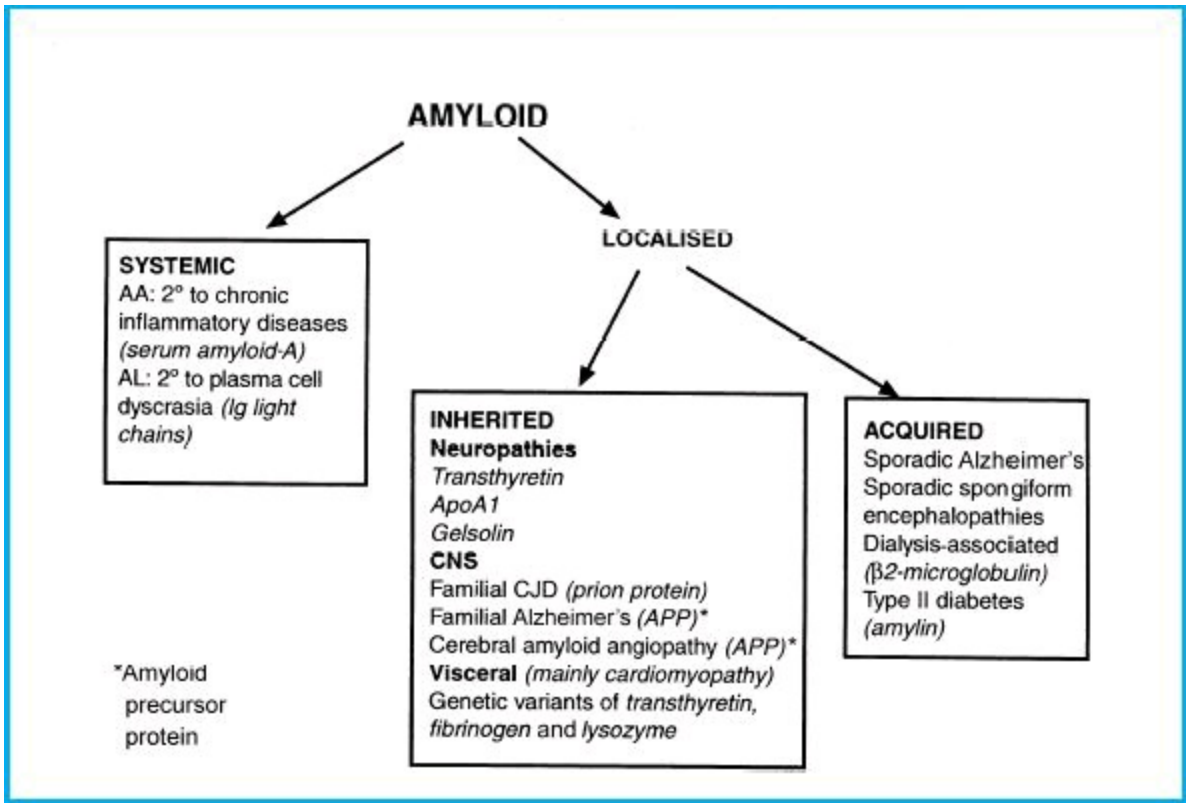
14.10 THE MOLECULAR BASIS OF SOME IMPORTANT DISEASES

The following conditions have been highlighted either because their molecular basis is well understood (eg **myasthenia gravis, α_1-antitrypsin deficiency**) or because they are caused by novel mechanisms (eg **trinucleotide repeat disorders**). Others are included because the identification of their molecular basis is historically important (as for dystrophin in **Duchenne muscular dystrophy**, which was the first disease to be worked out by identifying the gene through positional cloning). Overall, the following diseases serve to illustrate the importance of the molecular mechanisms of disease outlined in the above sections.

14.10.1 Amyloidosis

A pathological process characterised by the accumulation of extracellular fibrils of insoluble protein. The aggregated protein is specific to the different amyloid diseases listed overleaf, but in all cases the fibrillar component is associated with a non-fibrillar constituent called amyloid-P component which is derived from the acute-phase protein serum amyloid-P (SAP). Figure 14.17 outlines the classification of amyloidosis. (See also Section 15.12.1, Chapter 15, Nephrology.)

Figure 14.17 Classification of amyloidosis. The individual protein that associates with serum amyloid-P is shown in italics



Pathogenesis

Although the inherited forms of amyloid are rare, the accumulation of amyloid fibrils is a central part of the pathological process of a number of common diseases such as Alzheimer's disease and type 2 diabetes, in which amyloid is found in the islets of Langerhans. Many individuals on long-term haemodialysis eventually develop amyloid arthropathy. The key event in amyloid fibril formation is a change in conformation of the respective precursor protein that leads to its aggregation into an insoluble fibrillar form. The exact mechanism of this conformational change is unclear but it is thought to involve partial proteolytic cleavage of the precursor, and/or its overproduction. Using ^{131}I-labelled SAP, amyloid deposits can be localised using scintigraphy. Amyloid may cause organ dysfunction by progressive replacement of functional parenchyma or it may possibly be inherently cytotoxic.

14.10.2 α_1-Antitrypsin deficiency

Deficiency of α_1-antitrypsin is one of the most common hereditary diseases affecting White people. The prime function of the enzyme is to inhibit neutrophil elastase and it is one of the serpin

superfamily of protease inhibitors. Patients with deficiency present with emphysema (see Chapter 19, Respiratory medicine), because low protein levels fail to protect the lung from proteolytic attack. A proportion of individuals also develop liver cirrhosis, but this does not appear to be directly due to enzyme deficiency.

- The most common mutation that changes a glutamate residue to a lysine at position 342 of the protein (the Z mutation) results in the accumulation of protein in the endoplasmic reticulum of the liver
- The formation of these hepatic inclusions results from a protein–protein interaction between the reactive centre loop of one molecule and the β-pleated sheet of a second
- This leads to polymerisation and aggregation. Similar mechanisms have been found to be responsible for deficiency of C-1 esterase inhibitor (hereditary angioneurotic angiooedema) and antithrombin III
- Since not all patients who are homozygously deficient develop liver damage, other factors, such as the way the mutant protein is broken down in the liver, must be relevant to the manifestation of the liver component.

14.10.3 Alzheimer's disease

A neurodegenerative disease of inexorable cognitive decline characterised histologically by intraneuronal **neurofibrillary tangles** and extracellular **amyloid plaques**. Most cases are sporadic.

- About 5% of cases are inherited as an autosomal dominant with at least three genes responsible
- Mutations in the amyloid precursor protein (*APP*) gene on chromosome 21 are a rare cause of familial Alzheimer's disease (AD). The A4 protein is a proteolytic product of APP and the principal constituent of senile plaques
- Mutations in two closely related genes, the presenilins *PS1* and *PS2*, are responsible for other cases of AD
- Inheritance of the ε-4 allele of apolipoprotein E is an important determinant of age of onset in familial AD and a risk factor for sporadic AD (See also Chapter 16, Neurology).

Molecular markers

Neurofibrillary tangles consist of highly ordered intraneuronal structures called paired helical filaments (PHFs), which are assembled from the microtubule associated protein **tau**.

This suggests that neurons die because tau is handled in some abnormal way that leads to dysfunction of the microtubular network. Tau protein from PHFs is abnormally phosphorylated but it is not yet known whether this is part of the primary pathological process leading to AD. APP is cleaved into a β and a γ fragment. It is thought that plaque formation occurs when the Aβ fragment becomes insoluble and aggregates. Aggregated Aβ has been shown to induce free radical-mediated damage to neurons.

14.10.4 Trinucleotide repeat disorders

A new class of genetic disease has been recognised in recent years, in which the responsible genetic

mutation is a repetitive sequence of three nucleotides which can undergo expansion (and occasionally contraction). It has therefore become known as a dynamic mutation.

Examples of trinucleotide repeat disorders

- Huntington's disease
- Fragile X syndrome[a]
- X-linked bulbospinal neuronopathy (Kennedy syndrome)
- Myotonic dystrophy
- Friedreich's ataxia
- Spinocerebellar ataxias (there are a number of variants)

[a] See Chapter 7, Genetics.

As a consequence of dynamic mutation, mutant alleles arise from a population of premutant alleles that have a repeat number at the upper limit of the normal range (usually <35), which then become unstable and undergo sudden expansion into the mutant range (>50). Two key genetic characteristics are illustrated by trinucleotide repeat disorders.

Anticipation

The phenomenon whereby the severity of a disease becomes worse, and the age of onset earlier, in successive generations.

Somatic instability

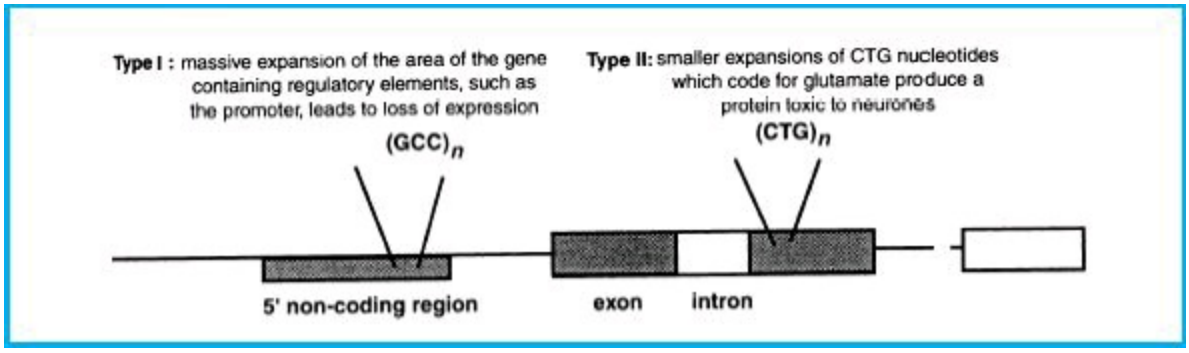
The length of the expansion continues to increase as cells divide throughout life. This may partly explain why a disease such as myotonic dystrophy gets worse as the patient gets older.

For a particular disease, the length of the expansion corresponds with the age of onset of the disease.

There are two main types of trinucleotide repeats (Figure 14.18): trinucleotide repeats can occur in the non-coding region or within exons, giving different effects.

It will be evident from Figure 14.18 that the consequence of a type I expansion is loss of gene expression because the gene cannot be transcribed due to stereochemical interference from the expanded region. Type II disorders are thought to be so-called **gain-of-function** dominant mutations, ie the trinucleotide expansion leads to the accumulation of an abnormal protein which is toxic to cells. In several of these disorders it has now been demonstrated that toxic protein accumulates in intraneuronal inclusions, which stain positive for ubiquitin. (See also Chapter 7, Genetics.)

Figure 14.18 Trinucleotide repeats



14.10.5 Mitochondrial disorders

The mitochondrial genome is circular and approximately 16.5 kb in length. It encodes genes for the mitochondrial respiratory chain and for some species of transfer RNA. Nucleic acids cannot move in and out of mitochondria, so all of the mRNA synthesised from the mitochondrial genome must be translated in the organelle itself. However, many nuclear-encoded proteins are transported into mitochondria and are absolutely necessary for mitochondrial function. (See also Chapter 7, Genetics.)

- Mitochondrial DNA (mtDNA) mutates 10 times more frequently than nuclear DNA; as there are no introns, a mutation will invariably strike a coding sequence
- **Maternal inheritance**: no mitochondria are transferred from spermatozoa at fertilisation, and so each individual only inherits mtDNA from the mother
- As there are 10^3–10^4 copies of mitochondrial DNA in each cell (each mitochondrion has 2–10 copies of mtDNA), normal and mutant mtDNA may coexist within one cell (known as heteroplasmy). This may be one explanation why mitochondrial diseases show a **poor genotype–phenotype correlation**
- There is evidence that mtDNA mutations are accumulated throughout life, as mtDNA has no protective DNA repair enzymes, and that this may contribute to the changes of ageing.

Phenotypes due to mitochondrial DNA mutations

- Sensorineural deafness
- Optic atrophy
- Stroke in young people
- Myopathy
- Cardiomyopathy and cardiac conduction defects
- Diabetes mellitus
- Chronic progressive external ophthalmoplegia
- Lactic acidosis
- Pigmentary retinopathy

Virtually all tissues in the body depend on oxidative metabolism to a greater or lesser extent, and so

these phenotypes can often occur together (eg diabetes and deafness). As mentioned above, the relationship between the mutations and the clinical features is poorly understood.

14.10.6 Myasthenia gravis

This relatively rare disease (incidence: 1 case per 8000–20 000) has a molecular pathogenesis that is well understood, and it serves as a model for other autoimmune diseases. Specific antibodies are directed against the nicotinic acetylcholine (ACh) receptor, which is present on the postsynaptic membrane of the neuromuscular junction (Figure 14.19). This results in:

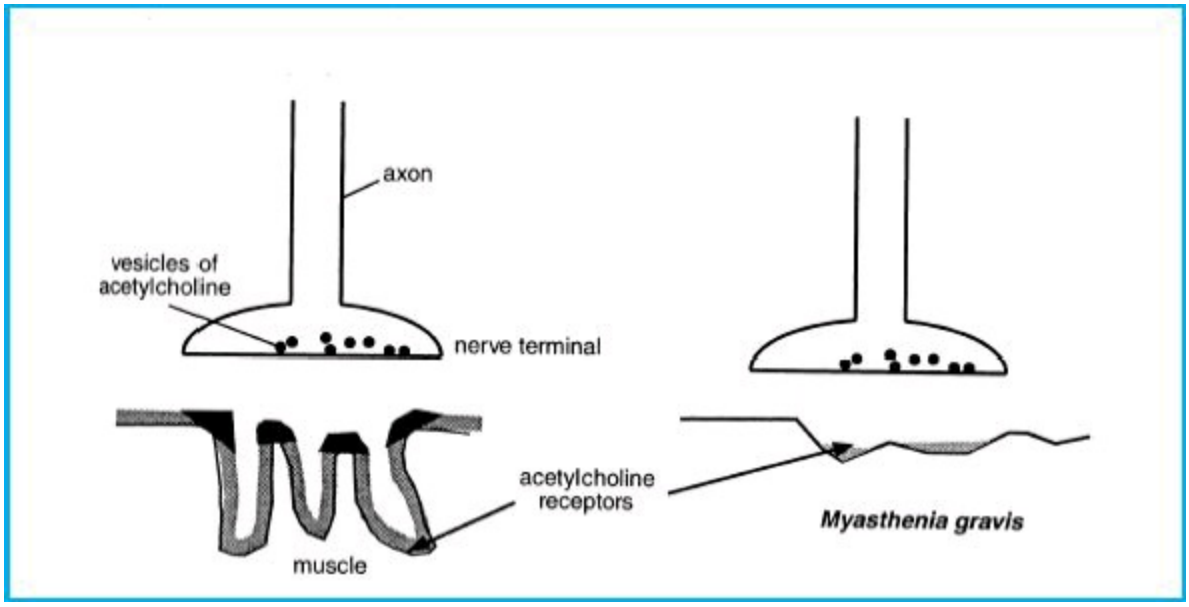
- Complement-mediated destruction of ACh receptors and a loss of the normal convolution of the muscle membrane (an important morphological hallmark of the disease); this leads to the loss of surface area for ACh to interact with its receptors
- Accelerated endocytosis and degradation of receptors
- Functional blockade of receptors.

These abnormalities lead to fatigable weakness (see also Chapter 16, Neurology). Ptosis and diplopia are the most common symptoms. In 10–15% of sufferers, symptoms are confined to the eyes (ocular myasthenia). Fatigability occurs because of a combination of the normal rundown of ACh release which occurs physiologically, and a decreased number of ACh receptors.

Over 80–90% of patients have detectable antibodies to the ACh receptor, and the others are presumed to have antibodies not detectable by current assays. Antibody negativity is more common in the ocular form.

- Passive transfer of antibodies from patients to mice reproduces the disease features
- Reduction of antibody levels by plasmapheresis or treatment with immune globulin ameliorates the disease
- The antibody titre in patients does not always correlate with disease severity, suggesting that anti-ACh receptor antibodies have different functional consequences depending on the exact epitope to which they are directed.

Figure 14.19 The neuromuscular junction in myasthenia gravis. There is loss of acetylcholine receptors and a decrease in postsynaptic folds



The origin of the autoimmune process is controversial, but 75% of patients have thymic abnormalities (hyperplasia in 85% and thymoma in 15%).

14.10.7 Duchenne muscular dystrophy

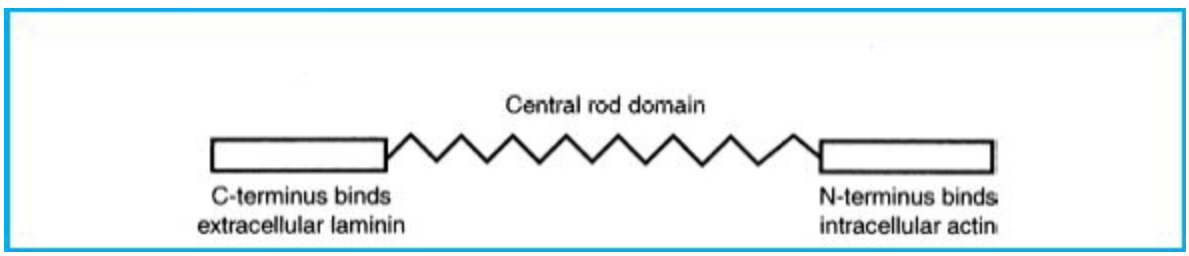
This is a genetic disease that is X-linked; it has the highest new mutation rate of any X-linked gene. It is caused by mutations in a protein called dystrophin, which is part of a large complex of membrane-associated proteins, defects in most of which can cause forms of muscular dystrophy.

Dystrophin is a very large protein indeed (>400 kDa) which is attached at its C-terminus to laminin on the inner aspect of the muscle membrane and at its N-terminus to actin, thus providing a connection between the extracellular matrix and the muscle cytoskeleton (Figure 14.20). Therefore, its role is probably structural.

The most common mutations are large deletions, which can be either of the following:

- **In frame**, in which the C-terminus and N-terminus of the molecule are preserved and a truncated form of dystrophin, missing some of the rod domain, is produced, leading to Becker dystrophy, a milder form of the disease compatible with a normal lifespan and prolonged ambulation
- **Out of frame**, which results in total abolition of dystrophin production because one or both of the binding sites for actin or laminin is disrupted. This is the abnormality which leads to typical Duchenne muscular dystrophy.

Figure 14.20 Dystrophin is an extremely large protein that links the cytoskeleton (actin) to the extracellular matrix of muscle



The very occasional finding of affected females can be due to the following:

- **Lyonisation**: X-chromosome inactivation occurring non-randomly and leading to preferential inactivation of the normal chromosome
- Very rarely, **X-autosome translocation**: the presence of a fragment of an autosome in the region where dystrophin is normally found leads to the preferential activation of this chromosome and inactivation of the normal chromosome.

The clinical features of Duchenne muscular dystrophy are described in Chapter 16, Neurology.

14.10.8 Sickle cell disease

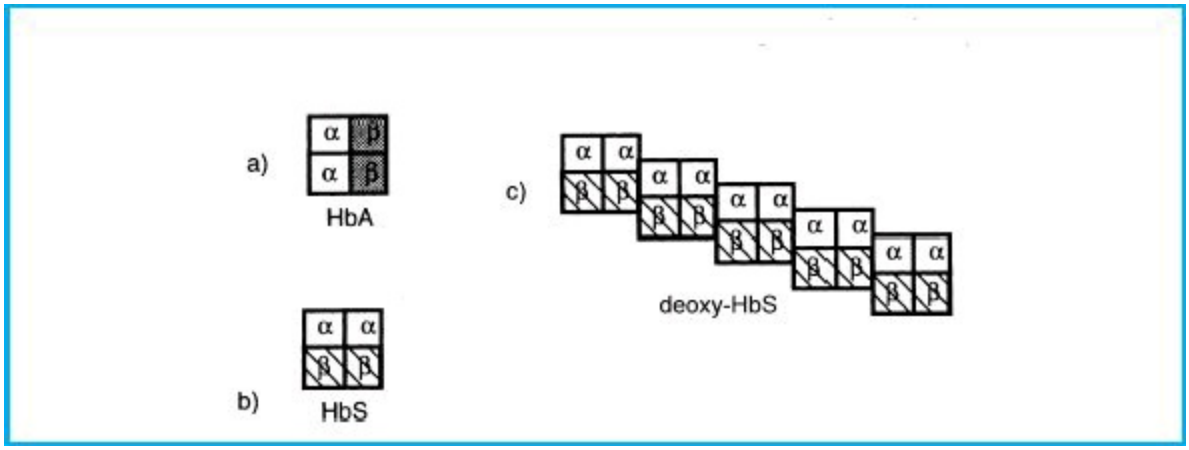
It has been known for five decades that haemoglobin from patients with this disease undergoes abnormal electrophoretic mobility. The basis for this is the presence, in all patients with the disease, of a single amino-acid substitution of valine for glutamic acid in the haemoglobin (HbS) β-globin subunit. Haemoglobin has to be highly soluble to pack into red cells at high concentrations and the sickle mutation leads to polymerisation of HbS and consequent loss of solubility.

The reason that polymerisation takes place is that, in its deoxygenated form, the HbS β-globin subunit can bind to a partner subunit on another strand, leading to the formation of large polymers (Figure 14.21), which deform the red cell by damaging the membrane and interfering with ion flux. The polymerisation process is a dynamic event under the influence of the oxygenation state of the cell and the intracellular concentration of haemoglobin, which accounts in part for the variable clinical manifestations of the disease.

- The unpredictable nature of the vaso-occlusive events observed in patients has been explained because the SS red cells have a greater propensity for attachment to vascular endothelium. The degree of stickiness to endothelium is determined primarily by the rapidity of polymer formation, which in turn is dependent on the rapidity of deoxygenation
- The binding of sickle red cells to endothelium appears to be mediated by the interaction between integrins on the cell membrane and adhesion molecules expressed on the vascular endothelial surface
- The presence of proinflammatory cytokines such as TNF stimulates this process, which explains why infection of any kind can provoke a sickle crisis
- One factor that has been shown to modify the rate of polymer formation is the presence of fetal haemoglobin (HbF), which slows the rate of polymer formation
- Certain ethnic subpopulations have higher amounts of HbF persisting in the circulation and milder SS disease

  This suggests that pharmacological upregulation of HbF could ameliorate the disease.
- Hydroxyurea has been shown to increase the amount of HbF and is now widely used in the prevention of sickle crises. The risk of tumours from this cytotoxic drug appears to be small and any myelosuppression is reversible.

Figure 14.21 Sickle cell disease: in sickle cell disease HbS undergoes abnormal polymerisation when deoxygenated



The clinical features of sickle cell disease are discussed in Chapter 9, Haematology.

14.11 GLOSSARY OF TERMS IN MOLECULAR MEDICINE

Allele	One of several different forms of a gene occupying a given genetic locus
Annealing	The pairing of complementary strands of DNA to form a double helix
Apoptosis	The morphological changes accompanying the process of programmed cell death
Autocrine	Secretion of substances by cells that then act on the cells themselves rather than on a distant target
cDNA	A single-stranded DNA complementary to an RNA, synthesised from it by the enzyme reverse transcriptase in vitro
Cell cycle	The period from one cell division to the next
Cytokines	Act locally and their effect can be positive or negative depending on the environment, other cytokines, the physiological state of the cell and the extracellular matrix. This variable response of cytokines underlies the ability of the organism to maintain a wide repertoire of responses to tissue injury
DNA polymerase	An enzyme that synthesises a daughter strand of DNA on a DNA template
ELISA	Enzyme-linked immunosorbent assay, a method of quantifying circulating proteins
Exon	Any segment of an interrupted gene that is represented in the mature RNA product
FISH	Fluorescent in situ hybridisation, a method of characterising gross chromosomal abnormalities
Gene family	Consists of a set of genes the exons of which are related; the members were derived from a common ancestral gene by duplication and subsequent variation
Gene targeting	The creation of animals (usually mice) that are null mutants for a particular gene, ie the gene has been ‘knocked out’ and the ‘knockout’ mouse contains no copy of the gene at all

G-protein	Heterotrimeric membrane protein that is activated by the exchange of GDP for GTP and dissociates on activation into α and βγ subunits. It has intrinsic GTPase activity which mediates its inactivation
Growth factor	A hormone that induces cell division and differentiation
Heterozygote	An individual with different alleles on each chromosome at a given locus
Housekeeping genes	Constitutively expressed genes in all cells because they provide basic functions needed for survival of all cell types
Hybridoma	A cell line produced by fusing a myeloma with a lymphocyte; it can indefinitely express the immunoglobulin of both cells, unless the myeloma has been selected to be deficient in Ig expression
Introns	Sequences of DNA that are transcribed but removed from nascent mRNA by splicing
Isoform	One of a number of different forms of a protein that may be derived from one gene by splicing, or from separate closely related members of a gene family
Oligonucleotide	A short sequence of (synthetic) DNA, typically 18–22 base pairs in length, which acts as a primer for PCR reactions or a molecular probe when detecting gene sequences
Oncogene	A gene the protein product (the oncoprotein) of which has the ability to transform eukaryotic cells so that they grow in a manner analogous to tumour cells
Paracrine	Secretion by one cell of substances that act on adjacent cells
Programmed cell death	The process whereby unwanted cells die under the control of a genetic programme
Promoter	A region of DNA involved in the binding of RNA polymerase to initiate transcription
Protein kinase	An enzyme that phosphorylates (adds a phosphate group) to a substrate (an amino acid in another protein)
Protein phosphatase	An enzyme that removes phosphate groups from substrates
Proto-oncogene	The normal counterpart in eukaryotic genomes of retroviral genes which can transform cells
Response elements	Specific nucleotide recognition sequences in the 59 regulatory regions of genes that recognise transcription factors which have been activated by upstream signals such as steroid hormones
Somatic cells	All the cells of an organism except the germ cells
Transcription factor	A protein that binds to the promoter region of a gene to influence its transcription
Tumour-suppressor gene	A gene that, when activated, will produce a protein that inhibits cell division. Mutations of these genes therefore lead to loss of control of cell division and contribute to tumorigenesis
UTR	Untranslated region

Chapter 15
Nephrology

CONTENTS

Nephrology

15.1 RENAL PHYSIOLOGY

The chief functions of the kidneys are:

- Excretion of water-soluble waste
- Maintenance of electrolyte balance
- Maintenance of water balance
- Acid–base homoeostasis
- Endocrine: renin–angiotensin–aldosterone system, erythropoietin secretion, vitamin D metabolism.

15.1.1 Glomerular filtration rate

Glomerular filtration is a passive process which depends on the net hydrostatic pressure acting across the glomerular capillaries, countered by the oncotic pressure; it is also influenced by the intrinsic permeability of the glomerulus (K_f); the latter may vary due to mesangial cell contraction, such as in response to angiotensin II. The mean values for the glomerular filtration rate (GFR) in normal young adults are 130 mL/min per 1.73 m^2 (men) and 120 mL/min per 1.73 m^2 (women), the 1.73 m^2 being mean body surface area of young adults. However, variation between individuals is large and accepted ranges of GFR at this age are 70–140 mL/ min per 1.73 m^2. In health, GFR remains stable until around 40 years of age, but thereafter declines at a rate of approximately 0.5–1 mL/min per year; by the age of 80 years the mean GFR is approximately 50% of that of a young adult.

- GFR increases by 50% during pregnancy due to plasma volume expansion (see Chapter 12, Maternal medicine)
- GFR has a diurnal rhythm, values being 10% greater in the afternoon than at midnight. This may be partly related to protein intake (which increases GFR)
- GFR falls transiently during exercise
- In patients with reduced renal reserve, GFR will be lower in the fasting than the fully hydrated state (relevant in the context of blood sampling).

There are several techniques for estimating GFR:

- **Plasma creatinine**: creatinine is produced from muscle cells at a constant rate, and so its plasma concentration at steady state depends on its excretion, which reflects GFR. However, plasma creatinine is an insensitive marker of early renal disease:

- When considering plasma creatinine values, the patient's age, sex and weight should be taken into account – elderly and malnourished patients may have low GFR but plasma creatinine close to the normal range
- Estimated GFR (eGFR) is routinely reported by all laboratories; it is calculated from the four-variable MDRD (Modification of Diet in Renal Disease) equation (which includes age and sex).

Creatinine clearance: calculated from a 24-hour urine collection with a consecutive blood sample – this is now rarely used. This tends to overestimate GFR, because creatinine is not just filtered but also secreted into the tubule from the post-glomerular circulation; the error increases with declining renal function. Note that certain drugs (eg trimethoprim and cimetidine) compete for this secretion mechanism, and so will increase plasma creatinine

- **Cockcroft and Gault formula**: this also assesses eGFR (based on creatinine clearance) and requires knowledge of the patient's age, weight and plasma creatinine:

$$\text{GFR (mL/min)} = \frac{(140 - \text{Age in years}) \times \text{Weight (kg)}}{\text{Plasma creatinine } (\mu\text{mol/L})} \times 1.23 \text{ (men) or } 1.04 \text{ (women)}$$

- This formula overestimates creatinine clearance in obese patients and in those patients adhering to a strict low-protein diet (in both these groups the endogenous creatinine production will be less than that predicted by overall body weight). A correction can be undertaken for body surface area.

The most accurate laboratory techniques for assessing GFR are:

- **Inulin clearance**: inulin is a small molecule, freely filtered by the glomerulus, with no tubular secretion
- **Chromium-labelled EDTA**: the most frequently used isotopic technique
- **Iohexol**: an iodine-based, non-ionic, water-soluble contrast agent which, similar to inulin, is freely filtered, and not secreted or absorbed by renal tubules.

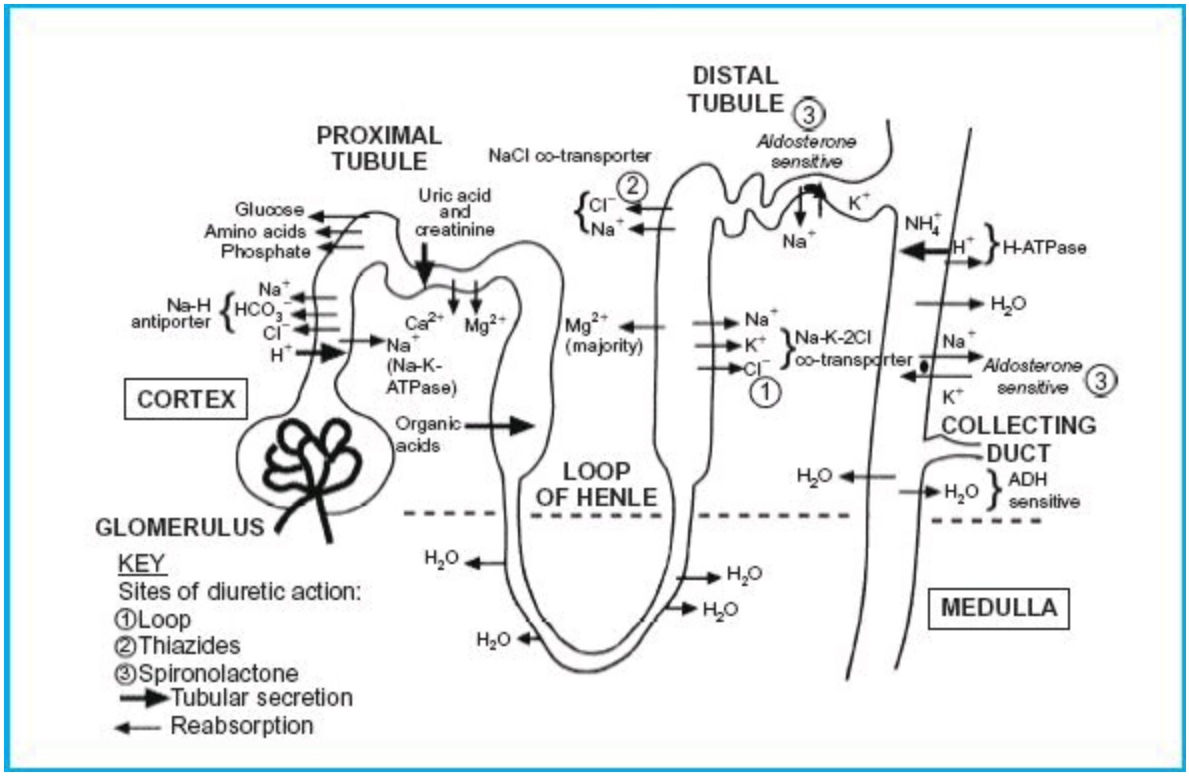
15.1.2 Tubular physiology

The renal tubule has many reabsorptive and secretory functions (Figure 15.1); these are energy consuming and hence, tubular cells are those most vulnerable to ischaemic damage (the acute tubular necrosis [ATN] of ischaemic acute kidney injury [AKI]).

Proximal tubule

Fifty per cent of filtered sodium is reabsorbed within the proximal tubule (via Na^+/K^+ ATPase); the Na^+/ H^+ antiporter secretes H^+ into the lumen and is responsible for 90% of bicarbonate and some chloride reabsorption. All of the filtered glucose and amino acids are reabsorbed here. Other important characteristics are as follows:

Figure 15.1 Schema of a nephron showing tubular physiology



- Phosphate reabsorption is modulated by parathyroid hormone (PTH), vitamin D and fibroblast growth factor-23 (FGF-23)
- Some important drugs are secreted into the tubular filtrate here: trimethoprim, cimetidine and most diuretics (note that thiazides, amiloride and loop diuretics are highly protein bound and are not filtered at the glomerulus)
- Creatinine and urate are secreted into the lumen.

Loop of Henle

The medullary thick, ascending limb is impermeable to water, and the medullary concentration gradient is generated here (allowing concentration of the urine). 40% of sodium is reabsorbed (via the $Na^+/K^+/2Cl^-$ co-transporter). Loop diuretics compete for chloride-binding sites on this transporter.

Distal tubule

In this segment of the nephron, 5% of sodium is reabsorbed (Na^+/Cl^- co-transporter); thiazide diuretics compete for these chloride-binding sites. As loop diuretics increase sodium delivery to the distal tubule, their combination with a thiazide (eg metolazone) can provoke a massive diuresis in resistant oedema. There are aldosterone receptors in both the distal and collecting tubules (see below).

Collecting duct

Aldosterone-sensitive sodium channels are responsible for 2% of all sodium reabsorption; spironolactone binds to the cytoplasmic aldosterone receptor. Atrial natriuretic peptide (ANP) is anti-aldosterone in action (and hence is increased in renal failure and in patients with congestive cardiac failure [CCF], in whom it is thought counteract secondary hyperaldosteronism). Other important collecting duct functions are as follows:

- H^+ is secreted into the lumen, so acidifying the urine by forming ammonia/NH_4^+
- Antidiuretic hormone (ADH, or vasopressin) increases water reabsorption by opening 'water channels'. Receptors on the basolateral membrane (non-luminal) of the collecting duct cell are stimulated by ADH, leading to insertion of **aquaporins** into the luminal membrane. The aquaporins then allow water uptake by the cell
- Lithium enters the collecting duct cells via the sodium channels and inhibits the response to ADH (hence, nephrogenic diabetes insipidus [NDI] can result).

15.1.3 Renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone (RAA) system is very important in normal health, helping to control blood pressure, sodium balance and circulating volume (see also Chapter 4, Endocrinology). However, it has a central role in the pathogenesis of secondary renal hypertension, and also in propagating progressive chronic kidney disease (CKD) (see Section 15.1.1). Remember that intrarenal perfusion will become critically dependent on the RAA system when hypovolaemia and hypotension supervene; this explains why patients can be vulnerable to AKI induced by agents blocking the RAA system (ie angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs] and renin inhibitors), even in the absence of renovascular disease.

- The RAA system is of key importance in the pathogenesis of progressive renal disease, irrespective of the primary disease aetiology
- Agents that block the RAA system are therefore now considered to be essential therapy in patients with a variety of chronic nephropathies.

15.2 RENAL INVESTIGATION

15.2.1 Urinalysis

Urinary dipstick

Standard dipsticks assess the presence of protein, blood and glucose. 'Multi-stix' will also assess pH (normally 5–6; pH >8 may suggest renal tubular acidosis), leukocytes (most commonly raised because of vaginal contamination of urine or urinary tract infection) and nitrite (broken down from nitrates by some bacteria, hence an indicator of infection):

- The sticks register positive for 'blood' in the presence of erythrocytes, as well as free myoglobin (eg in rhabdomyolysis) and haemoglobin
- Standard dipsticks do not detect Bence Jones proteins and so, if free urinary light chains are to be identified, immunoelectrophoresis of urine is necessary
- Microalbuminuria will usually not be detected with standard dipsticks.

Proteinuria

Normal urinary protein excretion is <150 mg/day, which should consist of <20 mg albumin, tubular-secreted proteins (40–60 mg), such as the Tamm–Horsfall or tubular glycoprotein and

immunoglobulin, and various filtered low-molecular-weight proteins.

- **Microalbuminuria**, which is the hallmark of early diabetic nephropathy, but is also prognostically important for cardiovascular disease and mortality risk when present in hypertensive patients, is defined as albumin excretion of 30–250 mg/day
- Proteinuria should be quantified by either **urinary albumin:creatinine ratio (uACR)** or **protein:creatinine ratio (uPCR)**. The uACR is routinely used in the screening of patients with diabetes. As average individuals pass around 10 mmol urinary creatinine each day:
  - A uPCR or ACR of 100 mg/mmol = 1000 mg protein or albumin/day (approximately)
  - A uACR of 5 mg/mmol = 50 mg albumin/ day = microalbuminuria (note that in this instance uPCR would be 'normal' and urine dipstick testing negative).

Significant non-nephrotic proteinuria (eg dipstick + to +++, 0.2–3.5 g/24 h) is usually indicative of renal parenchymal disease (unless due to urinary tract infection). **Nephrotic** range proteinuria (>3.5 g/ 24 h, dipstick ++++) is virtually always due to glomerular disease.

Non-renal causes of proteinuria:

- Fever
- Severe exercise
- Skin disease (eg severe exfoliation, psoriasis)
- Lower urinary tract infection (eg cystitis).

Orthostatic proteinuria

This describes proteinuria detectable after the patient has spent several hours in the upright posture; it disappears after recumbency, and so the first morning urine should test negative. Proteinuria is usually <1 g/24 h; there is no haematuria, and renal function and blood pressure are normal. Renal biopsy samples are usually normal and nephrological consensus suggests that this is a benign condition.

Urine microscopy

Microscopic examination of a fresh specimen of urine may yield many helpful pointers to intrinsic renal pathology:

- **Red cells**: >2–3/high power field is pathological (microscopic haematuria, now termed 'non-visible haematuria'); cells are usually dysmorphic in glomerular bleeding, but appear normal when derived from the lower urinary tract
- **Leukocytes**: infection, and some cases of glomerular and interstitial nephritis
- **Crystals**, eg oxalate, struvite (see Section 15.10.1), cystine and, with polarised light, uric acid
  - **Casts**: there are several types of cast:
  - *Tubular cells* – ATN or interstitial nephritis
  - *Hyaline* – Tamm–Horsfall glycoprotein (seen in normal individuals)
  - *Granular* – non-specific
  - *Red cell* – glomerulonephritis or tubular bleeding
  - *Leukocytes* – pyelonephritis or ATN.

Causes of urinary discoloration

- Haematuria
- Myoglobinuria (brown)
- Beetroot consumption
- Alkaptonuria (urine brown on exposure to the air)
- Obstructive jaundice (yellow)
- Haemoglobinuria
- Drugs (eg rifampicin, *p*-aminosalicylic acid)
- Porphyria (urine dark brown or red on standing)

15.2.2 Renal radiology

The essential first-line radiological investigation for AKI, CKD and most other nephrological conditions is **renal ultrasonography**, which will demonstrate the following:

- **Bipolar renal length**: in most cases of **CKD**, the kidneys are small (<8 cm) – the exceptions are polycystic kidney disease (very large, eg >16 cm with multiple cysts), and sometimes in diabetic renal disease and amyloid (normal size). In **AKI** the kidneys are usually normal size (8.5–13.5 cm), but slight enlargement is common due to swelling. Asymmetry (>1.5 cm disparity between kidneys) is seen in unilateral renal artery stenosis (RAS), but also in chronic pyelonephritis and other causes of renal atrophy
- **Obstruction**
- **Cortical scarring**: eg in reflux nephropathy or after segmental ischaemic damage
- **Calculi**: within the substance of the kidney and collecting systems
- **Mass lesions and cysts**, eg renal tumour, polycystic disease or simple renal cysts.

Doppler ultrasonography is useful to assess renal blood flow and to measure the resistive index within the kidney; specific patterns are observed in, for example, RAS (high peak arterial velocity) and acute rejection in transplant recipients (high resistive index).

CT urography has now replaced intravenous urography (IVU) for investigation of urinary tract bleeding (eg to detect urothelial tumours of the renal pelvis, ureters and bladder), urinary tract infection (UTI) and for some cases of obstructive uropathy.

Isotope renography

Two major types of renograms are commonly utilised:

1. **Static scans (eg DMSA)**: the isotope is concentrated and retained within the renal parenchyma, and elimination is slow. DMSA will therefore demonstrate aspects of structure (eg scars in reflux nephropathy) and split function of the two kidneys

   Dynamic scans (eg MAG_3, DTPA, Hippuran): these isotopes are rapidly taken up and

2. eliminated by the kidneys; such scans are used to assess renal blood flow and split function, and also to investigate obstruction (eg a diuresis renogram includes a dose of furosemide and shows whether urinary tract dilatation is due to obstruction).

Renal angiography

The most frequently used techniques are:

- **MR angiography (MRA)**: non-invasive and used in screening for RAS. Gadolinium (Gd) is used as the 'contrast' agent. MR scanning with Gd (Gd-MR) can occasionally lead to a serious condition, **nephrogenic systemic fibrosis (NSF)**, which has some similarities to scleroderma and can be fatal. The patients at greatest risk are those with stage 5 CKD receiving dialysis, or patients who have AKI; the nature of the Gd preparation (greater risk with linear structure, eg Magnevist and Omniscan) and use of multiple doses are additional risk factors. Current guidance recommends that Gd-MR should be used only with caution in patients with eGFR <30 mL/min
- **CT angiography (CTA)**: non-invasive and readily available, but risk of contrast nephropathy in AKI, CKD, people with diabetes, etc
- **Intra-arterial angiography**: provides excellent detail of intrarenal vasculature; invasive and risk of contrast nephropathy.

Renal tract CT and MR

These imaging modalities are commonly used in nephrourology in the investigation of many conditions including:

- Delineation of cause of obstruction
- Assessment of renal tract tumours, including staging
- Assessment of renal cyst structure.

15.3 ACID–BASE, WATER AND ELECTROLYTE DISORDERS

15.3.1 Acidosis and alkalosis

Respiratory acidosis (eg carbon dioxide retention due to chronic or acute-on-chronic lung disease) and **alkalosis** (eg due to hyperventilation) are common, and well understood by all.

Metabolic alkalosis and **metabolic acidosis** are covered in detail in Chapter 13, Metabolic diseases. The width of the anion gap can help differentiate the likely causes of a metabolic acidosis; the HCO_3^- will be low, and the anion gap can be either wide (normal chloride and exogenous acid) or normal (increased chloride and, hence, hyperchloraemic acidosis). Renal failure is associated with a wide gap acidosis (due to excess ammonia and organic acids), whereas **renal tubular acidosis** (RTA) is worth consideration as a cause of a normal gap acidosis.

15.3.2 Renal tubular acidosis

Distal or **type 1** RTA is fairly common, and can complicate many renal parenchymal disorders, particularly those that predominantly affect the medullary regions. Note that the latter may also be associated with nephrogenic diabetes insipidus, and sometimes with salt-wasting states. **Proximal** or **type 2** RTA is uncommon. GFR is often normal in both conditions.

Nephrocalcinosis and renal calculi formation: urinary calcium excretion is increased in severe acidosis, and calcium salts are more insoluble in alkaline urine, and hence calculi develop frequently in distal but not in proximal RTA (which is usually associated with a lower urinary pH and less severe acidosis).

The two types of RTA can be differentiated by several parameters (Table 15.1), the hallmark associations being severe acidosis, hypokalaemia and renal calculi/nephrocalcinosis in **distal RTA**, and proximal tubular dysfunction, osteomalacia/rickets and less severe acidosis in **proximal RTA**.

Treatment of RTA: this usually consists of oral potassium and bicarbonate replacement therapy. Close monitoring is needed to prevent major imbalances in electrolyte concentrations, especially during intercurrent illness.

Table 15.1 Differentiation between type 1 and type 2 renal tubular acidosis

	Type 1 (distal)	**Type 2 (proximal)**
Defect	Impaired urinary (H^+) acidification	Failure of HCO_3^- reabsorption
Urine pH	> 5.3 (ie urine never 'acidifies')	Variable
Plasma HCO_3^- (mmol/L)	<10	14–20
Plasma K^+	Usually ↓	Normal or ↓
Complications	Nephrocalcinosis	Osteomalacia (phosphate wasting)
	Calculi	Rickets
Other features	Growth failure Urine infection	Fanconi syndrome (ie phosphaturia, glycosuria, aminoaciduria)

Causes of distal RTA

- **Primary**: genetic (dominant) or idiopathic
- **Secondary to autoimmune diseases**: systemic lupus erythematosus (SLE), Sjögren syndrome, chronic active hepatitis
- **Tubulointerstitial disease**: chronic pyelonephritis, transplant rejection, obstructive uropathy, chronic interstitial nephritis
- **Nephrocalcinosis**: medullary sponge kidney, hypercalcaemia

- **Drugs and toxins**: lithium, amphotericin, toluene

Causes of proximal RTA

- **Occurring alone**: idiopathic
- **With Fanconi syndrome**: Wilson's disease, cystinosis, fructose intolerance, Sjögren syndrome
- **Tubulointerstitial disease**: interstitial nephritis, myeloma, amyloidosis
- **Drugs and toxins**: outdated tetracyclines, streptozotocin, lead and mercury (and other heavy metals), acetazolamide, sulfonamides

Type 4 RTA

This describes a metabolic acidosis that is associated with hyperkalaemia and CKD (eGFR usually >30 mL/min). It is commonly due to **mineralocorticoid deficiency**:

- **Low renin, low aldosterone** (hyporeninaemic hypoaldosteronism): diabetes mellitus and drugs (non-steroidal anti-inflammatory drugs [NSAIDs] and ciclosporin)
- **High renin, low aldosterone**: adrenal destruction, congenital enzyme defects and drugs (ACE inhibitors and ARBs).

Abnormal collecting duct function (eg due to absent/defective mineralocorticoid receptor, chronic tubulointerstitial disease or drugs such as spironolactone or amiloride) is responsible for other cases.

15.3.3 Polyuria

Polyuria (urine output >3 L/day) may result from:

- Diuretic usage
- Large fluid intake
- Alcohol: inhibits ADH release and alcohol is an osmotic diuretic
- Cranial diabetes insipidus: osmolality high
- Nephrogenic diabetes insipidus: osmolality high; note that polyuria (often manifests as nocturia) is often the first symptom of CKD
- Psychogenic polydipsia: osmolality low
- Atrial natriuretic peptide release: post-arrhythmia, cardiac failure.

The causes of **cranial** and **nephrogenic diabetes insipidus** are listed in Chapter 4, Endocrinology; **hyponatraemia** as well as other disorders of water balance, including the syndrome of inappropriate ADH secretion (**SIADH**), are also discussed in that chapter.

15.3.4 Hypokalaemia

Acute hypokalaemia can lead to muscle weakness and direct renal tubular cell injury. Chronic hypokalaemia is a cause of interstitial nephritis. The causes can be classified according to the

presence or **absence** of **hypertension** with reference also to the **plasma renin activity** and **urinary potassium excretion** (25–100 mmol/day in normal health).

Causes of hypokalaemia

With hypertension (potassium excretion usually <30 mmol/day)

High plasma renin activity:

- Renovascular disease
- Accelerated-phase hypertension
- Cushing syndrome
- Renin-secreting tumour

Low plasma renin activity:

- Primary hyperaldosteronism (including Conn syndrome)
- Carbenoxolone*
- Liquorice excess*
- 11-β hydroxysteroid dehydrogenase deficiency* ('apparent mineralocorticoid excess')
- Liddle syndrome (see text)
- Glucocorticoid-suppressible hyperaldosteronism (GSH)**

Without hypertension (usually high plasma renin activity)

High plasma renin activity:

- Diuretic usage (urinary potassium excretion may be high or low)
- Gastrointestinal tract losses (potassium excretion <30 mmol/day)
- Salt-wasting CKD (high sodium and potassium excretion)
- Bartter syndrome (high potassium excretion – see text)
- Gitelman syndrome (see text)
- Secondary hyperaldosteronism (eg cardiac or hepatic failure – increased potassium excretion)

*11-β hydroxysteroid dehydrogenase metabolises cortisol and prevents it from binding to the mineralocorticoid receptor. Acquired or congenital conditions in which this enzyme is inhibited have a Conn syndrome phenotype (including patients taking liquorice in excess, and carbenoxolone). Patients may have acidosis rather than alkalosis.

**GSH is rare and is due to a gene fusion which makes the hyperaldosteronism completely ACTH sensitive. The clue to diagnosis is a strong family history (autosomal dominant). Treatment is with glucocorticoids which lower the blood pressure.

Bartter syndrome

Severe hypokalaemia is consequent on a salt-wasting state (increased sodium delivery to the distal tubule) that is due to defective chloride reabsorption (at the $Na^+/K^+/2Cl^-$ co-transporter) in the loop of Henle; inheritance is usually autosomal recessive. Patients have normal or low blood pressure and severe hyperreninaemia (with hypertrophy of the juxtaglomerular apparatus) with consequent hyperaldosteronism; GFR is usually normal. Treatment is with large-dose potassium replacement;

NSAIDs may also be beneficial.

Liddle syndrome

This is an autosomal dominant syndrome of hypertension and variable degrees of hypokalaemic metabolic alkalosis. The patient appears to have primary hyperaldosteronism, but renin and aldosterone are suppressed and there is no response to spironolactone. The pathogenesis is associated with enhanced reabsorption of sodium in the distal nephron (amiloride-sensitive sodium channel). Treatment consists of salt restriction, potassium supplements and use of either amiloride or triamterene.

Gitelman syndrome

This condition can be either autosomal recessive or autosomal dominant, and is characterised by hypokalaemic metabolic alkalosis and also with hypocalciuria and hypomagnesaemia. Patients present at a later age than those with classic Bartter syndrome and, similar to the latter, the blood pressure is low or normal and patients have hyperreninaemic hyperaldosteronism. The metabolic abnormalities may lead to muscular weakness and tetany. Treatment is with magnesium and potassium supplements.

15.4. ACUTE KIDNEY INJURY

15.4.1 Pathogenesis and management of acute kidney injury

Reducing AKI and improving its management are now major targets within the NHS. Acute deterioration of renal function is seen in up to 5% of all hospital admissions. Oliguria is usual, and is defined as a daily urine output of <400–500 mL; this is the minimum volume to enable excretion of the daily waste products of metabolism.

Non-oliguric AKI accounts for about 10% of cases; this may be associated with drug toxicity (eg gentamicin or amphotericin), radiocontrast nephropathy and acute interstitial nephritis.

The majority (65%) of cases of AKI result from renal hypoperfusion and ischaemic damage, sepsis or systemic inflammation. With ischaemic damage, the renal histopathological lesion is **acute tubular necrosis** (**ATN**). However, when AKI is due to sepsis or inflammation, the kidney may be histologically normal, reflecting the pathophysiology with cytokine-mediated vasoconstriction and cellular dysfunction prominent.

Some patients have milder ischaemic insults to the kidneys, with an initial period of oliguria, but renal perfusion can then be restored by vigorous haemodynamic management before severe tubular injury ensues; this is termed ‘prerenal uraemia’. In the latter, physiological mechanisms (ie stimulation of the RAA system) are preserved within the kidney, and so the urinary manifestations of sodium and water reabsorption allow differentiation from established ATN (Table 15.2). In practice, the clinical response to fluid resuscitation provides the best means of confirming prerenal uraemia because these patients will usually start diuresing, whereas those with ATN (or sepsis or systemic inflammation) will remain oliguric. A large number of patients with ischaemic can be managed without the need for dialysis.

Table 15.2 Urinary findings in classic acute tubular necrosis (ATN) and prerenal uraemia

Urinary findings	ATN	Prerenal uraemia
Urine sodium (mmol/L)	>40	<20
Urine:plasma osmolality	<1.1:1	>1.5:1
Fractional sodium excretion (FeNa)[a] (%)	>1	<<1
Urine:plasma urea	<7:1	>10:1
Urine volume (L)	Oligoanuric or polyuria (recovery phase)	<1.5

[a]FeNa is the percentage of sodium that is filtered at the glomerulus (normally 1000 mmol/h), which actually appears in the urine (normal <6 mmol/h, ie <0.6%).

Many AKI patients with pre-existing CKD present with acute deterioration of renal function (**acute-on-chronic kidney disease**) and require similarly intensive support and clinical management.

The causes of AKI, with approximate relative frequency, are summarised below (excluding 'acuteon-chronic' cases).

Classification of AKI severity

There are several classification systems available, including RIFLE (**r**isk, **i**njury, **f**ailure, **l**oss, **e**nd-stage kidney disease), but the UK Renal Association recommends use of the international Kidney Disease: Improving Global Outcomes (KDIGO) staging classification (Table 15.3).

Table 15.3 KDIGO classification of severity of acute kidney injury

Stage	Serum creatinine (SCr) criteria	Urine output criteria
1	Increase ≥26 μmol/L within 48 h or Increase ≥1.5–1.9 × reference SCr	<0.5 mL/kg per h for >6 consecutive h
2	Increase ≥ 2.0–2.9 × reference SCr	<0.5 mL/kg per h for >12 h
3	Increase ≥ 3 × reference SCr or Increase ≥ 354 μmol/L or Started on renal replacement therapy irrespective of stage	< 0.3 mL/kg per h for >24 h or Anuria for 12 h

Causes of AKI

- **Disorders of renal perfusion** (65%):
  - Reduced circulating volume: blood loss; excess gastrointestinal (GI) losses; burns
  - Low cardiac output states: toxic or ischaemic myocardial depression

- Systemic sepsis
- Systemic inflammation
- Drugs inducing renal perfusion shutdown, eg ACE inhibitors, NSAIDs

- **Toxic ATN** (5%):
  - Rhabdomyolysis with urinary myoglobin
  - Drugs, eg gentamicin, amphotericin
  - Radiocontrast nephropathy
- **Structural abnormalities of renal vasculature** (<5%):
  - Large-vessel occlusion (renovascular disease)
  - Small-vessel occlusion: accelerated-phase hypertension, disseminated intravascular coagulation, haemolytic–uraemic syndrome, thrombotic thrombocytopenic purpura, preeclampsia, systemic sclerosis
  - Acute cortical necrosis
- **Acute glomerulonephritis** (15%):
  - Idiopathic crescentic glomerulonephritis
  - ANCA-positive vasculitis (ANCA is anti-neutrophil cytoplasmic antibody)
  - Goodpasture syndrome
  - Other proliferative glomerulonephritis (eg SLE, endocarditis, Henoch–Schönlein nephritis)
- **Interstitial nephritis** (<5%):
  - Idiopathic, immunologically mediated
  - Drug-induced hypersensitivity
  - Infection (eg pyelonephritis, leptospirosis, Hanta virus)
- **Myeloma/tubular cast nephropathy** (<5%)
- **Urinary tract obstruction** (10%)

Pathophysiology of AKI due to ischaemia, sepsis or inflammation

After an ischaemic insult there is intense afferent arteriolar vasoconstriction, mediated by the release of vasoconstrictors (particularly endothelin) and by loss of intrinsic vasodilators (nitric oxide and prostaglandin I_2 [PGI_2]); this contributes to the loss of GFR and the redistribution of blood flow within the kidney. Hypoxic injury to the energy-consuming cells of the proximal tubule and thick ascending limb of Henle occurs; calcium and oxygen free radical-mediated cell necrosis results in cell shedding from the tubular basement membrane, with the formation of casts that block urine flow. With sepsis and systemic inflammation there is believed to be cytokine (eg interleukin-6 [IL-6])-mediated intrarenal vasoconstriction and cellular dysfunction, but ATN is not a feature.

Investigation of AKI

The history may point to the cause of AKI (eg drugs, skin rash); assessment of the haemodynamic status is imperative and appropriate fluid resuscitation should be given.

Urinary examination: ATN and prerenal uraemia can sometimes be differentiated by urinary

- biochemistry (see Table 15.2); non-visible haematuria and red cell casts will point to acute glomerulonephritis as the cause
- A **renal ultrasound** scan will usually show normal-sized kidneys, and will identify obstruction (the latter should be urgently treated to reduce irreversible renal injury)
- **Autoantibody profile**: antinuclear factor (ANF), ANCA, anti-glomerular basement membrane (GBM), complement, and plasma and urinary electrophoresis should all be routinely performed (unless the cause of AKI is obvious, eg post-myocardial infarction or renal obstruction)
- **Percutaneous renal biopsy** is essential if an intrinsic lesion (eg vasculitis, other acute glomerulonephritis, interstitial nephritis) is suspected, or if no ischaemic, septic or systemic inflammatory cause is apparent, especially if there is no sign of improvement in renal function and/or if the oliguric phase is delayed.

Prevention of AKI

A National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report[(1)] in 2009 (*Adding Insult to Injury*) highlighted the late recognition and poor management of AKI within the UK, and that this was contributing to unnecessary mortality. As a consequence, education about AKI for all clinicians involved in the management of acutely sick patients is given high priority. Early recognition, monitoring and treatment (especially careful fluid balance, early treatment of sepsis and avoidance of potentially nephrotoxic drugs) of vulnerable patients can prevent many cases of AKI, and this should be the expected standard of care.

Management of AKI

For the patient with established AKI, the mainstay of treatment involves optimisation of fluid balance and avoidance of either hypovolaemia or fluid overload. Patients with single-organ AKI are best managed in a high-dependency unit (HDU) setting. Blood pressure should be controlled, haemoglobin maintained at or above 9 g/dL, and sepsis should be promptly and vigorously treated. 'Renal dose' dopamine has no place in clinical management. Some cases can be managed without renal replacement therapy (RRT), with the adoption of careful fluid balance, dietary control and use of loop diuretics for modest fluid overload; however, there is no evidence that diuretics alter the outcome of AKI. Many patients have AKI as part of a multi-organ dysfunction (MOD) and they can be managed only on an intensive care unit (ICU).

The key to AKI management is attention to intensive nutritional support of the sicker patients, and the use of continuous RRT (eg CVVH – continuous venovenous haemofiltration), which is less likely to provoke haemodynamic instability.

Other more specific treatments in AKI depend on the causative condition and include the following:

- Specific **immunosuppressive therapy**, and sometimes plasma exchange, may be appropriate for some conditions (eg Goodpasture syndrome, ANCA-positive vasculitis)
- **Obstruction**: bladder catheterisation for bladder outflow obstruction; nephrostomy drainage for renal obstruction
- **Other**, eg steroids in acute interstitial nephritis (AIN), plasma exchange in haemolytic–uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), chemotherapy in myeloma.

Indications for urgent RRT in AKI

- **Severe uraemia**: vomiting, encephalopathy, urea >60 mmol/L
- **Hyperkalaemia**: K^+ >6.5 mmol/L (or less, if ECG changes apparent)
- **Severe acidosis**: pH <7.1
- **Uraemic pericarditis**
- **Pulmonary oedema**

Prognosis of AKI

The overall survival for patients with AKI remains relatively poor: 55–60% of patients who require RRT survive, but this figure partly reflects the very poor outcome of patients who have AKI as a component of MOD who are managed on the ICU, eg only 10–20% of those with three- or four-organ failure will survive, yet 90% of patients who have AKI in isolation survive.

The prognosis for **recovery of renal function** varies according to the causative condition; renal recovery occurs in <50% of cases with autoimmune vasculitis. In survivors of ischaemic AKI, renal function will return to the normal range in 60%, whereas 30% will be left with CKD and 10% will be dialysis dependent.

15.4.2 Rhabdomyolysis

Muscle damage with release of myoglobin can cause severe, hypercatabolic AKI. Serum potassium and phosphate (released from muscle) rapidly rise, calcium is typically low and the creatine kinase massively elevated; serum creatinine may be disproportionately higher than urea. Primary management involves intravascular fluid expansion with the encouragement of diuresis. Sometimes the source of the rhabdomyolytic process requires specific therapy (eg fasciotomy for compartment syndrome, debridement of dead tissue and amputation of non-viable limbs).

Causes of rhabdomyolysis

- **Crush injury**: trauma; unconsciousness with compression
- **Metabolic myopathies**, eg McArdle syndrome
- **Infections**: viral necrotising myositis, infectious mononucleosis
- **Uncontrolled fitting**
- **Drugs**, eg statins
- **Overdose**: barbiturates, alcohol, heroin
- **Severe exercise, heat stroke, burns**
- **Inflammatory myopathies**: polymyositis
- **Malignant hyperpyrexia**

Prognosis of rhabdomyolysis

Patient survival in rhabdomyolysis depends on the nature and extent of the underlying causative pathology. However, in survivors, the prognosis for full renal functional recovery is usually good.

15.4.3 Contrast-induced nephropathy

Mild renal dysfunction may complicate up to 10% of angiographic and other radiological procedures using contrast agents. Contrast-induced nephropathy (CIN; also termed radiocontrast nephropathy) is manifested by non-oliguric AKI, typically occurring 1–5 days after the procedure. Intrarenal vasoconstriction, mediated largely by endothelin, and tubular cell toxicity (with ATN) are important in the pathogenesis. The AKI is usually fully reversible. Recent attention has been directed to prevention of radiocontrast nephropathy with:

- Pre-hydration of patients at greatest risk (eg for patients with eGFR <30 mL/min, administering 0.9% saline infusion before and during the procedure)
- Minimal evidence that *N*-acetylcysteine (given orally for 24 h before to 24 h after the procedure). Limited evidence of benefit in high-risk patients, but still part of some preventive protocols.

Risk factors for radiocontrast nephropathy

- High contrast load
- High iodine content of contrast
- Hypovolaemia
- Diabetes mellitus*
- Myeloma
- Hypercalcaemia
- Age
- Pre-existing CKD (particularly eGFR <30 mL/min)
- Hyperuricaemia

*Especially if the patient is taking metformin – this should be withdrawn before injection of radiocontrast.

15.5 CHRONIC KIDNEY DISEASE AND RENAL REPLACEMENT THERAPY

15.5.1 Chronic kidney disease

CKD is defined as evidence of kidney damage (eg urinary abnormality such as haematuria or proteinuria; scars or polycystic change on a renal scan) or eGFR <60 mL/min (see below). It is very

common, and latest data suggest that it affects about 9% of the UK adult population. The incidence of end-stage kidney disease (ESKD) patients joining RRT programmes in the UK is about 125/million each year; the figure is >300/million in parts of the USA (because of racial factors and increased population prevalence of diabetes mellitus and hypertension). The prevalence of patients on UK RRT programmes is >800/million and, as ageing constitutes one of the major risk factors for CKD and ESKD, the prevalence is greatest in elderly people (eg >2700/ million in the 75- to -79-year age group receive RRT).

Table 15.4 Classification of chronic kidney disease

Stage	Description	Estimated GFR (mL/min per 1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mildly ↓ GFR	60–89
3a	Moderate ↓ GFR	45–59
3b		30–44
4	Severe ↓ GFR	15–29
5	Kidney failure	≤15

GFR, glomerular filtration rate.

There are several recognised stages of **CKD** (Table 15.4):

- **Stage 1**: renal function is entirely normal (eGFR >90 mL/min); this group is identified by urinary or structural abnormalities (eg patients with type 1 diabetes and microalbuminuria). A proportion of patients will be at risk of progression of CKD in the future
- **Stage 2**: patients with eGFR 60–89 mL/min and urinary/renal structural abnormalities also require follow-up. Note that patients with CKD stages 1 and 2:
  - Will not have renal-related anaemia – if anaemia is present, another cause should be sought
  - Will not have CKD–mineral and bone disorder (CKD–MBD – see Section 15.5.3)
  - May have hypertension
- **Stage 3**: accounts for the largest proportion of CKD patients (eg 6% of the UK adult population). Over 95% of this group will not be at risk of future progressive CKD, because their eGFR is simply reduced as a result of their age (age being a denominator in the MDRD eGFR equation). In recognition of this, stage 3 has been divided into two stages, with stage 3a patients (eGFR 45–59 mL/min) being considered at low risk (unless they have associated proteinuria). However, a high proportion of stage 3 patients will be hypertensive, because this too is associated with ageing. Renal-related anaemia and secondary hyperparathyroidism may begin during stage 3b CKD, because it is at this level of renal function that perturbations in erythropoietin production and vitamin D metabolism start to occur (see Section 15.5.3). However, phosphate concentrations are normal
- **Stage 4**: most patients will be hypertensive, and many are anaemic. Hyperphosphatemia may develop during this stage. A far higher proportion of stage 4 patients will be at risk of CKD progression compared with those with stage 3 CKD. Hence, most patients will be referred to the

nephrology service, and those with progressive CKD will be given patient education with discussion of treatment options (ie RRT or conservative care)

- **Stage 5**: this is termed ESKD. Most patients will have progressive renal dysfunction such that consideration of treatment options becomes essential. The patient will normally be managed in secondary care, and attention will be given to the following:
  - In patients opting for haemodialysis therapy, a goal of management is to have a mature arteriovenous fistula in situ before dialysis commences
  - Suitable patients will be activated on the renal transplant waiting list (when eGFR ≤ 15 mL/min) or, where relevant, transplantation from a live kidney donor arranged
  - In those who have opted for treatment, and where a renal transplant is not imminent, most need to start dialysis when eGFR falls to <10 mL/min. The mean eGFR of patients commencing dialysis is 8.5 mL/min in the UK
  - Stages 5D and 5T refer to dialysis and transplanted patients, respectively.

Although many cases of CKD progress insidiously, such that very abnormal biochemistry is relatively well tolerated by the patient, 15–20% of ESKD patients initially present as uraemic emergencies (which carries a twofold worse prognosis). The key parameters that **differentiate CKD from AKI** are:

- Small kidneys at imaging
- Anaemia
- CKD–MBD
- Clinical tolerance of very severe uraemia.

Causes of progressive CKD (approximate relative frequencies)

- **Most common causes of ESKD in the UK**:*
  - Diabetic nephropathy (17%)
  - Chronic glomerulonephritis (15%)
  - Hypertension (15%)
  - Chronic pyelonephritis (10%) – most often due to reflux nephropathy, but also renal calculi (nephrolithiasis) with infection
  - Polycystic kidney disease (8%)
  - Obstructive uropathy (5%)
  - Post-acute kidney injury (5%)
  - Chronic tubulointerstitial nephritis (4%), eg sarcoidosis, lithium toxicity, myeloma
  - Amyloidosis (1%)
- **Rarer causes of CKD**:
  - Analgesic nephropathy
  - Other hereditary disorders, eg Alport syndrome
  - Toxic nephropathy

- After nephrectomy for renal tumours

*In at least 15% of cases of ESKD, the aetiology remains unknown. These are patients presenting with small kidneys on ultrasonography, and in whom renal biopsy will be diagnostically unhelpful. Most likely diagnoses are hypertension, chronic glomerulonephritis or pyelonephritis, or dysplastic kidneys.

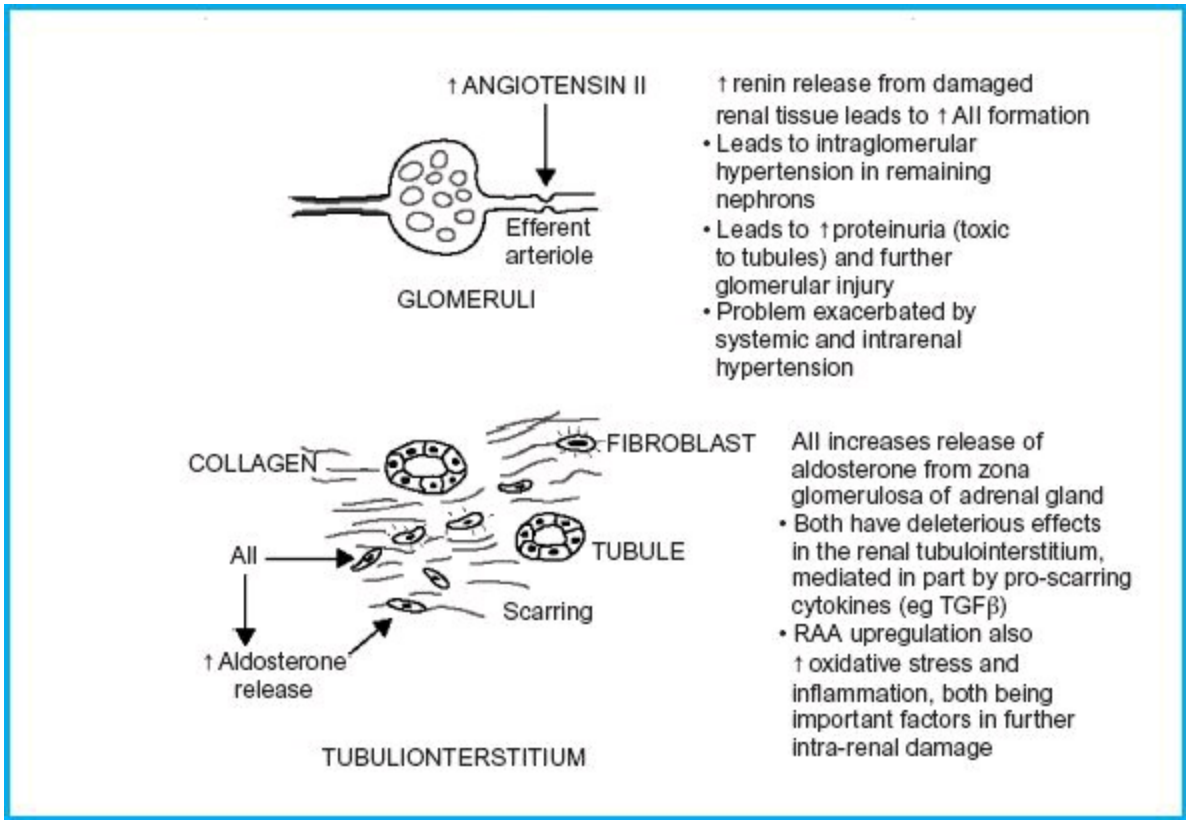
Pathogenesis and management of progressive renal dysfunction in CKD

Although most cases of advanced CKD are slowly progressive towards ESKD, patients with particular pathologies (eg post-obstructive atrophy and hypertension – when controlled) may manifest stable CKD for many years. When progression occurs, its pathogenesis is multifactorial. It is thought that the RAA system plays a major role: the vasoactive mediator angiotensin and aldosterone exacerbate the intraglomerular hypertension seen in the remaining nephrons, increasing proteinuria, which itself may also directly damage tubular cells. RAA system upregulation also provokes increased inflammation and oxidative stress, and stimulates fibrosis within the tubulointerstitium (Figure 15.2). Hence the **management** of patients with CKD requires attention to:

- **Control of blood pressure**: it is imperative to optimise blood pressure control. Target blood pressures for patients with CKD are <130/ 80 mmHg. Hypertension control can slow the progression towards ESKD, and **ACE inhibitors** and **ARBs** are indicated first line because of their effects on the RAA system. The importance of optimal blood pressure control has been shown in observational studies, eg patients with diabetes and optimal control may lose GFR at a rate of only 1–2 mL/min per year, whereas those with poor blood pressure and glycaemic control deteriorate rapidly towards ESKD, losing, for example, GFR at 8–16 mL/min per year. It is now recommended that dual therapy with ACE inhibitors and ARBs should be avoided except in selected patients monitored in nephrology clinics
- **Reduction of proteinuria**: heavy urinary protein losses are associated with an increased rate of progression in many cases of CKD. Amelioration of proteinuria by blockade of the RAA system may also slow progression
- **Dietary modification**: patients with advanced CKD should maintain a normal protein and high calorie intake to avoid malnutrition (and a consequent increased likelihood of morbidity) in the phase leading up to RRT. Restricted protein intakes are used as a conservative means of limiting uraemia only in a minority of patients. However, phosphate restriction and dietary modification of salt and potassium intake should be instituted in most with CKD stages 4 and 5
- **Endocrine complications**: anaemia and CKD–MBD may begin during CKD stages 3 and 4, and hence early attention should be directed to these endocrine complications (see Section 15.5.3)
- **Cardiovascular (CVS) disease prevention**: CKD creates a proatherogenic environment due to factors such as hypertension, mixed hyperlipidaemia and, when present, diabetes mellitus, with increased rates of coronary artery disease, stroke and peripheral vascular disease. Statins have been proven to reduce macrovascular thrombotic complications in non-dialysis CKD patients in the SHARP (Study of Heart And Renal Protection) trial.[(2)] However, other structural cardiovascular complications develop in CKD and these include left ventricular hypertrophy (LVH), vascular calcification (which results in arterial stiffness and is part of CKD–MBD) and congestive cardiomyopathy. Patients with CKD therefore have a marked increase in CVS mortality compared with the general population; sudden cardiac death accounts for around 25%

of all ESKD mortality.

Figure 15.2 Role of angiotensin II (AII) in the pathogenesis of progressive chronic kidney disease (CKD)



15.5.2 Anaemia of CKD

The anaemia of CKD usually first appears when GFR <45 mL/min; if untreated, it is a major contributor to morbidity in patients with advanced CKD. The major cause is the lack of endogenous erythropoietin secretion by the damaged kidneys, but other factors that predispose to the anaemia are listed below:

- Reduced dietary iron intake due to anorexia
- Impaired intestinal absorption of iron
- Impaired iron utilisation (see below)
- Uraemia has a toxic effect on precursor cells in bone marrow
- Occult GI blood loss due to capillary fragility and platelet dysfunction
- Reduced red blood cell (RBC) survival (particularly in haemodialysis patients).

In general, haemodialysis patients have more severe anaemia, and a poorer response to erythropoiesis-stimulating agents (ESAs) than their counterparts receiving peritoneal dialysis. Haemodialysis represents an 'inflammatory state', with cytokine release being stimulated by interaction of blood cells with the artificial dialysis membranes.

Recombinant erythropoiesis-stimulating agents and intravenous iron

Endogenous erythropoietin is normally synthesised by renal peritubular cells; it stimulates proliferation and maturation of erythroid lines within the marrow. Recombinant ESA preparations are

widely available and are used to correct anaemia in patients with CKD. It is imperative that these patient groups avoid repeated blood transfusion, so that future renal transplantation will not be precluded by allosensitisation.

Before initiation of an ESA, the patient should be iron replete. The serum ferritin (a measure of storage iron) and the transferrin saturation (available functional iron) need monitoring because most patients require supplemental intravenous iron. Targets for treatment include:

- **Target haemoglobin**: 10–12 g/dL. Several randomised controlled trials (RCTs) have shown that trying to normalise haemoglobin with use of high ESA doses is associated with increased risk of CVS disease in CKD patients
- **Ferritin**: >200 µg/L in all RRT and CKD patients. Although this target is greater than in the general population, it enables a reduction in ESA dose. Almost all haemodialysis patients receive regular boluses of intravenous iron during dialysis; although patients with stage 3a CKD may respond to oral iron, intravenous therapy is needed for those with more advanced CKD
- **Transferrin saturation**: >20% (a figure of less than this may indicate functional iron deficiency).

Some patients remain poorly responsive to ESA therapy despite achieving target iron parameters. They are likely to have high hepcidin levels – this is an inflammatory cytokine that diminishes transfer of usable iron from ferritin into transferrin. One of the key aims of therapy is to limit or reverse the LVH that is prevalent in RRT patients. Haemoglobin correction will also have a positive effect on sexual function and other quality-of-life measures.

Causes of resistance to ESA therapy

- Iron deficiency
- Severe hyperparathyroidism
- Sepsis or chronic inflammation (these raise hepcidin levels)
- Aluminium toxicity (rare)
- Occult GI tract blood loss
- Pure red cell aplasia (PRCA; see below)

Main side effects of ESA therapy: accelerated hypertension with encephalopathy (aim for a monthly Hb increase of <1.5 g/dL), bone aches, flu-like syndrome, fistula thrombosis (rare) and PRCA (see below). Very high doses in the TREAT (Trial to Reduce cardiovascular Events with Aranesp Therapy) study were associated with stroke and recurrence of cancer.

Pure red cell aplasia

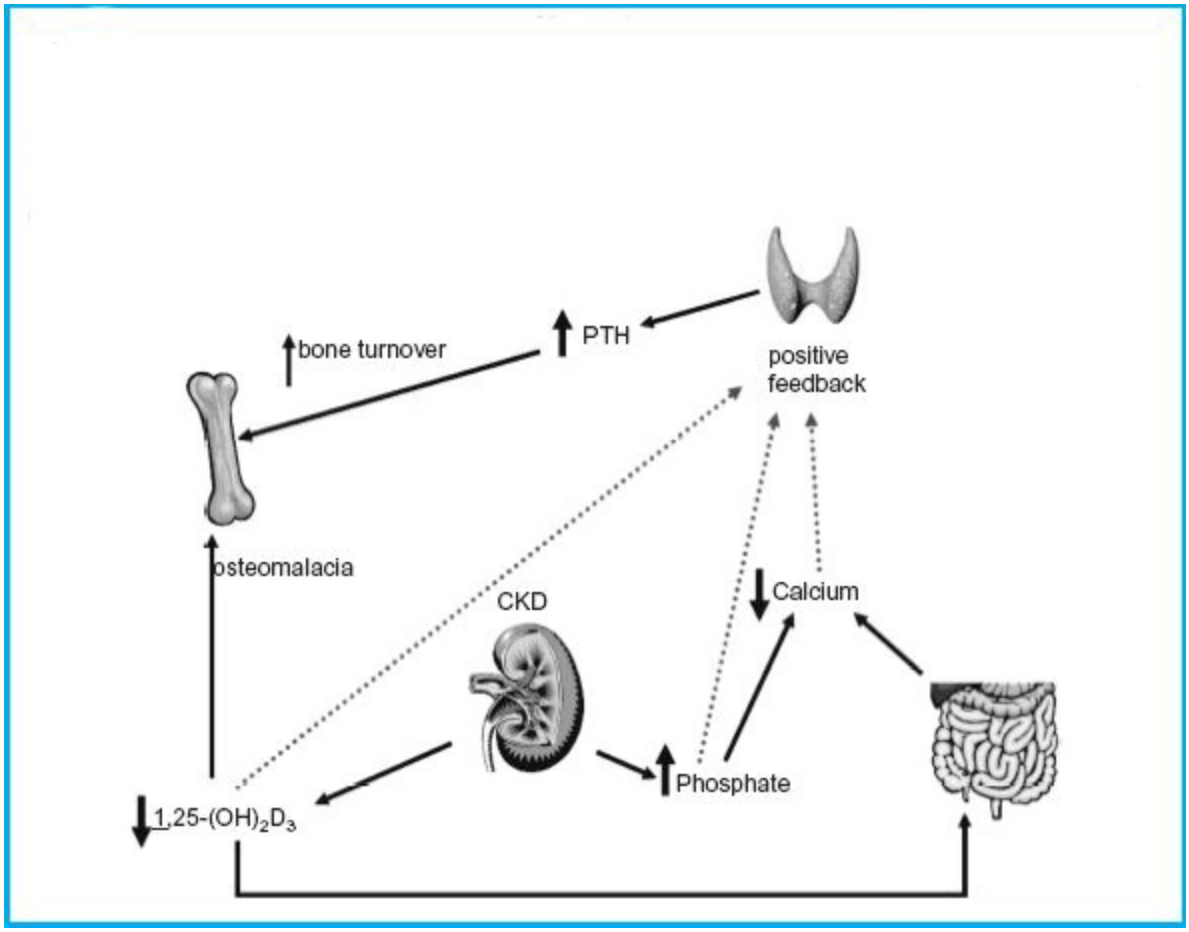
A few cases of unresponsive and progressive severe anaemia have been identified in patients treated with ESAs, who have antibodies directed at endogenous and exogenous erythropoietin; they become transfusion-dependent. Other marrow functions remain intact.

15.5.3 CKD–mineral and bone disorder

The regulation of vitamin D and parathyroid hormone (PTH) metabolism are discussed in Chapter 13, Metabolic diseases. The importance of renal bone disease has increased with an understanding that it can be intricately related to vascular disease, and hence the term 'CKD–mineral and bone disorder' (CKD–MBD). This is common in patients with CKD and those receiving dialysis. The pathogenesis is fairly complex (Figure 15.3) but the most important components are:

- **High serum phosphate**: phosphate clearance is reduced in renal failure. In earlier CKD, the hormone, FGF-23, acts as a phosphotonin (inhibiting renal tubular reabsorption of phosphate) controlling phosphate concentrations. High FGF-23 concentrations are associated with LVH development in CKD and with mortality in dialysis patients
- **Low plasma ionised calcium**: due to several factors. There is lack of 1,25-dihydroxy-vitamin D (the 1α-hydroxylation, which increases activity of vitamin D, normally occurs in the kidney). Malnutrition and hyperphosphataemia also contribute
- **Stimulation of PTH release**: **secondary hyperparathyroidism** is very common and is the direct response of the glands to hypocalcaemia, hyperphosphataemia and low native and 1,25-dihydroxy-vitamin D levels. These factors feed back independently to the parathyroid glands to stimulate PTH release, and hence a balanced correction of all of them is necessary before the hyperparathyroidism can be optimally controlled. PTH has end-organ effects on bones (leading to osteoclastic resorption cavities) and also the heart, contributing to LVH, and it is also a major cause of ESA resistance
- **Tertiary hyperparathyroidism**: defined by the presence of elevated PTH and non-iatrogenic hypercalcaemia; it is due to autonomous PTH secretion from generally hyperplastic parathyroid glands (90%) or an adenoma (10%). Note that **primary hyperparathyroidism** is only rarely associated with renal failure (due to either the nephrotoxic effects of hypercalcaemia or renal calculus disease)
- **Low vitamin D levels**: this results not only in reduced absorption of calcium by the gut, but also in osteomalacia
- **Acidosis**: increases the severity of bone disease.

Figure 15.3 Pathogenesis of CKD–mineral and bone disorder (CKD–MBD). In CKD there is phosphate retention and reduced 1α-hydroxylation of 25-hydroxy-vitamin D. These abnormalities lead to reduced plasma [Ca^{2+}], and all three factors independently stimulate parathyroid hormone (PTH) release from the parathyroid glands. The net effect is demineralisation of bone with release of calcium and more phosphate into the circulation; bony abnormalities include osteomalacia and high-turnover bone disease. Vascular calcification, arterial stiffness and LVH are prominent cardiovascular associations



Histological findings at bone biopsy in CKD–MBD

Bone biopsies are now seldom performed in dialysis patients; different histological lesions can coexist in the same patient:

- **Osteomalacia**: due to vitamin D deficiency
- **Hyperparathyroid bone disease** (high-turnover bone): osteoporosis and cystic resorption; also termed 'osteitis fibrosa cystica' (von Recklinghausen's disease of bone). Subperiosteal erosions on the radial border of the phalanges are characteristic
- **Osteoporosis**: due to relative malnourishment, steroid use and hyperparathyroidism
- **Osteosclerosis**: a component of the 'rugger-jersey' spine appearance on a radiograph (bone denser at the vertebral end-plates and thin in the middle of the vertebrae)
- **Adynamic bone disease**: bone with low turnover; PTH levels (and serum alkaline phosphatase) are usually subnormal. Over-treatment of secondary hyperparathyroidism with excess vitamin D (totally suppressing PTH release) may be contributory. These patients have limited buffering capacity of phosphate and calcium, and adynamic bone disease is associated with increased vascular calcification and a greater likelihood of bone fractures
- **Aluminium bone disease**: now rare with the use of specially treated water supplies for dialysis (reverse osmosis) and non-aluminium-containing phosphate binders.

Prevention and treatment of CKD–MBD

The basic principles are to improve the diet (particularly phosphate restriction), reduce hyperphosphataemia and acidosis and reduce the PTH level. This is brought about by use of

phosphate binders, oral bicarbonate, dialysis where necessary and giving vitamin D at doses that do not provoke hypercalcaemia:

- **Phosphate binders**: the mainstay of treatment has traditionally involved calcium-based binders (eg calcium carbonate or acetate). However, with the awareness that CKD patients are at risk of vascular calcification and valvular calcification, non-calcimimetic agents (eg sevelamer, a polymer, and lanthanum carbonate) are increasingly used, and calcium intake is limited to 1.5 g/day. Aluminium-containing binders are now infrequently used, although they are efficacious
- **Treatment targets**: the KDIGO (Kidney Disease Improving Global Outcomes) guidelines[3] recommend aiming for normal range serum phosphate (<1.5 mmol/L), calcium low–normal range (2.2–2.45 mmol/L) and PTH maintained at 2–9 times the normal range (normal range up to 6.9 pmol/L, hence approximately 14–63 pmol/L) in dialysis patients. The trend (ie increasing or decreasing) is of equal importance to the absolute level of phosphate or PTH for deciding on intervention. A PTH greater than 'normal' is recommended to avoid the risk of inducing adynamic bones. However, these guidelines have a limited evidence base.

Most cases (>97%) of secondary hyperparathyroidism can be controlled with this standard medical treatment. For resistant cases (usually those with large parathyroid gland mass [eg >1 cm^3], who have had chronic and poorly treated secondary hyperparathyroidism) and in patients with tertiary disease, the treatment options are now:

- Cinacalcet (a calcium-sensing receptor agonist)
- Selective vitamin D receptor agonist (eg paricalcitol)
- Parathyroidectomy.

15.5.4 Maintenance dialysis

In the UK, the dialysis population is approximately 28 000, or 475/million; approximately 85% of patients receive **haemodialysis**, and the remainder peritoneal dialysis (**continuous ambulatory peritoneal dialysis [CAPD] or automated PD [APD]**). Ideally, patients should be given the opportunity to choose a dialysis modality according to lifestyle factors (employment, home environment), their capability and local resources.

Factors that would favour haemodialysis in preference to peritoneal dialysis

- Recent abdominal surgery or irremediable hernias
- Recurrent or persistent (eg *Pseudomonas* spp. or fungal) peritonitis associated with previous PD
- Peritoneal membrane failure: inability to ultrafiltrate the necessary fluid volume to maintain fluid balance in the patient
- Age and general frailty (ie physically or mentally incapable of PD): some such patients are now able to manage with assisted APD
- Severe malnutrition: protein losses in the dialysis effluent may be 3–10 g/day in CAPD
- Intercurrent severe illness with hypercatabolism
- Chronic severe chest disease: respiratory function may be compromised by PD

- Loss of residual renal function: some patients only obtain adequate dialysis with PD during the early stages after development of ESKD. As residual function is lost, underdialysis becomes a reality, especially in those with larger muscle mass

Peritoneal dialysis

A standard **CAPD** regimen would involve four 2L exchanges/day. The concentration of dextrose within the dialysate can be altered so that differing ultrafiltration requirements can be addressed. Polymers (eg icodextrin) are used to maintain ultrafiltration during the long night-time dwell. Although a few patients manage CAPD for many years, in most there is a finite length of time (eg 3–6 years) for its efficacy as a form of RRT. This is determined by gradual loss of **residual renal function** (ie a patient will start CAPD with a GFR of 8–10 mL/min, which is a major contributor to waste product clearance; over time, the GFR falls to zero, with corresponding inadequacy of the CAPD technique) and deterioration of peritoneal membrane function. **APD** is performed overnight, and can maintain fluid homoeostasis in patients with ultrafiltration failure (see below). APD may also be chosen for its convenience by some patients with normal peritoneal membrane characteristics. In some dependent patients, assisted APD enables them to dialyse at home. This involves health-care assistants visiting to start and disconnect the APD session.

The main **complications of PD** treatment are:

- **Bacterial peritonitis**: most cases are treatable. The most common infecting organisms are coagulase-negative staphylococci, Gram-negative bacteria and *Staphylococcus aureus*. The rate of PD peritonitis should be no greater than 1 episode/30 patient-months. Patients who have repeated episodes of peritonitis, and hence several courses of intraperitoneal antibiotics, are prone to develop resistant organisms (eg pseudomonas or fungal peritonitis) and catheter loss, necessitating a switch to haemodialysis. If the dialysis fluid culture yields more than one organism (especially Gram-negative organisms and anaerobes) during a peritonitis episode, then intra-abdominal pathology (eg bowel perforation, diverticular abscess) should be suspected, and expediently diagnosed and treated
- **Ultrafiltration failure**: some patients are identified as 'high transporters' of glucose; the osmolar benefit of their PD dialysate is rapidly lost and hence these patients have difficulty with fluid removal (ultrafiltration). The latter may also develop after several years of PD treatment. APD and polymer-based dialysis solutions may help maintain fluid balance in such patients
- **Encapsulating peritoneal sclerosis (EPS)**: a serious complication of long-term PD. Risk factors include repeated episodes of peritonitis and duration of PD (eg 5% incidence in patients treated with PD for >3 years). The peritoneal membrane thickens and encases the bowel. Clinical features include PD ultrafiltration failure, but, in more severe cases, life-threatening bowel obstruction and malnutrition. Surgery is generally indicated and can be lifesaving
- **Malnutrition**: renal failure is an anorexic condition; patients may need nutritional supplements.

Haemodialysis

Haemodialysis is an intrinsically more efficient means of RRT than PD, and many patients have lived for >20 years while being supported by haemodialysis. As this is usually an intermittent therapy (typically, 4 h of dialysis three times each week), water restriction and dietary modification are even

more important than for patients receiving PD (who with CAPD would be receiving continuous dialysis). Successful haemodialysis relies on adequate **vascular access**:

- This is ideally provided by arteriovenous fistulae. An appropriate blood flow rate would be 250–400 mL/min into the dialyser circuit. Fistulae take 4–6 weeks to mature, and so vascular access surgery should be planned in timely fashion, when possible
- Patients who present late with severe uraemia and those with fistula complications inevitably require use of temporary or semi-permanent (tunnelled) vascular access catheters. The most frequent complication is line-related sepsis (in particular, *S. aureus* and coagulase-negative staphylococci), and the incidence of bacterial endocarditis is increased in haemodialysis patients. Repeated use of antibiotic courses increases risk of methicillin-resistant *S. aureus* (MRSA) and *Clostridium difficile* infection in dialysis patients
- The other main complication of haemodialysis catheters is venous stenosis or occlusion. Temporary catheters are inserted into the femoral or internal jugular veins, and only left in situ for <1 week; the jugular veins are the preferred sites for tunnelled catheter insertion. Subclavian catheters are no longer recommended
- Standard of care minimises insertion-related complications by ultrasound scanning for vein localisation, and the use of fluoroscopy with left internal jugular vein insertion (because anatomical variants are common).

Long-term complications in dialysis patients

Although dialysis therapies will keep patients alive and, with the additional use of ESA, relatively well, many of the metabolic abnormalities of the uraemic condition persist and these patients are at increased risk of the following:

- **Vascular disease**: dialysis patients have a high risk of cardiovascular events and death compared with the general population, the relative risk of mortality being >100 in dialysis patients aged <30 years, and it remains threefold that of the general population in patients aged >80 years. The risk is greatest in diabetic dialysis patients (eg mean survival of 3 years). Pathogenetic factors have been discussed earlier in this section. Most deaths are due to cardiac disease but this is more often due to arrhythmia (sudden cardiac death) or congestive cardiomyopathy (which is exacerbated by fluid overload) than to overt myocardial infarction. **Vascular calcification** is a major component of the vascular disease and is associated with arterial stiffness and LVH, which in turn correlate with increased mortality
- **Cardiac valve calcification**: this affects the aortic valve in particular, and is frequently seen in haemodialysis patients. As with vascular calcification, it is thought to be associated with perturbations in serum phosphate and calcium product
- **Dialysis-related amyloid**: β_2-microglobulin is a small-molecular-weight (about 11 000 Da) protein normally metabolised and excreted by the kidney. Plasma levels increase greatly in patients on long-term (eg >10 years) haemodialysis, and the protein is deposited as amyloid within carpal tunnels, joints and bones. Dialysis with more biocompatible membranes can alleviate the β_2-microglobulin burden
- **Arthritis**: pyrophosphate arthropathy (pseudogout) and gout (see Section 15.5.5 below) are common in patients with renal failure.

15.5.5 Renal transplantation

About 2500 UK patients benefit from renal transplantation each year, and over half of transplants derive from **cadaveric donors**. However, a shortage of organs available for transplantation persists and the rate of **living-donor transplants** (related or unrelated) is ever increasing. All potential living renal donors have to be screened carefully to ensure that they are clinically fit; absolute contraindications include pre-existing renal disease, a disease of unknown aetiology (eg multiple sclerosis or sarcoidosis), recent malignancy and overt ischaemic heart disease (IHD). Hypertensive patients may be considered provided that they have no evidence of end-organ damage, and the blood pressure is well controlled. All donors require careful counselling before the donor operation.

Screening and preparation of potential recipients

All dialysis patients and those with advanced CKD are considered for transplantation. Approximately half will be suitably fit for listing:

- Exclusion criteria include current or recent malignancy (eg <2 years) and severe comorbidity (eg debilitating chronic obstructive pulmonary disease [COPD] or stroke, dementia, etc). Advanced age is not a contraindication but few patients aged >80 years are eventually listed
- As the transplant is inserted in the iliac fossa, anastomosed to the iliac vessels, long-standing dialysis patients and those with a history of peripheral vascular disease should be screened for vascular calcification with pelvic radiography
- Patients with risk factors (eg patients with diabetes aged >50 years, previous IHD, heavy smoking) should undergo **CVS screening** before referral. This includes echocardiography (LV ejection fraction must be >30%) and noninvasive imaging for reversible coronary ischaemia (eg myocardial perfusion imaging or stress echocardiography). Selected patients then undergo coronary angiography and, if necessary, coronary revascularisation before transplantation
- Patients with persistently or recurrently infected urinary tracts (eg severe reflux, patients with spina bifida) need bilateral native nephrectomy before transplantation.

Matching and incompatible transplants

Most cadaveric organs are transplanted to blood group-compatible patients with the best available tissue match, but the national allocation scheme will give preference to 'long waiters' who are often highly sensitised to most HLA allotypes.

- HLA antigens are coded from chromosome 6 (see also Chapter 10, Immunology)
- Class 1 antigens are A, B and C; class 2 are the D group antigens
- Relative importance of HLA matching: DR > B > A > C
- Transplants to 'incompatible' recipients (eg blood group incompatibility or those presensitised to donor antigens) are possible with use of 'desensitisation therapy' (eg plasma exchange and B lymphocyte-suppressive therapy) for the recipient a week or so before a planned living-donor transplantation.

Combined kidney–pancreas transplantation

This is performed for patients with type 1 diabetes mellitus; recipient fitness is of paramount

importance. The pancreas is usually transplanted onto the opposite iliac vessels to the kidney, with its duct draining into the bladder.

- Acute rejection of the pancreas is manifest by worsening of glycaemic control and a rise in urinary amylase, but responds to pulsed steroid therapy
- Long-term results are encouraging – normalisation of glycaemic status is expected, and most diabetic microvascular complications (particularly retinopathy and neuropathy) can be stabilised, but not reversed
- Sometimes a two-stage transplant regimen (eg kidney months or years after pancreas) is necessary because of limited organ availability.

Indications for recipient nephrectomy before transplantation

- Pyonephrosis or any suppuration within the urinary tract (see above). If this is due to bladder dysfunction (eg spina bifida) a resting ileal conduit will need to be created before transplantation
- Massive polycystic kidneys
- Uncontrollable hypertension (rare with modern drug therapies)
- Renal/urothelial malignancy: patients must remain free of recurrence for >2 years before transplantation

Post-transplantation renal function

It is common to see **acute renal transplantation dysfunction**, especially in the first 2 weeks after engraftment. Nevertheless, the overall graft survival rate is 95% at 1 year, 70% at 7 years and 50% at 14 years. **Chronic graft dysfunction** is common and is responsible for most graft losses beyond 1 year after transplantation. The causes of acute and chronic graft dysfunction are shown in Table 15.5.

Acute transplant rejection

This is very common, and should be anticipated in the early weeks after transplantation. The risk of acute rejection episodes has been reduced with current induction immunosuppressive regimens. Most cases respond rapidly to pulsed intravenous methylprednisolone therapy. Steroid-resistant rejection occurs in about 5% and usually requires monoclonal antibody therapy (eg ATG or OKT3).

Table 15.5 Causes of graft dysfunction after transplantation

Acute graft dysfunction (1 day to 4 months after transplantation)
• **Delayed graft function** (ATN of the graft): increased with prolonged cold ischaemia time (seen in about 20% of all transplants – usually resolves by 2–3 weeks)
• **Ureteric leakage** (breakdown of anastomosis)
• **Vascular thrombosis** (arterial or venous thrombosis of the transplant vessels – usually irremediable); this may be associated with primary non-function (ie the transplant never functions)

- **Urinary tract infection**
- **Acute calcineurin inhibitor** (CNI: ciclosporin or tacrolimus) toxicity – resolves rapidly with alteration in dosage
- **Cytomegalovirus infection** (diagnosed with polymerase chain reaction (PCR) for the virus)
- **Acute rejection**: occurs in about 25% of all transplants (see below)

Chronic graft dysfunction (4 months after transplantation onwards)

- **Chronic renal allograft nephropathy**: by far the most common cause of chronic dysfunction of the transplant (see below)
- **Recurrent primary disease** within the graft (see below)
- **CNI nephrotoxicity**: changes on transplant biopsy are rarely pathognomonic. Withdrawal of the CNI in such patients may stabilise graft function
- **Polyomavirus infections** (eg BK or JC virus – see below)
- **Donor-specific antibodies (DSA)**: these are directed at mismatched donor antigens that are not considered in the matching process. An increase in immunosuppression is often indicated; outcome is uncertain

---

Chronic renal allograft nephropathy

This accounts for the majority of graft losses occurring beyond the first year after transplantation. It is usually manifest by the development of proteinuria and slowly progressive graft dysfunction, and has multifactorial causes including both low-grade immunological ('chronic antibody-mediated rejection') and non-immunological (hypertension, hypercholesterolaemia, vascular disease within the graft, CNI toxicity) factors. Other terms have been used to describe it in the past, including chronic rejection, transplant glomerulopathy and chronic allograft nephropathy (CAN). Management involves:

- Optimising hypertension control
- Limiting proteinuria (use of ACE inhibitors and ARBs)
- **Modification of immunosuppressive therapy**: despite their excellent track record in transplantation, CNI can contribute to allograft nephropathy in some patients, perhaps because of adverse microvascular effects within the graft. Reduction or complete withdrawal of CNI dose can ameliorate, or even stabilise, progressive graft dysfunction in certain patients with chronic renal allograft nephropathy.

Polyomavirus infection

Graft dysfunction can be due to polyomavirus infection within the graft. BK virus and JC virus are the initials of the patients in whom they were first identified. The mainstay of treatment is a reduction in immunosuppressive therapy, particularly the antiproliferative drugs (eg mycophenolate mofetil [MMF]); specific antiviral therapy with cidofovir may be beneficial in selected cases. Successful treatment allows stabilisation of graft function but return to baseline graft function is rare.

Post-transplantation: non-renal complications

Although the quality of life of most patients is significantly improved after transplantation, patients are still at risk of the following:

- **Malignancy**: **non-Hodgkin's lymphoma** (usually Epstein–Barr virus-associated) is 20–50 times and **skin cancer** 5–20 times more common in transplant recipients than in age-matched general populations, and the increased incidence is thought to be due to the effects of immunosuppression (especially azathioprine with skin and CNI with lymphoma). All other malignancies are slightly more prevalent (1.5-fold increased)
- **Cardiovascular**: IHD is 10–20 times more prevalent (due to effects of immunosuppression and hyperlipidaemia, as well as persistence of the CVS risk accompanying the patient's previous 'uraemic state') than in an age-/sex-matched equivalent population. Mortality rate is 2% in the first year after transplantation, half of which is due to CVS disease and half to infection (see below)
- **Infections**: all infections are more common, but patients are also at risk from opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP), and especially cytomegalovirus (CMV)
    - **CMV**: about 50% of the general population will have had CMV infection. Around 20% of recipients develop CMV disease, typically 6–12 weeks after transplantation. CMV antibody-negative recipients of a CMV-positive graft are at risk and are given prophylaxis with oral valganciclovir (a prodrug of ganciclovir); this is also used to treat mild infections (leukopenia and mild pyrexia are typical). Severe infections can be associated with myocarditis, encephalitis, retinitis and renal dysfunction; these cases require treatment with intravenous ganciclovir
    - **PJP** is uncommon but very serious; patients receive co-trimoxazole prophylaxis for the first 6 months post-transplantation
    - Patients of Asian origin, or those with a previous TB history, are given anti-tuberculous prophylaxis with isoniazid for the first year after transplantation
- **Osteoporosis**: due to immunosuppressant (particularly steroid) usage. Many patients receive bisphosphonate prophylaxis
- **Gout**: all patients with CKD are at increased risk of hyperuricaemia and acute gout. However, prophylaxis with allopurinol or febuxostat is not widely implemented. Treatment of acute gout in patients with CKD is problematic: there are no non-nephrotoxic NSAIDs available, and patients with transplants (or with CKD) are at risk of serious renal dysfunction with their usage. Colchicine is used, but it has frequent GI side effects; temporary treatment with steroids (eg a single intramuscular injection of 125 mg methylprednisolone or 30 mg prednisolone orally for 2 weeks) will provide an excellent anti-inflammatory effect and provides cover for the introduction of prophylaxis (eg allopurinol)
- **New-onset diabetes after transplantation (NODAT)**: the incidence is increased in transplanted patients (3–5% may develop it per year); immunosuppressants (particularly tacrolimus) are thought to be responsible.

Recurrent renal disease after transplantation

Patients with Alport syndrome are at risk of developing anti-GBM antibody syndrome after

transplantation, because they have no prior tolerance to the Goodpasture antigen. Vasculitis may recur, and serum monitoring is recommended in ANCA +ve patients. All types of primary glomerulonephritis may recur in the graft, but particularly:

- **Focal segmental glomerulosclerosis (FSGS)**: 15% recurrence rate, with graft loss in 50% of these
- **IgA nephropathy**: 30–60% have evidence of histological recurrence; graft loss in 15% of these
- **Membranous glomerulonephritis**: <10% recurrence rate, but 50% graft loss if affected
- **Mesangiocapillary glomerulonephritis**: >50% risk of recurrence.

Immunosuppression for renal transplantation

Immunosuppressive regimens vary from centre to centre. Most now involve induction with a monoclonal antibody (eg basiliximab, directed against CD25, given at induction and day 4), followed by a CNI-based regimen (eg tacrolimus with MMF). Patients who have at least two steroid-responsive acute rejections will usually receive oral corticosteroids for up to 12 months after transplantation. Particular considerations with immunosuppressants are:

- **Tacrolimus**: similar to ciclosporin, this agent inhibits a T-cell phosphatase, calcineurin, which is needed for T-cell activation, and hence the term 'CNI'. It is now the central component of most transplant immunosuppressive regimens, because there is a lower incidence of acute rejection episodes compared with ciclosporin; hypertension may be less frequent or severe. There is a risk of chronic renal allograft nephropathy with long-term use and also the development of diabetes mellitus (NODAT)
- **Ciclosporin**: its introduction around 1980 completely revolutionised the outcome of transplantation. Common side-effects include hirsutism, liver dysfunction and gum hypertrophy, hypertension and chronic renal allograft nephropathy. It now tends to be used in patients intolerant of tacrolimus
- **Azathioprine**: traditional antiproliferative agent; commonly associated with mild bone marrow suppression. This is exacerbated in patients receiving allopurinol, and the two agents should not be used together
- **MMF**: the main side-effects of this antiproliferative agent are gastrointestinal, in particular diarrhoea (Myfortic is a more GI-friendly analogue), and bone marrow suppression (but less frequently than azathioprine). It is usually used in combination with a CNI; in the management of chronic renal allograft nephropathy, its use facilitates reduction or withdrawal of the CNI
- **Sirolimus (rapamycin)**: this is related to erythromycin, and it inhibits T-cell division. It is not associated with nephropathy, but it can provoke hyperlipidaemia
- **Corticosteroids**: these agents have been the mainstay of immunosuppressive regimens for several decades, but now long-term dosing is generally avoided to reduce cardiovascular complications and post-transplantation osteoporosis.

Optimal immunosuppressive regimen

Transplant centres tailor immunosuppressive regimens in order to maximise the chances of good long-term graft function, but with limitation of recipient vascular risk; this involves reducing or complete withdrawal of CNI dose, and sparing steroid use. A typical approach might be:

- Induction with monoclonal antibody, a large CNI dose and MMF
- Maintenance therapy with CNI coupled with MMF (or sirolimus)
- If more than one steroid-sensitive acute rejection episode, prednisolone for 6–12 months
- At 1–2 years post-transplantation, reduce CNI dose
- If chronic renal allograft nephropathy develops, then reduce/withdraw CNI, and introduce MMF or sirolimus (if not receiving one or other).

15.6 GLOMERULONEPHRITIS AND ASSOCIATED SYNDROMES

15.6.1 Clinical presentation of glomerulonephritis

The term 'glomerulonephritis' implies inflammatory disease primarily affecting the glomeruli (but note that no inflammation is seen in minimal change disease), but other **glomerular** diseases exist that do not involve glomerulonephritis (eg diabetic nephropathy). Most glomerulonephritis develops as a result of **immune dysregulation**, due either to an inappropriate immune response to a 'self-antigen' (autoimmunity, eg anti-GBM disease, ANCA-positive vasculitis), or to an inappropriate or exaggerated response to a foreign antigen (eg membranous glomerulonephritis secondary to hepatitis B infection).

- This 'immune dysregulation' pathogenesis explains why there is a genetic predisposition to some forms of glomerulonephritis (eg IgA nephropathy)
- Immune complexes are often deposited in the glomeruli (eg SLE nephritis, mesangiocapillary glomerulonephritis), but in some glomerulonephritides, immune complexes form in situ within the glomerulus (eg anti-GBM disease)
- Inflammation leads to proliferation of cellular structures (mesangial, endothelial or epithelial cells) and/or scarring
- Glomerulonephritis may be **idiopathic** (**primary**) or **secondary** to systemic disease (eg malignancy, infections or drugs)
- The long-term clinical outcome often depends more on the severity of tubulointerstitial damage rather than the extent of glomerular injury
- The type of glomerulonephritis is defined by light microscopic, immunofluorescent and electron microscopic (ultrastructural) characteristics (see Section 15.6.2)

Screening for glomerulonephritis

- Dipstick for proteinuria; urinary ACR or PCR
- Dipstick for haematuria; urine microscopy for red cells and casts
- Hypertension.

Attenuation of progression of glomerulonephritis

- Control blood pressure (≤130/80 mmHg) for all types of glomerulonephritis
- ACE inhibitors and ARBs: decrease proteinuria and blood pressure, and may ameliorate progressive scarring (see Section 15.5)

- Progression depends on degree of coexistent scarring in the tubulointerstitium.

Classification of glomerulonephritis

Diabetes mellitus is the most common cause of glomerular pathology, but it causes glomerulosclerosis and is therefore not a 'glomerulonephritis'. The more common forms of glomerulonephritis (GN) are:

- Minimal change disease
- Membranous GN
- Focal segmental glomerulosclerosis (FSGS)
- IgA nephropathy (mesangioproliferative GN)
- Crescentic GN (eg associated with Goodpasture syndrome or vasculitis)
- Focal segmental proliferative GN (eg associated with vasculitis or endocarditis)
- Mesangiocapillary GN
- Diffuse proliferative GN (eg post-streptococcal).

Renal syndromes and their relationship to glomerulonephritis

There is often confusion about the relationship of the various glomerulonephritides to the different renal syndromes. A particular type of GN may manifest several different clinical syndromes (Table 15.6), eg membranous GN may be responsible for CKD, persistent proteinuria, nephrotic syndrome and hypertension; any combination of these may be present during the course of the disease. However:

- Certain glomerulonephritides are characteristically associated with typical clinical presentations (eg minimal change disease and nephrotic syndrome, IgA nephropathy and recurrent visible haematuria)
- It should also be borne in mind that a particular syndrome can be due to some conditions other than GN (eg the nephrotic syndrome can be due to accelerated phase hypertension, preeclamptic toxaemia or amyloid).

Table 15.6 Clinical presentation of glomerulonephritis (GN)

	Proteinuria	Nephrotic	Nephritic	Haematuria	AKI	CKD
Minimal change disease	+	+++	–	–	–	–
Membranous GN	+++	++	–	±	–	++
Focal segmental glomerulosclerosis	++	++	±	–	±	++
Mesangioproliferative (IgA)	++	+	+	+++	±	++
Mesangiocapillary GN	++	++	+	+	+	++
Diffuse proliferative GN	+	±	+++	++	+++	+
Crescentic nephritis	+	±	+++	++	+++	+
Focal segmental proliferative GN	+	++	++	++	++	+

+++, very common presentation; –, never seen/extremely rare.
AKI, acute kidney injury; CKD, chronic kidney disease.

Definitions of the common renal syndromes

- **Asymptomatic proteinuria**: <3 g/day
- **Nephritic syndrome**: characterised by hypertension, oliguria, haematuria and oedema (usually with accompanying AKI)
- **Hypertension**
- **Nephrotic syndrome**: >3 g proteinuria/day with serum albumin ≤25 g/L; oedema; hypercholesterolaemia
- **Haematuria**: Non-visible or visible (formerly termed ‘microscopic’ or ‘macroscopic’)
- **Acute kidney injury**
- **Chronic kidney disease**

Causes of the nephrotic syndrome

- **Common**:
  - Primary GN

- Diabetes mellitus
- Basement membrane nephropathy (eg Alport syndrome)
- Infections (eg leprosy, malaria, hepatitis B – associated with secondary GN)
- Pre-eclampsia
- Accelerated hypertension
- Myeloma
- Amyloidosis
- Drugs (associated with secondary GN): NSAIDs; gold, penicillamine, captopril and mercury; now rarely seen
- Connective tissue disease (eg SLE – secondary GN)

- **Rare**:
  - Vesicoureteric reflux
  - Constrictive pericarditis
  - Sickle cell disease
  - Allergies (eg bee sting, penicillin)
  - Hereditary GN (eg 'Finnish type' nephrotic syndrome)

Causes of visible haematuria*

- Urinary infections
- Renal papillary necrosis
- Acute GN
- Loin-pain haematuria syndrome
- IgA nephropathy
- Prostatic hypertrophy (dilated prostatic veins)
- Renal calculi
- Urinary tract malignancy

*It is imperative to exclude urinary tract malignancy (urine cytology, cystoscopy, CT urography and ultrasonography) in patients aged >40 years presenting with haematuria.

15.6.2 Notes on particular glomerulonephritides

Minimal change disease

The clinical presentation is almost always nephrotic. Although most common in children (causing >80% of nephrotic syndrome due to GN in under 15 year olds), it also accounts for 28% of nephrotic syndrome in adults. Highly selective proteinuria (ie loss of mainly smaller protein molecules – see below) is typical, and most cases are steroid responsive. Other features include:

- Normal renal function and renal histology (by light microscopy – but epithelial cell foot-process fusion seen on electron microscopy)
- May be due to NSAIDs or gold; rare associations are with Hodgkin's lymphoma and thymoma
- May frequently relapse (10%), but renal functional prognosis is excellent.

Monitoring: patients with frequently relapsing disease are taught to dipstick their urine on a regular basis; three consecutive days of +++ proteinuria is the trigger to commence steroids, which are continued at high dose until urinalysis has remained negative for 3 consecutive days.

Treatment: the mainstay is with short courses of high-dose prednisolone. Most relapses are steroid sensitive; cyclophosphamide (usually orally in children, pulsed intravenously in adults) is used for frequent relapsers or steroid-resistant disease. A subgroup of frequently relapsing (eg ≥2 episodes per year) teenagers enter adult nephrological care and prove quite difficult to manage. Avoidance of long-term steroid side-effects (particularly osteoporosis) is important, and so the relapse rate can be reduced by treatment with CNIs and/or MMF (taken for several years). In most of these patients the presumed underlying immune perturbation resolves by their late 20s. However, some patients are eventually found to have FSGS (see below).

Urinary protein selectivity

The index of urinary protein selectivity is used mainly in paediatric nephrological practice; highly selective proteinuria is likely to result from minimal change disease, and so its detection may obviate the need to perform renal biopsy in the child. In adults, the range of possible renal diagnoses in patients with significant proteinuria usually makes biopsy essential. The index is calculated from the respective concentrations of different molecular weight proteins within the urine:

$$\frac{\text{IgG (mol. wt 150 kDa)}}{\text{Transferrin (mol. wt 40 kDa)}}.$$

Highly selective (ie minimal change) proteinuria is defined as an index of <0.1, and unselective proteinuria >0.3.

Membranous glomerulonephritis

This is one of the most common types of GN in the adult; there are two peaks of disease: patients in their mid-20s and those aged 60–70 years. The clinical presentation may be nephrotic syndrome, asymptomatic proteinuria or CKD.

- Renal histology is characterised by granular IgG and complement deposition on the GBM; immune complexes are subepithelial (outer aspect of basement membrane) and appear as 'spikes' with silver stain
- 70% have primary or idiopathic disease and around 75% of these have an autoantibody, anti-PLA_2R (anti-phospholipase A_2 receptor) antibody, in plasma. The level of anti-PLA_2R antibody seems to correlate with disease activity, including recurrence in transplant recipients
- In all proteinuric membranous GN patients, the cornerstone of treatment is optimal blood pressure control and limitation of proteinuria with ACE inhibitors or ARBs. A 6-month trial is typical
- Immunosuppression is indicated for those with persistent nephrotic syndrome after 6 months of renin–angiotensin blockade and/or evidence of progressive CKD. About a third will progress

- through CKD to ESKD, a third respond to immunosuppressive therapy (eg cytotoxic regimens such as the modified Ponticelli regimen: monthly cyclophosphamide alternating with corticosteroids for 6 months), and the disease remits spontaneously in a third
- Renal vein thrombosis may occur in up to 5% of patients. Patients at greatest risk are those with serum albumin <20 g/L, and these should receive anticoagulation
- 30% of membranous GN cases are secondary to other conditions (see box below)
- The condition can recur in renal transplant recipients.

Secondary causes of membranous glomerulonephritis

- **Malignancy**: bronchus, stomach, colon, lymphoma, chronic lymphoid leukaemia (CLL) (screening indicated in patients aged >65 years)
- **Connective tissue disease**: SLE, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disease
- **Chronic infections**, eg hepatitis B or C, malaria, syphilis
- **Drugs**: gold, penicillamine, captopril, NSAIDs
- **Others**: sarcoidosis, Guillain–Barré syndrome, primary biliary cirrhosis (all rare)

Causes of renal vein thrombosis

- **Acute thrombosis**:
  - Infantile gastroenteritis
  - Acute pyelonephritis
  - Renal cell carcinoma (with renal vein invasion)
- **Chronic thrombosis**:
  - Amyloidosis
  - Nephrotic syndrome due to GN (particularly membranous GN)
  - Thrombophilic syndromes (see Chapter 9, Haematology)

Focal segmental glomerulosclerosis (FSGS)

The **primary** form of FSGS accounts for <10% of nephrotic syndrome in children and elderly people, but up to 20% in young adults. It can also frequently present with proteinuria and/or CKD. In childhood the clinical pattern is often identical to minimal change disease, and it may be misdiagnosed as such. There are also familial forms of FSGS. Focal glomerular deposits of IgM are seen at biopsy.

Secondary FSGS: this can be seen in patients who abuse heroin, or have HIV infections and AIDS, and it is recognised in patients with obesity or when the functioning renal mass is reduced (eg after nephrectomy). In the latter cases, the glomerulosclerosis probably occurs as a result of haemodynamic stress and/or ischaemic changes within the glomeruli, and immune complexes are not

seen.

Treatment of primary FSGS: it is important to make the clinical distinction between primary and secondary FSGS. Those with secondary disease should not be treated with immunosuppression, but with optimal blood pressure control using RAA system blockade. In nephrotic patients with primary disease, >40% will respond to moderate-dose steroids given for 3–6 months. Frequent relapsers are treated in a similar way to those with minimal change nephropathy (eg with cyclophosphamide or CNI).

Outcome of FSGS: a rapidly deteriorating clinical course is seen in 2%, whereas 25% of all patients will eventually progress to ESKD. There is a high rate of recurrence in transplant recipients.

Mesangioproliferative glomerulonephritis (IgA nephropathy or Berger's disease)

This is a very frequent condition, the most common primary GN in adults. It typically affects young adults, presenting with non-visible or visible haematuria. The haematuric episodes are usually 'synpharyngitic' (ie occurring 0–3 days after an upper respiratory tract infection [URTI]). The condition is under-recognised because most nephrologists would not undertake renal biopsy in patients with isolated non-visible haematuria. The serum IgA is increased in 50% of patients; the condition is considered to be autoimmune, and there is evidence that the glycosylation of the IgA molecule is abnormal in some affected individuals, with this predisposing to GN. The following are other features of IgA nephropathy:

- An increased incidence in the Far East, especially Japan (associated with HLA-DQW7)
- IgA nephropathy can be associated with cirrhosis, dermatitis herpetiformis, coeliac disease and mycosis fungoides. It occurs in the Wiskott–Aldrich syndrome
- Renal biopsy features show proliferation of mesangial areas of the glomerulus; immunological staining is strongly positive for IgA. A similar histological picture may be seen in **Henoch–Schönlein nephritis**, and the pathogenesis is thought to be similar in the two conditions. Crescents may be present during haematuric episodes.

Treatment of IgA nephropathy: the mainstay of treatment is optimal blood pressure control with RAA system blockade, as for other chronic nephropathies. Nephrotic presentations should be treated as for minimal change nephropathy. Patients with progressive CKD may show stabilisation of renal function with immunosuppression (steroids, CNI or MMF).

Outcome of IgA nephropathy: 25% of patients presenting with CKD or significant proteinuria will progress to ESKD by 20 years after disease onset; however, the overall prognosis for IgA nephropathy is certain to be better than this because the mildest cases are likely to remain undiagnosed. Clinical criteria help identify patients with better prognosis – those with proteinuria <1 g/24 h at presentation have a 98% renal survival rate at 15 years, compared with 65% of patients with proteinuria >1 g/24 h. The disease frequently recurs in transplant recipients.

Mesangiocapillary glomerulonephritis

There are three forms of mesangiocapillary (also called membranoproliferative) GN (MCGN):

Type I: immune deposits in the subendothelial space and mesangium. This can occur in association with or without mixed **cryoglobulinaemias**, and **hepatitis C** may underlie the

- problem in 70–90%; other causes are hepatitis B, subacute bacterial endocarditis (SBE), shunt nephritis, malaria, SLE, Sjögren syndrome, sickle cell disease, α_1-antitrypsin deficiency, hereditary complement deficiencies and malignancy (CLL, non-Hodgkin's lymphoma)
- **Type II**: dense deposits in the mesangium ('dense-deposit' disease) leading to characteristic double-contouring of the basement membrane on renal biopsy. This is usually familial, and associated with partial lipodystrophy or factor H deficiency. Patients have reduced serum complement and the presence of circulating C3 nephritic factor. The latter binds to the alternative pathway C3 convertase, preventing its inactivation by factor H; continued complement activation results
- **Type III**: immune deposits diffusely present in subendothelial space and the mesangium. Often associated with hepatitis C or B infections (and the secondary causes as for type I MCGN).

Patients present with non-visible haematuria and dipstick proteinuria (most common), nephrotic syndrome (35%), CKD or rapidly deteriorating renal function (10%).

Treatment: steroids are only occasionally effective, but are used in childhood nephrotic presentations. The complement inhibitor, eculizimab, will be of benefit for patients with type II MCGN, but therapy is expensive.

The overall renal functional prognosis is fairly poor, with 50% progressing to ESKD. There is a high rate of recurrence of MCGN in transplant recipients.

Diffuse proliferative glomerulonephritis

This is the histological pattern of the classic post-streptococcal GN which usually presents with the nephritic syndrome or AKI; children and young adults are most often affected. The disorder is typically preceded (by 10–21 days) by a sore throat or by skin disease (eg impetigo – most often in developing countries).

- Serum C3 is low and there is diffuse proliferation within glomeruli at biopsy
- Post-infectious cases usually recover spontaneously with restoration of full renal function
- A similar histological picture may be seen in patients with SLE nephritis (but immune complex deposition is characteristic in the latter).

Rapidly progressive glomerulonephritis, including Goodpasture syndrome

The term 'rapidly progressive GN' (RPGN) is a clinical description of rapidly deteriorating renal function due to an underlying GN. The histological counterpart is a **crescentic GN**, and so the two terms are (sometimes incorrectly) used interchangeably. They refer to the renal lesions that excite great interest from the nephrologist, not least because patients are often very sick with hypercatabolic AKI and possibly associated systemic disease (eg pulmonary haemorrhage), but also because the underlying disease processes are potentially treatable provided that investigation and therapy are expedient. All age groups may be affected, and the presentation is usually with AKI or nephritic syndrome.

- Causes of RPGN include Goodpasture syndrome, ANCA-positive vasculitis and lupus nephritis
- Crescentic nephritis may be 'idiopathic' but is more often associated with Goodpasture syndrome, ANCA-positive vasculitis or SLE; crescents can also be seen during haematuric

episodes with IgA nephropathy and in Henoch–Schönlein disease.

ANCA-positive vasculitis and lupus nephritis are both considered in detail in Section 15.12, and hence the remainder of this section will concentrate on Goodpasture syndrome and its treatment, which is similar to that for all of these conditions.

Goodpasture syndrome

This is characterised by the presence of circulating anti-GBM antibodies (the GBM antigen is a component of type IV collagen), which localise to the glomerular and pulmonary capillary basement membranes. The condition is rare (<1 case/million per year), tends to affect elderly people or patients in their 20s to 30s, is more common in smokers and in some cases may be triggered by inhaled hydrocarbons.

- **Pulmonary haemorrhage** occurs in 50% of patients with Goodpasture syndrome; the most vulnerable are young male smokers. It is also seen in ANCA-positive disease (Wegener's granulomatosis and microscopic polyangiitis), which is considered later. The occurrence of pulmonary haemorrhage confers a greater mortality and is a definitive indication for plasma exchange
- Specific biopsy changes are seen in Goodpasture syndrome, with IgG deposited on the GBM in a linear pattern. The GN is of the diffuse proliferative type, and typically there is extensive crescent formation (epithelial cell proliferation arising from Bowman's capsule)
- **Prognosis**: renal functional recovery is rarely seen if the patient presents with advanced AKI (eg creatinine >600 μmol/l) and/or anuria. The overall mortality rate is 20%. Elderly patients are at particular risk from infective complications after immunosuppression; patients who have pulmonary haemorrhage are at greatest risk of mortality. Transplantation is possible once the patient is rendered autoantibody-negative.

Treatment of RPGN and crescentic nephritis

The following is applicable to most diseases causing RPGN and/or crescentic GN (an exception being IgA disease during a haematuric episode). Treatment is with immediate high-dose immunosuppressive therapy with or without **plasma exchange**. The latter is essential for patients with pulmonary haemorrhage who have a circulating autoantibody (ie anti-GBM or ANCA) in high titre, and it is used in most cases of Goodpasture syndrome and those with ANCA-positive disease who have severe AKI. The aim of plasma exchange is to rapidly remove these autoantibodies, allowing time for the immunosuppressive drugs to act to reduce their formation (eg cyclophosphamide) or to diminish tissue inflammation (with steroids). A typical regimen for severe ANCA-positive vasculitis and Goodpasture syndrome would be as follows:

Induction therapy: high-dose steroids (intravenous methylprednisolone 1 g on 3 consecutive days, followed by prednisolone 1 mg/kg) with 7–10 × 4L plasma exchanges within the first 10–14 days. Pulsed intravenous cyclophosphamide (10–15 mg/ kg every 2, and later 3, weeks for the first 6 months – the 'CYCLOPS' regimen), by which stage the steroid dose will have been tapered to around 10–20 mg/day. The chosen cyclophosphamide dose depends on age and severity of renal dysfunction.

Maintenance therapy: low-dose steroid and azathioprine (or MMF) are continued for a further 12–18 months (or even longer in some cases of cANCA-positive vasculitis [see later], or Goodpasture

syndrome with persistence of anti-GBM antibody).

Plasma exchange in renal disease

- **Agreed benefit**:
  - Goodpasture syndrome
  - ANCA-positive diseases: especially with pulmonary–renal presentation (mandatory with pulmonary haemorrhage); also for severe AKI
  - Idiopathic crescentic GN
  - Cryoglobulinaemias
  - Myeloma: cases with hyperviscosity
  - TTP
- **Possible benefit**:
  - SLE nephritis: severe lupus with AKI
  - Henoch–Schönlein nephritis: with crescentic forms and AKI
  - Myeloma: with AKI due to cast nephropathy (see Section 15.12.7)
  - HUS

Hypocomplementaemia and glomerulonephritis

The following disorders are often associated with GN coupled with *low serum complement* (C3):

- **SLE**
- **Shunt nephritis** (rare): focal segmental proliferative GN (or MCGN); classically associated with coagulase-negative staphylococcal infection of ventriculoatrial shunts
- **Primary complement deficiency** (eg C1q, C2 or C4 deficiency): associated with lupus-like syndromes, GN (usually mesangiocapillary type) and increased risk of bacterial infection
- **Endocarditis**: focal segmental proliferative glomerulonephritis
- **Post-streptococcal glomerulonephritis**
- **Mesangiocapillary glomerulonephritis**: see earlier
- **Cryoglobulinaemia**: especially type II (see below).

Cryoglobulinaemia

Immunoglobulins that precipitate on cooling may be monoclonal or polyclonal (for classification see Chapter 10, Immunology). They can induce a small-vessel vasculitis, particularly affecting the skin and kidneys. Type II (mixed monoclonal) and type III (polyclonal) cryoglobulinaemias are associated with GN (mesangiocapillary or membranoproliferative).

15.7 INHERITED RENAL DISEASE

The most common inherited renal diseases are polycystic kidney disease and Alport syndrome. Rarer disorders include other renal cystic disease, disorders of amino acids and familial GN; the latter conditions are encountered much more frequently in paediatric nephrology.

15.7.1 Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal condition, and the genes have now been identified:

- ***PKD1***: chromosome 16 in 86% of PKD patients (mean age of ESKD: 57 years)
- ***PKD2***: chromosome 4 in 10% (mean age of ESKD: 69 years).

The diagnosis is generally made by ultrasonography; cysts usually develop during the teenage years so that first-degree relatives aged >20 years, with a normal scan, can be >90% confident of being disease free; the confidence level rises to 98% at 30 years of age. Cysts develop from all segments of the nephron. The prevalence of ADPKD is 1 in 1000; the condition accounts for about 8% of RRT patients in the UK.

Diagnostic criteria for ADPKD

In a patient known to be at 50% risk because of family history, diagnosis would be suggested by the following ultrasound findings:

- Two cysts, either unilateral or bilateral, if aged <30 years
- Two cysts in each kidney in patients aged 30–59 years
- Four cysts in each kidney in patients aged >60 years.

Sporadic cases (no family history) are also commonly seen.

Clinical features

Patients may present with abdominal pain or mass, hypertension, UTI, renal calculi (10%), macroscopic haematuria or CKD.

- The age of onset of CKD varies widely (eg 25–60 years); not all patients develop ESKD
- In patients known to have ADPKD, intermittent severe abdominal pain is common, but, apart from UTI and calculi, the exact cause may be difficult to identify (possible causes being cyst expansion, cyst rupture, intracystic haemorrhage).

Treatment

Treatment of the progressive CKD in ADPKD is as for other chronic nephropathies (ie hypertension control, RAA system blockade, prevention of CVS complications). Tolvaptan, an ADH-receptor antagonist, has been shown to limit cyst development and expansion, and it is hoped that it will have an effect on progressive CKD; trials are still ongoing.

Associations of ADPKD*

- Liver cysts: 70%
- Hepatic fibrosis (rare)
- Berry aneurysms: 5% (see below)
- Diverticular disease
- Pancreatic cysts: 10%
- Mitral valve prolapse or aortic incompetence

*There is no increased incidence of renal malignancy in ADPKD (see von Hippel–Lindau syndrome Section 15.7.2).

Intracranial aneurysms in ADPKD

These occur in 5% of ADPKD patients, but familial clustering is seen (ie if family history of aneurysms, then >20% of patients with ADPKD will have them). The majority are asymptomatic; the risk of rupture increases with aneurysm size (eg 4% per year if >10 mm). Rupture is associated with a 30–50% chance of severe morbidity/mortality due to subarachnoid haemorrhage. Most patients have normal renal function at the time of rupture. There is debate as to the value of screening (with MRA) for intracranial aneurysms in ADPKD.

15.7.2 Other renal cystic disorders

- **Autosomal recessive PKD**: rare (1/10 000 births). The gene is localised to chromosome 6. ESKD develops early in childhood; 100% have hepatic fibrosis. The prognosis is poor
- **The von Hippel–Lindau (VHL) syndrome**: autosomal dominant; the gene is localised on chromosome 3. Renal cysts are premalignant (>50%) and prophylactic bilateral nephrectomy is often necessary. It is likely that patients previously thought to have renal malignancy in association with ADPKD actually had VHL. Patients are also at risk of multiple spinocerebellar haemangioblastomas (which can be severely debilitating and are the main determinant of outcome in patients who are successfully transplanted), retinal angiomas, pancreatic cysts, islet cell tumours and phaeochromocytomas
- **Tuberous sclerosis**: dominantly inherited (either chromosome 9 or 16), and affects 1 in 10 000 individuals; patients develop epilepsy (80%), learning disability (50%), hamartomas, renal cysts and angiomyolipomas (usually do not require surgery; sirolimus can diminish growth). Skin lesions include shagreen patches, ash-leaf spots and adenoma sebaceum
- **Juvenile nephronophthisis–medullary cystic disease complex**: two different terms are used for two similar diseases that differ only in their age of onset and mode of transmission. Cysts occur in the renal medulla, and patients have chronic tubulointerstitial nephritis, salt wasting and progressive CKD. **Juvenile nephronophthisis (NPH)** occurs in children, is autosomal recessive, and accounts for up to 15% of childhood ESKD; 10–15% of children have retinal abnormalities (a form of retinitis pigmentosa). In adults, a histopathologically identical disease, **autosomal dominant medullary cystic disease**, leads to ESKD in the third and fourth decades; it is uncommon and not associated with extrarenal abnormalities
- **Medullary sponge kidney (MSK)**: sporadic; the cysts develop from ectatic collecting ducts. These may calcify, leading to the classic nephrocalcinosis associated with MSK. Patients have a

benign course, except that renal calculi and upper tract UTI are commonly associated

- **Acquired cystic disease**: cystic change is common in the rudimentary kidneys of dialysis patients, and especially in scarred kidneys; most cysts develop from proximal tubules. They are present in >5% of patients at the onset of RRT, and in >80% after 10 years of dialysis. Malignant change is thought to occur with an annual incidence of about 1%
- **Simple cysts**: fluid-filled, solitary or multiple, these are usually harmless, incidental findings at ultrasonography. The cysts may grow to considerable size (eg >10 cm). They occasionally require percutaneous drainage because of persistent loin pain. Simple cysts are very common, affecting 2% of patients aged <50 years, 11% aged 50–70 years and >20% of elderly people.
- The **Bosniak** system is used to classify the malignant risk of renal cysts (categorisation depends on the presence of cyst wall thickening, calcification, septations and solid components). A Bosniak I cyst is simple, category IV malignant. Category II and III cysts are 'indeterminate' and may require prolonged follow-up.

15.7.3 Alport syndrome

The prevalence of Alport syndrome is 1/5000 individuals. Genetic associations vary; 85% have X-linked dominant inheritance, but other families may show dominant or recessive inheritance. Many different gene defects have been recognised, which explains the clinical heterogeneity. The primary defect is an abnormal GBM (seen at electron microscopy) with variable thickness and splitting ('basket weave' appearance); the Goodpasture antigen is absent in the GBM (hence the predisposition of patients to anti-GBM glomerulonephritis after transplantation).

- Clinical presentation is with deafness (see below), persistent non-visible haematuria, proteinuria and CKD; 30% develop nephrotic syndrome
- CKD develops in all affected males; the rate of progression is heterogeneous between families (ie ESKD before 30 years in some, yet only by 60 years in others)
- Carrier females may have urinary abnormalities (haematuria, proteinuria), and usually do not develop CKD
- **Bilateral sensorineural deafness** is characteristic, but the hearing loss may be only mild; familial progressive nephritis may occasionally occur without deafness
- **Other extrarenal manifestations**: ocular abnormalities occur in 40% (**lenticonus** – conical or spherical protrusion of the surface of the lens into the anterior chamber, retinal flecks or cataracts), macrothrombocytopenia, leiomyomas (rare)
- The molecular defects involve the gene encoding for the α_5-chain of type IV collagen; alteration of this chain is thought to prevent integration of the α_3-chain into the GBM.

15.7.4 Thin basement membrane nephropathy

Up to 25% of patients referred to a nephrologist for investigation of non-visible haematuria have thin basement membrane nephropathy (TBMN). It is common in families, when it has also been termed 'benign familial haematuria' (BFH); the inheritance pattern is dominant although the gene has not been identified. The normal thickness of the GBM is around 450 nm; patients with TBMN/BFH have an

average GBM thickness of <250 nm. Patients usually have normal blood pressure and renal function; long-term follow-up is recommended because there appears to be a very small risk of CKD (perhaps because some patients have variants of Alport syndrome, or IgA nephropathy may coexist).

15.7.5 Other inherited disorders associated with renal disease

The list is far from comprehensive because many rare disorders have been described:

- **Conditions associated with renal structural disorders:**
  - Cystic renal diseases (see Section 15.7.2)
  - Branchio-otorenal syndrome (AD)
  - Dandy–Walker syndrome (polycystic kidneys [AR])
- **Inherited conditions with glomerular disease:**
  - Alport syndrome and variants (see Section 15.7.3)
  - Congenital nephrotic syndrome (eg Finnish type [AR])
  - Nail–patella syndrome (AD)
  - Familial GN (eg some forms of FSGS or IgA nephropathy; Wiskott–Aldrich syndrome [X-linked or XL])
  - Inherited complement deficiency
  - Charcot–Marie–Tooth disease (mostly AD; some variants AR or XL)
- **Metabolic disorders with renal involvement:**
  - Fabry's disease (XL)
  - Primary amyloidosis (AD)
  - Familial Mediterranean fever (AR)
  - Cystinosis (AR)
  - Primary oxalosis (AR)
- **Inherited tubular disorders:**
  - Cystinuria (AR)
  - Swachman syndrome (AR)
  - Marble brain disease (AR)
  - Hypophosphatasia (AR)
- **Renal diseases that have genetic influence:**
  - Benign familial haematuria (AD)
  - Reflux nephropathy (AR).

AD = autosomal dominant
AR = autosomal recessive

15.8 RENAL INTERSTITIAL DISORDERS

15.8.1 Interstitial nephritis

Inflammation of the renal tubulointerstitium may be acute or chronic; a recognised precipitating cause can be found in most patients.

Acute interstitial nephritis

AIN accounts for about 2% of all AKI cases, but for 25% of all drug-induced AKI cases. Most are due to an immunologically induced hypersensitivity reaction to an antigen – classically a drug (see box below) or an infectious agent. The presentation is usually with mild renal impairment and hypertension or, in more severe cases, AKI which is often non-oliguric. Systemic manifestations of hypersensitivity may occur and include fever, arthralgia, rash, eosinophilia and raised IgE.

- **Diagnosis**: urinalysis may be unremarkable (eg minor proteinuria), although urinary eosinophils may be present. If >1% of urinary white cells are eosinophils, then this suggests the diagnosis. Renal biopsy shows oedema of the interstitium with infiltration of plasma cells, lymphocytes and eosinophils; there is often ATN with variable tubular dilatation. Occasionally there is a granulomatous reaction (sarcoidosis can cause AIN). Note that AIN may need to be distinguished from acute pyelonephritis, in which condition most of the inflammatory infiltrate will be composed of neutrophils
- **Treatment**: cessation of precipitating cause (eg drugs). Most cases will improve without further treatment, but studies show that moderate-dose oral steroids (eg 1 mg/kg, tapered over 1 month) can hasten recovery of renal function. Most patients make a near-complete renal functional recovery.

Causes of acute interstitial nephritis

- **Idiopathic** (rare – can be associated with anterior uveitis)
- **Infections**: viral (eg Hanta virus), bacterial (eg leptospirosis), mycobacterial
- **Drugs**, eg rifampicin, allopurinol, methicillin, **penicillin**, **cephalosporins**, sulfonamides, furosemide, thiazides, cimetidine, amphotericin, aspirin, **NSAIDs**
- **Other**, eg sarcoidosis, Sjögren syndrome

Chronic tubulointerstitial nephritis

Many diverse systemic and local renal conditions can result in chronic inflammation within the tubulointerstitium. Patients present with CKD or ESKD; some patients may also manifest RTA (usually type 1), nephrogenic diabetes insipidus or salt-wasting states. Renal biopsy findings involve a chronic inflammatory infiltrate within the interstitium (granulomatous in sarcoid and tuberculosis [TB]), often with extensive scarring and tubular loss; the latter indicates that renal function can never be fully recovered.

Certain common causes of CKD are associated with tubulointerstitial nephritis (TIN) and

macroscopically abnormal kidneys, eg reflux nephropathy, analgesic nephropathy, obstructive and cystic renal disease. However, **TIN with macroscopically normal kidneys** accounts for about 3% of all cases of ESKD, and is seen with Sjögren syndrome, lithium toxicity, urate nephropathy, heavy metal nephropathy and Balkan nephropathy (see box).

Causes of chronic tubulointerstitial nephritis

- **Immunological diseases**, eg SLE, Sjögren syndrome, rheumatoid arthritis, systemic sclerosis
- **Haematological disorders**: myeloma, light-chain nephropathy, sickle cell disease
- **Heavy metals (and other toxins)**, eg lead, cadmium, Chinese herb nephropathy (see Section 15.13.3)
- **Metabolic disorders**, eg hypercalcaemia, hypokalaemia, hyperuricaemia
- **Other**: irradiation, chronic transplant rejection
- **Granulomatous disease**: Wegener's, TB, sarcoidosis
- **Drugs**: ciclosporin, cisplatin, lithium, iron, analgesics (see Section 15.8.2)
- **Chronic infections**: chronic pyelonephritis (TB)
- **Hereditary disorders**, eg nephronophthisis, Alport syndrome
- **Endemic disease**: Balkan nephropathy (see below)

Treatment of TIN

This is of the underlying condition (or drug/toxin withdrawal); steroids may be beneficial in some autoimmune or inflammatory disorders. The progressive CKD is treated as for other chronic nephropathies.

Balkan endemic nephropathy

A chronic renal interstitial disease endemic in rural villages along the tributaries of the river Danube (eg in Romania, Bulgaria, Serbia, Bosnia, Croatia). There is extensive scarring and patients progress to ESKD.

- Urothelial malignancy is increased 200-fold
- Patients have coppery yellow pigmentation of palms and soles
- **Aetiology**: this chronic interstitial disease is thought to be a slowly progressive toxic nephropathy. There is marked clustering of disease in the villages, and individuals moving to endemic disease can develop Balkan endemic nephropathy after 15 years. The most favoured aetiological factor is exposure to aristolochic acid, from seeds of the European birthwort, which can contaminate wheat used for bread making. Aristolochic acid is also responsible for Chinese herb nephropathy.

15.8.2 Analgesic nephropathy and papillary necrosis

Analgesic nephropathy

In the 1950s to 1970s analgesic nephropathy was the most common cause of both AKI and CKD in parts of Europe and Australia (eg 25% of ESKD cases in Australia), and was associated with excess phenacetin use. The condition is now uncommon, but occasional cases are seen in association with aspirin and NSAID overuse. The hallmarks of the condition are the history of chronic analgesic usage (eg for backache, pelvic inflammatory disease, headache) and of addictive or dependent personality traits, renal pain (due to papillary necrosis) and CKD. When IVU was in frequent use 'cup-and-spill' calyces due to papillary necrosis, with renal scarring, were the classic radiological features.

- Renal biopsy is of no diagnostic value
- Women are affected more often than men (4:1)
- As with other TIN, nephrogenic DI, salt wasting and distal RTA can be associated
- Increased risk of urothelial malignancy (there may be multiple synchronous lesions in the urinary tract).

Papillary necrosis

Causes of renal papillary necrosis

- **Toxic**:
  - Classic analgesic nephropathy
  - TB
- **Ischaemic**:
  - Sickle cell disease
  - Acute pyelonephritis
  - Accelerated hypertension
  - Profound shock
  - Diabetes mellitus
  - Urinary tract obstruction
  - Hyperviscosity syndromes
  - NSAID induced

15.9 REFLUX NEPHROPATHY AND URINARY TRACT INFECTIONS

15.9.1 Vesicoureteric reflux and reflux nephropathy

'Reflux nephropathy' is the term applied when small and irregularly scarred kidneys (**chronic pyelonephritis**, CPN) are associated with **vesicoureteric reflux** (VUR). It is the most common cause of CPN, but other disorders, such as obstructive injury and analgesic nephropathy, can also result in

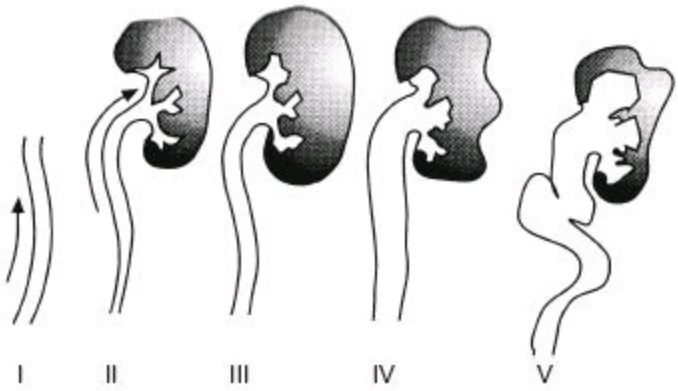
CPN. Renal scarring is necessary for the diagnosis of reflux nephropathy and this almost always occurs only during the first 5 years of life, when it is termed 'primary reflux nephropathy'. The end result of reflux nephropathy is hypertension, proteinuria, CKD and, sometimes, ESKD; reflux nephropathy still accounts for at least 10% of adult patients entering RRT programmes, and is a common cause of ESKD in children.

- **Epidemiology**: VUR is very common in utero, and 0.5% of all neonates are affected. Around 1% of children will have VUR, but this disappears in 40% by the age of 2 years. In young children, VUR usually presents with a complicating UTI. About 30% of children with a UTI will have some degree of VUR and 10% will have evidence of reflux nephropathy. Of women with symptomatic UTI, 5% will have reflux nephropathy; however, documented UTI occurs in <50% of adults with reflux nephropathy
- **Grading**: reflux can be graded – from grade I (involving reflux into ureter only) to grade V (gross dilatation and tortuosity of ureter, renal pelvis and calyces with severe scarring) – Figure 15.4
- **Diagnosis** is by micturating cystography (radionuclides can be used in children); scarring can be demonstrated by ultrasonography and DMSA
- **Pathogenesis of renal scarring**: scars will form only if there is intrarenal reflux accompanied by urinary infection. The scars form at the sites of the intrarenal reflux; severity of scarring is proportional to the degree of VUR. UTI occurring without VUR rarely leads to scarring
- **Genetic predisposition**: siblings of patients with reflux have a 30–50% chance of having VUR; parent-to-child transmission is 66%. Hence, offspring or siblings (if a child) of affected patients should undergo screening. The gene is thought to be dominant with variable penetrance due to environmental factors; the gene frequency has been estimated to be 1:600
- **Associated renal abnormalities**: abnormalities such as renal dysplasia are increased in children with VUR
- **Secondary VUR**: this is seen in patients with neurogenic bladders or other causes of bladder obstruction.

Management ofVUR and reflux nephropathy

All children with a UTI should be investigated for VUR with the aim of preventing renal scars. As these occur early in life, there is no place for anti-reflux surgery to prevent renal scars in adults who have VUR. Children with grade I–III reflux usually do not require surgery because it tends to resolve spontaneously; those with grade II or worse reflux should receive prophylactic antibiotic therapy (eg low-dose nitrofurantoin, trimethoprim or co-trimoxazole, or cefalexin in those with CKD) for several years in order to limit UTIs.

Figure 15.4 Classification of vesicoureteric reflux



Grade I: Ureter only
Grade II: Up to pelvis and calyces, but with no dilatation
Grade III: Mild-moderate dilatation, but with only minimal blunting of fornices
Grade IV: Moderate dilatation, with obliteration of sharp angles of fornices
Grade V: Gross dilatation and tortuosity of ureter and pelvi-calcyceal system. Calyces severely clubbed

For patients with grade IV and V VUR, treatment options include surgery (eg endoscopic injection of collagen behind the intravesical ureter, lengthening of the submucosal ureteric tunnel and ureteric reimplantation) or long-term antibiotics, depending on progression of scarring and patient choice. Whichever the approach, a UTI should be treated promptly and, as with all forms of chronic, potentially progressive renal disorders, hypertension must be controlled properly (with RAA system blockade favoured). Patients with reflux nephropathy have an increased incidence of renal calculi.

15.9.2 Urinary tract infection

Apart from the outer third of the female urethra, the urinary tract is normally sterile. UTIs are the most common bacterial infections managed in general practice; they predominantly affect women (except in infants, patients aged >60 years and those with co-morbid diseases). Coliforms are the most common pathogens. Several important definitions are applied:

- **Acute uncomplicated UTIs**: **acute cystitis** and **acute pyelonephritis**. The incidence of cystitis is 0.5% per year in sexually active women. It may recur in 40% of healthy women, even when their urinary tracts are normal. Three-day antibiotic treatment regimens are recommended for acute cystitis because of cost, compliance and efficacy. In those with recurrent cystitis, attention to hygiene, post-coital micturition and fluid intake is recommended; in postmenopausal women, intravaginal oestrogen pessaries that alter vaginal flora may be beneficial
- **Complicated UTIs**: this term is used when UTIs occur in patients with abnormal urinary tracts (eg stones, obstruction, ileal conduits, VUR, neuropathic bladder) or (very commonly) in patients with urinary catheters (see below). The definition also incorporates UTIs in patients with advanced CKD and renal transplants
- **Asymptomatic bacteriuria**: two separate urinary specimens showing bacterial colony counts of $>10^5$/mL of the same organism in an asymptomatic patient. The prevalence is 3–5% in adult women (and 0.5% in men); it increases greatly in elderly people (eg 50% of women) and institutionalised patients. The vast majority of cases require no treatment, but it should always be

treated if detected in pregnant women, because 15–20% will otherwise develop acute pyelonephritis

- **Urethral syndrome**: patients have 'abacterial' cystitis. Causes include true recurrent UTIs (but with low bacterial counts) and genital (eg *Chlamydia* sp.), vaginal (eg *Trichomonas* or *Candida* sp.) or fastidious organism (eg *Ureaplasma* or *Lactobacillus* sp.) infections. Postmenopausal women may develop the syndrome because of atrophic vaginitis due to oestrogen deficiency.

Long-term antibiotic treatment regimens: these may be appropriate for patients prone to recurrent UTIs, and especially in those with an underlying predisposition (except those with urinary catheters). The regimens may involve rotating monthly antibiotic courses (eg amoxicillin, quinolone and then a cephalosporin) or low-dose, once-daily, long-term therapy (eg nitrofurantoin or trimethoprim).

Predispositions to urinary tract infection

- **Abnormal urinary tract**: eg calculi, VUR, reflux nephropathy, analgesic nephropathy, obstruction, atonic bladder, ileal conduit, in-dwelling catheter
- **Pregnancy**: where the urinary tract abnormality – eg ureteral dilatation – is temporary
- **Impaired host defences**: immunosuppressive therapy (including transplanted patients), diabetes mellitus, atrophic vaginitis
- **Virulent organisms**: eg urease-producing *Proteus* sp.

Other specific forms of UTIs

- **Urinary catheter-associated infection**: up to 5% of all hospital admissions may be due to nosocomial UTIs, and most of these occur in patients with long-term in-dwelling catheters. The incidence of bacteriuria is 3–10% per day of catheterisation, and so the duration of catheterisation is the greatest risk factor. Avoidance of prolonged catheter use is now a prominent goal in hospitals. Most infections are asymptomatic, but catheter-associated infections are the most common source of Gram-negative septicaemia in hospitalised patients. Most cases of 'infection' do not require treatment; if lower urinary tract symptoms occur, a single antibiotic dose may be as effective as a full course of therapy (which predisposes to bacterial resistance), and the catheter should be changed. For prevention of UTIs in patients with long-term catheters, regular (eg 3-monthly) catheter change is recommended because organisms are harboured within the biofilm lining of the catheter
- **Prostatitis**: prostatitic symptoms are experienced by 50% of men, but are caused by bacteria in only a minority. **Acute bacterial prostatitis** is rare; patients present with symptoms of cystitis and the prostate is swollen and tender. There will be pyuria and a positive urine culture. The most common pathogens are the Gram-negative bacilli, *E. coli*, and *Proteus* and *Klebsiella* spp. Antibiotic treatment is needed for 1 month. **Chronic prostatitis** is manifest by recurrent UTIs with the same organism. It is characterised by a qualitative difference in the first voided urine (no pyuria), compared with that passed after prostatic massage (>10 white blood cells per high-power field, bacterial colony count 10-fold greater). Treatment is with quinolone antibiotics for 1–3 months

- **Renal abscess**: usually due to *Staphylococcus aureus* after haematogenous spread to the kidney. May present as a renal mass, but renal abscesses are often insidious and non-specific. CT is needed for diagnosis. Treatment is with antibiotics, percutaneous drainage for larger abscesses and sometimes nephrectomy
- **Emphysematous pyelonephritis**: this is a necrotising, life-threatening form of acute pyelonephritis caused by gas-forming organisms (including *E. coli*, and *Pseudomonas*, *Klebsiella* and *Proteus* spp.). 90% of cases occur in patients with diabetes. A plain film will demonstrate the gas, but CT will localise this better. Emergency nephrectomy and broad-spectrum antibiotics are required, but even then the mortality rate is 20%
- **Xanthogranulomatous pyelonephritis**: this is a rare, chronic, renal infection that is associated with obstruction and staghorn calculi. Renal tissue is replaced with lipid-laden infiltrating macrophages (foam cells); the xanthomatous tissue may extend beyond the renal capsule into neighbouring structures. Patients are usually middle-aged women with flank pain, fever, a palpable renal mass and positive MSU (midstream urine specimen). Nephrectomy provides the only chance of cure.

15.9.3 Tuberculosis of the urinary tract

TB reaches the urinary tract via haematogenous spread. Most patients are aged 20–40 years, with men affected twice as commonly as women. 25% of patients are asymptomatic; a further 25% have asymptomatic pyuria or non-visible haematuria, and painless visible haematuria is common. Hypertension is unusual, but genital involvement (epididymitis and prostatitis in men, salpingitis and pelvic pain in women) is commonly associated.

- The renal medullary regions are most commonly affected. In the early stages, ulcerating lesions and granulomas are seen in the renal pyramids and collecting systems; renal histology shows chronic interstitial nephritis with granulomas
- As the disease progresses, scarring occurs with ureteric strictures, hydronephrosis, subcapsular collections, perinephric abscesses or renal atrophy. The bladder may be fibrotic and small. The caseating material may eventually calcify
- **Treatment**: standard anti-tuberculous therapy is recommended. Surgery may be indicated for obstruction and strictures. Nephrectomy for non-functioning kidneys is no longer routine because prolonged anti-TB therapy can render the calcified, caseous masses (‘cement kidney’) sterile.

15.10 RENAL CALCULI AND NEPHROCALCINOSIS

15.10.1 Renal calculi (nephrolithiasis)

Renal stones are common, with an annual incidence of approximately 2 per 1000 and a prevalence of 3% in the UK; the lifetime risk is 10–15% in the West. Calcium-containing stones account for >70%.

Stone composition

- Calcium oxalate: 25%
- Mixed calcium oxalate/phosphate: 40%
- Calcium phosphate: 5%
- Urate: 10% (radiolucent)
- Cystine: 2%
- Xanthine: 1% (radiolucent)
- Staghorns ('struvite' containing magnesium ammonium phosphate and sometimes calcium): 20%; associated with infection with urease-producing bacteria (eg *Proteus* spp.)

Basic investigation

This should include stone analysis, MSU, assessment of renal function, serum calcium and phosphate, and a qualitative test for urinary cystine. The 24-hour urinary excretion of oxalate, calcium, creatinine and uric acid may also be helpful, and RTA should be excluded (urine pH).

Conditions predisposing to urolithiasis

- **Metabolic abnormalities**:
  - Idiopathic hypercalciuria (most common)
  - Primary hyperparathyroidism (and other causes of hypercalcaemia)
  - Renal tubular acidosis
  - Cystinuria
  - Hyperoxaluria (primary or secondary)
  - High dietary oxalate intake (eg glutinous rice or leafy vegetables in Thailand)
  - Uric aciduria
  - Hypocitraturia (eg chronic diarrhoea, excess laxative and diuretic use)
- **Renal structural abnormalities**:
  - Polycystic kidney disease
  - Medullary sponge kidney
  - Reflux nephropathy
  - Nephrocalcinosis (see Section 15.10.2)
- **Other causes**:
  - Chronic dehydration – common (eg chronic diarrhoea, warm climates)
  - Triamterene (less soluble in urine pH <6)
  - Industrial exposure to cadmium

Treatment

General measures: increased fluid intake and low-protein diet; reduced dietary oxalate intake.

Associated urinary infection should be eradicated where possible (very difficult with staghorn calculi). Treat other underlying causes (eg allopurinol for urate stones, surgery for hyperparathyroidism).

Thiazide diuretics (eg chlortalidone): increase tubular reabsorption of calcium in patients with hypercalciuria; they will therefore reduce the likelihood of supersaturation of calcium products within the urine. Citrate may be beneficial for calcium oxalate stones.

The specific treatment of patients with **cystinuria** is described in Chapter 13, Metabolic diseases.

Stone removal: ureteric calculi <0.5 cm may be passed spontaneously. Lithotripsy alone may be used for larger ureteric stones and for pelvicalyceal stones <4 cm (obstruction being prevented by double J-stent insertion); larger calculi can be 'de-bulked' by this technique before surgical extraction.

15.10.2 Nephrocalcinosis

This is defined as the deposition of calcium salts within the renal parenchyma; it may be associated with urinary calculi.

Causes of nephrocalcinosis

- **Cortical nephrocalcinosis**:
  - Cortical necrosis – after very severe acute ischaemic injury to the kidneys ('tramline' calcification)
  - Chronic glomerulonephritis
- **Medullary nephrocalcinosis**:
  - Hypercalcaemia (eg primary hyperparathyroidism, sarcoidosis, hypervitaminosis D, milk–alkali syndrome)
  - Hypoparathyroidism
  - Idiopathic hypercalciuria
  - Renal tubular acidosis
  - Primary hyperoxaluria
  - Berylliosis
  - Medullary sponge kidney
  - TB

15.11 URINARY TRACT OBSTRUCTION AND TUMOURS

15.11.1 Urinary tract obstruction

Chronic urinary tract obstruction (most often due to prostatic disease, calculi and bladder lesions) is a common cause of CKD; obstruction must also be excluded in every case of unexplained AKI. The

causes of renal tract obstruction are shown in the box below. The term 'obstructive nephropathy' refers to pathological renal damage resulting from obstruction.

Acute obstruction

This is often painful due to distension of the bladder, ureter(s) or pelvicalyceal systems. Complete obstruction will result in anuria and AKI; anuria may also occur even when obstruction is unilateral, due to an intense afferent arteriolar vasoconstriction (similar to that seen in ischaemic AKI).

- **Diagnosis**: obstruction is one of the few truly reversible causes of renal failure, but diagnosis and treatment need to be expedient in order to allow renal functional recovery. Ultrasonography is the chief mode of diagnosis, but it may show only minimal pelvicalyceal dilatation in the early stages of acute obstruction
- **Treatment and prognosis**: an obstruction at the bladder outlet should be relieved with catheterisation if feasible. For ureteric or vesicoureteric obstruction (eg due to bladder tumour), temporary drainage can often be achieved by percutaneous nephrostomy or endoscopic ureteric stenting, pending definitive surgical correction. Relief of obstruction may be followed by massive diuresis (temporary nephrogenic DI), and if within 2 weeks, full renal functional recovery is likely, unless there is complicating pyonephrosis.

Chronic obstructive nephropathy

This is usually associated with CKD or ESKD and it is often complicated by chronic UTIs. Obstruction accounts for 5% of all cases of ESKD. Salt-wasting nephropathy and chronic metabolic acidosis are common complications.

- **Differential diagnosis**: there may be diagnostic uncertainty when the upper tracts are dilated (but non-obstructed). This is seen in VUR, post-obstructive atrophy, congenital megacalyces and megaureters, and some cases of CPN. In such cases, diuresis renography or retrograde pyelography will exclude obstruction. Occasionally, Whitaker's test, which involves puncture of the collecting system followed by pressure flow studies, is necessary to diagnose obstruction
- **Pathology and outcome**: there is permanent renal histopathological damage that results from a combination of parenchymal compression, renal ischaemia and sometimes infection. In severe cases, severe tubular loss, interstitial fibrosis and cortical atrophy are observed. If the obstruction is relieved (eg in <12 weeks), renal functional decline can stabilise and dialysis may be prevented.

Causes of urinary tract obstruction

- **Within the lumen**:
  - Tumour (eg urothelial lesions of bladder, ureter or renal pelvis)
  - Renal calculi
  - Papillary necrosis (sloughed papilla)
  - Blood clot
- **External compression**:

- Malignancy: retroperitoneal neoplasia including para-aortic lymphadenopathy and pelvic cancer (eg cervical or prostatic carcinoma)
- Other 'tumours': aortic aneurysm; pregnancy (hydronephrosis of pregnancy is very common, is usually asymptomatic and resolves fully after delivery); haematomas
- Aberrant arteries (pelviureteric junction [PUJ] obstruction)
- Retroperitoneal fibrosis (eg malignant, idiopathic, peri-aortitis, drugs [see Section 15.11.2])
- Prostatic disease: benign hypertrophy or malignancy
- Inflammatory disorders (eg diverticulitis, Crohn's disease, pancreatitis)
- Iatrogenic (eg accidental surgical ligation of ureter)

- **Within the wall of urinary tract structures**:
  - Neuromuscular dysfunction (eg PUJ obstruction, neuropathic bladder [spina bifida, spinal trauma – see below])
  - Ureteric or vesicoureteric stricture: TB, schistosomiasis, previous calculi, after surgery, congenital, irradiation (eg for seminoma of testis), malignancy, ureterocele
  - Urethral stricture: infection (eg gonococcal), following instrumentation
  - Posterior urethral valves (see below)
  - Congenital bladder neck obstruction

Neuropathic bladder

In childhood**, spina bifida** with myelomeningocele is by far the most common cause of a neuropathic bladder. Spina bifida has an incidence of around 1–2 per 1000 births; siblings of affected individuals have a 10- to 20-fold increased chance of having the condition. Urinary tract complications are present at birth in 15%, and will develop in 50%, often over many years. Most of these patients have incomplete bladder emptying due to urethral sphincter dyssynergia, but those with the mildest neurological lesions are paradoxically able to generate very high pressures within the bladder, with the greatest risk of renal damage.

- The main urinary tract abnormalities are incontinence, infection and reflux with upper tract dilatation, the latter leading to CKD and ESKD
- Patients often have associated bowel dysfunction
- **Treatment**: with anticholinergic drugs, intermittent self-catheterisation and, in more severe cases, urinary tract diversion into an ileal conduit. Note that chronically infected urinary tracts will need to be removed before renal transplantation.

Posterior urethral valves

These occur in male infants and account for 10% of childhood hydronephrosis; the valves are mucosal diaphragms in the posterior urethra at the level of the prostate. Posterior urethral valves can now be detected antenatally using ultrasonography. 50% of patients present before the first year of life with poor urinary stream, distended bladder and failure to thrive (due to renal failure). Most have VUR and dilated upper tracts.

Treatment: urinary diversion should be avoided; self-catheterisation is usually necessary.

Approximately 20% of affected individuals will progress to ESKD, largely because of late initial presentation.

15.11.2 Retroperitoneal fibrosis

An uncommon, progressive condition in which the ureters become embedded in dense fibrous tissue (the ureters are drawn medially), often at the junction of the middle and lower thirds of the ureter, leading to obstruction. Most cases are thought to result from an immunologically mediated periaortitis, and steroids are of benefit in these 'idiopathic' forms of retroperitoneal fibrosis (RPF); they may need to be continued for 2 years.

- **Other associations**: retroperitoneal malignancy (eg colonic, bladder or prostatic cancer, lymphoma), previous irradiation, inflammatory abdominal aortic aneurysm, other fibrosing conditions (eg mediastinal fibrosis, sclerosing cholangitis), drugs (eg methysergide and some β blockers) and granulomatous disease (TB or sarcoidosis)
- **Investigation**: erythrocyte sedimentation rate (ESR) is often very high; CT urography will show medial deviation of the ureters and a peri-aortic mass.
- **Treatment**: ureterolysis (with tissue biopsy) with long-term steroid therapy in inflammatory cases (because relapse is common). Malignant RPF can be palliated with ureteric stenting or percutaneous nephrostomy.

15.11.3 Urinary tract tumours

Benign renal tumours: include adenomas, which are very common (however, just as with thyroid adenoma and carcinoma, their histological differentiation from malignant lesions can be difficult), hamartomas, angiomyolipomas (associated with tuberous sclerosis) and renin-secreting (juxtaglomerular cell) tumours.

Renal cell carcinoma (hypernephroma): arise from the tubular epithelium; they are more likely in smokers, and at least 50% of patients with von Hippel–Lindau syndrome will develop them (usually multiple and bilateral). As mentioned previously, **acquired cystic kidney disease** in patients with renal failure is also a risk factor; the cumulative incidence of malignant change is about 1%, and these account for 80% of renal cell carcinomas in dialysis patients.

- Renal cell carcinoma has a propensity to invade the renal veins, with passage of tumour emboli to the lung
- Other unusual clinical features include pyrexia of unknown origin (PUO), left varicocele (renal vein invasion leads to left testicular vein occlusion), and endocrine effects (secretion of erythropoietic factor resulting in polycythaemia [3%], PTH-like substance, renin and ACTH). The 5-year survival rate is about 50%.

Wilms' tumours (nephroblastomas): these are tumours of early childhood, derived from embryonic renal tissue (so containing combinations of poorly differentiated epithelium and connective tissues). They can become enormous and metastasise early. Treatment is with nephrectomy and actinomycin D, providing a 5-year survival rate of 90%.

Urothelial tumours: very common and usually derived from transitional epithelium, although squamous carcinoma (worse prognosis) is recognised. The usual presentation is with bleeding or urinary tract obstruction. Tumours can be multiple, and so investigation of the complete urinary tract is indicated.

- Several carcinogens (eg smoking, rubber and aniline dye exposure), and analgesic nephropathy have been aetiologically linked to this type of malignancy
- Other risk factors include renal calculi, cystic kidney disease, chronic cystitis and *Schistosoma haematobium* infection (note that *Schistosoma mansoni* is associated with GN)
- Nephroureterectomy is indicated for lesions of the ureter or renal pelvis, and cystectomy with resection of the urethral mucosa for advanced bladder cancer; surgery combined with radiotherapy provides a 5-year survival rate of 50%. Survival is much better for lower-stage lesions.

Metastatic disease (involving the kidney): most commonly from breast, lung, stomach, lymphoma or melanoma.

15.12 SYSTEMIC DISORDERS AND THE KIDNEY

15.12.1 Amyloidosis

Amyloidosis occurs when certain proteins, most of which are normal constituents of plasma, develop a particular conformational pattern (β-pleated sheet) and are deposited in an organised formation within organs. Many different amyloid proteins are now recognised; some are abnormal, others genetically derived, and in the more common forms of amyloid, there is overproduction of the protein. Kidney involvement leads to presentation with proteinuria, nephrotic syndrome or CKD; biopsy demonstrates characteristic Congo red-staining extracellular fibrillar material within the mesangium, interstitium and vessel walls. Radionuclide scan (amyloid fibrils labelled with ^{123}I localise to amyloid deposits after injection) is used to demonstrate the full extent of disease in all organs. Amyloid is now classified according to the amyloid proteins involved.

Light chain amyloid (AL-amyloidosis)

The incidence of AL-amyloidosis is 9 per million per year. This is a monoclonal plasma cell disorder closely related to myeloma; some patients fulfil the diagnostic criteria for myeloma. Free immunoglobulin light chains, or light chain fragments (hence the 'L'), are secreted by a clone of B cells. Median age of presentation is >60 years.

- Nephrotic syndrome, postural hypotension and peripheral neuropathy are more likely in cases without myeloma
- AL-amyloid may infiltrate any organ other than the brain, eg heart (restrictive cardiomyopathy in 30%, sick sinus syndrome and arrhythmias), macroglossia, GI tract (motility disturbance, malabsorption, haemorrhage), neuropathy (peripheral and autonomic) and bleeding diathesis
- **Treatment**: mirrors the management of myeloma with high-dose melphalan and then autologous bone marrow transplantation in selected cases. Other treatments include thalidomide and

dexamethasone

- **Prognosis**: when patients present with renal complications prognosis is poor, with a median survival of 12 months, and only 25% alive at 3 years. Survival is shorter in those with myeloma, heart disease and autonomic neuropathy. Cardiac involvement accounts for half of deaths.

AA-amyloidosis

This was previously termed 'secondary amyloid'. Chronic infections (eg TB, empyema) now account for fewer AA-amyloid cases than previously; 70% are due to autoimmune inflammatory conditions (eg rheumatoid arthritis). In these conditions, the amyloid protein A is derived from acute phase reactants, and is made in the liver. In AA-amyloidosis, the kidney is the main target organ – cardiac involvement and neuropathy are uncommon. Prognosis is slightly better than for AL-amyloidosis, with median survival of 25 months, and a 40% 3-year survival rate.

Treatment: the underlying inflammatory or infective disorder should be treated. Colchicine has been shown to prevent disease progression in **familial Mediterranean fever** (another form of AA-amyloidosis), which is encouraging. It has undergone trials in patients with rheumatoid arthritisrelated amyloid with some success. A few patients with AA-amyloidosis have received renal transplants; recurrent amyloid is seen in >10%.

Classification of amyloidosis

AL, AA and dialysis-related amyloid are systemic amyloidoses.

AL type, which is serum amyloid protein A coupled with immunoglobulin light chains:

- Myeloma; monoclonal disorder with paraproteinaemia

AA type: serum amyloid protein A binds to high-density lipoprotein (HDL)

- **Chronic suppurative disorders**
  - TB, osteomyelitis, empyema, bronchiectasis, syphilis, leprosy
- **Chronic inflammatory disorders (fibrils derived from acute phase proteins)**
  - **Rheumatological conditions**: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Still's disease, Reiter syndrome, Sjögren syndrome, Behçet's disease
  - **Gastrointestinal conditions**: Whipple's disease, inflammatory bowel disease
  - Familial Mediterranean fever
- Other causes:
  - Paraplegia
  - Renal cell carcinoma.

Many hereditary amyloidoses are recognised (see below):

Dialysis-related amyloid

This does not deposit in the kidneys, because it is a complication of long-term dialysis. It is due to

failure of clearance of β_2-microglobulin (see Section 15.5.4).

Hereditary renal amyloid: a group of rare conditions related to a mutation in a specific protein, most commonly transthyretin amyloid. Other forms include abnormalities in lysozyme, fibrinogen and apolipoproteins ApoA1 and ApoA2.

15.12.2 Renovascular disease

Atherosclerotic renovascular disease

Atherosclerotic renovascular disease (ARVD) accounts for >90% of all renovascular disease. It increases with ageing and is associated with common atherogenic risk factors (ie hypertension, hypercholesterolaemia, smoking, diabetes), as well as with the presence of generalised vascular disease. It can be demonstrated in >10% of patients with IHD undergoing coronary angiography, >30% with peripheral vascular disease and it affects 30% of patients with congestive heart failure (CHF). With ever-ageing RRT programmes, ARVD is commonly detected in ESKD patients (15–20%), although it probably accounts for the renal failure (then termed 'ischaemic nephropathy') only in the minority (see below).

Clinical presentation is with hypertension, CKD or ESKD, 'flash' pulmonary oedema (5%), and AKI due to acute arterial occlusion or related to renin–angiotensin blocker use. Prognosis is poor (5-year survival rate <20%) due to co-morbid vascular events. Many cases of ARVD are thought to be incidental, the arterial narrowing occurring in association with prior hypertension and CKD (proatherogenic state), rather than being the cause of them. 90% of RAS lesions are 'ostial' (occurring within the first centimetre of the renal artery origin).

- **Flash pulmonary oedema**: sudden onset of acute heart failure in the absence of a myocardial ischaemic event. Patients typically have LVH, severe hypertension and severe bilateral renal artery disease. The episodes of pulmonary oedema are more common at night, presumably because of posture-related redistribution of fluid and diurnal variations in vasoactive peptides
- **Pathogenesis of CKD**: the correlation between severity of proximal lesions (ie degree of RAS or occlusion) and renal function is poor; this explains why only a minority of revascularisation procedures lead to clinical improvement. Parenchymal disease, manifested by intrarenal atheroma, ischaemic change, hypertensive damage and cholesterol embolisation, is usually the major determinant of renal functional outcome
- **Radiological diagnosis**: **MRA** can be performed safely in most patients with CKD stages 3 and 4; the possibility of gadolinium-related nephrogenic systemic fibrosis (see Section 15.2.2) limits its use in more severe CKD. **CTA** is commonly used, but prophylaxis against contrast-induced nephropathy may be necessary. **Duplex ultrasonography** combines measurement of proximal renal artery blood flow velocity with intrarenal resistive index and, although time-consuming and highly operator dependent, it is an accurate test for detection of ARVD and assessing RAS severity. **Conventional intra-arterial angiography** is now reserved for confirming RAS severity before revascularisation
- **Revascularisation**: around 10% of ARVD patients undergo revascularisation therapy, and endovascular techniques (renal angioplasty with stenting) account for >95% of procedures (surgical reconstructions are reserved for complicated lesions, eg related to aortic aneurysm).

- Two large RCTs, the ASTRAL and CORAL trials, between them totalling >1750 patients, have shown that revascularisation added to standard medical therapy (statins, aspirin and antihypertensives) does not improve renal function, blood pressure control, CVS event rate or mortality when compared with medical therapy alone. However, these RCTs did not enrol specific patient sugroups such as those with AKI or flash pulmonary oedema, and these are considered definitive indications for revascularisation.

Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) accounts for 10% of all renovascular disease; it occurs in young people (20–35 years), and most patients are female. The RAS lesions may be long and can be distal in the renal artery, sometimes appearing as a 'string of beads' at angiography. Patients usually present with severe hypertension, but renal failure is unusual. As the kidney beyond a fibromuscular stenosis is usually healthy, revascularisation may cure the hypertension. FMD is associated with other arterial lesions (eg carotid stenosis in 15%).

15.12.3 Connective tissue disorders and the kidney

Most of the connective tissue disorders have the propensity to cause renal disease, and characteristic features are described below (see also Chapter 20, Rheumatology); lupus nephritis and systemic sclerosis merit more detailed coverage.

- **Mixed connective tissue disease**: membranous or diffuse proliferative GN (uncommon)
- **Sjögren syndrome**: renal involvement is most often manifest by renal tubular dysfunction (RTA 1 or 2) with interstitial nephritis; cryoglobulinaemia and membranous or focal proliferative GN are less common
- **Rheumatoid arthritis**: renal disease is common, and usually due to amyloid or less often the effects of drug therapy. Rheumatoid-related GN (typically mild mesangioproliferative change) is manifest by microscopic haematuria and mild proteinuria. Membranous GN is also recognised (cases due to gold or penicillamine therapy are now rare because of the use of modern disease modifying anti-rheumatic drugs (DMARDs)
- **Seronegative spondylarthropathies**: ankylosing spondylitis and Reiter syndrome can be associated with IgA nephropathy
- **Relapsing polychondritis**: this rare disorder is associated with cartilage inflammation, leading to destruction and deformity (eg saddle nose, floppy ears). Crescentic, mesangioproliferative or membranous GN may occur.

SLE nephritis

Over 5% of patients with SLE have renal involvement at presentation, and around 60% of patients will develop overt renal disease at some stage. Lupus nephritis is more common in Black patients and women (10-fold greater than in men), and 90% will have ANF antibodies. Renal disease can be manifest by any syndromal picture (eg proteinuria, nephrotic syndrome, rapidly progressive GN with AKI, CKD) but proteinuria is present in most patients with nephritis. Similarly, many different patterns of glomerular disease are recognised (the histological picture may even change over time

within the same individual). Note that drug-induced SLE only rarely affects the kidneys. Although lupus nephritis can present with marked patient morbidity, most cases respond well to prompt immunosuppressive treatment.

Renal histology: the histological pattern has some prognostic value, with focal proliferative disease having a favourable renal outcome; advanced sclerosing cases have the worst renal prognosis. 'Wire loop' lesions (thickened capillary walls – electron microsopy shows electron-dense deposits) are characteristic; immunofluorescence is positive for most immunoglobulins (IgG, IgM, IgA) and complement components (C3, C4, C1q). A synopsis of the ISN (International Society of Nephrology) and RPS (Renal Pathology Society) classification is as follows:

- Class I: minimal mesangial changes
- Class II: mesangioproliferative changes
- Class III: focal proliferative GN (variable severity)
- Class IV: severe diffuse proliferative GN
- Class V: membranous GN
- Class VI: advanced sclerosis.

Treatment: patients with mild disease (eg classes I and II) usually require no treatment. However, irrespective of class, most patients with significant proteinuria are likely to receive at least prednisolone and ACE inhibitor therapy. Acute SLE with AKI (classes III and IV) should be treated as for RPGN/ crescentic nephritis (see Section 15.6.2), with an intense induction regimen (high-dose steroid, and usually pulsed intravenous cyclophosphamide, or MMF in young women), followed by maintenance therapy. Patients with class V histology who present with the nephrotic syndrome are treated similarly, although there is less evidence of benefit. Although plasma exchange has been used in patients with crescentic disease and those with severe extrarenal manifestations of SLE, there is again little evidence of improved outcome.

- MMF is favoured over cyclophosphamide in treatment of women of childbearing age
- In many patients the immunosuppression can be tapered, and withdrawn by 5 years, even in those presenting with severe AKI.

Prognosis of renal lupus: <10% of cases with nephritis now progress to ESKD (historically, renal disease used to be the most common cause of death in SLE). The SLE syndrome often becomes quiescent once the patients reach RRT. Lupus nephritis rarely recurs in renal transplant recipients.

Systemic sclerosis

Renal disease is always accompanied by hypertension; the hallmark presentation is 'scleroderma renal crisis' with accelerated hypertension, microangiopathic haemolytic anaemia and AKI. Prominent pathological changes are seen in the interlobular arteries (severe intimal proliferation with deposition of mucopolysaccharides – so-called 'onion skin' appearance); fibrinoid necrosis of afferent arterioles and secondary glomerular ischaemia are common. The essential treatment is with RAA system blockade for hypertension control; some patients develop ESKD, but renal function sometimes recovers in patients who presented with renal crisis. The overall prognosis is poor because of other organ involvement (especially restrictive cardiomyopathy and pulmonary fibrosis).

15.12.4 Diabetic nephropathy

Diabetic nephropathy is now the most common cause of ESKD in the UK, accounting for 17% of patients. In recent years there have been advances in the understanding of the natural history, pathogenesis and treatment of diabetic nephropathy, but the mortality of this group remains high, largely because of associated CVS disease.

Epidemiology

Established or clinical nephropathy (see below) is associated with macroalbuminuria (>300 mg albumin/24 h, which equates to >500 mg/24 h of total proteinuria), and occurs with a cumulative incidence of 30% after 40 years in patients with type 1 diabetes. In those with type 2 diabetes, nephropathy is already prevalent in 10% at the time of diagnosis (reflecting previous 'subclinical' hyperglycaemia), but the cumulative incidence of nephropathy is similar to that for type 1. About 80% of patients with type 2 diabetes and nephropathy will succumb to other complications (usually CVS or infections) before they develop significant CKD and ESKD. As type 2 diabetes is 10–15 times more common than type 1 in Western populations, it accounts for 75% of the patients with diabetes seen in CKD clinics or on RRT programmes. In a UK diabetic clinic, the prevalence of patients with nephropathy is about 5%.

- Genetic influence: patients in certain racial groups who have diabetes have a far greater risk of developing nephropathy (eg Asians, Pima Indians). In the UK, the likelihood of ESKD is threefold greater in Asian and African–Caribbean people with diabetes than in White people
- Nephropathy is usually associated with retinopathy (common basement membrane pathology); renovascular disease and other arterial pathology are common.

Natural history of nephropathy

In type 1 diabetes, the stages of development of nephropathy have been well characterised:

- **Stage 1**: at the time of diabetes diagnosis the GFR is elevated by >20% compared with age-matched controls. Urinary albumin excretion rate (UAER) is also increased; both are reduced by commencement of insulin
- **Stage 2**: GFR remains elevated (due to hyperfiltration) and kidneys are hypertrophied, but blood pressure and UAER are normal. The GFR appears to be linked to glycaemic control, with greatest hyperfiltration associated with worse control. There are early histological changes with thickening of GBMs and mesangial expansion. This stage typically lasts for 5–15 years after diabetes diagnosis
- **Stage 3**: microalbuminuria (or 'incipient nephropathy') is present (UAER 30–300 mg/day, or uACR 3–30 g/mol). The GFR remains elevated or returns to the normal range. Blood pressure starts to rise (in 60%). Microalbuminuria occurs in 30–50% of patients at 5–10 years after diabetes onset, and 80% of these patients go on to develop overt nephropathy (stage 4) by 10–15 years. Histological changes progress from those seen in stage 2
- **Stage 4**: 'established' (also known as 'clinical' or 'overt') nephropathy is associated with increasing macroproteinuria, which may become nephrotic in 30%, and declining GFR (eg average 2–10 mL/min per year). Hypertension is present in 80% and is correlated with the rate of decline of GFR. Renal histology typically shows diffuse glomerular sclerosing lesions (all

patients) and vascular changes; 10% have Kimmelstiel–Wilson nodules (focal glomerular sclerosis)
- **Stage 5**: development of ESKD occurs at an average of 7 years from onset of stage 4.

It is thought that the development of nephropathy occurs in a similar fashion in type 2 diabetes, but increased GFR is rarely seen because of age-related renal vascular changes and co-morbidity.

Screening and prevention

Patients should be **screened** for microalbuminuria in the diabetic clinic; the urinary ACR can be assessed in an early morning specimen or equally well in random spot urine samples. An ACR >2.5 (men) and 3.5 (women) g/mol is generally taken as the cut-off for microalbuminuria (equivalent to a UAER >25 mg/24 h).

- Studies in patients with type 1 diabetes have shown that tight glycaemic control can reduce the likelihood of patients developing microalbuminuria (by 40%); intensive insulin regimens may prevent or delay some microalbuminuric patients progressing to overt nephropathy
- The latter has been clearly shown in trials using ACE inhibitors in type 1 diabetes, and with ARBs in type 2. These agents also slow the time of doubling of serum creatinine and hence the time to ESKD in patients with established nephropathy; comparisons with other antihypertensive agents suggest that their renoprotective effects are partly independent of hypertension control
- It is now accepted that blood pressure should be targeted to 130/80 mmHg in patients with stage 4 nephropathy – this will slow, but not prevent, the inexorable decline of GFR in patients with overt nephropathy.

Outcome

The mortality of these patients is very high (eg patients with type 1 diabetes have a 20-fold greater mortality than the general population), and this relative risk may be magnified a further 25-fold in those with proteinuria. The 2-year mortality rate is 30% in patients with ESKD, largely due to co-morbid cardiovascular disease. As mentioned, more patients with type 2 diabetes and stage 4 nephropathy will die than reach ESKD.

- Microalbuminuria confers an excess risk of mortality compared with patients with normoalbuminuria, eg 4-year mortality rate 28% in patients with type 2 diabetes with microalbuminuria, compared with 4% in those without. It is thought that microalbuminuria represents the renal manifestation of a generalised vascular endothelial dysfunction
- All patients who reach ESKD are considered for RRT. Most patients require screening for coronary artery disease before listing for transplantation; combined renal and pancreatic transplantation is now feasible in selected patients (see Section 15.5.5). The 5-year survival rate of transplanted patients with diabetes is 45–75%, compared with around 20% for those who remain on dialysis

15.12.5 Thrombotic microangiopathies

Haemolytic–uraemic syndrome and **thrombotic thrombocytopenic purpura** share similar renal histological features and microangiopathic haemolytic anaemia (MAHA), but the causative factors

underlying these processes are different (see also Chapter 9, Haematology). There is endothelial damage with leukocyte and platelet activation, widespread inflammation and RBC fragmentation with schistocytes, a raised lactate dehydrogenase (LDH) and reduced haptoglobin level. Platelet clumping occurs within intravascular thrombi, and hence thrombocytopenia is a major feature. The typical renal histological lesions include intraglomerular thrombi with ischaemia and arteriolar lesions.

Haemolytic–uraemic syndrome (HUS)

HUS is the most common cause of AKI in children (because AKI is rare in children), but it is also seen in adults (5 cases/million per year). Children aged <4 years account for 90% of cases. Two main forms of HUS are recognised.

Shiga-like toxin producing E. coli HUS (STEC-HUS)

Previously termed 'diarrhoea-associated HUS'. The onset is explosive, with AKI, severe anaemia and thrombocytopenia, and epidemics of the disease occur. A third of UK cases are due to shiga-like toxin producing *E. coli* O157:H7; the toxin damages vascular endothelium, predisposing to the microangiopathy. *Shigella dysenteriae* can also be associated.

Treatment is supportive with transfusions, dialysis, plasma and plasma exchange, although the benefit of the latter has not been proven in clinical trials. Assessing RBC fragmentation and the platelet count are the best means of monitoring disease activity. The survival rate is 90% and most recover renal function.

Atypical HUS

This tends to affect older children and adults and accounts for 10% of all HUS cases; atypical HUS (aHUS) is thought to result from genetic defects leading to chronic, uncontrolled complement activation, which initiates the endothelial damage. Familial forms exist and neurological complications (stroke and encephalopathy) are more likely than with STEC-HUS.

Treatment is initially supportive during the acute presentation. Thereafter, eculizamab, a terminal complement inhibitor, has been shown to provide longer-term stabilisation. Thirty per cent either die or reach ESKD in the first clinical presentation.

Thrombotic thrombocytopenic purpura (TTP)

In TTP the presentation can be indolent, and neurological abnormalities occur in 65% (due to formation and release of microthrombi within the brain vasculature). Idiopathic and secondary forms are recognised. Idiopathic TTP is thought to be an autoimmune disease with antibodies directed against a metalloproteinase, ADAMTS13, which normally breaks down multimers of von Willebrand's factor (vWF). With low levels of ADAMTS13, vWF builds up and triggers platelet activation and intravascular thrombosis.

Treatment: plasmapharesis or plasma exchange, with supportive RBC/platelet transfusion and plasma infusion. Untreated, the mortality rate is >90%; with optimal treatment, 80% survive.

Secondary causes of HUS and TTP

These include:

- Pregnancy-associated thrombotic microangiopathy (see Chapter 12, Maternal medicine)
- TTP
- HELLP syndrome (HELLP = **h**aemolysis, **e**levated **l**iver enzyme, **l**ow **p**latelet count)
- Post-partum HUS
- HIV-associated thrombotic microangiopathy
- Cancer-associated thrombotic microangiopathy
- Drugs (eg ciclosporin, aciclovir, quinine)
- Bone marrow transplantation.

Differential diagnosis of STEC-HUS, a HUS and TTP

As the clinical presentations and haematological features are very similar, but aetiology and treatments differ significantly, early and correct diagnosis is essential. The ADAMTS13 test and testing for shiga toxin and enterohaemorrhagic *E. coli* (EHEC) are indicated.

- TTP: ADAMTS13 <5%
- STEC-HUS: normal or slightly reduced ADAMTS13 but positive test for shiga toxin or EHEC
- Atypical HUS: normal ADAMTS13 and negative tests for shiga toxin/EHEC.

15.12.6 Hypertension and the kidney

A detailed description of hypertension is beyond the scope of this chapter, but see Chapter 1, Cardiology. The kidney is often damaged by essential hypertension, or it can be central to the pathogenesis of many cases of secondary hypertension.

Primary (essential) hypertension and renal damage

End-organ renal damage is common and is usually manifested as asymptomatic proteinuria and/or CKD (**hypertensive nephrosclerosis**). Microalbuminuria develops in 20–40% of patients with essential hypertension, and persistent proteinuria (occasionally nephrotic) in a smaller proportion. Typical histological lesions include vascular wall thickening and luminal obliteration, with widespread interstitial fibrosis and glomerulosclerosis.

- CKD develops in 10–20% of patients; the risk is greater in African–American individuals who develop intrarenal small-vessel disease (nephroangiosclerosis)
- Progression to ESKD occurs in 2–5% over 10–15 years. Isolated hypertension accounts for about 30% of all cases of ESKD in the USA (where African–American individuals are four times more likely to develop ESKD than White people) and 10–15% in the UK
- It is thought that many patients who present with ESKD of unknown aetiology, especially with small, smooth kidneys visible on ultrasonography, actually have long-standing hypertensive renal disease.

Treatment and targets: all patients should have their blood pressure controlled to <140/85 mmHg. In those with CKD, or with significant proteinuria, the blood pressure target should be <130/80 mmHg. RAA system blockers are specifically indicated for the reasons described earlier in the

chapter.

Hypertensive emergency (previously termed 'malignant' or 'accelerated hypertension'): this refers to presentation with severe diastolic (DBP >120 mmHg) and/or systolic (SBP >180 mmHg) hypertension in association with acute end-organ damage (eg grade 3 or 4 retinopathy, with haemorrhages and/or exudates (grade 3) with/without papilloedema, AKI, cardiac failure or stroke). The condition constitutes a medical emergency. Typical histological lesions include arterial fibrinoid necrosis (which also accounts for the retinal abnormalities) coupled with severe tubular and glomerular ischaemia.

Secondary hypertension

Over 90% of hypertension is idiopathic, approximately 5% is due to renal disease, 3% is due to primary hyperaldosteronism and <1% has either an alternative rare endocrine or other cause.

Hypertension due to renal disease

Renal disease accounts for most cases of secondary hypertension. The pathogenesis involves stimulation of renin release with activation of the RAA system, reduced natriuretic capacity (in advanced CKD) and disorganisation of intrarenal vascular structures. Most patients with CKD are hypertensive, and it is evident in at least 90% of the dialysis population and >60% of transplant recipients. It is a chief contributor to the LVH and associated high cardiovascular mortality of these patients.

- Most forms of renal disease are complicated by hypertension, but exceptions are some patients with chronic pyelonephritis who have salt wasting (typically with normal blood pressure despite advanced CKD)
- Although cases of RAS are invariably associated with hypertension, the stenosis will be causative only in the minority
- **Coarctation of the aorta**: hypertension is seen in the upper limbs only. Rib notching may be seen on radiography
- **Endocrine**: Cushing syndrome, phaeochromocytoma, acromegaly and apparent mineralocorticoid excess (see section 15.3.4) are all rare causes. It is now believed that **primary hyperaldosteronism** (associated with bilateral or unilateral adrenal hyperplasia) may account for about 3% of all hypertension (see Chapter 1, Cardiology and Chapter 4, Endocrinology)
- **Other secondary hypertension**: alcohol, obesity.

15.12.7 Myeloma and the kidney

Myeloma occurs with an incidence of 30–40 cases/ million, and at a median age of 70–80 years. Renal involvement may present with AKI, CKD and/or proteinuria. Note that Bence Jones proteinuria is not detected by standard urinary dipsticks.

Renal failure due to myeloma

AKI: some degree of renal impairment is observed in 50% of patients with myeloma; this is reversible in the majority (in those in whom it is secondary to hypercalcaemia, hypovolaemia,

infection or nephrotoxic drugs), but 10% of patients may need dialysis. The latter cases are usually due to myeloma cast nephropathy.

CKD: due to amyloidosis, and cast nephropathy associated with chronic interstitial nephritis.

Myeloma cast nephropathy

In this, free κ (the most nephrotoxic) and λ light chains excreted in the urine damage the tubules by direct nephrotoxicity and cast formation. The intratubular casts are composed of hard, needle-shaped crystals and excite an interstitial infiltrate, often with multinucleate giant cells. ATN and tubular atrophy occur, and hence the potential for some recovery from an AKI episode.

- Patients with light chain only myeloma are more likely to have renal involvement
- Cast nephropathy may also be seen in patients with MGUS (see below).

Treatment: is with rehydration and supportive therapy. Hypercalcaemia should be treated with intravenous bisphosphonates. AKI may improve with plasma exchange – the results of an RCT are awaited. The myeloma should be treated with bortezomib (Velcade) and dexamethasone-based initiation regimens; other therapies include cyclophosphamide, melphalan and thalidomide. Younger patients, and those with lower tumour bulk and few complications, may be considered for autologous stem cell transplantation.

Prognosis: renal recovery is seen in only about 15–20% of patients with myeloma cast nephropathy who require dialysis. The remainder need RRT – the prevalence of myeloma patients on dialysis programmes is about 2%. Renal transplantation is not appropriate. Patients with myeloma and ESKD have poor survival rates (<50% at 1 year). Those with the greatest tumour mass have the worst prognosis.

Monoclonal gammopathy of undetermined significance

See also Chapter 9, Haematology.

Formerly known as benign monoclonal gammopathy, MGUS may be associated with light chain nephropathy, interstitial nephritis, amyloid and also mesangiocapillary GN. A proportion of patients with MGUS will develop myeloma during long-term follow-up (typically 1% per year).

15.12.8 Renal vasculitis

The kidney is often involved in systemic vasculitic illness. Several disorders are recognised (see also Chapter 20, Rheumatology).

Small vessel pauci-immune vasculitis

These conditions affect small vessels (arterioles and veins) and are associated with GN, and pulmonary and skin vasculitis. They are usually associated with positive serum ANCA. Incidence is 10–20 cases/ million each year. The major conditions are defined as follows:

Wegener's granulomatosis: respiratory tract disease is characteristic, and this involves necrotising granulomas within the upper respiratory tract (leading to sinusitis and nasal

- discharge, as well as damage to the nasal septum) and lungs (with haemoptysis). About 70% of patients are cANCA (which is directed against proteinase 3; PR_3) positive and 25% pANCA (directed against myeloperoxidase; MPO) positive
- **Churg–Strauss syndrome**: vasculitis that is associated with asthma, eosinophilia and necrotising inflammation; 60% have positive pANCA; 30% are ANCA negative
- **Microscopic polyangiitis (MPA)**: vasculitis occurring in the absence of evidence for the above two conditions (ie no asthma, eosinophilia or necrotising granulomatous inflammation); 50% are pANCA positive and 40% cANCA positive.

In all conditions, **AKI** is the usual renal presentation; renal histology shows necrotising glomerulitis typically associated with focal proliferative and/or crescentic GN. Pulmonary involvement is common, but blood pressure may be normal. Various forms of vasculitic skin rash (ranging from purpura to skin necrosis) are seen.

Treatment: all of the above three conditions normally merit high-dose immunosuppressive therapy; typical regimens are described in 'Treatment of RPGN and crescentic nephritis' in Section 15.6.2. Patients with cANCA-positive disease are more likely to relapse after the cessation of maintenance therapy. In such cases, immunosuppression is continued for several more years.

Prognosis: 1-year renal and patient survival rate is >80%. Poorer renal prognosis is seen in patients with severe renal failure and/or oligoanuria at presentation. Mortality is increased in patients with pulmonary haemorrhage. The risk of vasculitic relapse in transplanted patients is 20%.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a rare, medium-sized arterial vasculitis that results in microaneurysm formation; hypertension is usually severe, and renal infarcts rather than GN are characteristic. Patients are usually ANCA negative (unless there is also small-vessel involvement, ie PAN–MPA overlap – these patients can develop GN). Pulmonary (infiltrates and haemorrhage), GI tract (infarcts), neurological (mononeuritis multiplex) and systemic features (myalgia, PUO) are recognised, but the condition is notoriously difficult to confirm. A few cases are associated with hepatitis B infection.

Treatment is as for small-vessel vasculitis/crescentic nephritis.

Other vasculitides that can affect the kidney

- **Henoch–Schönlein nephritis**: in addition to the typical systemic features of this condition, some patients develop renal disease as a result of small-vessel (typically postcapillary venulitis with IgA deposition) vasculitis. Glomerular lesions range from mild mesangial hypercellularity (similar to idiopathic IgA nephropathy) through to crescentic nephritis
- **Kawasaki disease**: acute febrile illness, usually in children, associated with a desquamating erythematous rash and necrotising arteritis in some patients. It is the most common cause of myocardial infarction in childhood, but significant renal disease is uncommon
- **Takayasu arteritis**: this can be associated with RAS and renovascular hypertension
- **Giant-cell arteritis**: has been associated with RPGN, but such cases may represent Wegener's granulomatosis with temporal artery involvement.

15.12.9 Sarcoidosis and the kidney

Sarcoidosis (see Section 15.8.1) can be associated with:

- **AKI**: due to AIN; 90% of patients have systemic manifestations of sarcoidosis (eg hepatosplenomegaly, hypercalcaemia)
- **CKD**: associated with CIN and hypercalcaemia. Glomerular disease (membranous or proliferative GN) may rarely occur, and is associated with microscopic haematuria and significant proteinuria.

Treatment: most patients respond promptly to oral steroids, which can be tapered at 3–6 months. Relapses occur, but are usually steroid-responsive. Serum ACE may be useful for monitoring disease activity and predicting likelihood of relapses.

15.13 DRUGS AND THE KIDNEY AND TOXIC NEPHROPATHY

See also Chapter 2, Clinical pharmacology, toxicology and poisoning.

15.13.1 Renal elimination of drugs

Drugs may be eliminated via the kidneys by two main mechanisms:

- **Glomerular filtration**: a passive process; such drugs will be water soluble
- **Active tubular secretion**: drugs act as substrates for secretory processes that are designed to eliminate endogenous molecules; the tubular pathways are different for organic anions (basolateral tubular membrane) and cations (located on the luminal brush border).

Examples of drugs that are secreted by the tubule

- **Anionic drugs**:
  - Acetazolamide
  - Cephalosporins
  - Penicillin
  - Loop diuretics
  - Thiazide diuretics
  - Probenecid
  - Salicylates
- **Cationic drugs**:
  - Amiloride
  - Cimetidine
  - Ranitidine

- Metformin
- Morphine
- Quinine

15.13.2 Drug nephrotoxicity

Drugs can lead to renal damage in a number of different ways, and examples are given below.

Alterations in renal blood flow

- **NSAIDs**: alteration in prostaglandin metabolism can lead to a critical reduction in glomerular perfusion (particularly when there is reduced renal reserve or CKD). Interstitial nephritis may also result from NSAIDs
- **ACE inhibitors and ARBs**: AKI occurring in patients who are critically dependent on the RAA system – those with reduced renal perfusion (eg CCF, loop diuretics, hypovolaemia and severe RAS) – is well recognised with these agents
- **Ciclosporin and tacrolimus**: toxicity can be acute (due to renal vasoconstriction) or chronic. The latter is a common cause of transplant dysfunction, and is associated with arterial damage (intimal proliferation and hyaline degeneration of the vascular media), tubular vacuolation and atrophy, and interstitial fibrosis.

Direct tubular toxicity

- **Aminoglycosides**: disturbance of renal function is seen in up to a third of patients receiving aminoglycosides. 5% of filtered gentamicin is actively reabsorbed by proximal tubular cells, within which the drug is concentrated; binding to phospholipid results in disturbed intracellular regulation, with inhibition of microsomal protein synthesis and, eventually, cellular necrosis (ATN)
- **Cisplatin**: selectively toxic to proximal tubular cells, by inhibiting nuclear DNA synthesis; ATN results. The platinum component may not be the major damaging influence because carboplatin is less nephrotoxic
- **Amphotericin**: this is toxic to distal tubular cells in a dose-dependent manner; ATN results and is accompanied by non-oliguric AKI. Liposomal formulations minimise the nephrotoxic risk.

Glomerulonephritis

- **Gold**: now rarely used in rheumatoid treatment; previously, gold led to proteinuria in 5% of patients in a non-dose-related manner within 6 months of the start of therapy. On cessation of the gold, resolution of proteinuria is seen by 6 months. Gold is found in mesangial cells at renal biopsy; it is believed to induce an immune-complex GN (usually membranous, but occasionally minimal change nephropathy)
- **Penicillamine**: risk of membranous GN greater than with gold; it is dose related, and the onset of proteinuria may be later (18 months after the start of treatment).

Other nephrotoxic effects of drugs

Interstitial nephritis and RPF have been covered in earlier sections, and drug-induced SLE syndromes in Chapter 20, Rheumatology. **Lithium** is commonly associated with CKD due to an interstitial fibrosis; this usually stabilises with dose reduction or drug withdrawal. Nephrogenic DI can also occur.

15.13.3 Toxic nephropathy

This refers to renal damage resulting from drugs (as above), or radiocontrast media (see section 15.4.3) or environmental toxins (eg heavy metals) and poisons (eg Paraquat).

Causes of environmental and occupational toxic nephropathy

- **Heavy metals**:
  - Mercury: AKI, proteinuria and nephrotic syndrome (minimal change or membranous nephropathy)
  - Lead: acute poisoning leads to AKI with ATN; chronic interstitial nephritis and Fanconi's syndrome are seen with chronic exposure
  - Cadmium: similar renal pathology and clinical presentation as for lead
  - Arsenic: acute poisoning causes AKI with ATN and cortical necrosis; interstitial fibrosis leads to CKD with chronic exposure
  - Bismuth: proteinuria, Fanconi syndrome and AKI have been described
- **Hydrocarbons and organic solvents**:
  - Carbon tetrachloride
  - Ethylene glycol: this is rapidly metabolised to oxalic acid which crystallises within the renal tubules; ATN results
  - Petroleum-based hydrocarbons: these can predispose to GN (eg Goodpasture syndrome or membranous GN)
  - Paraquat: AKI, but usually lethal due to accompanying irremediable pulmonary disease
- **Plant and animal toxins**:
  - Snake, spider and hornet venoms: directly nephrotoxic, or induce ATN, cortical necrosis (often associated with disseminated intravascular coagulation), or muscle necrosis and rhabdomyolysis
  - Bee sting: rare cause of nephrotic syndrome
  - Mushroom poisoning: AKI
  - Poison ivy or oak: rare causes of nephrotic syndrome

REFERENCES

Acute Kidney Injury – NCEPOD report (Adding insult to injury):

1) http://www.ncepod.org.uk/2009aki.htm

2) The SHARP study: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial, Lancet 2011; 377: 2181–92

3) KDIGO CKD-mineral and bone disorder guidelines: http://www.kdigo.org/pdf/KDIGO%20CKD-MBD%20GL%20KI%20suppl%20113.pdf

Chapter 16
Neurology

CONTENTS

Neurology

16.1 NEUROLOGICAL ASSESSMENT

The purpose of neurological assessment can be focused on answering the following three questions:

1. Is there a neurological lesion?
2. Where is the lesion (neuroanatomical localisation)?
3. What is causing the lesion (pathophysiological process)?

16.1.1 Neurological history

The importance of a careful and structured neurological history cannot be overemphasised. In general, if one does not have a clear idea of the level(s) of the nervous system that are likely to be involved, to inform the subsequent examination, then the history should be retaken.

The structure of neurological history taking is similar to that in general medicine, but some aspects deserve emphasis:

- Age: can be fundamental in formulating the likely differential diagnoses, eg in a patient with a first seizure
- Occupation: can be fundamental in contextualising the impact of the patient's presenting symptoms, eg a loss of consciousness in a group 2 vehicle driver
- Handedness: assesses likelihood of cerebral dominance (94% of right-handers are left hemisphere dominant, whereas only 50% of left-handers are) and the impact of symptoms, eg tremor or weakness in a dominant or non-dominant hand.

The time course of the neurological symptoms, their frequency and pattern of evolution (shape) can yield useful information as to the underlying aetiology (Figures 16.1 and 16.2).

Figure 16.1 Time course of onset neurological symptoms by aetiology

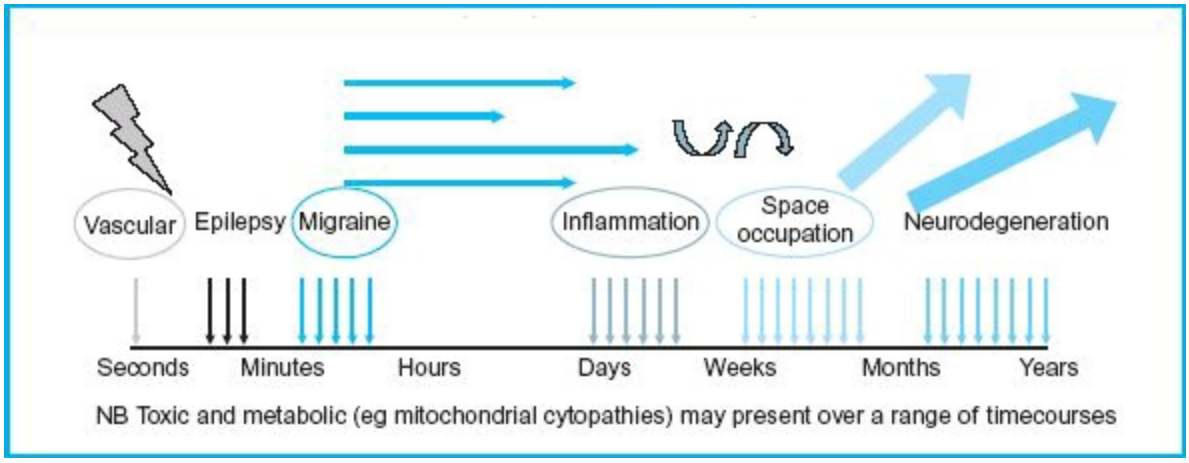
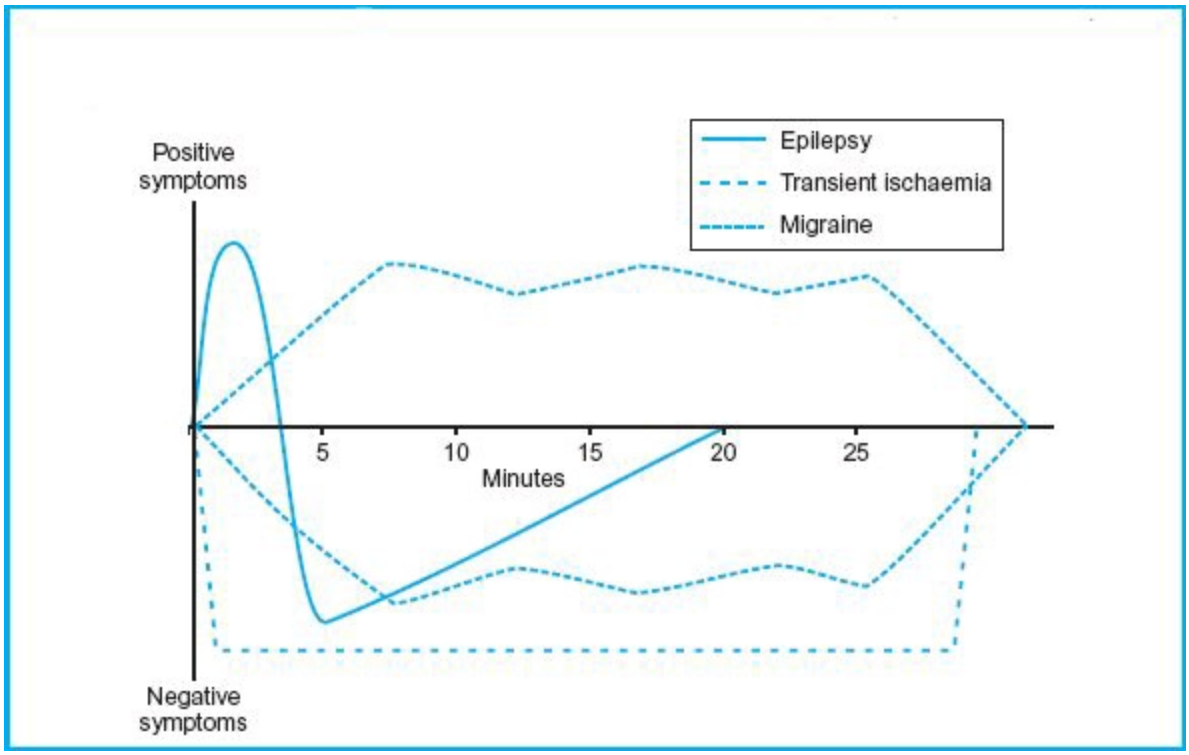


Figure 16.2 Demonstrating how the 'shape' of three common neurological conditions – seizures, transient ischaemic attacks and migraine – and their positive and negative neurological features in the history help to differentiate them



- Acute (seconds to minutes): may imply a vascular aetiology
- Subacute (hours to days): may imply an inflammatory aetiology
- Chronic (weeks to months): may imply a structural lesion
- Chronic (months to years): may imply a degenerative aetiology
- Metabolic (including mitochondrial cytopathies, see Section 16.8.3) and toxic aetiologies: can present with any of the above time courses and acute-on-chronic phenomena can occur, eg a bleed into a cerebral tumour could cause a sudden exacerbation of a slowly progressive deficit

Transient ischaemic attacks, for example, are typically sudden in onset and cause negative symptoms – loss of vision, numbness and/or weakness – which peak over seconds as a result of arterial occlusion. Seizures, caused by synchronous electrical discharge of cortical neurons, when focal, typically cause positive symptoms initially, such as limb jerking, tingling or coloured visual

phenomena, but may leave short-lived post-ictal deficits, such as numbness, weakness or blindness, which resolve rapidly. Migraine, due to slow (2–3 mm/ min) spreading of a depressive wave across the cerebral cortex, can cause a mixture of positive and negative phenomena, eg bright visual phenomena followed by blurred vision, tingling of a limb followed by heaviness and weakness. Seizures and migrainous phenomena are typically stereotyped, and this can be a useful feature in determining whether recurrent pathophysiological phenomena affecting the nervous system are occurring, compared with patients who describe random phenomena that do not locate reliably to a location in the nervous system.

16.1.2 Neuroanatomical localisation

It is useful to consider the levels of the nervous system that are involved by history and examination findings (Table 16.1).

Table 16.1 Useful questions or features in detecting deficits at particular levels of the nervous system

Level of nervous system	Questions
Cerebral cortex	Dominant hemisphere (if the patient retains insight) Do you have problems with speech, reading, writing, comprehension? Non-dominant: visuospatial (*usually found on examination)*? Neglect, denial, inattention,[a] apraxia (dressing)
Cerebellum	Arm clumsiness: Do you struggle to insert/turn a key in a lock/light a cigarette! Leg clumsiness: Do you stagger/walk as if you are drunk? Ask about brainstem symptoms, because blood supply is shared and there are numerous interconnections
Brainstem	Brainstem symptoms: Do you have double vision, decreased facial sensation, droopiness of the face, vertigo, slurred speech, problems swallowing
Spinal cord	Distal arm weakness: Do you drop things and/or have a poor grip? Leg weakness: Do you trip or drag your feet or wear out the tips of your shoes? Symmetrical **Sensory level**: Do you have a feeling similar to a band of tightness or a belt or girdle around your trunk? **Sphincter dysfunction**: Are you incontinent of urine or do you feel that you haven't emptied your bladder properly? Have you noticed a change in your bowel habit (usually constipation)? Have you noticed any changes in your sexual function? Is the feeling normal?
Root	Do you experience shooting pain in a particular body area or pins and needles or numbness

Peripheral nerve	Distal arm weakness: Do you drop things and/or have a poor grip? Distal leg weakness: Do you trip or drag your feet or wear out the tips of your shoes? Asymmetrical: Is your weakness or changes in sensation confined to an area or areas of your body? Denervation changes: Have you noticed any thinning and/or twitching of your muscles? Sensory: Have you noticed any numbness or tingling or pins and needles?
Neuromuscular junction	Does your strength wax and wane? Is your weakness worse at end of day/on sustained action – reading, looking up, talking for long periods, chewing meat?
Muscle	Proximal arm weakness: Do you have problems lifting grocery bags, your young children or books? Proximal leg weakness: Do you have problems getting out of the car or standing from a chair without using your hands?

[a]For example, ask patients to perform a task with each hand in turn (they will continually use one hand). Alternatively test sensation separately on each side of the body in turn and the patient will detect these. Then test on both sides simultaneously; the patient will perceive the stimulus only on one side. Similar tests are possible for the visual fields.

16.1.3 Differences between upper and lower motor neuron lesions

A fundamental distinction in neuroanatomical localisation is the differentiation between lesions of the upper and lower motor neurons. The upper motor neuron (UMN) runs from area 4 of the cerebral cortex to the anterior horn of the spinal cord. Fifteen per cent of fibres decussate in the lower medulla to form the anterior corticospinal tract, and 85% decussate to form the lateral corticospinal tract. The lower motor neuron (LMN) runs from the anterior horn of the spinal cord to the neuromuscular junction. Familiarity with the differences in clinical signs produced by lesions of the UMN and LMN are a fundamental skill of neurological assessment (Table 16.2).

16.2 BRAIN DISORDERS

Dementia

- Degenerative
- Non-degenerative

Acute and subacute confusional states (delirium)

- Systemic causes
- CNS-specific causes

CNS infections

- Encephalitis
- Meningitis
- Myelitis – infective

Antibody-mediated encephalitis

Table 16.2 Differences in clinical features between upper and lower motor neuron lesions

	Upper motor neuron lesion	**Lower motor neuron lesion**
Symptoms noticed by patient	May be long before clinical evidence	Short
Muscle wasting	Mild	Marked
Fasciculations (visible **spontaneous** contraction of groups of muscle fibres)	No	Yes
Tone	Increased[a]	Decreased/Normal
Weakness	Pyramidal Upper limb – extensor weakness Lower limb – flexor weakness	Either root/peripheral nerve
Reflexes	↑ ± clonus	**↓/absent**
Plantar responses	Extensor or normal	Normal
Superficial reflexes	Absent (abdominal reflexes lost in lesions above T9)[b]	

[a]In the *acute* phases of stroke or in spinal shock, for example, there may be flaccid tone and depressed reflexes, and it takes days to weeks for the tone and reflexes to increase.

[b]Only relevant in young, thin patients with an unscathed abdomen.

16.2.1 Cerebral cortex and cognition

The cortex and cognition

Cognition is the mental act of acquiring knowledge and understanding via thought, experience and sensation. A wide range of neurological and general medical disorders may affect this process.

The cortex is the outer, grey matter portion of the brain. It is connected to deep structures (such as the thalamus and basal ganglia) by ascending and descending white matter tracts, and a rich network of corticocortical pathways connects cortical regions to each other.

Cortical localisation

Cortical localisation refers to the concept that specific areas of cortex are involved in specific

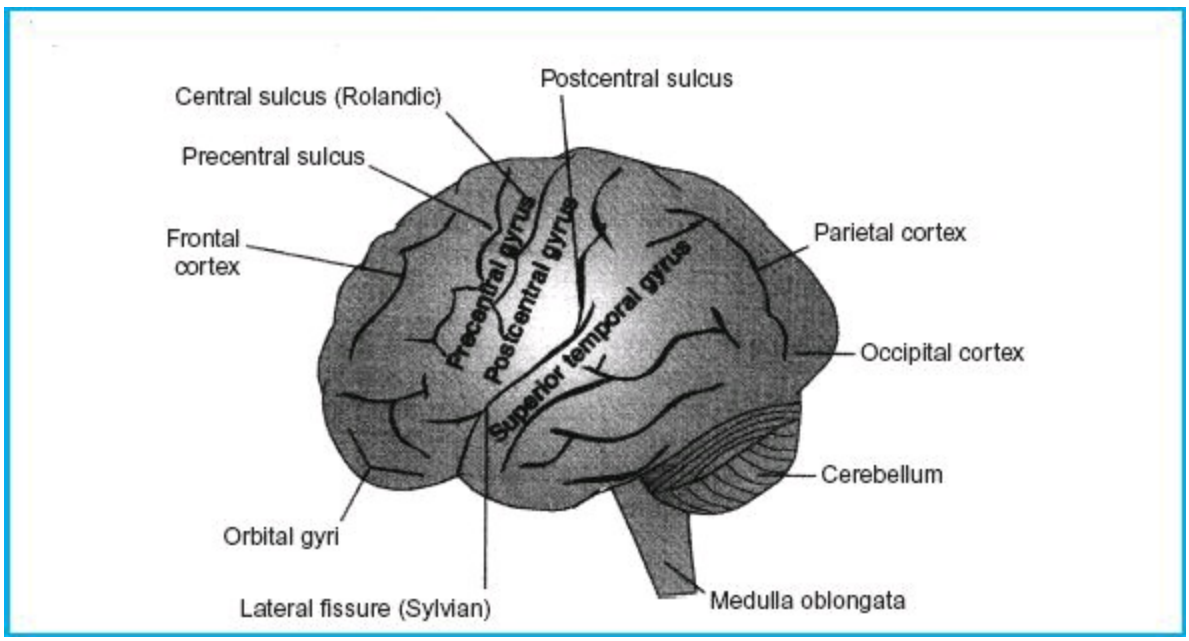
neurological and cognitive functions. Although over-simplistic, this concept serves as an excellent model for beginning to understand why certain brain lesions produce certain patterns of clinical symptoms and signs. The cortex of each hemisphere can be divided into four main lobes: frontal, parietal, temporal and occipital. Each of these lobes contains a 'primary' cortical area. The motor cortex is in the precentral gyrus of the frontal lobe, the somatosensory cortex in the postcentral gyrus of the parietal lobe, the auditory cortex in the superior temporal gyrus and the visual cortex in and around the calcarine fissure of the occipital lobe. Association cortices that support the primary function of that part of the cortex surround each primary cortical area. In addition to this, there are cortical regions throughout the brain involved in higher cognitive functions, and these too can be broadly split up according to which lobe they are in (Figure 16.3).

Frontal lobe

The frontal lobe is closely associated with executive function, ie the process by which we are able to plan, carry out, evaluate and alter our approach to complex tasks. It controls our regulation of the other cognitive functions. The frontal lobe is also involved in regulation of behaviour and social conduct. It is important in motivation and goal-directed behaviour. Frontal lobe damage can cause alterations in behaviour that may be characterised by either apathy or disinhibition.

The left hemisphere is responsible for language in most people. Broca's area, in the inferior frontal gyrus, is critical for speech production and many other aspects of speech output are controlled by the dominant frontal lobe.

Figure 16.3 Surface anatomy of the brain



Parietal lobe

Parietal lobe functions can be broadly split into dominant and non-dominant features. In the dominant (usually left) parietal lobe there are regions that are critical for reading, writing and calculation. Praxis, the ability to perform learned skilled tasks, is also subserved largely by the dominant parietal lobe. This is a significant oversimplification; this complex function probably involves a distributed network of regions throughout the brain. The non-dominant (usually right) parietal lobe is critical for visuospatial tasks and lesions here may result in spatial neglect, where the patient ignores the left side of space. More commonly, lesions will result in problems with visual construction and dressing.

Anosognosia describes the phenomenon whereby patients do not recognise their own neurological deficit and occurs in non-dominant parietal lobe lesions.

Temporal lobe

Once again, it simplifies matters to consider dominant and non-dominant temporal lobes separately. In the dominant temporal lobe there are cortical areas critical for word knowledge and semantic memory. In the posterior dominant temporal lobe is Wernicke's area which is responsible for comprehension of spoken language. Cortical regions needed for face and object recognition are found in the non-dominant temporal lobe. On the medial aspect of both temporal lobes are found the hippocampi, and these structures are required for memory formation.

Occipital lobe

The major functions found here are visual and important with regard to perception of colour and motion (see Section 16.3, Neuro-ophthalmology).

16.2.2 Dementia

Dementia is a syndrome defined as loss of mental functions, due to brain disease, that is sufficiently severe to interfere with daily functioning. Consciousness is not affected. Most dementias are chronic, progressive conditions. It is an umbrella term and many different diseases can cause the syndrome of dementia; it is not a feature of normal ageing. In contrast, delirium is an alteration in mental function with fluctuating levels of consciousness and arousal. Once again, this is a syndrome and not a specific diagnosis; there are many causes of delirium and these differ from the causes of dementia.

Neurodegenerative disease accounts for the greatest proportion of dementia cases. The principal neurodegenerative causes of dementia are:

- Alzheimer's disease
- Dementia with Lewy bodies
- Parkinson's disease
- Frontotemporal dementia
- Primary progressive aphasia.

Rarer causes of neurodegenerative dementia include:

- Progressive supranuclear palsy
- Huntington's disease
- Prion disease.

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative dementia and usually affects people aged >65 years, with incidence rising with increasing age. It is associated with well-described pathological changes in the brain comprising extracellular amyloid β plaques and intracellular hyperphosphorylated tau tangles. Multiple neurotransmitter deficits are seen, particularly a loss of cholinergic function. Progressive atrophy of the brain occurs, often predominantly affecting

medial temporal regions and the parietal cortex.

The apolipoprotein E (*APOE*) gene on chromosome 19 is a risk factor for AD. There are three alleles (e2, e3 and e4), and having one or two copies of the e4 allele increases the chance of an individual developing AD. In addition to this risk gene, there are three main genes known to cause rare autosomal dominant forms of AD. Presenilin 1, presenilin 2 and amyloid precursor protein genes all cause early-onset hereditary AD.

The presenting symptom of AD is usually amnesia, but patients also develop other cognitive problems in language, praxis, calculation and visuospatial functioning. Occasionally these other cortical symptoms can be the presenting complaint. Patients initially have preserved insight into their condition. Personality and behaviour are not significantly affected in the earlier stages of the disease, reflecting relative sparing of the frontal lobe functions. Patients often have a normal neurological examination although, as the disease progresses, mild parkinsonism and myoclonus may be seen.

There is no treatment to alter the progression of AD at the current time. Cholinesterase inhibitors (eg donepezil) are licensed for the treatment of AD and are supported by national UK guidelines (NICE). They work by increasing levels of acetylcholine in the brain. A further drug, memantine, has now been licensed for use in AD.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementia and similar to AD, predominantly affects people aged >65 years. Pathologically, the hallmark is the accumulation of Lewy bodies, which are intracellular aggregates made up of α-synuclein. These accumulate in the brainstem and cortex. From a pathological point of view, these Lewy bodies are the same as the aggregates seen in Parkinson's disease and also in multiple system atrophy (MSA). In DLB there are multiple neurotransmitter deficiencies, but notably affected are the cholinergic and dopaminergic systems.

The clinical presentation of DLB may be similar to AD with problems in memory, language and visuospatial functioning. However, there are some characteristic features that set it apart. Patients with DLB tend to have a fluctuating level of arousal that produces variations in levels of cognitive impairment; at times patients may seem acutely confused and at other times quite lucid. In addition, patients with DLB frequently hallucinate and typically see well-formed, non-threatening, visual hallucinations. Many patients have symptoms of rapid eye movement (REM) sleep behaviour disorder and this can be present for years before the other features of DLB manifest. On examination the patient may be parkinsonian, although at presentation this can be subtle. As the disease progresses, the parkinsonism becomes more obvious.

Cholinesterase inhibitors are used to treat the cognitive symptoms and dopaminergic medication can be used to treat the parkinsonism, although a balance must be struck because too much dopaminergic medication tends to worsen confusion and hallucinations.

Patients with Parkinson's disease may develop very similar cognitive impairments to patients with DLB, and this is termed 'Parkinson's disease dementia' (PDD).

Frontotemporal dementia

This is the second most common form of degenerative dementia in the people aged <65 years, AD still being the most common. It is a heterogeneous condition and there are multiple types of

pathological change associated with it. Approximately half of frontotemporal dementia (FTD) cases are caused by tau pathology (commonly Pick's bodies) and most of the rest are associated with transactive response DNA-binding protein 43 (TDP-43) inclusions. A small number of patients have fused-insarcoma (FUS) pathology. Pathologically FTD is linked to many other neurodegenerative conditions; the pathological changes of progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), both tauopathies, may be seen post-mortem. Progressive atrophy of the frontal and temporal lobes is seen on neuroimaging.

Cases of FTD are more likely to be hereditary than the other neurodegenerative dementias. Up to 40% of patients with FTD have a family history of dementia or a related neurodegenerative condition. The first two genes identified were both on chromosome 17: microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*). More recently, a hexanucleotide repeat expansion in *C9orf72* was discovered and is now the most common genetic cause of FTD. Mutations in *C9orf72* can also cause familial motor neuron disease (MND) and some patients develop a combination of FTD and MND.

FTD presents with alterations in behaviour, personality and social conduct. Neuropsychological testing may reveal executive difficulties. Patients may appear disinhibited or apathetic. Many patients have a disorder of language production associated with their behavioural syndrome. Although patients are typically free of focal neurological deficits, on bedside examination, some patients do exhibit frontal release signs such as the grasp reflex. In time patients may develop parkinsonism and, as mentioned above, some patients develop signs of MND.

There are currently no licensed treatments for FTD and management is based on optimising social care and educating caregivers to cope with the patient's behaviours.

Primary progressive aphasia

Primary progressive aphasia (PPA) refers to a progressive disturbance in language, sufficiently severe to interfere with daily activities. Three clinical syndromes are currently recognised. Non-fluent variant PPA and semantic variant PPA correspond closely to the older terms of progressive non-fluent aphasia (PNFA), and semantic dementia (SD). These syndromes are typically associated with the same range of pathologies that are seen in FTD. A newly described subtype, logopenic variant PPA, is more commonly associated with AD pathology. Left hemisphere atrophy, particularly around the perisylvian fissure, is seen on neuroimaging, with different regional variations corresponding to the different clinical syndromes. These syndromes are typically sporadic with only rare hereditary cases.

Non-fluent variant PPA presents with effortful speech production problems characterised by deficits in speech sound production (apraxia of speech) and/or agrammatism (inability to speak in grammatically correct sentences). Left-sided inferior frontal atrophy is usually seen. Semantic variant PPA presents with fluent, effortless speech that is empty of meaning due to loss of semantic knowledge – patients do not know what words mean and cannot name items on neuropsychological testing. Atrophy of the anterior temporal lobes, left more than right, is usually seen. Logopenic variant PPA presents with word-finding difficulties in spontaneous speech, difficulty repeating sentences and sound-based speech errors (phonological paraphasia), particularly for longer words. The condition is associated with atrophy of the left posterior temporal and parietal lobes.

There are no licensed treatments, although some patients find speech and language therapy of benefit.

Prion disease

The prion diseases are fatal, transmissible spongiform encephalopathies, with the prion acting as the transmissible or 'infectious' agent. Prion disease may occur sporadically or be transmitted; some forms may also be inherited. Prions are misfolded proteins that induce the abnormal misfolded state in other neighbouring proteins, thus propagating the disease. Prions are resistant to standard sterilisation techniques including heat, irradiation and autoclaving, so transmission through contaminated medical and surgical appliances is a risk.

The most common form of prion disease is sporadic Creutzfeldt–Jakob disease (CJD). Hereditary prion diseases are associated with a broad range of mutations in the prion protein (*PRNP*) gene on chromosome 20. Variant CJD became prominent in the 1990s due to disease being passed to humans by the ingestion of meat from cattle with bovine spongiform encephalopathy (BSE).

Sporadic CJD usually presents between the ages of 45 and 75 with ataxia, rapidly progressive dementia and myoclonus. Variant CJD presents earlier in life (average age 26), may have a psychiatric prodrome and is also associated with painful sensory symptoms, often before the onset of the dementia.

Well-characterised abnormalities can be seen on MRI, with hyperintense signal change in the basal ganglia and cortex in sporadic CJD and thalamic signal change in variant CJD. Cerebrospinal fluid (CSF) analysis may reveal abnormally high levels of the proteins 14-3-3 and S100B (S100 calcium-binding protein) proteins in sporadic CJD, although this test is less sensitive in variant CJD. The EEG in sporadic CJD typically shows periodic sharp wave complexes but this may not occur in variant CJD. A blood-based assay test has recently been developed for variant CJD.

Non-degenerative dementia

The most common cause of non-degenerative dementia is vascular dementia (VaD). This is a heterogeneous condition because vascular disease in the brain can cause dementia in a number of ways.

A large stroke, or a small strategic infarct, can cause dementia due to loss of cognitive functions in the affected brain area. In this instance, there are usually other physical symptoms and signs of stroke, such as weakness, sensory loss, visual field defect and aphasia.

Multiple small strokes can cause a multi-infarct dementia with progressive stepwise deteriorations in cognition, often accompanied by focal neurological symptoms and signs according to the lesion locations.

Diffuse small-vessel disease can cause gradually worsening subcortical dementia with progressively worsening white matter lesions. In such cases, slowness of thought processing and a dysexecutive syndrome (a failure of planning and abstract thinking) characterise the dementia. There is often evidence of impaired gait and balance due to the vascular disease as well.

MRI is helpful in delineating the distribution of vascular disease and can aid diagnosis.

'Normal' pressure hydrocephalus

The famous triad of dementia, gait failure and incontinence defines the syndrome of normal pressure hydrocephalus. The precise aetiology remains unknown. The cognitive syndrome is usually that of a subcortical dementia with slowing and poor executive function. The gait is 'magnetic', with feet that

seem to stick to the floor; there is reduced stride length and impaired balance. True ataxia does not usually occur. Neuroimaging reveals dilated lateral ventricles, although this is a non-specific finding and can be seen in degenerative dementias due to brain atrophy. Removal of a large volume of CSF via a lumbar puncture may produce transient improvements in the symptoms, and such patients can be considered for ventriculoperitoneal shunt insertion to treat their symptoms over the long term.

16.2.3 Acute and subacute confusional states (delirium)

In contrast to dementia, in which there is no disorder of arousal, acute confusional states, 'encephalopathy' and delirium are all terms that describe a disorder of cognition in which arousal is impaired and may fluctuate. This syndrome may present acutely or subacutely. As all cognitive functions rely on intact levels of arousal, patients with delirium have a broad range of cognitive symptoms that can lead to the misdiagnosis of dementia. To avoid this mistake, clinical assessment must look for the hallmarks of delirium that include combinations of the following features:

- Fluctuation
- Disorientation
- Poor attention
- Altered sleep–wake patterns
- Agitated behaviour
- Apathy
- Hallucinations, misperceptions and delusions.

Delirium is not an aetiological diagnosis, and when the clinical syndrome is identified, it is necessary to assess for the underlying cause. The range of causes is broad and is most easily divided initially into systemic medical illnesses and CNS disorders.

Systemic causes

- **Metabolic and endocrine:**
  - Hypo-/hypernatraemia
  - Hypo-/hyperglycaemia
  - Hepatic failure
  - Renal failure
  - Hypercalcaemia
  - Hypo-/hyperthyroidism
  - Hyperammonaemia
  - Hypoxaemia
  - Hypercapnia
  - Acidosis
  - Vitamin deficiency (eg thiamine, vitamin B_{12})

- **Infection:**
  - Any sufficiently severe infection (eg pneumonia, urinary tract infection)
- **Toxic and drug-induced:**
  - Alcohol (excess and withdrawal)
  - Benzodiazepines
  - Lithium
  - Carbon monoxide

CNS-specific causes

- **Infection:**
  - Meningitis (viral, bacterial, fungal)
  - Encephalitis (viral, bacterial, fungal)
  - Cerebral or parameningeal abscess
- **Malignant:**
  - Cerebral metastases
  - Malignant meningitis
  - Primary brain tumour (eg high-grade glioma)
- **Inflammatory:**
  - Vasculitis
  - Systemic lupus erythematosus
  - Neurosarcoid
  - Multiple sclerosis
  - Acute disseminated encephalomyelitis (ADEM)
  - Behçet's disease
- **Antibody-associated encephalitis:**
  - Paraneoplastic
  - Non-paraneoplastic
  - Hashimoto's encephalitis (now called steroid-responsive encephalopathy associated with autoimmune thyroiditis – SREAAT)
- **Vascular:**
  - Stroke (especially thalamic or multiple infarcts)
  - Cerebral venous sinus thrombosis

Antibody-mediated encephalitis

Over the last decade there have been significant advances in our understanding of immune-mediated encephalitis with ever more antibodies being identified. Broadly, these conditions can be split into paraneoplastic and non-paraneoplastic encephalitis.

Classic paraneoplastic encephalitis was described in the 1980s and is a rare complication of cancer (particularly lung and breast), associated with a number of onconeural antibodies (anti-Hu, CV2, Ma1/2, amphiphysin). The antibodies are directed against intracellular targets, and are not deemed pathogenic because the pathology appears predominantly T-cell driven. The typical phenotype is 'limbic' encephalitis characterised by seizures, amnesia and confusion. Such patients are often poorly responsive to immunomodulatory therapy, but removal of the underlying tumour can result in clinical improvement.

More recently, a more common non-paraneoplastic form of immune-mediated encephalitis has been described, with antibodies directed against cell surface proteins. These antibodies are deemed pathogenic and most patients respond to immunomodulation, typically with steroids, intravenous immunoglobulin and/or plasma exchange.

The two best-described antibodies are directed against the voltage-gated potassium channel complex (VGKC) and the *N*-methyl-D-aspartate (NMDA) receptor. The clinical features of each syndrome can be seen in Table 16.3. Although often not associated with cancer, a significant minority of VGKC antibody (Ab) cases will have a thymoma or small-cell lung cancer. In young women with NMDA receptor encephalitis there are a significant number of cases with ovarian teratomas.

Wernicke's encephalopathy

Dietary deficiency, specifically lack of thiamine (vitamin B_1), leads to Wernicke's encephalopathy. It is traditionally associated with alcoholism but it may develop in association with numerous other conditions, including:

- Cancer
- Gastrointestinal surgery
- Gastrointestinal disease (eg Crohn's disease, coeliac disease)
- Hyperemesis gravidarum
- Starving/fasting.

The classic clinical triad consists of confusion, ataxia and abnormal eye movements, although only a minority of patients exhibit all three. Several other features may be present, including seizures, reduced conscious level, pupillary abnormalities, peripheral neuropathy and hypothermia. A high index of suspicion is required and if the diagnosis is even a consideration, then parenteral thiamine should be administered. This remains a clinical diagnosis, although some characteristic MRI changes have been described.

16.2.4 Coma

Impaired consciousness can be considered a problem with alertness, awareness of self or both. These are interrelated but can be dissociated. Diminished alertness arises from a disturbance of arousal – mainly a function of the brainstem reticular formation. Diminished awareness – an inability to accurately integrate what is perceived – is a function of multiple cortical areas.

Coma is anatomically considered as interruption of the ascending reticular activating system in the midbrain and pons projecting to the thalamus and cortex. Clinically, it is best defined as a completely

unaware patient unresponsive to external stimuli with only eye opening to pain and no eye tracking or fixation, and limb withdrawal to a noxious stimulus at best (often with reflex motor movements). Brainstem reflexes can be partly absent or absent.

Table 16.3 Clinical features of antibody-mediated encephalitis

Antibody	VGKC	NMDA
Demographics	>50 years, male predominance	<50 years, female predominance
Common features	Temporal lobe seizures Amnesia Disorientation	Psychiatric prodrome Seizures Amnesia and disorientation Reduced conscious level Autonomic instability
Characteristic features	Faciobrachial dystonic seizures may precede frank encephalitis	Choreoathetoid movement disorder and orofacial dyskinesias Catatonia with waxy flexibility
MRI findings	Medial temporal lobe high signal (>60%)	Often normal or non-specific
Blood and CSF findings	Usually normal CSF Hyponatraemia (60%)	Increased cell count and detection of NMDA receptor antibody in CSF

Note: ensure that the patient is not 'locked in' by asking the patient to open his or her eyes and look up, down and from side to side. For such patients, although having impaired motor tracts from a lesion in the ventral pons, there is sparing of the ascending reticular activating system, and therefore they can hear, see and perceive pain. Classically, patients have open eyes, move their eyes vertically and can blink to command.

Practically, one can ask the following questions in a comatose patient: could this be major anoxic–hypoxic brain injury (including basilar artery stroke), intoxication, CNS infection, major metabolic or endocrine derangement, or non-convulsive status epilepticus?

Causes of coma

- Structural injury of the cerebral hemisphere(s)
- Intrinsic brainstem injury, or extrinsic compression from neighbouring damaged tissue
- Acute metabolic or endocrine derangement (eg hypoglycaemia, hyperglycaemia, nonketotic hyperosmolar):
  - Hyponatraemia
  - Hypernatraemia

- Addison's disease
- Hypercalcaemia
- Acute hypothyroidism
- Acute panhypopituitarism
- Acute uraemia
- Hyperbilirubinaemia
- Hypercapnia

- Diffuse physiological brain dysfunction (eg seizures, drug intoxication or poisoning, hypothermia, acute catatonia, malignant neuroleptic syndrome)

The degree of coma is more difficult to define precisely, eg what does drowsy or stuporous really mean?

It is better to choose some key findings and relate how they change over time in the patient. Comatose patients have several potential outcomes. They may:

- Make a good recovery
- Become fully conscious but disabled
- Remain in a minimally conscious state (MCS)
- Remain unconscious (persistent vegetative state [PVS])
- Lose all brain function (brain death).

The RCP have published guidelines on the assessment, management, prognosis and end-of-life ethical and medicolegal decisions in prolonged disorders of consciousness – https://www.rcplondon.ac.uk/resources/prolonged-disorders-consciousness-national-clinical-guidelines#attachments

Persistent vegetative state is defined as:

- No awareness of self or environment
- No sustained reproducible, purposeful or voluntary behavioural response to visual, auditory, tactile or noxious stimuli
- No language comprehension or expression
- Mostly intact cranial nerve reflexes
- Roving nystagmoid eye movements
- Presence of sleep and wake cycles; eyes often open during the day
- Stable, unsupported blood pressure and intact respiratory drive
- Bowel and bladder incontinence.

Minimally conscious state is defined as:

- Patients make eye contact or turn head when being talked to
- An abulic emotionless state but with eye-tracking movements
- May mouth words and fend off pain

- Eyes following moving person
- Some intelligible verbalisation
- May hold object or use object when asked.

A routine set of clinical tests is necessary to assess the depth of coma, the location of the lesion and possibly the underlying cause.

Examination in comatose patients

General inspection and vital signs: signs of trauma, rash, intravenous drug use stigmata, etc, BP (both hypertension and hypotension) and temperature may indicate infection, and arrhythmias could suggest drug intoxication or a potential cause of basilar artery embolus, for example.

General neurological examination (eg to determine if there are focal lateralising signs such as asymmetry in muscle tone, reflexes or plantar responses): with specific emphasis on:

- Meningism
- Fundoscopy, eg papilloedema, subhyaloid haemorrhage in subarachnoid haemorrhage (SAH); other causes of rapid rise in intracranial pressure
- Eardrums – for trauma
- Assessment of level of unconsciousness (Glasgow Coma Scale)
- Response to painful stimuli, eg nail-bed pressure:
  - Decorticate responses are defined by slow flexion of the elbow, wrist and fingers – usually upper brainstem lesion
  - Decerebrate responses are defined by adduction and internal rotation of the shoulder, arm extension and wrist pronation with fist formation – usually reflective of bilateral midbrain or pontine lesions.

Glasgow Coma Scale (rated between 3 and 15)

Eye opening

4 = spontaneous
3 = to speech
2 = to pain
1 = none

Best motor response

6 = obeying
5 = localising pain
4 = withdrawal
3 = abnormal flexing
2 = extensor response
1 = none

Best verbal response

5 = oriented
4 = confused conversation
3 = inappropriate words
2 = incomprehensible sounds
1 = none

Brainstem responses

Pupils (will be normal in lesions above the thalamus and below the pons)
Pinpoint (2 mm): opioid intoxication or pontine lesion
Fixed midpoint (4–6 mm): midbrain lesion or compression
Dilated pupil(s) (>8 mm): sympathomimetic drugs or third nerve or midbrain lesion

Spontaneous eye movement abnormalities (ping-pong, ocular dipping) localise mostly to bihemispheric dysfunction, except ocular bobbing (rapid downward eye movements, with slow return to the mid-horizontal position), which localises to the pons.

Horizontal deviation of the eyes to one side might be a sign of non-convulsive status epilepticus, but also possibly of an ipsilateral hemispheric or contralateral pontine stroke. Sometimes only subtle movements of the eyelids, tongue, jaw or face occur.

Roving eye movements, slow conjugate lateral to-and-fro movements, indicate that the brainstem is intact and imply a toxic, metabolic or bilateral hemisphere cause for the coma.

Skew deviation of the eyes suggests a posterior fossa lesion.

Oculocephalic 'doll's eye' reflexes: if absent, can proceed to more sensitive caloric testing (check tympanic membrane is intact beforehand).

Corneal reflexes: if the pons is intact, the eyelids will close; if the pons and midbrain are intact, Bell's phenomenon occurs (upward movement of the globe on eyelid closure).

Evaluation of breath (eg foetor hepaticus) should be made, and check the breathing pattern for abnormalities, which can be difficult to assess, especially once mechanical ventilation is involved, and Cheyne–Stokes breathing can occur with any type of reduced alertness.

Tests

Imaging: both CT and MRI have a role in determining the cause of the coma (eg mass, haemorrhage, oedema, stroke and contusions)

A detailed metabolic (including acid–base anion and osmolar gap calculation for exogenous toxins), drug and infection screen (see Section 16.2.5) should be undertaken

Cerebrospinal fluid: see Section 16.2.5

An EEG could be invaluable if there is the possibility of non-convulsive status epilepticus or the diagnosis remains unclear

Once the patient has been stabilised, it offers the opportunity to re-examine the history and check for systemic causes of coma.

Treatment

If CNS infection remains a possibility, start full coverage according to local guidelines, usually with antimicrobial third-generation cephalosporin, vancomycin and ampicillin in combination with intravenous aciclovir, and strongly consider intravenous dexamethasone 0.6 mg/kg daily before administration of antibiotics, and continue for 4 days.

Supportive therapy, eg optimisation of electrolytes, blood glucose, acid–base balance, thiamine administration if appropriate, prevention of infection, pressure areas, venous thromboembolism and contractures are all important in the longer-term management of the patient.

Determination of brain death

This will vary according to local guidelines and will usually require more than one examination by more than one competent individual (eg ICU intensivist).

Brain death is declared when brainstem reflexes, motor responses and respiratory drive are absent in a comatose patient with an irreversible widespread brain lesion of known cause, along with satisfactory temperature, oxygenation, absence of hypercapnia and pharmacological influences (eg sedation and neuromuscular blocking agents) and no contributing metabolic derangements or reversible medical condition.

16.2.5 CNS infections

Encephalitis

Infection of the brain parenchyma is termed ‘encephalitis’ and is typically due to viruses or bacteria. The common clinical features are:

- Fever
- Headache
- Seizures
- Lethargy
- Behavioural change.

Herpes simplex virus type 1 is the most common cause of encephalitis in the UK, although many other infectious agents may be seen:

Viruses

- Herpes simplex virus type 1 (HSV1)
- Varicella-zoster virus (VZV)
- Enterovirus
- Adenovirus
- Parechovirus

- HIV

Bacteria

- *Mycobacterium tuberculosis*
- *Listeria* spp.
- *Streptococcus pneumoniae* (direct spread from meningitis)
- *Neisseria meningitidis* (direct spread from meningitis)
- Syphilis

Other

- *Cryptococcus neoformans* (immunocompromised)
- *Toxoplasma gondii* (immunocompromised)
- Remember the non-infectious causes of encephalitis (see Section 16.2.3)

Patients suspected of having encephalitis require rapid assessment and treatment. Prompt lumbar puncture for CSF analysis is required, although some patients may need urgent CT first to ensure that this is safe.

Clinical features of herpes simplex encephalitis

- Fever
- Focal symptoms (eg musical hallucinations)
- Confusion
- Focal signs (eg right-sided weakness and aphasia)

Indications for urgent CT before lumbar puncture

- Reduced conscious level
- Focal neurological signs
- Signs of raised intracranial pressure (papilloedema, bradycardia with hypertension)
- Uncontrolled seizures
- Sepsis
- Significant clotting abnormality
- Immunocompromise
- Note that **a change in existing neurological signs** may warrant a repeat scan even if a previous scan was normal.

The lumbar puncture must measure the opening pressure, and CSF is sent for cell count, glucose, protein, Gram stain and viral polymerase chain reactions (PCRs) with a contemporaneous paired plasma glucose. Additional tests may be necessary in certain circumstances, particularly the immunocompromised patient and the returning traveller, in whom the list of potentially causative

organisms is much greater. MRI can be a useful adjunct to CSF analysis and may show typical temporal and medial frontal lobe changes in HSV1 encephalitis, or may reveal an alternative diagnosis. It is good practice to test patients presenting with symptoms and signs of any CNS infection for HIV.

Aciclovir is an effective and safe treatment for HSV1 encephalitis, proven to reduce morbidity and mortality. For this reason it is often given even before confirmation of HSV1 infection (which may take several days with PCR testing). Other treatments are cause-specific and rely on the outcome of investigations and the weight of clinical probabilities.

Meningitis

Infection and inflammation of the lining of the brain and spinal cord (meninges) are called meningitis. The cardinal symptoms and signs are:

- Headache
- Fever
- Neck stiffness
- Photophobia
- Vomiting.

Clearly there is significant overlap with the features of encephalitis, and indeed the two may occur together – meningoencephalitis. Infective causes of meningitis are equally broad but may be divided in a similar way:

Viral

- Enterovirus
- HSV2
- HIV
- VZV
- Mumps

Bacterial

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *Mycobacterium tuberculosis*
- *Borrelia burgdorferi* (Lyme disease)

Other

- *Cryptococcus neoformans* (immunocompromised)
- *Toxoplasma gondii* (immunocompromised).

Remember that there are many non-infectious causes of meningitis such as drug-induced, autoimmune inflammatory diseases and carcinoma.

Bacterial meningitis is a medical emergency and patients may have signs of systemic sepsis. A patient with meningococcal disease may develop the classic petechial rash. Immediate management revolves around the assessment of vital signs and stabilising the patient. Blood cultures must be taken and are a good way of confirming the diagnosis. Whole blood PCR testing can also be done for the major bacterial pathogens. Lumbar puncture can be very helpful, but the same precautions for CT must be taken. In cases of suspected bacterial meningitis, early antibiotic administration is recommended, and a lumbar puncture should not delay this. When CSF is obtained, Gram staining may rapidly identify the causative bacteria.

Table 16.4 describes typical patterns of CSF findings that help with the differential diagnosis of both meningitis and encephalitis, guiding further specialist testing and treatment.

Infectious myelitis

A number of different organisms are known to cause infectious myelitis (see box).

Acute viral myelitis

- Enterovirus
- VZV
- HSV
- Cytomegalovirus (CMV)
- Hepatitis C virus

In these cases, the clinical syndrome is usually characterised by pain, fever, meningism and a combination of lower motor neuron signs (due to grey matter/anterior horn involvement) and upper motor neuron signs (due to corticospinal tract involvement). Patients have sensory loss in various patterns as a result of differential involvement of spinothalamic and dorsal column tracts. Some of these patients probably have a post-viral inflammatory myelitis rather than direct infection.

MRI may reveal cord signal change. CSF usually reveals lymphocytic pleocytosis, and viral PCR may be positive.

Table 16.4 Typical cerebrospinal fluid findings in central nervous system infections

Test	Normal	Bacterial	Viral	Tuberculous	Fungal
Opening pressure (cm)	10–20	High	Normal	High/very high	Very high
Cells	<5	100–50 000 (neutrophils)	5–1000 (lymphocytes)	5–500 (lymphocytes)	0–1000 (lymphocytes)
Protein (g/L)	<0.45	>1.0	0.5–1.0	1.0–5.0	0.5–2.0
Glucose (% plasma)	50–66	<40	50–66	<33	30–50

Treatment is usually with combination antiviral agents and steroids.

Chronic viral myelopathy

- HIV

- HTLV1 (human T-lymphotrophic virus type 1)

HIV causes a vacuolar myelopathy that is chronically progressive. Management is based on optimising treatment for HIV and excluding any opportunistic infections.

HTLV1 causes 'tropical spastic paraparesis', rare in the UK. Patients develop a slowly progressive spastic paraparesis with prominent bladder dysfunction.

HTLV1 antibodies can be detected in the CSF. There is no good evidence-based treatment currently.

Bacteria

- Syphilis
- *Mycobacterium tuberculosis*

'Tabes dorsalis' is the term given to describe tertiary syphilis affecting the spinal cord. Dorsal columns are predominantly involved, producing a sensory ataxic syndrome. Usually a late complication of syphilis, this syndrome can occur with a shorter latency in the context of co-infection with HIV.

TB can cause myelitis due to spread of infection from the spinal column or tuberculomas in the cord.

Parasites

- *Schistosoma* spp.

This can cause an acute transverse myelitis presentation and eosinophilia is commonly seen. Praziquantel and steroids are the treatment of choice.

16.2.6 Headache

The current International Headache classification is available online at: www.ihs-classification.org/_downloads/mixed/International-Headache-Classification-III-ICHD-III-2013-Beta.pdf

Headache is the most common symptom that has a multiplicity of causes. Important neurological causes of chronic recurrent headache include:

- Migraine without aura
- Migraine with aura
- Tension headache
- Cluster headache
- Headaches in association with raised intracranial pressure
- Subarachnoid haemorrhage.

Migraine

Migraine without aura

This is a recurrent headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity,

aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria of migraine without aura

- A At least five attacks, fulfilling criteria B–D
- B Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C Headache has at least two of the following four characteristics:
  - 1 Unilateral location
  - 2 Pulsating quality
  - 3 Moderate or severe pain intensity
  - 4 Aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)
- D During headache at least one of the following:
  - 1 Nausea and/or vomiting
  - 2 Photophobia and phonophobia
- E Not better accounted for by another ICHD-3 diagnosis

Migraine with aura

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other CNS symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria for migraine with aura

- A At least two attacks fulfilling criteria B and C
- B One or more of the following fully reversible aura symptoms:
  - 1 Visual
  - 2 Sensory
  - 3 Speech and/or language
  - 4 Motor
  - 5 Brainstem
  - 6 Retinal
- C At least two of the following four characteristics:
  - 1 At least one aura symptom spreads gradually over <5 min, and/or two or more symptoms occur in succession
  - 2 Each individual aura symptom lasts 5–60 min
  - 3 At least one aura symptom is unilateral
  - 4 The aura is accompanied, or followed within 60 min, by headache

D	Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded

The neurological symptoms suggest a vascular origin, and a popular hypothesis is that of 'spreading depression' of cortical blood flow. However, although changes in cerebral perfusion undoubtedly occur, it is currently not clear whether these are primary or brainstem neuroregulatory abnormalities of serotoninergic or noradrenergic neurotransmitters are more important. Therapy is aimed at stopping an attack (abortive) or, if the frequency of attacks is high enough (eg two or more per month), regular medication is given as a prophylactic agent.

Migraine therapy

- **Abortive**
  - Paracetamol
  - Non-steroidal anti-inflammatories (eg high-dose aspirin 900 mg) with antiemetic
  - Triptan, eg sumatriptan ($5HT_1$ agonist) oral, intranasal or subcutaneous or sublingual wafer (eg rizatriptan, eletriptan)
  - Ergotamine[a]
- **Prophylactic**
  - β blocker (eg propranolol)
  - Amitriptyline or other tricyclic antidepressants
  - Topiramate
  - Other anticonvulsants (eg sodium valproate, gabapentin)
  - Candesartan
  - Methysergide[a]

[a]Rarely used now due to adverse events.

Cluster headache

Males are more often affected than females, and onset of attacks is typically between age 25 and 50 years.

Attacks occur in series lasting for weeks or months (so-called cluster periods) separated by remission periods, usually lasting months or years. About 10–15% of patients have chronic cluster headache, without such remission periods. Attacks consist of severe, strictly unilateral pain, which is orbital, supraorbital or temporal, or in any combination of these sites, lasting 15–180 min and occurring from once every other day to eight times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or with restlessness or agitation.

Diagnostic criteria for cluster headache

A At least five attacks fulfilling criteria B–D

B Severe or very severe, unilateral, orbital, supraorbital and/or temporal pain lasting 15–180 min (when untreated)

C Either or both of the following:

1 At least one of the following symptoms or signs, ipsilateral to the headache:

- conjunctival injection and/or lacrimation
- nasal congestion and/or rhinorrhoea
- eyelid oedema
- forehead and facial sweating
- forehead and facial flushing
- sensation of fullness in the ear
- miosis and/or ptosis

2 A sense of restlessness or agitation

D Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active

The aetiology is not known and treatment is difficult. Management of the acute attack includes inhaled oxygen (via face mask) and subcutaneous sumatriptan. A reducing course of steroids may be helpful, and intranasal lidocaine and occipital nerve blocks or stimulation have been used with some effect. Verapamil, topiramate and lithium can be used for prophylaxis. Rarely, symptomatic cluster headaches can occur.

16.2.7 Idiopathic intracranial hypertension

This term refers to a group of patients who present with headaches and profound papilloedema, yet have no focal neurological signs or no lesion (eg space-occupying or cerebral venous thrombosis) on imaging. The most common presentation is in overweight young women and comprises:

- Headache
- Blurred vision
- Dizziness
- Transient visual obscurations
- Horizontal diplopia from non-localising nerve VI palsy
- Pulsatile tinnitus (rhythmic whooshing sound synchronous with the patient's heartbeat – which may occur only when lying down).

Papilloedema is found on examination, with peripheral constriction of the visual fields and enlarged blind spots. The CSF pressure is elevated.

Diagnostic criteria for idiopathic intracranial hypertension (IIH)

A	Papilloedema
B	Normal neurological examination except for cranial nerve abnormalities
C	Neuroimaging: normal brain parenchyma without hydrocephalus, mass or structural lesion, and no abnormal meningeal enhancement or venous sinus thrombosis on MRI and MR venography; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
D	Normal CSF composition
E	Elevated CSF opening pressure (≥25 cmH_2O) in a properly performed lumbar puncture[a]

A diagnosis of IIH is definite in patients fulfilling A–E; the diagnosis is probable if A–D are met but the CSF pressure is lower than specified

[a]The patient must be comfortable because talking, crying and flexed legs compressing an obese abdomen, and Valsalva's manoeuvre, may artificially raise the CSF pressure reading.

Iatrogenic (drug-induced) causes include:

- Oral contraceptive pill
- Steroids
- Tetracycline
- Vitamin A
- Nitrofurantoin
- Nalidixic acid.

Treatment of IIH

This consists of weight loss, acetazolamide or topiramate, and repeated lumbar puncture to reduce the CSF pressure. Bariatric surgery as a potential treatment is currently the subject of a clinical trial. In more resistant cases or those associated with regular recurrence, a ventriculoperitoneal shunt may be necessary. Optic nerve sheath fenestration can be performed in patients whose sight is threatened.

16.2.8 Epilepsy

An epileptic seizure is an intermittent *stereotyped* disturbance of consciousness, behaviour, emotion, or motor or sensory function which, on *clinical* grounds, is believed to result from cortical neuronal discharge.

Epilepsy is a liability to clinically manifested seizures of any type and a condition in which seizures recur, usually spontaneously.

The prevalence of epilepsy is relatively constant at different ages and is around 0.7%, whereas the incidence follows a U-shaped curve, with the highest incidence in young and elderly people.

A simplified classification of epilepsy

- Generalised seizures
  - Tonic–clonic
  - Absences (3 Hz spike-and-wave activity in ictal EEG)
  - Partial seizures secondarily generalised
- Partial seizures
  - Simple partial seizures
  - Complex partial seizures
- Others, eg myoclonic or atonic

- A typical tonic–clonic seizure begins without warning. After loss of consciousness and a short tonic phase, the patient falls to the ground with generalised clonic movements. There may be tongue biting and incontinence (which is unhelpful diagnostically), and there is post-ictal confusion – often the patient's first recollection is waking up in the ambulance or hospital.
- Simple partial seizures may affect any area of the brain, but consciousness is not impaired and the ictal EEG shows a local discharge starting over the corresponding cortical area. Any simple seizure may progress (eg motor seizures may show a Jacksonian march) and become secondarily generalised with a resulting tonic–clonic seizure
- Consciousness is impaired by complex partial seizures that typically have a medial temporal (often hippocampal) focus. An aura (sense of déjà vu, strong smell or rising sensation in the abdomen) may precede the seizure, followed by loss of consciousness. There may be automatisms (repetitive stereotyped semipurposeful movements).

Imaging is usually carried out in most if not all patients with seizures; focal seizures usually imply a focal pathology and imaging, ideally MRI, is mandatory in such circumstances. A 12-lead ECG should be performed in adults with suspected epilepsy. The purpose of an electroencephalograph (EEG) is to define type of seizure and the epilepsy syndrome, NOT to diagnose 'epilepsy', and is best avoided in patients with a low probability of a seizure(s) from clinical assessment.

Anticonvulsant agents are discussed in Chapter 2, Clinical pharmacology, toxicology and poisoning.

Treatment of epilepsy

Patients presenting with a first seizure have an overall risk of recurrence of about 35% at 2 years. Most neurologists therefore do not advocate routine treatment for a first seizure that does not also affect long-term prognosis. However, some groups have a higher recurrence risk (eg 65% at 2 years for patients with a remote neurological insult – which may be apparent on appropriate cranial imaging – and an EEG with epileptiform features), and in these subgroups treatment may be considered:

- After the second or subsequent seizures, drug treatment is routinely advised as the recurrence risk is much higher. NICE have updated their treatment recommendations for epilepsy: http://guidance.nice.org.uk/CG137/

NICEGuidance/pdf/English

- Lamotrigine and carbamazepine (or oxcarbazepine) are widely accepted as drugs of first choice for partial seizures, and sodium valproate for generalised seizures (but a good option for virtually any seizure type or unclassified epilepsy syndrome), with newer anticonvulsants such as levetiracetam gaining acceptance as a broad-spectrum alternative in both scenarios. Ethosuximide can be used for absences and topiramate is a useful broad-spectrum adjunctive or alternative agent, but use is limited due to adverse events, liver induction and drug–drug interactions. Other anticonvulsants are best initiated by specialists
- Note that 40% of patients with epilepsy will be women of childbearing age. As valproate exposure in utero is associated with a higher incidence of neural tube defects and cognitive impairments than other agents, the choice of monotherapy may need to be reviewed (see Chapter 2, Clinical pharmacology, toxicology and poisoning).

Any antiepileptic should be introduced at a low dose and the clinician must be vigilant for idiosyncratic reactions. The dosage can then be escalated until either control is achieved or the maximum allowed dose is reached. If control is not achieved with monotherapy, then at least one additional trial of monotherapy is recommended before combination therapy is considered. In patients with complex or refractory epilepsy, specialist referral should be considered if the epilepsy is not controlled with medication within 2 years or management is unsuccessful after two drugs have been tried in adequate courses.

Epilepsy and driving

Current UK regulations (https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals) are such that after a first unprovoked or isolated seizure, if an EEG and imaging are normal, a 6-month cessation of driving for a Group 1 (motor cars and motor cycles) licence is required. If either or both investigations are abnormal, then 12 months off driving is required. Loss of consciousness, for which investigations have not revealed a cause, is treated in the same way as a solitary seizure.

Patients with epilepsy may be allowed to drive if they have been free from any epileptic attack, including auras, for 1 year, or if they had an epileptic attack while asleep >3 years ago and attacks subsequently only when asleep.

To obtain a vocational driving licence (group 1 licence) or group 2 (lorries and buses) licence, patients should have been free of epileptic attacks AND off all antiepileptic medication AND free from a continuing liability to epileptic seizures (eg structural intracranial lesion) for 10 years.

Patients should be reminded that they have a legal obligation to report their seizure(s)/aura(s) to the DVLA.

Epilepsy and pregnancy

Seizure rate in pregnancy is predicted by seizure rate before pregnancy. All epileptic drugs have potential teratogenic effects including:

- Cleft lip/palate
- Congenital heart defects

- Urogenital defects
- Neural tube defects (especially valproate).

Exposure to sodium valproate in utero has been demonstrated to lead to learning impairments in childhood. Teratogenic effects are more likely if more than one drug is used. Antiepileptic drugs are not contraindicated in pregnancy, because the effects of uncontrolled epilepsy may be more risky. The UK Pregnancy and Epilepsy Register (www.epilepsyandpregnancy.co.uk) collects information prospectively from women with epilepsy and publishes results on a regular basis.

There is no increase in infant mortality for mothers with epilepsy. Folic acid supplementation, 5 mg daily, ideally started before conception and continued throughout the first two trimesters, decreases the incidence of malformations.

16.2.9 Stroke

- Transient ischaemic attacks (TIAs)
- Stroke
- Subarachnoid haemorrhage.

Stroke is the most prevalent neurological disorder in those aged <85 years, of whom 29% will die of complications and a further 25% will remain dependent, so optimal management, particularly in prevention and of TIAs is crucial. In White populations, the most frequent causes are large-artery atherosclerosis (about 50%), atrial fibrillation (about 25%) and small-vessel disease of the deep perforators (about 20%). In young patients, the leading cause is arterial dissection (see below).

Transient ischaemic attacks

A TIA is a focal CNS or monocular disturbance developing over seconds and fading over minutes or hours to give full recovery within 24 hours. Most TIAs are caused by embolism.

Differential diagnosis of TIA

- Migraine aura:
- focal epilepsy with post-ictal paralysis
- transient global amnesia
- structural brain lesions (eg subdural haematoma, meningioma)
- Hypoglycaemia
- MS paroxysmal phenomena (unusual)

Risk factors for stroke

- Diabetes (doubles risk of ischaemic stroke)
- Hypertension (risk of stroke doubles for every 7.5 mmHg increase in diastolic BP)
- Smoking (doubles risk of ischaemic stroke)

- Hypercholesterolaemia
- Cardiac arrhythmia
- Atheroma (eg carotid, aortic arch)
- Exogenous oestrogen – oral contraception and hormone replacement therapy
- Cocaine abuse
- Previous TIA or stroke
- Male sex
- Increased Hb, haemoglobinopathy
- Family history

Comprehensive guidelines for the assessment and management of stroke have been published: www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf

A completed stroke is a focal CNS disturbance due to a vascular cause where the deficit persists. The aetiology may be embolic, thrombotic or haemorrhagic. The presenting symptoms depend on the vascular territory involved.

Lacunar strokes

Lacunar infarctions occur where small intracerebral arteries are occluded by atheroma or thrombosis. Typically, small low-density subcortical lesions are seen in the area of the internal capsule.

- Lacunar syndromes:
  - no visual field defect
  - no new disturbance of higher cortical or brainstem function
  - pure motor hemiparesis, or pure sensory deficit of one side of the body, or sensorimotor
  - hemiparesis, or ataxic hemiparesis (dysarthria clumsy hand syndrome or ipsilateral ataxia with crural hemiparesis)
- Lacunar infarcts have a low mortality and relatively good prognosis for recovery, and lower risk of recurrence than large-vessel occlusions. They are primarily associated with hypertension
- Other types of stroke involve either the anterior or the posterior cerebral circulation
- Posterior circulation syndromes (POCSs): any one of:
  - cranial nerve impairment
  - unilateral or bilateral motor or sensory deficit
  - disorder of conjugate eye movement
  - cerebellar dysfunction
  - homonymous hemianopia
  - cortical blindness
- Total anterior circulation syndromes (TACSs):
  - hemiplegia and homonymous hemianopia contralateral to the lesion
  - either aphasia or visuospatial disturbance
  - sensory deficit contralateral to the lesion

- Partial anterior circulation syndromes (PACSs):
  - one or more of unilateral motor or sensory deficit, aphasia or visuospatial neglect (combined or not with homonymous hemianopia)
  - motor or sensory deficit may be less extensive than in lacunar syndromes (eg hand alone)
- Intracerebral haemorrhage is primarily associated with the rupture of microaneurysms situated in the basal ganglion or brainstem and account for about 10% of strokes.

Factors associated with a poor prognosis in stroke

- Complete paralysis of a limb (MRC grade 0 or 1)
- Loss of consciousness at onset of stroke
- Higher cerebral dysfunction
- Coma or drowsiness at 24 hours
- Old age

TIA and subsequent stroke risk

There are several scoring systems designed to stratify the short-term risk of stroke after TIA, perhaps the most widely used being the ABCD^2. A score of ≥4 equates to a substantially increased risk of early stroke.

***A**ge* ≥60	1 point
*Elevated **b**lood pressure*	1 point
Systolic ≥140 mmHg Diastolic ≥90 mmHg	
***D**iabetes*	1 point
***C**linical features of the TIA*	
Unilateral weakness	2 points
Speech impairment	1 point
Other symptoms	0 points
*Symptom **d**uration*	
≥60 min	2 points
10–59 min	1 point
<10 min	0 points
Total possible score	7 points

Management of TIA

All patients with a suspected TIA should receive aspirin or clopidogrel (each as a 300 mg loading dose and 75 mg thereafter) and a statin, eg simvastatin 40 mg started immediately.

Those at high risk of a stroke: ABCD^2 ≥4 or those with crescendo TIA (two or more TIAs in a week),

atrial fibrillation or on anticoagulants irrespective of $ABCD^2$ score, should receive specialist assessment and investigation within 24 hours of onset of symptoms; those at lower risk, $ABCD^2 \leq 3$, as soon as possible, but definitely within 7 days.

All patients should receive measures for secondary prevention, introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

For patients confirmed to have had an ischaemic stroke or TIA, the following risk factors should also be checked for:

- Atrial fibrillation and other arrhythmias
- Carotid artery stenosis (only for people likely to benefit from surgery)
- Structural and functional cardiac disease.

Antiplatelets in secondary prevention

For patients in sinus rhythm: for patients with ischaemic stroke or TIA in sinus rhythm, clopidogrel 75 mg once daily should be the standard anti-thrombotic treatment (RCP's guideline outside of licence). Aspirin 75 mg daily with modified-release dipyridamole 200 mg twice daily can be used if clopidogrel is not tolerated. If both clopidogrel and modified-release dipyridamole are contraindicated or not tolerated, offer aspirin 75 mg daily. If both clopidogrel and aspirin are contraindicated or not tolerated, offer modified-release dipyridamole 200 mg twice daily. Aspirin and clopidogrel are not recommended for long-term prevention after a TIA or stroke unless there is another indication such as acute coronary syndrome or recent coronary stent procedure.

For patients with any form of atrial fibrillation: for patients with ischaemic stroke or TIA in paroxysmal, persistent or permanent atrial fibrillation (valvular or non-valvular), anticoagulation should be the standard treatment.

Anticoagulation:

- Should not be given after stroke or TIA until brain imaging has excluded haemorrhage
- Should not be started in patients with uncontrolled hypertension
- Of patients with disabling ischaemic stroke, should be deferred until at least 14 days have passed from the onset; aspirin 300 mg daily should be used until this time
- Of patients with non-disabling ischaemic stroke, should be deferred for an interval at the discretion of the prescriber, but no later than 14 days from the onset
- Should be commenced immediately after a TIA once brain imaging has ruled out haemorrhage, using an agent with a rapid onset such as low-molecular-weight heparin or an oral direct thrombin or factor Xa inhibitor.

Lipid lowering in secondary prevention of stroke and TIA

This should be intensified if a total cholesterol <4.0 mmol/L or LDL-cholesterol <2.0 mmol/L is not attained with initial therapy, and should be used with caution, for other indications, only in patients with recent primary intracerebral haemorrhage.

Intravenous thrombolysis

Patients with a suspected stroke should be taken to a recognised stroke centre, assessed clinically and

imaged as soon as possible, to assess their suitability for thrombolysis by staff expert in its administration, post-thrombolysis monitoring and in units that have appropriate neuroradiological, neurosurgical and intensive care support.

Within 3 hours of known symptom onset: any patient, regardless of age or stroke severity, who has been shown not to have an intracerebral haemorrhage or other contraindications (such as co-morbidities or high levels of pre-stroke disability), should be considered for treatment using alteplase.

Between 3 and 4.5 hours of known stroke symptom onset: patients aged <80 years, who have been shown not to have an intracerebral haemorrhage or other contraindication, should be considered for treatment with alteplase.

Between 3 and 6 hours of known stroke symptom onset: patients should be considered for treatment with alteplase on an individual basis, recognising that the benefits of treatment are likely to be smaller than for those treated earlier, but that the risks of a worse outcome, including death, will on average not be increased.

As implied by the above RCP recommendations, the benefits of treatment rapidly diminish with time and beyond 4.5 hours the benefits are unproven, although subject to ongoing research, as is using advanced imaging to select patients up to 9 hours after onset. Therefore one should take specialist up-to-date advice if uncertain.

Mortality from thrombolysis at 6 months is not increased, despite the higher risk of early (within 7 days) fatal and non-fatal intracerebral haemorrhage.

There is no upper age limit for treatment, as such, particularly within the first 3 hours, but careful attention to co-morbid conditions and levels of disability should be considered in the holistic assessment of the patient's suitability for thrombolysis.

Patients with severe stroke and those with early signs of infarction on the initial scan also benefit from treatment (as long as these early radiological signs are subtle and consistent with the stated time of onset and do not suggest a lesion older than 6 hours).

Every patient treated with thrombolysis should be started on an antiplatelet after 24 hours, unless contraindicated (eg after significant haemorrhage has been excluded).

All people presenting with acute stroke who have had the diagnosis of primary intracerebral haemorrhage excluded by brain imaging should, as soon as possible but certainly within 24 hours, be given:

- An antiplatelet orally if they are not dysphagic
- An antiplatelet rectally or by enteral tube if they are dysphagic.

Thereafter, aspirin 300 mg should be continued until 2 weeks after the onset of stroke, at which time definitive long-term antithrombotic treatment should be initiated. People being discharged before 2 weeks can be started on long-term treatments earlier.

Any person with acute ischaemic stroke, for whom previous dyspepsia associated with an antiplatelet is reported, should be given a proton pump inhibitor in addition to aspirin.

Carotid artery stenosis and endarterectomy

The two major predictors of risk of ipsilateral ischaemic stroke in patients with internal carotid artery stenosis are recent relevant ipsilateral cerebrovascular symptoms and the degree of stenosis.

Carotid endarterectomy provides extra benefit over and above best medical therapy, irrespective of gender and type of qualifying event (cerebral or ocular), for symptomatic carotid stenosis of ≥70%.

There is some benefit of surgery for 50–70% carotid stenosis, except in women and those with ocular events.

There is no benefit of surgery for carotid stenosis <50%.

Acute cervical arterial dissection

A small proportion of patients with acute ischaemic stroke, who are usually younger or may present with a history of neck trauma, will have experienced a dissection of a carotid or vertebral artery as the underlying cause.

There is currently no adequate evidence to guide treatment of carotid or vertebral artery dissection. There is no evidence to suggest that thrombolysis carries any greater risk in these patients than stroke due to other causes.

Patients should be investigated using non-invasive angiographic techniques, eg CT-A, MRA, and patients with stroke secondary to arterial dissection and who meet the indications for thrombolysis should receive it. Patients with dissection should be treated with either anticoagulants or antiplatelet agents, preferably as part of a randomised clinical trial.

Subarachnoid haemorrhage

Around 5% of all strokes are due to subarachnoid haemorrhage (SAH). Causes include:

- Ruptured arterial aneurysm
- Trauma
- Ruptured arteriovenous malformation
- Cocaine or amphetamine abuse
- Hypertension.

Eighty per cent of intracranial aneurysms are located in the anterior circulation, most on the anterior communicating artery, and 15% are bilateral.

Investigation of subarachnoid haemorrhage

SAH is typically investigated with CT and lumbar puncture (LP):

- CT may be negative in up to 20% of suspected cases of SAH, so a normal CT does not exclude the diagnosis
- LP shows xanthochromia (due to red cell breakdown products, only visible >4 hours after haemorrhage)
- Other recognised findings include transient glycosuria, low CSF glucose or lengthening of the QT interval (leading to tachyarrhythmias or torsades de pointes).

Treatment of SAH

The management of SAH depends on making the diagnosis, locating the underlying aneurysm and occluding it. About a quarter of patients will die within a day of presentation, and a third of those who survive the first day will subsequently die of complications or rebleeding. At presentation, several factors have prognostic value for poor outcome, the most important of which are decreased level of consciousness, increasing age (>65) and amount of blood visible on CT scan.

Every patient presenting with sudden severe headache and an altered neurological state should have the possible diagnosis of SAH investigated by:

- Immediate CT brain scan (positive in 98% of cases within 6 hours, but only 50% within a week of onset)
- LP between 12 hours and 14 days if the CT brain scan is negative and does not show any contraindication
- Spectrophotometry of the CSF for xanthochromia.

Lumbar puncture in suspected SAH

Refer to your local guidelines, but in general the following apply.

After haemorrhage into the CSF, red blood cells undergo lysis and phagocytosis; the liberated oxyhaemoglobin is converted in vivo in a time-dependent manner into bilirubin and sometimes methaemoglobin. Of these three pigments, only bilirubin arises solely from in vivo conversion.

An LP should only be performed a minimum of 12 h after the onset of presenting symptoms, as best evidence suggests that bilirubin forms 9–15 hours after a bleed. State the date and time of the onset of suspected SAH on the request form to aid interpretation.

Minimise the rate of bilirubin decay in direct light; whenever possible collect sequential specimens and protect them from light (eg put them in a thick brown envelope outside the specimen bag and send by hand to the lab as soon as possible).

Minimise the possibility of in vitro lysis of red cells and production of oxyhaemoglobin by: always ensuring that the least blood-stained CSF sample taken (usually the fourth/last) is sent for bilirubin analysis.

Note that at least 1 mL or 20 drops, or minimum stipulated under local requirements, should be sent.

Avoid vacuum tube transport systems, if possible.

A simultaneous blood specimen should be taken for serum bilirubin and total protein measurement (CSF bilirubin will also be increased when CSF total protein or serum bilirubin is increased).

Always use spectrophotometry in preference to visual inspection for xanthochromia (Figure 16.4).

An increase in CSF bilirubin is the key finding, which supports the occurrence of SAH but is not specific for this.

In most positive cases, bilirubin will occur with oxyhaemoglobin.

Every patient diagnosed as having an SAH should be referred immediately to a tertiary neuroscience centre and:

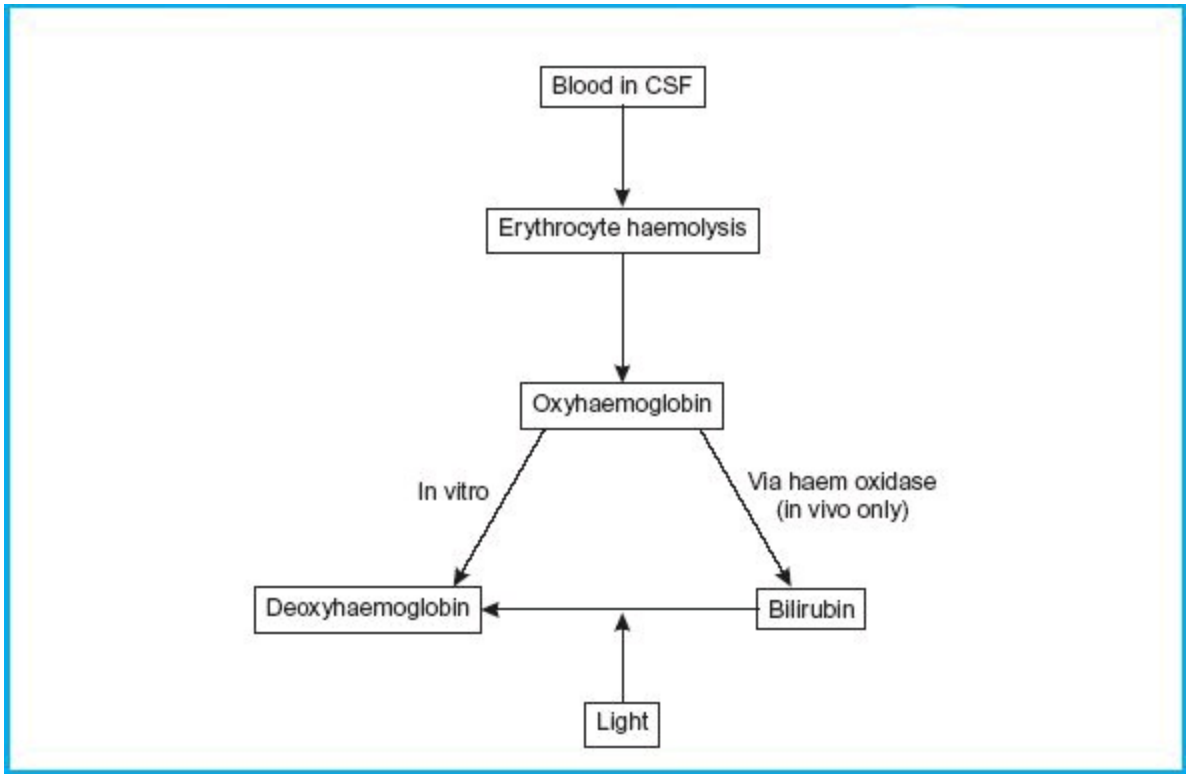
- Be started on oral nimodipine 60 mg 4-hourly unless there are specific contraindications, to reduce intracranial vasospasm and prevent delayed cerebral ischaemia
- Not be given anti-fibrinolytic agents or steroids

Recommend that they be given early CT or catheter angiography, followed by clipping or coiling
- of any aneurysm related to the haemorrhage, within 48 hours of the ictus, especially for good grade (high GCS) patients.

Complications of subarachnoid haemorrhage

- **Neurological:**
  - Rebleeding
  - Hydrocephalus
  - Focal ischaemic injury from cerebral vasospasm
- **Systemic:**
  - Fever
  - Tachyarrhythmias secondary to catecholamine release
  - Neurogenic pulmonary oedema (rarely)
  - Hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Figure 16.4 Formation of oxyhaemoglobin and bilirubin in the CSF after subarachnoid haemorrhage



Prevention of SAH

Every patient with a strong family history of two or more affected first-degree relatives and/or a history of polycystic renal disease should:

- Be advised that their family may be at increased risk of SAH
  Be considered for a referral to a neurovascular and/or neurogenic specialist for up-to-date

- information and advice.

Intracranial aneurysms are associated with:

- Polycystic kidney disease
- Ehlers–Danlos syndrome
- Fibromuscular dysplasia causing renal artery stenosis
- Medium-vessel arteritides (eg polyarteritis nodosa)
- Coarctation of the aorta.

16.2.10 Central nervous system vasculitis

Primary CNS vasculitis

There are many causes of vasculitis that are classified in section 20.5 of Chapter 20. The nervous system may be involved as part of a vasculitis, with systemic inflammatory markers such as giant-cell arteritis (see section 20.5.3 of Chapter 20) or as part of any of the multisystem vasculitides, such as granulomatosis with polyangiitis (GPA; Wegener's granulomatosis), Churg–Strauss syndrome and ANCA-related vasculitis (see section 20.5 of Chapter 20). When the peripheral nervous system is involved, a mixed sensory and motor neuropathy is found, which is usually rapidly progressive and painful, initially asymmetrical, with a mononeuritis multiplex picture, in the context of a known multisystem vasculitis and/or with raised inflammatory markers (ESR/CRP). In these circumstances, an urgent combined nerve and muscle biopsy, ideally before starting high-dose corticosteroids, eg 1 g methylprednisolone daily for 3–5 days with an oral prednisolone taper of 60 mg daily or 1 mg/kg without unnecessary delay, can improve diagnostic yield. Appropriate secondary immunosuppression can be contemplated in light of the patient's overall health status.

Involvement of the CNS can occur as part of systemic vasculitides, when cranial nerve palsies, often multiple, can occur. Primary (isolated) CNS vasculitis can be more of a diagnostic challenge.

Three broad presentations are recognised:

1. **Multiple sclerosis-like with atypical features**: relapsing–remitting course, eg optic neuritis and/or brainstem episodes, but with less common features of MS such as encephalopathy, persistent headaches, seizures and stroke-like episodes
2. **Acute or subacute encephalopathy**: headache and acute confusional state with drowsiness and coma
3. **Intracranial mass lesion**: mimicking a tumour with headache and focal neurological signs.

It is important to pursue and exclude other causes of vasculitis, because investigations may yield non-diagnostic results in primary CNS vasculitis. ESR and CRP are often normal, CSF may yield abnormal protein and cell counts, and cerebral imaging may be normal or demonstrate non-specific vascular white matter changes. Angiography (CT, MR or formal catheter) may demonstrate beading but can be non-specific. Cerebral biopsy may be required, but yield may be reduced if the patient has already been treated urgently with high-dose corticosteroids and secondary immunosuppression such

as cyclophosphamide. Azathioprine and other agents may be considered after the condition has entered remission, and establishing this can be challenging if the paraclinical test results were initially non-specific

For giant-cell arteritis, see section 20.5.3.

Cerebral venous sinus thrombosis

Cerebral venous thrombosis (CVT) should be considered in the following groups of patients:

- Patients presenting with new, subacute headache suggestive of raised intracranial pressure (ICP):
  - Pregnant patients in the third trimester or puerperium who present with new headache suggestive of raised ICP
  - Patients with new headache suggestive of raised ICP who have a history of venous thromboembolism
  - Patients presenting with progressive neurological decline including any of headache, focal neurological signs, seizures, altered mentation, ENT infection, meningism
  - Patients with atypical site of intracerebral haemorrhage (ICH)/multiple sites of haemorrhage
  - Patients with ischaemic stroke crossing arterial territories/bilateral stroke
- Patients in whom CVT is considered should undergo urgent imaging of the brain and cerebral venous system, usually with a CT of the brain and CT venogram due to ease of access and the superiority of venous imaging over MRI.

Once diagnosed, investigations for the causes of CVT will include: FBC/renal/liver/bone/clotting profile, D-dimer (if pre-imaging), full thrombophilia screen (protein C and protein S, and antithrombin III should be tested after cessation of anticoagulant therapy because results are unreliable in acute thrombosis and with anticoagulation), full drug history (in particular history of taking the oral contraceptive pill), inflammatory marker screen; LP should be considered and discussed with neurologists before initiation of anticoagulation, but should not lead to a prolonged delay.

Anticoagulation should be started as soon as possible after diagnosis unless an LP is indicated. Usually low-molecular-weight heparin in the same doses used to treat pulmonary embolus are used; however, in some cases (large haemorrhage with mass effect, possibility of need for LP, need for surgical intervention, other active bleeding risk), intravenous unfractionated heparin may be more appropriate.

Patients with seizures should be treated with appropriate antiepileptic medications because recurrent seizures would risk exacerbating raised ICP. Early neurological deterioration can be seen in up to 25% of cases. If deterioration occurs despite optimum anticoagulation, then surgical/radiological intervention should be considered.

Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterised by severe, recurrent, sometimes thunderclap, headaches with or without seizures and focal neurological deficits, and constriction of cerebral arteries, which is monophasic and resolves spontaneously in 1–3 months. Mean age of onset is around 45 years, with a female:male ratio of 2–10:1. Over half the cases are

secondary, post-partum (two-thirds in first week post-partum) or after exposure to vasoactive, sympathomimetic or serotoninergic substances. The major complications are localised cortical SAH (22%), and parenchymal ischaemic or haemorrhagic strokes (7%). Diagnosis requires demonstration of the 'string-of-beads' appearance of cerebral arteries on angiography, with complete or almost complete resolution on repeat angiography 12 weeks after onset. Nimodipine seems to reduce thunderclap headaches within 48 h, but has no definite effect on the haemorrhagic and ischaemic complications

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is a syndrome caused by rapid development of vasogenic intracerebral oedema; it presents with a combination of altered mentation with confused, lethargic and slowed motor responses, or deep stupor, seizures including status epilepticus, visual disturbance including cortical blindness, and/or non-severe headache. This constellation should prompt an early brain MRI to reveal the typical bilateral hyperintensities on fluid-attenuated inversion recovery (FLAIR) imaging, predominantly in the parieto-occipital region, and diffusion-weighted imaging (DWI) changes consistent with vasogenic oedema. CT shows changes only in about 50%.

Triggers include: abrupt arterial hypertension, impaired renal function, pregnancy, immunosuppressive drugs, especially ciclosporin and tacrolimus post-transplantation, and inflammatory conditions, such as GPA, systemic lupus erythematosus (SLE), polyarteritis nodosa (PAN) and systemic sclerosis. The clinical outcome is usually excellent, with recovery within a few days, although the MRI abnormalities resolve much more slowly. Little is known about the best management, but withdrawal of trigger factors and intense blood pressure monitoring are recommended. Seizures do not normally progress to chronic epilepsy, so antiepileptic drugs should be discontinued after about 3 months. PRES may coexist with RCVS in about 10% of cases, with associated intracerebral or SAH.

16.2.11 CNS inflammation

Multiple sclerosis

Clinical presentation of MS

Multiple sclerosis (MS) (incidence 1 in 800) is the most common non-traumatic cause of disability in young adults and is thought to be a cell-mediated autoimmune disease associated with immune activity directed against CNS antigens, principally myelin. The aetiology of MS remains unclear but there is an increased relative risk in offspring (about 4%) compared with the general population, although concordance rates in monozygotic twins of about 25% suggest an additional environmental component, with Epstein–Barr virus (EBV) and low vitamin D levels receiving much attention.

Diagnosis of MS

A diagnosis of MS requires evidence of dissemination of lesions of the CNS, brain and/or spinal cord, in time and space *with no better explanation*. Paraclinical, including blood and CSF, tests are aimed at excluding differential diagnoses.

Typical first clinical presentations that may progress to MS include: optic neuritis, brainstem and/or

cerebellar syndromes, or partial spinal cord syndromes. The largest predictor of a further clinical episode occurring within 20 years (82%) is MRI evidence of dissemination in space, with additional silent lesions also being present (eg cerebellar lesions at the time of an optic neuritis).

MRI diagnostic criteria

Current diagnostic criteria allow for a diagnosis of MS to be made in the context of a *typical* clinical attack plus MRI evidence of dissemination in space (typical lesions in two or more of these areas: *periventricular, juxtacortical, infratentorial* and/or *spinal cord*) and any new lesions (a mixture of gadolinium-enhancing and non-enhancing lesions in the requisite areas on a single scan), or any new typical T1 or T2 lesion on a subsequent scan: 'any two, any new'. MS white matter lesions are typically ovoid in shape, 3–5 mm in size and oriented perpendicular to the long axis of the lateral ventricles, which can differentiate them from vascular lesions, for example. Typically, given the availability of multiple MR scans, current UK practice is still to wait until a second clinical attack, disseminated in time and space, occurs before confirming a diagnosis of MS.

Other paraclinical tests

Unpaired *oligoclonal bands in the CSF*, but not serum, indicate intrathecal immunoglobulin synthesis. These are not specific to MS and occur in about 85% of cases. Other causes include neurosarcoidosis, CNS lymphoma, SLE, neurosyphilis, SAH (rare) and subacute sclerosing panencephalitis (SSPE) – a rare, late complication of measles.

Clinical consensus identifies four different subtypes of MS, which may reflect different immunological subtypes:

1. **Relapsing–remitting multiple sclerosis** (RRMS): the most common form (80–85% of patients); onset 20–40 years of age, typically 2–3:1 female:male. Short-lasting acute attacks (relapses), eg optic neuritis, brainstem/cerebellar disorder or spinal cord syndrome, lasting 4–8 weeks, followed by clinical remission, a relatively steady baseline state between relapses. The average number of relapses is around 0.8/year, with residual disability as a result of incomplete recovery from relapses common
2. **Secondary progressive disease**: untreated, up to 50% of patients with relapsing–remitting disease will subsequently show progressive irreversible deterioration, with relapses becoming less prominent within about 10 years of MS disease onset
3. **Primary progressive disease**: 10–15% of patients show progressive deterioration from onset without any superimposed relapses. Age of onset is typically older (in 50s) than for relapsing–remitting disease, 1:1 male:female and presentation is typically myelopathic
4. **Progressive–relapsing disease**: a very small number of patients with primary progressive disease also experience superimposed relapses associated with gradual disease progression.

Symptoms of MS

A patient with MS will commonly experience fatigue and cognitive deficits, in addition to neurological symptoms such as visual disturbance (from optic neuritis), myelopathic symptoms such as spasticity, weakness, walking impairment, numbness, neuropathic pain, sphincter disturbance such as urinary frequency, hesitancy and nocturia, constipation and sexual dysfunction. Cerebellar and brainstem dysfunction such as tremor, dysarthria and ataxia are also common.

Treatment of MS

A multidisciplinary approach to the management of MS, including physiotherapy, is recommended by NICE. Pharmacological treatment of MS can be divided into:

- Symptomatic treatment (see Chapter 2)
- Treatment of relapses
- Disease-modifying treatment.

Treatment of relapses

A relapse is typically defined as new or recurring neurological symptoms lasting at least 24–48 hours in a patient with MS, whose condition has been stable or improving for the previous 30 days, in the absence of infection or systemic upset.

It is recommended that infection be excluded before steroids are considered. As steroids only accelerate natural recovery from relapse and have no long-term effect on disease course, and can cause well-recognised complications, it is prudent to ask patients what benefit, if any, they achieved from the last course of steroids and whether they feel that they have platueaued or are recovering from the current relapse.

If patients are receiving disease-modifying treatments apart from interferon-β and glatiramer acetate, given the possibility of opportunistic infection such as progressive multifocal leukoencephalopathy (PML), it is prudent to discuss steroids with the neurology team before starting them in these patients.

Typical relapse treatment regimens would be:

- 1 g methylprednisolone daily for 3 days
- 500 mg oral methylprednisolone for 5 days.

Disease-modifying treatment (DMT) for MS

It is unclear currently whether drugs that reduce relapses more effectively in the short term may reduce entry into the secondary progressive phase of MS and longer-term disability, unrelated to relapse. Clinical trial results guide recommendations for therapy, which should be offered to patients (aged ≥18 years), who are ambulant and have no contraindications to therapy, such as pregnancy, in the following clinical situations:

1. Patients with active RRMS (two or more relapses in the last 2 years): interferon-β, glatiramer acetate, dimethyl fumarate or teriflunomide (reduces the relapse rate by a third in RRMS)
2. Patients with highly active RRMS (defined as ongoing severe relapses or unchanged or increased relapse rate despite treatment with interferon-β or glatiramer acetate) should be considered for fingolimod (reduces relapse rate by half)
3. Patients with rapidly evolving severe RRMS (two or more disabling relapses in the last year and new brain MRI lesions) should be considered for natalizumab (reduces relapses by 80%).

In patients with relapsing secondary progressive MS, treatment with interferon-β only, should be considered only when relapses are the dominant cause of the increasing disability. Treatment for primary progressive MS is not recommended.

Patients within 12 months of a clinically significant, clinically isolated syndrome, when MRI evidence of dissemination in space predicts a high likelihood of development of clinically definite MS, and patients with only a single major relapse in the preceding 2 years, but combined with MRI

evidence of continuing disease activity, can also be considered for treatment with interferon-β or glatiramer acetate.

Decisions on change of treatment are generally made clinically, on the basis of increasing severity of relapses or lack of relapse reduction on treatment compared with pretreatment (underpinned by an assessment of the degree of new MRI activity).

Decisions on withdrawing treatment are usually made clinically, on the basis of the development of non-relapsing secondary progressive MS, with loss of the ability to walk.

Clinical vigilance should be maintained for new symptoms occurring in patients with MS who are taking the following drugs:

- **Natalizumab (Tysabri):** a monoclonal antibody to α_4,β_1-integrin that prevents binding of lymphocytes to the vascular endothelium of the blood–brain barrier; it is associated with the occurrence of progressive multifocal leukoencephalopathy, an infection of oligodendrocytes by the John Cunningham (JC) virus. Typically, patients present with more indolent progressive symptoms than relapses, developing over months, such as cognitive decline, homonymous visual field defects and hemiparesis or hemianaesthesia. New neurological symptoms in such patients should be discussed with the neurology team
- **Fingolimod (Gilenya):** a sphingosine 1 phosphate receptor (S1P) modulator that blocks the egress of lymphocytes through lymph nodes, reducing their passage into the CNS. The drug is associated with transient AV conduction slowing, macular oedema and reactivation of herpes viruses
- **Alemtuzumab (Lemtrada):** a monoclonal antibody to CD52 that causes a rapid depletion of B and T lymphocytes, which lasts approximately 3 and 12 months, respectively, after each dose. It is associated with a variety of autoimmune diseases indicated for patients with active MS, either clinically or radiologically determined, including thyroid disorders in about 30% of patients, idiopathic thrombocytopaenic purpura and, rarely, Goodpasture syndrome.

Neuromyelitis optica

Neuromyelitis optica (NMO or Devic's disease) is an antibody-mediated condition of the optic nerves, brain and spinal cord, which is about 200 times less common than MS in Western populations, but much commoner in the Far East. It is important to diagnose, however, because some MS DMTs have been shown to trigger devastating attacks in NMO and also, unlike MS, the accumulation of disability seems to occur largely as a result of relapses, with much less neurodegeneration. NMO IgG, an NMO-specific autoantibody directed against aquaporin-4 (AQP4), the major water channel in the CNS, clearly identified NMO as a separate disease from MS. The term 'NMO spectrum disorders' (NMOSDs), describes restricted forms of the disorder which include recurrent optic neuritis (ON), relapsing transverse myelitis (TM) and some encephalitic presentations in children. NMO is clinically characterised by acute, severe episodes of optic neuritis and transverse myelitis. Clinically, patients with MS have a partial myelitis, whereas patient with NMO-related myelitis may appear 'sawn off', with profound weakness and loss of sensation and sphincter control. Similarly, patients with NMO-related optic neuritis may show little visual recovery, or sequential optic neuritides, whereas a good visual recovery would be the norm in MS. Only about 60% of NMO patients have brain MRI lesions, including causing hypothalamic disorders, where

SIADH has been described. Spinal lesions are typically three or more vertebral segments in length, may cause cord swelling and, in the cervical area, can extend into the brainstem causing intractable hiccups and vomiting. The serum NMO IgG AQP4 antibody is present in about 70% of cases and, when found in a patient presenting with longitudinally extensive transverse myelitis (LETM), predicts a further episode of either myelitis or optical neuritis within a year in about half the patients. Treatment of NMO and NMOSDs acutely is with steroids and sometimes plasma exchange or intravenous immunoglobulin, and long-term steroids (unlike MS) and a steroid-sparing agent such as azathioprine or mycophenolate, with other therapies such as rituxumab reserved for refractory cases.

Neurosarcoidosis

Neurosarcoidosis is a multisystem granulomatous disorder that affects the nervous system in about 5% of cases. Involvement of the nervous system includes:

- Optic neuritis (including bilateral cases)
- Other cranial nerve palsies including bilateral facial palsy and hearing loss
- Seizures
- Chronic meningitis
- Headache
- Encephalopathy
- Ataxia
- Vertigo
- Hypopituitarism
- Myelopathy
- Peripheral neuropathy.

Diagnosis involves determination of multisystem sarcoidosis by serum angiotensin-converting enzyme (ACE) levels, chest radiograph for hilar lymphadenopathy and/or infiltrates, CT of the thorax, abdomen and pelvis, and CSF (can show lymphocytosis, raised protein, low glucose and raised ACE levels, in addition to oligoclonal bands). MRI with gadolinium contrast may show inflammatory changes mimicking MS, meningeal enhancement or even a mass lesion in the cerebrum and/or myelitis. Defining a peripheral target to obtain tissue for a firm diagnosis is the aim, although challenging. Gallium scans and/or muscle biopsy may be helpful. Treatment is immunosuppression with corticosteroids and steroid-sparing agents, commensurate with the severity of the patient's illness.

Cerebral tumours

Primary brain tumours account for approximately 2% of adult cancers, with an incidence of around 10–20 per 100 000 per annum, and overall carry a 25% mortality rate, being the most common cancer-related death in men aged <45 years and women aged <35 years. The common tumours are gliomas and meningiomas; CNS lymphoma can also occur. Brain tumours are usually sporadic but rare causes include previous exposure to ionising radiation, neurocutaneous syndromes (eg neurofibromatosis, tuberous sclerosis, von Hippel–Lindau syndrome) and genetic tumour syndromes (eg Li–Fraumeni syndrome). Twenty per cent of patients with cancer outside the nervous system, most

commonly lung, breast and melanoma, develop secondary brain metastases.

Primary brain tumours are classified based on histological appearances into four grades, I—IV, with low-grade (I and II) and high-grade (III and IV) tumour subdivisions. These grades correlate with presentation, prognosis and guide management. Prognosis is also related to younger age, performance status and molecular factors, eg loss of heterozygosity at chromosome 1p/19q occurs in about 70% of oligodendrogliomas and anaplastic oligodendrogliomas, and is associated with prolonged progression-free survival and response to chemotherapy.

Low-grade tumour may present with seizures, evolving personality change or minor neurological deficits, or occasionally be found incidentally on imaging, whereas high-grade tumours may present subacutely with rapidly evolving neurological deficits, symptoms of raised ICP, rapid cognitive decline or seizures. Surgery or surveillance is usually recommended for low-grade gliomas, whereas surgery and/or chemotherapy and radiotherapy are utilised for high-grade gliomas. Low-grade astrocytomas have a median survival of 5–7 years and oligodendrogliomas 10–15 years, compared with a median life expectancy of 2–3 years for anaplastic astrocytomas and 1–2 years for a grade IV glioblastoma multiforme.

The possibility of high-grade transformation of a previously low-grade lesion should prompt reimaging if such a patient presents with rapidly evolving clinical signs.

Idiopathic intracranial hypertension

See Section 16.2.7.

Motor neuron disease

Motor neuron disease (MND) is a progressive degenerative, usually asymmetrical, motor syndrome, with clinical involvement of UMNs (spasticity, brisk reflexes, extensor plantar responses) and LMNs with denervation (muscle wasting, weakness and fasciculations), supplying bulbar, limb and respiratory muscles. Cognitive, sensory and autonomic involvement is described.

The prevalence is 7 per 100 000; 10% present at age <45 years and 20% >70 years.

The aetiology is largely unknown, although 5–10% of patients report a first-degree relative with MND, and genetic mutations in *C9orf72* are described in MND in association with frontotemporal dementia, and 85% of amyotrophic lateral sclerosis (ALS) cases have ubiquitinated inclusions in spinal cord neurons.

There are three principal clinical phenotypes, reflecting the pattern and progression of the degenerative motor neuronopathy:

1. **Amyotrophic lateral sclerosis**: both LMNs and UMNs are involved; a typical clinical picture would be LMN signs in the arms and bilateral UMN signs in the legs; intermediate prognosis
2. **Progressive bulbar palsy**: bulbar musculature affected with poor prognosis
3. **Progressive muscular atrophy**: typically presents with LMN signs affecting a single limb which then progress; best prognosis (still poor).

Diagnosis of MND

Diagnosis is largely clinical but requires careful exclusion of other, potentially treatable, disorders such as compressive myeloradiculopathy or multifocal motor neuropathy (MMN) with conduction block. Brisk reflexes in wasted, fasciculating limbs are highly suspicious. Confirmatory investigations include imaging to exclude structural pathology (eg brainstem lesion, spondylotic myeloradiculopathy), nerve conduction studies (NCS) and electromyography (EMG), which may show evidence of chronic partial denervation and widespread fasciculation with normal sensory nerves and preserved motor nerve conduction velocities (these latter features distinguish the disorder from motor peripheral neuropathies). Serum CK and CSF protein concentration may be slightly increased. Prognosis is poor with only a 15–20% 5-year survival rate.

Revised El Escorial criteria for diagnosis of amyotrophic lateral sclerosis (ALS) variant of motor neuron disease

Definite ALS

- UMN signs and LMN signs in three regions (bulbar, arm, leg)

Probable ALS

- UMN signs and LMN signs in two regions, with at least some UMN signs rostral (superior in the neuroaxis) to LMN signs

Probable AL: laboratory supported

- UMN signs in one or more regions and LMN involvement defined by EMG (denervation) in at least two regions

Possible ALS

- UMN signs and LMN signs in one region
- UMN signs in two or more regions
- UMN signs and LMN signs in two regions with no UMN signs rostral to LMN signs

Management of motor neuron disease

Regular multidisciplinary management, including speech and language therapy, nutritional advice (including consideration of percutaneous endoscopic gastrostomy [PEG] with radiologically inserted gastrostomy [RIG]) and respiratory assessment (eg for non-invasive positive pressure ventilation or NIPPV), avoids complications, improves quality of life and allows for forward planning. Riluzole, a glutamate antagonist, is usually well tolerated, although it can cause bone marrow suppression and deranged LFTs, and is associated with a modest improvement in survival (about 2–3 months at 18 months) and NICE-approved for treatment of probable or definite MND.

16.2.12 Movement disorders

Movement disorders are classified clinically as hypokinetic disorders, characterised by poverty of voluntary movement, and hyperkinetic syndromes in which excessive involuntary movements occur.

Hypokinetic disorders

Parkinson's disease

The prototypical hypokinetic movement disorder is idiopathic Parkinson's disease (PD), which typically presents with the classic triad:

- Resting tremor (can be absent in up to 30%)
- Rigidity
- Bradykinesia (progressive reduction in amplitude and speed of repetitive movements).

Parkinson's disease results from pathological lesions called Lewy bodies containing the protein α-synuclein within the dopaminergic neurons of the substantia nigra pars compacta. There is a substantial genetic contribution to PD, with monogenic forms common in young-onset patients aged <40 years (commonly recessive due to a *parkin* mutation) and in certain ethnic groups. Loss of dopamine input to the basal ganglia results in poverty of movement, or bradykinesia. Lewy body pathology also occurs in neocortical and non-dopaminergic brain regions, giving rise to other non-motor features of PD, some of which (*) may precede the onset of clinical symptoms:

- Depression*

- Sleep disorders*
- Pain and other sensory disorders
- Bowel dysfunction*
- Dementia.

PD is a clinical diagnosis, but may be inaccurate in 10%, even in specialist centres. Clinical features supporting PD and those suggesting an alternative parkinsonian syndrome are shown in Table 16.5. MRI may be useful in differentiating PD from atypical parkinsonian syndromes (see below). Dopamine transporter SPECT imaging may be helpful in differentiating PD from non-PD tremor syndromes or drug-induced parkinsonism, but is not useful in distinguishing neurodegenerative parkinsonian syndromes.

Table 16.5 Supportive features and 'red flags' for diagnosis of idiopathic Parkinson's disease (PD)

Supportive of PD	'Red flags' for PD diagnosis	Alternative diagnosis
Unilateral onset and persistent asymmetry	Prominent early autonomic failure (postural hypotension, urinary incontinence, erectile failure)	MSA DLB
Resting tremor	Cerebellar signs	MSA
Good response to levodopa	Prominent pyramidal signs	MSA Vascular parkinsonism CBS
Levodopa-induced dyskinesia	Vertical supranuclear gaze palsy	PSP
Long disease course (>10 years)	Early falls (within first year)	PSP Normal pressure hydrocephalus
	Neuroleptic use	Drug-induced parkinsonism
	Poor levodopa response	MSA PSP/CBS
	Early dementia	DLB PSP/CBS
	Toxin exposure (rare)	Manganese Carbon monoxide MPTP

CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine); MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

Treatment of Parkinson's disease

The dopamine precursor levodopa, first used clinically in 1967, remains the most effective symptomatic treatment for PD. Levodopa therapy leads to the development of motor complications, including end-dose 'wearing off' and abnormal involuntary movements, or dyskinesia, in around 50%

of patients after 5 years of therapy (Table 16.6).

Table 16.6 Relative adverse effects of levodopa and dopamine agonists

Adverse effect	Levodopa	Dopamine agonists
Dyskinesia	+++	+
Motor fluctuations	+++	+
Oedema	+	+++
Somnolence	+	++
Postural hypotension	++	+++
Nausea	++	+++
Hallucinations	+	++
Impulse control disorders	+	+++

Dopamine receptor agonists stimulate predominantly striatal dopamine D_2 receptors and produce clinical anti-parkinsonian effects.

- Ropinirole and pramipexole tablets, as well as the rotigotine patch, are the most common in clinical use
- Apomorphine subcutaneous infusion is helpful in patients with motor fluctuations
- The magnitude of anti-parkinsonian effects is lower than with levodopa in clinical trials, although the use of dopamine agonists is associated with a lower incidence of dyskinesia in the short and longer term
- Dopamine agonists are less well tolerated than levodopa, with more common side-effects, including ankle oedema, somnolence, nausea and postural hypotension.

Adjunctive therapies (Figure 16.5)

- Monoamine oxidase B inhibitors, eg selegiline and rasagiline, may have mild neuroprotective effects in early PD; more often used as adjunctive therapies to improve 'on' time
- Catechol-*O*-methyltransferase inhibitors, eg entacapone, improve 'on' time when added to levodopa
- Amantadine, a glutamatergic N-methyl-Daspartate (NMDA) receptor antagonist, improves dyskinesia by about 40% in PD.

Surgery for movement disorders

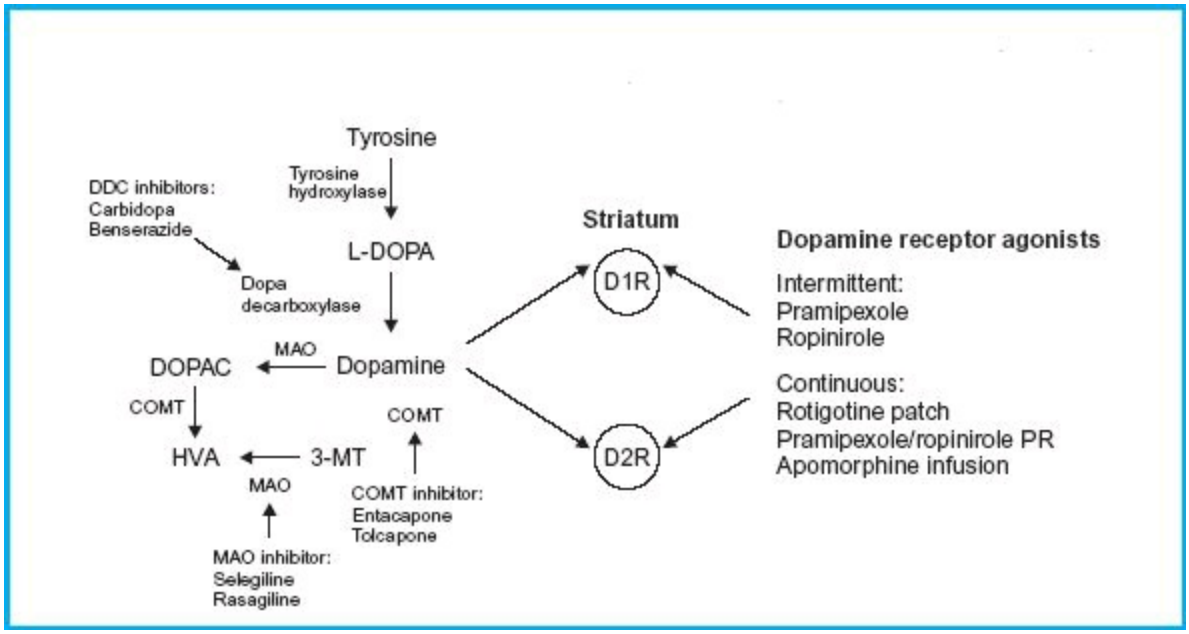
Deep brain stimulation (DBS) surgery is a procedure in which electrodes are implanted in targets such as the internal globus pallidus or subthalamic nucleus, and continuously stimulated via an implantable pulse generator. Stimulation of both targets improves motor fluctuations and extends 'on' time in patients with PD, allowing a reduction in dyskinesia. Surgical treatment of PD with motor complications has been proved to improve quality of life more than best medical therapy, have good long-term efficacy, and there is increasing evidence for its use earlier in the disease course.

However, non-dopaminergic features such as gait impairment do not respond as well long term to DBS.

Atypical parkinsonian syndromes

These conditions are neurodegenerative disorders, typically with a more aggressive disease course and poorer response to dopaminergic therapy compared with PD. Clues to their clinical diagnosis are given in Table 16.5.

Figure 16.5 Sites of action of drugs used in the treatment of Parkinson's disease. COMT, catechol-*O*-methyltransferase; DDC, dopa decarboxylase; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; MAO, monoamine oxidase; 3-MT, 3-methoxytyramine.



Progressive supranuclear palsy (PSP) typically presents with early backward falls, vertical gaze palsy, predominantly axial parkinsonian features, dysarthria, dysphagia and frontal–subcortical cognitive impairment. Underlying tau pathology in the basal ganglia, thalamus and midbrain is the underlying cause. Progression is typically within the seventh decade and is more rapid than seen in PD. Atrophy of the midbrain ('hummingbird sign') is seen on sagittal MR of the brain.

Corticobasal degeneration is a related tauopathy with significant overlap with PSP, although the clinical corticobasal syndrome frequently has other pathological substrates such as Alzheimer's disease pathology. Typical presentation is with asymmetrical, pyramidal and dystonic signs, myoclonus and cortical sensory loss.

Multiple system atrophy (MSA) is an α-synucleinopathy, but unlike PD, pathologically involves the basal ganglia, cerebellum and brainstem. The core feature is early autonomic failure, with urinary incontinence, constipation, orthostatic hypotension and sleep disorders, including rapid eye movement (REM) sleep behaviour disorder and sleep-disordered breathing. The mean age of presentation is around 55 years (younger than PD and PSP), and presentation over the age of 75 is unusual. The response to levodopa may be good at an early stage, but typically wanes later in the disease course. Mean survival from symptom onset is 7–8 years. Dysphagia and sleep-disordered breathing including stridor are common contributors to mortality.

Hyperkinetic movement disorders

Hyperkinetic movement disorders are characterised by excessive involuntary movements. Clinical clues to their diagnosis and some conditions associated with particular syndromes are given in Table 16.7.

Table 16.7 Hyperkinetic movement disorders and associated clinical conditions

Movement disorder	Phenomenology	Conditions
Tremor	Rhythmic oscillation around a body part	Essential tremor Dystonic tremor Drug-induced tremor Symptomatic, eg Wilson's disease
Dystonia	Sustained or intermittent muscle contractions Abnormal movements/ postures Patterned, twisting, tremulous	Inherited, eg *DYT1* primary dystonia, myoclonus– dystonia, dopa-responsive dystonia Acquired, eg neurode generative (PD, MSA, PSP), drug induced, dystonic cerebral palsy, Wilson's disease
Chorea	Random 'dancing' movements Flit from one body part to another	Huntington's disease Drug induced, eg levodopa-induced dyskinesia in PD Post-streptococcal (Syndenham's chorea) Antiphos pholipid syndrome Neuroacan thocytosis Wilson's disease
Myoclonus	Brief sudden jerks Positive myoclonus Negative myoclonus	Physiological, eg hypnic jerks Metabolic disease, eg uraemia, liver failure Post-anoxic brain injury Physiological myoclonus Genetic, eg myoclonus–dystonia, mitochondrial disease Neurodegenerative, eg sporadic CJD, corticobasal syndrome, Alzheimer's disease Myoclonus epilepsy syndromes, eg juvenile myoclonic epilepsy
	Brief, sudden, stereotyped movements	

Tics	Premonitory urge Can be simple motor, complex motor, vocal Temporarily suppressible Often worsening of symptoms after suppression	Gilles de la Tourette syndrome (often associated with neuropsychiatric features, eg OCD) Secondary causes

CJD, Creutzfeldt–Jakob disease; MSA, multiple system atrophy; OCD, obsessive–compulsive disorder; PD, Parkinson's disease; PSP, progessive supranuclear palsy.

Tremor

Tremor is assessed at rest and with action (including posture holding and kinetic movements). A pure rest tremor is most suggestive of PD, particularly when asymmetrical and with lower limb involvement. Although a classic 4–6 Hz resting tremor is described in PD, the range can be greater than this.

Essential tremor

Symmetrical upper limb tremor presents mainly on posture holding and terminal intention is characteristic of essential tremor:

- Autosomal dominant family history often seen but no gene identified
- Improvement following alcohol may be seen
- Pronounced asymmetry and lower limb tremor are suggestive of an alternative diagnosis (eg dystonic tremor or PD)
- Propranolol is first-line treatment; primidone and topiramate are alternatives
- Deep brain stimulation surgery to the thalamus may be effective in severe refractory cases.

Huntington's disease

Huntington's disease is an autosomal dominant neurodegenerative disorder with typical onset in the third to fourth decades. It is due to mutations in the huntingtin gene on chromosome 4, encoding a CAG-repeat expansion within the gene. Huntington's disease shows genetic characteristics of complete penetrance and anticipation, whereby earlier age of onset occurs in later generations due to expansion of the CAG repeat. Genetic testing in at-risk individuals with a family history is available with appropriate genetic counselling. Pathological findings are of neurodegeneration in cortex and striatum, especially the caudate nucleus, in which selective loss of dopamine D_2 receptor-bearing medium spiny neurons occurs. Early caudate atrophy is often seen on MRI of the brain.

- Chorea, with random 'dancing' movements flitting from one body part to another, is the characteristic movement disorder of this condition, although parkinsonism is also seen
- In younger-onset patients a hypokinetic rigid picture with parkinsonism is commonly seen
- Slow saccadic eye movements are characteristic
- Frontal-subcortical cognitive impairment is typically present in Huntington's disease, and a number of behavioural disturbances occur.

No disease-modifying treatment has been proven in Huntington's disease, although several putative agents are in development. Symptomatic treatment includes management of mood and behavioural changes with SSRIs, and management of chorea with anti-dopaminergic agents such as tetrabenazine.

Overall this is a progressive disease with limited survival.

Wilson's disease

This is an autosomal recessive disorder of copper metabolism, arising from a mutation in the *ATP7B* gene on chromosome 13. This leads to impaired biliary copper excretion with consequent accumulation of copper in organs including the liver, brain and cornea. Although children are more likely to present with hepatic manifestations, those in their late teens or older may present with neurological complications, including:

- Dystonia: characteristic risus sardonicus facial expression
- Tremor: variable, may resemble essential tremor. Classic 'wing-beating' tremor is rare
- Dysarthria: may be ataxic or spastic
- Chorea: typically in younger patients and associated with other signs
- Parkinsonism: rarely sole feature of Wilson's disease
- Frontal–subcortical cognitive and behavioural syndrome: executive dysfunction, impulsivity, emotional lability
- Kayser–Fleischer rings (copper deposits in Descemet's membrane of cornea): seen in 98% of patients with neurological Wilson's disease
- MRI of the brain typically shows hyperintensity on T2-weighted images in the basal ganglia.

Consideration of Wilson's disease in young patients presenting with extrapyramidal features is important because this is a potentially treatable cause. Management is with copper chelation therapy (eg Dpenicillamine), although symptomatic treatment of movement disorders, eg dystonia, may also be necessary.

16.3 NEURO-OPHTHALMOLOGY

16.3.1 Visual fields

The optic pathway and visual field defects resulting from various lesions at different sites are illustrated in Figure 16.6.

The optic nerve is formed from retinal nerve fibres, which exit the eye and travel in the optic nerve to the optic chiasm. Lesions of the retina and optic nerve produce field defects in the ipsilateral eye alone.

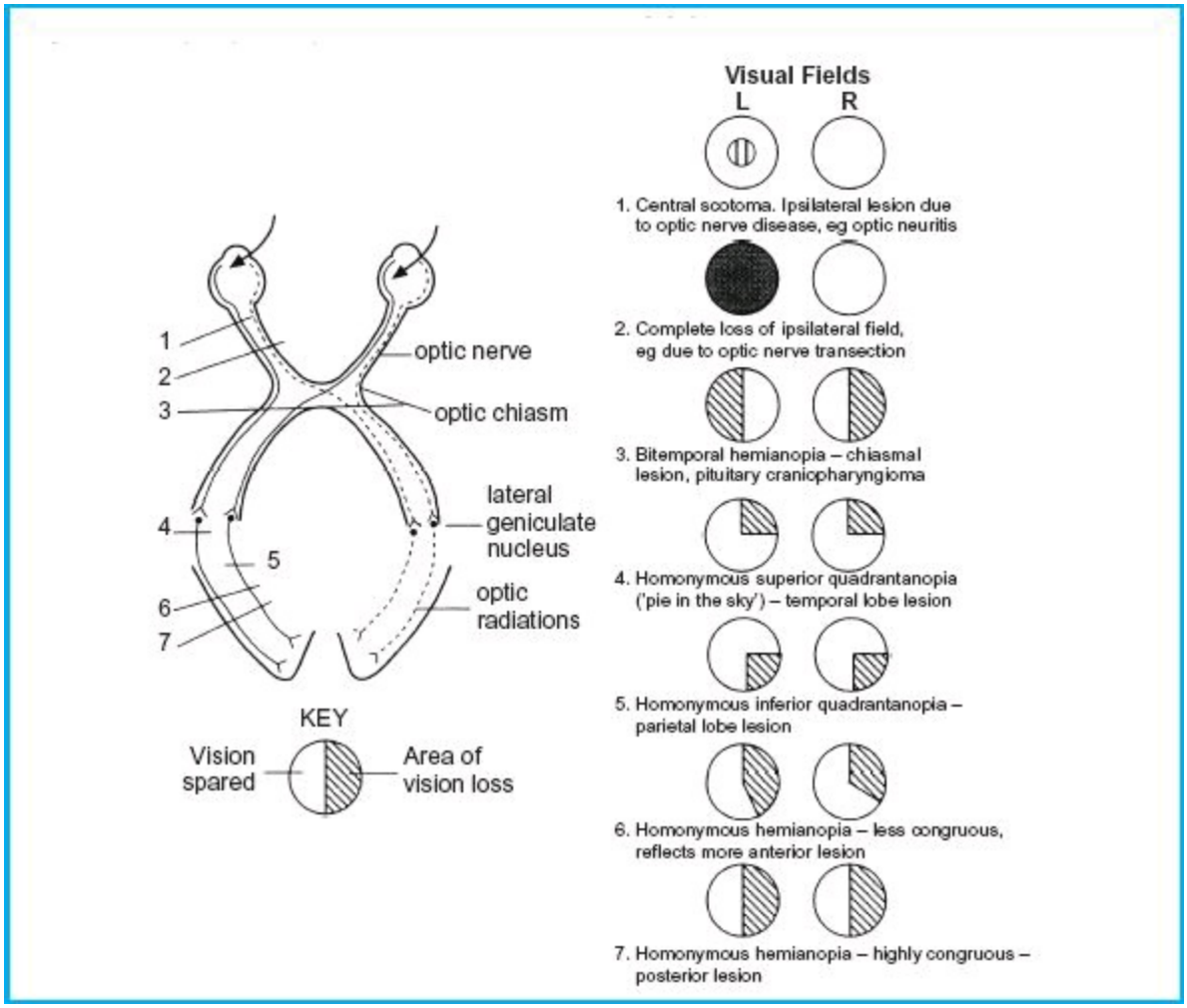
Lesions at the optic chiasm typically produce a bitemporal hemianopia. Causes include the following:

- Pituitary tumour – compression from below
- Craniopharyngioma
- Intracranial aneurysm
- Meningioma
- Dilated third ventricle.

From the optic chiasm, fibres run in the optic tract to the lateral geniculate nucleus in the thalamus. Retrochiasmal lesions produce homonymous field defects, the degree of congruity (similarity between

the two sides) increasing with more posterior lesions. From the lateral geniculate nucleus, fibres pass in the optic radiation to the primary visual cortex, in the occipital cortex. The fibres from the lower and upper quadrants of the retina diverge, the upper fibres (lower half of the visual field) passing through the parietal lobes, the lower fibres (upper half of the visual field) through the temporal lobes. Hence:

Figure 16.6 Optic pathway abnormalities and associated defects



- Temporal lobe lesions may cause a superior homonymous quadrantanopia
- Parietal lobe lesions may cause an inferior homonymous quadrantanopia.

The decussation of fibres at the optic chiasm means that the right visual field is represented in the left occipital cortex and vice versa.

Within the calcarine sulcus of the occipital lobe, there is topographic representation of the visual field with the more peripheral regions represented anteriorly, and the more central or foveal regions located posteriorly.

At the very tip of the occipital lobe, the representation of the fovea is a vascular watershed, supplied by both the middle and the posterior cerebral arteries. A posterior cerebral artery cerebrovascular accident may be associated with sparing of this area because of the dual blood supply – macular sparing (see below).

Cortical blindness

This is usually due to bilateral occipital infarcts and results in severe or complete loss of vision.

Pupillary responses are preserved.

Other features may include:

- Subjective denial of visual loss (Anton syndrome)
- Macular sparing: a tiny island of preserved central field, which may allow useful reading vision, but be so small as to be useless for distance vision
- Charles–Bonnet syndrome (formed visual hallucinations).

16.3.2 The pupils

Pupil size depends on both pupillodilator (sympathetic) and pupilloconstrictor (parasympathetic) fibres. Pupils of unequal sizes are not related to optic nerve disease. Newline pupilloconstrictor fibres travel from the Edinger–Wesphal nucleus in the midbrain to the orbit on the third nerve.

The sympathetic (pupillodilator) fibres follow a complex path:

- **First order**: from the posterior hypothalamus, through the brainstem to the C8–T2 level of the spinal cord – the ciliospinal centre of Budge
- **Second order**: preganglionic neurons from the cord pass to the paravertebral sympathetic chain and terminate in the superior cervical ganglion
- **Third order**: postganglionic fibres traverse with the internal carotid artery to enter the skull, pass to the cavernous sinus and thence to the orbit, where fibres innervate the dilator pupillae.

Relative afferent pupillary defect

This is detected by the swinging flashlight test. An afferent pupillary defect is a sign of asymmetrical disease anterior to the chiasm.

If the amount of 'light information' carried by one eye is less than that from the contralateral side, when a light is swung from the normal to the abnormal side, pupil dilatation is the first movement of the pupil observed. This is also known as a Marcus Gunn pupil. It is important to ensure that the patient is fixating a distant object during this examination to separate out the light response from accommodative response.

Causes

- Retinal disease, eg detachment, arterial or venous occlusion
- Optic nerve disease, eg optic neuritis, glaucoma with asymmetrical nerve damage

Causes of a small pupil (miosis)

- **Senile miosis**
- **Pontine haemorrhage**
- **Horner syndrome**

- **Argyll Robertson pupil:** bilateral, may be asymmetrical, small irregular pupils which accommodate normally but do not react to light. They dilate poorly in the dark and in response to mydriatics. Classically seen in tertiary syphilis. Lesion is in the rostral midbrain near the sylvian aqueduct, such that the light fibres are disrupted but the more ventral near fibres are spared
- **Drugs:** systemic (opiates), topical (pilocarpine)
- **Myotonic dystrophy**

Horner syndrome

Interruption of the sympathetic pupillomotor fibres, due to a lesion anywhere along the three-neuron sympathetic pathway, results in Horner syndrome.

Clinical characteristics

- **Miosis**: more evident in dim light 'dilatation lag'
- **Ptosis** – partial: levator palpebrae is 30% supplied by sympathetic fibres
- **Anhidrosis**: often not obvious, feature of first-order lesions
- **Vasodilatation**
- **Enophthalmos**: due to narrowing of the palpebral aperture by ptosis and elevation of the lower lid

Congenital Horner syndrome is associated with heterochromia – a difference in iris colour – as the development of eye colour is thought to be sympathetically mediated.

Causes

- **First order**: brainstem space-occupying lesion, syringomyelia, brainstem stroke, spinal cord tumour, demyelinating disease, cervical spondylosis
- **Second order**: apical lung (Pancoast's) tumour, cervical rib, mediastinal mass, internal carotid artery dissection, iatrogenic, eg neck surgery, angiography
- **Third order**: internal carotid artery dissection, cavernous sinus syndrome, Raeder's paratrigeminal neuralgia, cluster headaches

Pharmacological testing for Horner syndrome

- Apraclonidine hydrochloride is an α-adrenergic receptor agonist. Instillation of 1% apraclonidine into both eyes produces mydriasis in the affected eye only to become larger than the healthy side, whereas the size of the pupil on the unaffected side remains unchanged.
- **Hydroxyamphetamine test**: this differentiates between a first- and second- OR third-order neuron. The drug leads to dilatation of the pupil as a result of noradrenaline release from the intact, presynaptic, myoneural junction. Therefore, if there is a first- or second-order cause of

Horner's syndrome, pupil dilatation occurs, but not with a third-order cause.

Causes of a large pupil (mydriasis)

- **Adie's (tonic) pupil**: idiopathic dilated pupil with poor reaction to light and slow constriction to prolonged near effort; 70% female, 80% initially unilateral, 4% per year becoming bilateral
- **Third nerve weakness**
- **Drugs**: topical mydriatics, eg tropicamide, atropine, systemic tricyclic antidepressant in overdose
- **Trauma**: rupture of sphincter pupillae

16.3.3 The oculomotor system

Eye movements are controlled by supranuclear, internuclear and infranuclear control systems.

The supranuclear and internuclear systems act to maintain stability on, or bring the eyes to, a desired position. Supranuclear eye movement disorders occur due to abnormalities of the cerebral hemispheres, cerebellum or brainstem. Apart from convergence, the movements are all conjugate. With movement deficits of supranuclear aetiology, the vestibulo-ocular reflex produces a greater range of movement than voluntary gaze. This is seen when the patient fixes on a target while the head is passively moved, resulting in a greater range of movement (doll's head movement). This implies that, while the oculomotor nuclei are intact, in that the eyes can be driven into eccentric positions within the orbit, the supranuclear descending control of voluntary eye movements is impaired.

Examples of more common **supranuclear** deficits include the following:

- **Progressive supranuclear palsy** (Steele–Richardson–Olszewski syndrome): the ophthalmoplegia is a paresis of vertical conjugate gaze. This is commonly associated with dementia and a parkinsonian syndrome
- **Gaze palsy**: the eyes are unable to look in a particular direction – either horizontal or vertical:
  - A horizontal gaze palsy is due to a nuclear sixth nerve lesion in the pons such that the ipsilateral sixth nerve does not fire and interneuron communication to the contralateral medial rectus is also lost, resulting in a failure of lateral gaze of both eyes
  - Vertical gaze palsy, with loss of up- and downgaze, occurs due to dorsal midbrain lesions
- **Tonic deviation of the eyes** occurs with cerebral damage to the frontal area, resulting in ocular deviation to the side of the lesion
- **Parinaud (dorsal midbrain) syndrome**: damage to the midbrain and superior colliculus causes:
  - Impaired upgaze and accommodation
  - Retraction of the eyelids
  - Loss of the pupillary light reflex with preserved convergence (light near dissociation)
  - Convergence retraction nystagmus: on attempted upgaze

- Relative mydriasis
- Causes include pineal tumour, haemorrhage, infarction, hydrocephalus and demyelination.

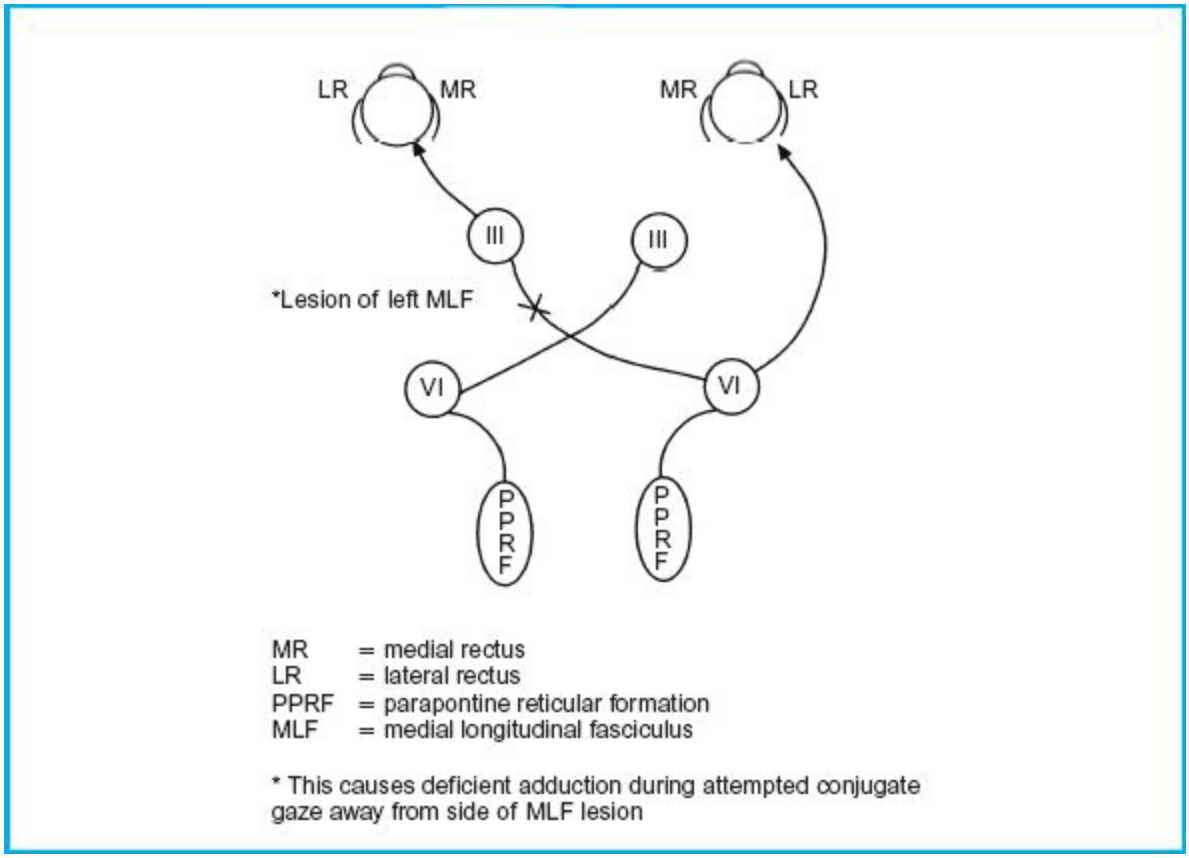
The **internuclear** system serves to connect the nuclei of the cranial nerves, resulting in conjugate gaze.

Internuclear ophthalmolplegia (INO; Figure 16.7) is a disorder of horizontal eye movements due to a lesion in the medial longitudinal fasciculus (MLF) in the dorsal midbrain. The MLF is a bilateral structure, near the midline, and connects the third and sixth nerve nuclei in the pons, so that both eyes move synchronously to look to either the left or the right simultaneously.

Features of INO

- Impaired adduction of the eye ipsilateral to the lesion
- Abducting nystagmus in the contralateral eye
- Convergence normal
- Diplopia is not usually a feature even though the eyes are not parallel

Figure 16.7 Pathology of internuclear ophthalmoplegia



Causes of INO

- Demyelinative disease 30% – usually young people, often bilateral
- Vascular – usually 60 years+, usually bilateral

- Trauma
- Occlusion of basilar artery
- Miller Fisher syndrome
- Vasculitis
- Drug overdose, eg barbiturates, phenytoin, amitriptyline
- Wernicke's encephalopathy

Bilateral INO is almost always due to MS.

In the **infranuclear** system, eye movement is mediated by the following:

- **The sixth nerve**: innervates the lateral rectus
- **The fourth nerve**: innervates the superior oblique
- **The third nerve**: innervates the medial, superior and inferior recti and inferior oblique (and levator palpebrae).

16.3.4 Conjugate gaze abnormalities

Conjugate eye movements are symmetrical and synchronous.

Defects of the third, fourth and sixth nerves will cause defects of oculomotility and therefore diplopia in most patients.

Causes of third, fourth and sixth nerve palsies will be given in the appropriate sections:

- Ischaemia
- Diabetes
- Intracerebral aneurysm/haemorrhage
- Head trauma
- Tumour (primary and secondary)
- Demyelination
- Arteritides
- Meningitides, eg tuberculous, syphilitic
- Lymphoma
- Orbital cellulitis
- Sarcoidosis
- Myaesthenia gravis
- Ophthalmoplegic migraine.

Other causes of ophthalmoplegia (extraocular muscle dysfunction)

- Dysthyroid eye disease
- Myositis

- Myasthenia gravis
- Guillain–Barré syndrome
- Midbrain tumour or infarction
- Basal menigitides
- Wernicke's encephalopathy

The effects of paresis on diplopia are predicted by:

- Paresis of horizontally acting muscles causes horizontal diplopia and vertical muscle paresis results in vertical diplopia
- The direction of gaze in which the separation of images is maximum is the direction of action of the paretic muscle
- Diplopia is a disturbing symptom. Symptoms can be alleviated by patching one eye, either the one with worse vision or the one with the palsy. There is no fear of patching inducing amblyopia in adults. More definitive treatment involves fitting prism on to spectacles, the use of botulinum toxin and surgery to realign eyes when the defect has been stable for some months.

Cavernous sinus and orbital apex disease cause multiple cranial nerve palsies affecting the oculomotor system because nerves III, IV and VI are all anatomically close to each other in these areas. Pathology here is discussed before the effects of the individual nerves.

Cavernous sinus syndrome

The cavernous sinuses are dural venous sinuses, located on either side of the pituitary fossa and body of the sphenoid bone. The internal carotid artery, with the sympathetic carotid plexus and nerve VI pass through the body of the sinus. The nerves III, IV and VI, pass through the lateral wall of the sinus. Lesions in this area may therefore produce total internal and external ophthalmoplegia.

The main causes of cavernous sinus syndrome are as follows:

- **Trauma**
- **Vascular**: intracavernous aneurysm – nerve VI is generally affected first because it is within the sinus, adjacent to the artery; the other structures are affected later
- **Cavernous sinus thrombosis**
- **Caroticocavernous fistula**
- **Neoplastic**: primary intracranial tumours, direct spread from nasopharyngeal tumours or metastatic
- **Inflammatory**: due to infection, eg sinusitis, tuberculosis or inflammatory disease such as Wegener's granulomatosis.

Caroticocavernous fistula

This may be either high or low flow.

High-flow shunt is due to a fistula between the cavernous sinus and the intracavernous artery. It is usually secondary to trauma and causes marked proptosis which may be pulsatile, nerve III, IV and VI palsies, or an orbital bruit with an injected chemotic eye, often with elevated intraocular pressure due

to raised episcleral venous pressure.

Low-flow shunt occurs in arteriosclerotic disease, often spontaneously, due to communication between the dural branches of the internal or external carotid arteries and the cavernous sinus, resulting in a milder clinical picture.

Oculomotor nerve (III)

The third nerve has a large nucleus located in the midbrain at the level of the superior colliculus. Fibres pass through the red nucleus and the pyramidal tract in the cerebral peduncle. The nerve then passes between the posterior cerebral and superior cerebellar arteries, through the cavernous sinus, and splits into superior and inferior branches as it enters the orbit via the superior orbital fissure – one of these branches may be affected in isolation:

- The superior branch innervates the superior rectus and levator palpebrae
- The inferior branch innervates the medial and inferior recti, inferior oblique and sphincter pupillae.

The large size of the nerve III nucleus means that a complete nerve III palsy is rarely due to a central lesion, the cause usually being a peripheral lesion.

Features of complete nerve III palsy

- Ptosis
- Eye abducted: due to unopposed lateral rectus function, and slightly depressed due to unopposed superior oblique function – although this muscle has more influence in an adducted eye
- Fixed dilated pupil

Lateral gaze is intact and attempted downward gaze causes intorsion due to preservation of superior oblique function. Intorsion is inward rotation of the eye, best seen by observing a conjunctival blood vessel.

Pupil-sparing nerve III palsies more frequently have a 'medical' or vascular cause, eg diabetes mellitus, hypertension because the parasympathetic pupillomotor fibres run on the peripheral surface of the nerve and have their own vascular supply via pial vessels. However, by virtue of this peripheral position, the pupil fibres are affected early with a compressive cause, when pupil dilatation is seen in 95% cases. Note therefore that imaging is still required to definitively exclude a compressive III palsy.

Causes of an oculomotor nerve III palsy

- Posterior communication artery aneurysm (posterior cerebral and basilar aneurysms can also cause a III palsy) – usually painful
- Diabetes – 75% pupil sparing

  Cavernous sinus pathology, eg thrombosis, aneurysm, fistula, pituitary mass. Frequently

- associated with lesions of nerves IV, V and VI
- Orbital apex disease, eg tumours, thyroid disease, orbital cellulitis, granulomatous disease – often associated with nerve IV and VI palsies and optic nerve dysfunction
- Trauma
- Uncal herniation: nerve III travels anteriorly on the edge of the cerebellar tentorium and may be compressed in increased intracranial pressure due to a supratentorial cause as it is compressed by the temporal lobe

Trochlear nerve (IV)

The trochlear nerve (IV) nucleus lies in the midbrain at the level of the inferior colliculus. It is the only nerve to exit from the dorsal aspect of the brainstem and has the longest intracranial course of any cranial nerve. It passes between the posterior cerebral and superior cerebellar arteries, lateral to nerve III, through the cavernous sinus and into the orbit via the superior orbital fissure. A trochlear nerve (IV) palsy is the most common cause of vertical diplopia. An acquired trochelar nerve (IV) palsy is frequently associated with torsion, when the images, as well as being separated vertically and horizontally, are rotated in relation to each other. Superior oblique action is maximal with the eye depressed in adduction, and patients classically experience maximal symptoms coming down stairs or reading.

Causes of trochlear nerve (IV) palsy

- **Congenital**: decompensation occurs in 30%, typically with no torsion
- **Trauma**: susceptible to contrecoup injuries, eg whiplash due to dorsal brainstem exit. This is frequently bilateral

Abducens nerve (VI)

The abducens nerve (VI) nucleus lies in the mid-pons, inferior to the fourth ventricle and is motor to the lateral rectus. The abducens nerve (VI) nucleus is surrounded by the facial colliculus, so a nuclear abducens nerve (VI) weakness is associated with weakness of an ipsilateral lower motor neuron in facial nerve VII. A nerve VI weakness causes a convergent deviation of the eyes in primary position, with diplopia maximal with attempted gaze towards the side of the lesion and in distant gaze.

Causes of abducens nerve (VI) weakness

- Increased intracranial pressure: due to stretching of the nerve as the brainstem is downwardly displaced and the nerve is fixed where it exits the pons. This can be a false localising sign

16.3.5 Nystagmus

Nystagmus is a defect of control of ocular position leading to an involuntary to-and-fro oscillation of the eye. It is associated with reduced vision due to the image not staying on the fovea during fixation. It also occurs in some ocular conditions associated with reduced vision, eg albinism, retinal dystrophies.

- **Pendular nystagmus**: both phases of equal velocity, no fast or slow phase
- **Jerk nystagmus**: distinct fast and slow phases – the amplitude usually increases with gaze towards the direction of the fast phase. The nystagmus is named according to the fast phase of the movement.

Congenital nystagmus

Patients with congenital nystagmus are unaware of the ocular oscillations. Congenital nystagmus is horizontal. The following are among the causes:

- Idiopathic
- X-linked or autosomal dominant
- Secondary to visual impairment, eg albinism, optic nerve hypoplasia, retinal dystrophy.

Acquired nystagmus

This is associated with oscillopsia, a disturbing sensation of the world moving in time with the nystagmus. Nystagmus may vary in different directions of gaze:

- **Downbeat nystagmus**: associated with foramen magnum lesions, eg Arnold–Chiari malformation, spinocerebellar degeneration, syringobulbia, platybasia, demyelinative disease
- **Upbeat nystagmus**: typically due to intrinsic brainstem disease, cerebellar vermis lesions, organophosphates, Wernicke's encephalopathy
- **Pendular nystagmus**: demyelinative disease.

Treatment is directed at reducing the amplitude and frequency of the oscillation, so increasing the time the image stays on the fovea and improving acuity.

Gabapentin and memantine are used as first-line agents.

16.4 OTHER CRANIAL NERVE DISORDERS

The brainstem and locations of the other principal cranial nerve nuclei are illustrated in Figure 16.9.

16.4.1 Facial nerve

The facial nerve has the following functions:

- Motor to the muscles of facial expression

- Taste fibres from the anterior two-thirds of the tongue (in the chorda tympani)
- Taste from the palate (nerve of the pterygoid canal)
- Secretomotor parasympathetic fibres to parotid, submandibular and sublingual glands
- Nerve to stapedius.

Taste fibres, the nerve to stapedius and the facial muscles leave the nerve below the geniculate ganglion.

Causes of a facial nerve palsy

- Bell's palsy
- Neurosarcoidosis (bilateral)
- Cerebellopontine angle lesions (eg vestibular schwannoma)
- Cholesteatoma
- Lyme disease
- Stroke
- Multiple sclerosis
- Otitis media
- Ramsay Hunt syndrome
- Diabetes
- Guillain–Barré syndrome
- Brainstem tumour

If the palsy is bilateral, exclude myasthenia gravis, facial myopathy (look for ptosis) and neurosarcoidosis. Weakness of frontalis (forehead) indicates a nuclear or intranuclear (LMN) lesion.

Bell's palsy

An isolated lower motor neurone facial nerve palsy of acute onset, thought to be secondary to viral infection:

- Unilateral facial weakness
- Absent taste sensation on anterior two-thirds of tongue
- Pain behind the ear.

Usually recovery begins by 2 weeks, but the palsy may be prolonged, and 10% have residual weakness. Electrophysiological tests can help predict the outcome, and tapering dose of steroids (given from onset) improves the outcome. Tarsorrhaphy may be needed to prevent corneal damage, and the patient's inability to fully close the eye should be assessed.

Figure 16.8 Main structures passing through the cavernous sinus

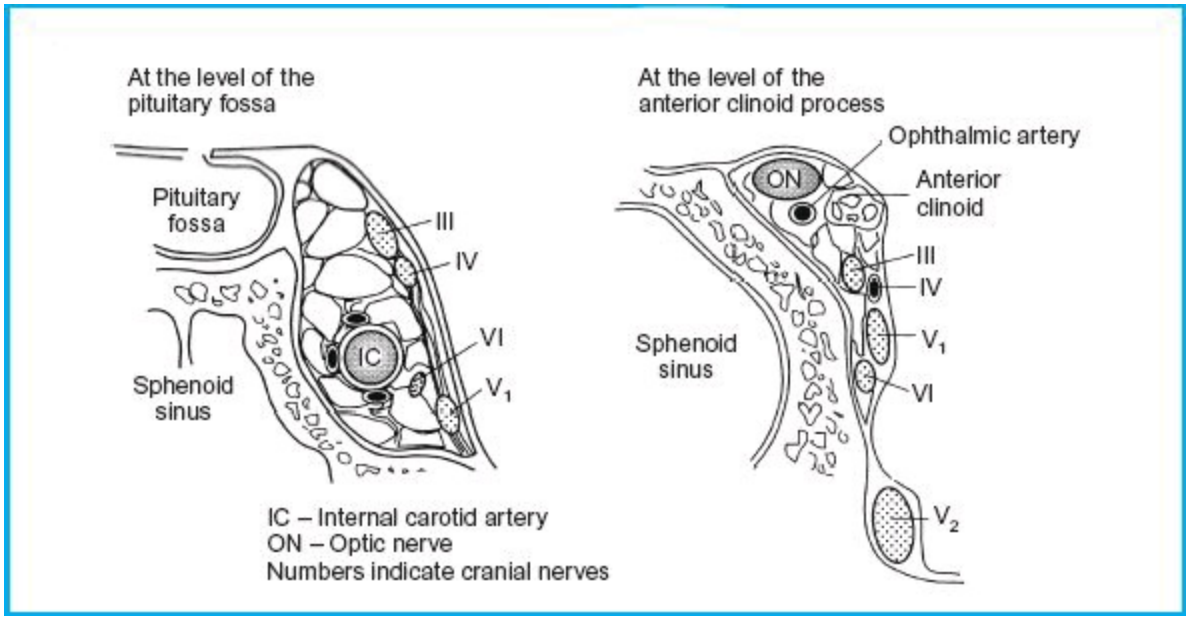
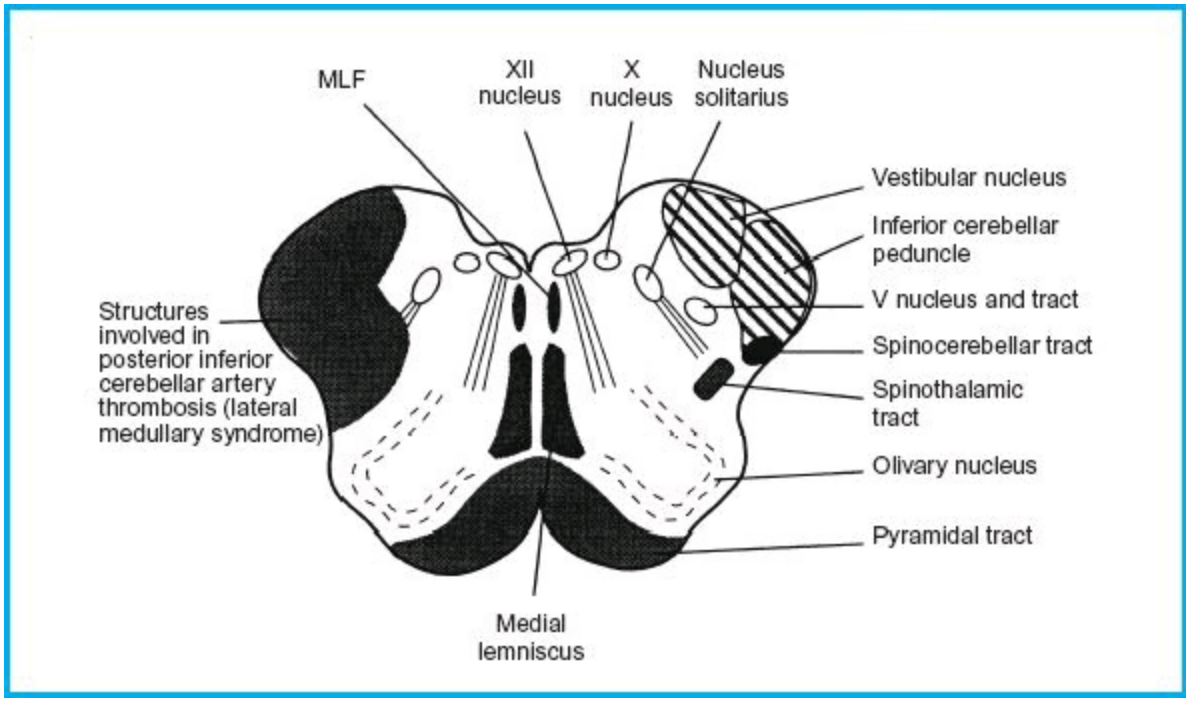


Figure 16.9 Locations of the principal cranial nerve nuclei within the brain stem



Ramsay Hunt syndrome

Features include herpes zoster, affecting the geniculate ganglion, and facial palsy with herpetic vesicles in the auditory meatus. Deafness is a complication.

16.4.2 Trigeminal neuralgia

This is characterised by brief lancinating pain in the distribution of one of the divisions of the trigeminal nerve. It is more common in patients aged >50 and in women. Maxillary and mandibular divisions are most often affected; it is almost always unilateral and trigger points are common. It may be caused by neurovascular conflict or be a presenting symptom of MS in younger patients.

Treatment includes:

- Carbamazepine/phenytoin
- Clonazepam
- Baclofen
- Thermocoagulation of trigeminal ganglion
- Surgical microvascular decompression.

16.4.3 Vestibulocochlear nerve

Damage to the eighth cranial nerve may result in deafness or vertigo (see below). At the bedside sensorineural and conductive deafness are distinguished by Rinne's and Weber's tests.

Rinne's test

- Air > bone conduction normally
- Hearing decreased and bone < air conduction in conduction deafness
- Hearing decreased and air > bone conduction in sensorineural deafness.

Weber's test

- Central normally
- Lateralises to normal side in sensorineural deafness
- Lateralises to deaf side in conduction deafness.

Causes of deafness

- **Conduction**
  - Ear wax
  - Otosclerosis
  - Middle-ear infection
- **Sensorineural**
  - Vestibular schwannoma
  - Paget's disease
  - Central lesions (MS/CVA/glioma)
  - Congenital (maternal infections, congenital syndromes)
  - Ménière's disease
  - Head trauma
  - Drugs and toxins (aminoglycoside antibiotics, furosemide, lead)

Several drugs may cause tinnitus, including aspirin, furosemide and aminoglycosides.

Vertigo

Neurological disorders causing vertigo are typically due to pathology of the labyrinthine structures of the middle ear, the brainstem vestibular nuclei or the vestibulocochlear nerve that connects the two.

Common causes of vertigo

- **Labyrinthine (peripheral)**
  - Benign paroxysmal positional vertigo (BPPV)
  - Trauma (including barotrauma)
  - Ménière's disease
  - Acute viral infections
  - Chronic bacterial otitis media
  - Occlusion of the internal auditory artery
- **Brainstem (central)**
  - Acute vestibular neuronitis
  - Vascular disease
  - MS
  - Space-occupying lesions (eg brainstem glioma)
  - Toxic causes (eg alcohol, drugs)
  - Hypoglycaemia

Vestibular schwannoma

Vestibular schwannoma is a benign tumour arising on the eighth cranial nerve as it emerges from the brainstem in the cerebellopontine angle. It is a common cause of a cerebellopontine angle syndrome:

- Cranial nerve VIII is affected early, but the patient may not report hearing loss, tinnitus and vertigo
- Corneal reflex (cranial nerve V) is absent
- Facial sensation is abnormal (V nerve)
- The facial nerve is affected late.

Investigation is by use of MRI or high-resolution CT scanning, and treatment is surgical removal.

16.4.4 Lateral medullary syndrome

The lateral medullary (Wallenberg's) syndrome is usually due to vertebral artery or posterior inferior cerebellar artery occlusion, which damages the dorsolateral medulla and inferior cerebellar peduncle (Figure 16.9).

Features of the lateral medullary syndrome

- Ipsilateral loss of pain and temperature sensation on the face (V)
- Ipsilateral paralysis of palate, pharynx and vocal folds (IX, X)
- Ipsilateral ataxia (inferior cerebellar peduncle)
- Contralateral loss of pain and temperature sensation on the body (spinothalamic tract)
- Ipsilateral Horner syndrome (descending sympathetic outflow)
- Vertigo, nausea and vomiting, nystagmus (vestibular nuclei)

16.5 SPINAL CORD DISORDERS

16.5.1 Neuroanatomy

The spinal cord extends from the craniocervical junction at the top of the C1 vertebra to the conus medullaris opposite the bottom of the L1 vertebra, a length of approximately 45 cm, whereas the spinal column is 70 cm long. There are enlargements of grey matter between C5 and T1 and from L1 to S3 which supply the motor neurons to the arms and legs, respectively. Below the lumbar enlargement, the spinal cord narrows and ends as the conus medullaris. A fine pial thread, the filum terminale, attaches to the first coccygeal segment. The lower group of lumbosacral roots within the spinal theca is known as the cauda equina.

The grey matter forms an H-shaped column in the centre of the cord, containing the cell bodies of motor, sensory and autonomic neurons. These are grouped into zones (Rexed's laminae). Surrounding the grey matter are the white matter pathways or long tracts. The principal descending motor pathway, the corticospinal tract, crosses in the midbrain. The two principal ascending sensory pathways are the dorsal columns, which carry vibration and joint position sense, and the spinothalamic tract, which carries pain and temperature. Light touch is carried in both tracts and is therefore non-localising.

Ascending sensory pathways

- Dorsal (posterior) columns:
  - Joint position sense and vibration
  - Synapse in the brainstem at the cuneate (arm) and gracilis (leg) nuclei, then decussate:
    - Sacral and lumbar fibres lie medially
- Spinothalamic tracts:
  - Pain and temperature:
    - Incoming fibres cross immediately or within a few spinal segments
    - Crossed tract results in lamination, with fibres from legs outside fibres from the arms
  - Sacral and lumbar fibres lie laterally.

Blood supply of the spinal cord

The anterior spinal artery receives six to eight major radicular branches and branches of the cervical

and vertebral arteries to supply the cervical and thoracic cord. The radicular artery of Adamkiewicz arises from the aorta and enters the spinal cord between T9 and L2. Small central arteries penetrate the cord to supply the anterior columns and ventral grey matter, with circumferential branches supplying the anterior two-thirds of the cord. Paired dorsolateral arteries extend the length of the cord and supply the posterior third of the cord.

The simplified cross-sectional anatomy of the spinal cord is highlighted in Figures 16.10 and 16.11, and helps to conceptualise the more common clinical spinal cord scenarios that follow.

Clinical spinal cord scenarios

1. Complete transection of the cord. This may arise from trauma or severe inflammation, eg NMO. This leads to complete loss of all modalities distal to the transection, including motor, all sensory and sphincter function
2. Hemisection of the cord (Brown–Séquard syndrome): trauma, a glioma or MS can result in a cord hemisection. There is loss of motor function and dorsal column sensation *ipsilateral* to the hemisection, because both the corticospinal tracts and the dorsal columns decussate superiorly in the medulla, whereas there is *contralateral* loss of pain and temperature as the spinothalamic tract decussates at the level or within two segments of it entering the spinal cord
3. Central cord lesions, eg syringomyelia. A syrinx is a cystic cavity that develops within the substance of the spinal cord which may extend into the brain stem (syringobulbia). The cause of primary syringomyelia is unknown; secondary causes include: intramedullary tumour, trauma or central necrosis secondary to ischaemia. Classically, syringomyelia occurs in the cervical and thoracic region leading to dissociated sensory loss (of pain and temperature with preserved dorsal column function) and LMN weakness, atrophy and fasciculations as a result of anterior horn grey matter involvement. Long tract (UMN) signs below the lesion indicate that a sympathetic involvement (Horner syndrome) may occur. The results of surgical decompression and shunting of the syrinx are often disappointing
4. Posterolateral column dysfunction: vitamin B_{12} deficiency (and now copper deficiency sometimes secondary to zinc toxicity) is characterised by vacuolar degeneration of the corticospinal tracts and dorsal columns. A concomitant peripheral neuropathy contributes to one of the causes of mixed UMN and LMN signs, eg extensor plantar responses and absent ankle jerks
5. Posterior column syndrome: tabes dorsalis is the classic, though now rare, cause of loss of dorsal column function only, with significant deafferentation of the limbs
6. Anterior horn cell syndrome: causing LMN signs – weakness, atrophy, fasciculations and possible reflex loss – is classically the result of poliomyelitis
7. Combined anterior horn cell and pyramidal tract syndrome, producing UMN signs below the level of the lesion and LMN signs at the level of the lesion, is typically caused by the ALS variant of MND. Similar signs could be caused by extrinsic compression of both the spinal cord and the exiting motor nerve root (myeloradiculopathy) by spondylosis
8. Anterior spinal artery syndrome: the anterior spinal artery supplies approximately the anterior two-thirds of the spinal cord and occlusion causes a flaccid paralysis with dissociated sensory loss (commonly with a thoracic spinal level), impairment of pain and temperature and intact dorsal column function.

Figure 16.10 Anatomy of the spinal cord (cross-section)

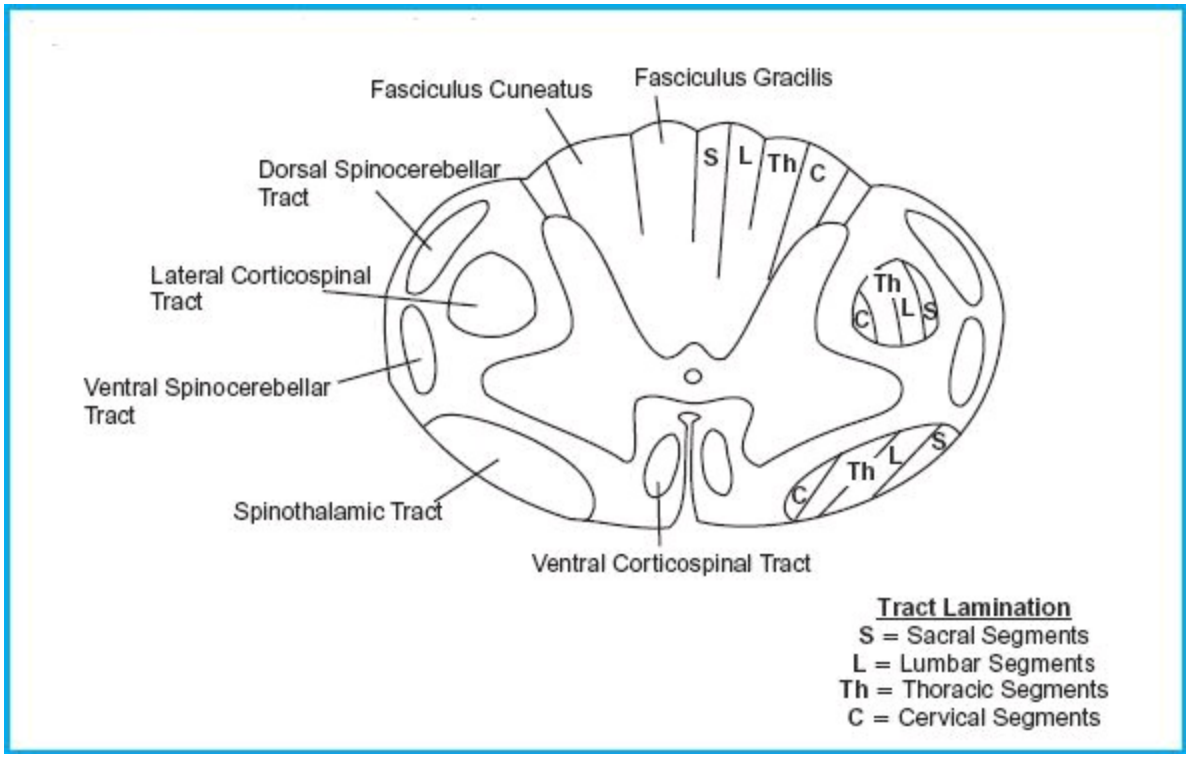
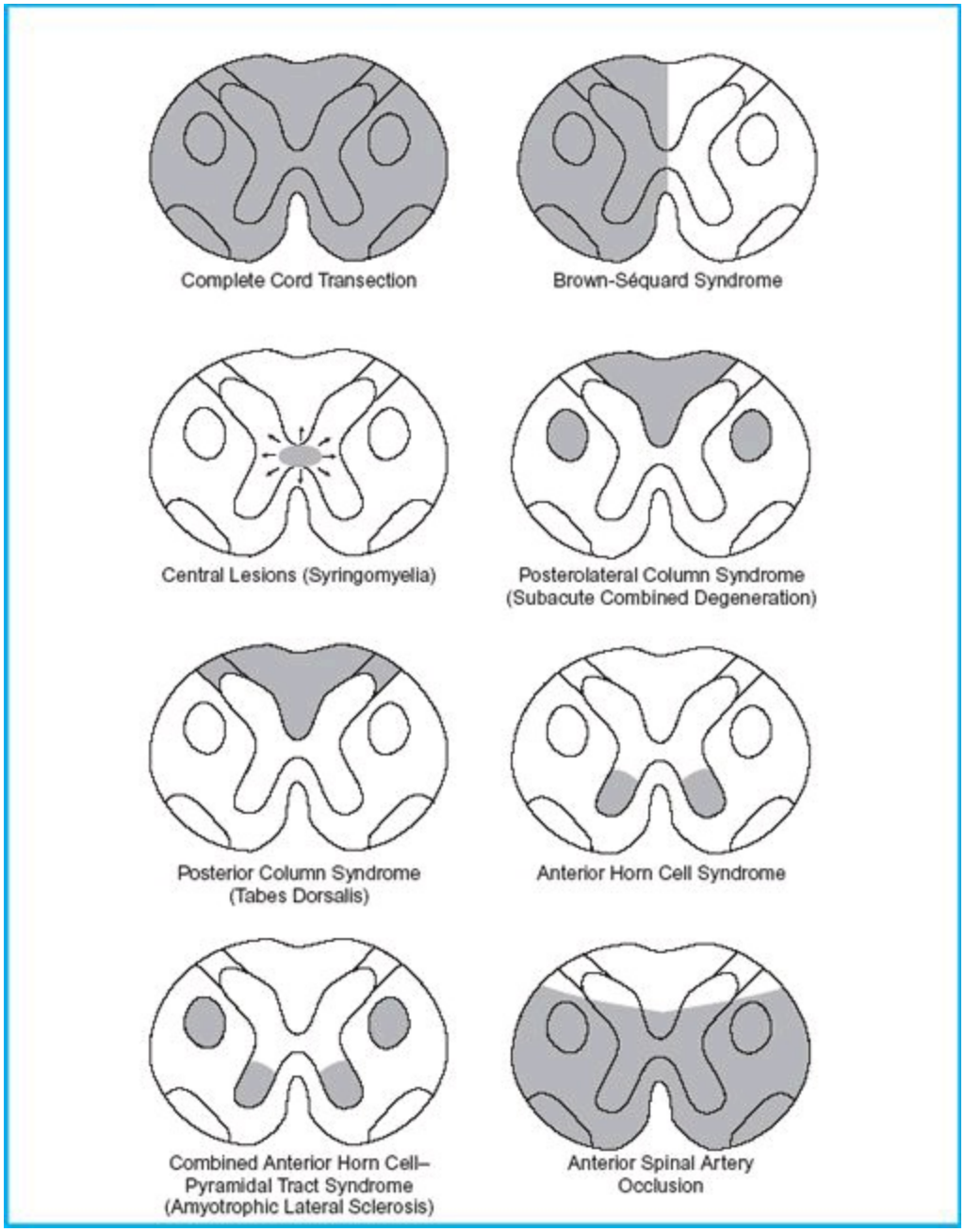


Figure 16.11 Clinical spinal cord scenarios



Lhermitte's symptom or sign

Lhermitte's symptom or sign is 'a transient, short-lasting sensation felt at the back of the neck, lower back or other parts of the body after neck movement, commonly flexion'. The sensation is usually electric-like but can be tingling, buzzing or otherwise. It propagates rapidly and disappears on resuming 'normal posture'. It localises the lesion to the dorsal cervical spinal cord. Common causes include MS and spondylosis; less common causes are vitamin B_{12} and radiation myelopathy.

Cauda equina vs conus medullaris lesion

It is estimated that about 0.12% of herniated lumbar discs cause cauda equina syndrome, ie dysfunction of multiple sacral and lumbar nerve roots in the lumbar vertebral canal, leading to impairment of bladder, bowel or sexual function, and perianal or 'saddle' numbness.

Other possible symptoms include:

- Back pain (with or without sciatic-type pains)
- Sensory changes or numbness in the lower limbs

- Lower limb weakness
- Reduction or loss of reflexes in the lower limbs
- Unilateral or bilateral symptoms.

Differences between cauda equina and conus medullaris lesions are shown in Table 16.8.

16.5.2 Absent knee jerks and extensor plantars

Causes of absent knee, ankle jerks and extensor plantar responses include:

- Subacute combined degeneration of the cord – vitamin B_{12} deficiency
- Conus medullaris lesion
- UMN and peripheral neuropathy cauda equina compression, eg stroke in someone with alcohol problems
- Friedreich's ataxia
- MND
- Syphilis
- HTLV-1 infection.

Table 16.8 Differences between cauda equina and conus medullaris lesions

Features	Cauda equina	Conus medullaris lesion
Vertebral levels affected	L2 to sacrum	L1–2
Spinal levels affected	Lumbosacral nerve roots	Distal spinal cord
Symmetry of symptoms/ signs/pain	Asymmetrical, severe radicular pain	Symmetrical, perineal pain
Motor deficit	Flaccid paralysis	Normal to mild-to-moderate distal loss
Sensory loss	Saddle anaesthesia	Saddle anaesthesia, pinprick and temperature loss, with preserved tactile stimulation
Reflex loss	Asymmetrical hyporeflexia	Hyperreflexia
Impotence	Infrequent	Frequent
Sphincter loss	Late urinary retention	Early urinary retention and atonic anal sphincter

16.6 PERIPHERAL NERVE DISORDERS

Disorders of the peripheral nerve can be divided into mononeuropathies, multiple mononeuropathies and polyneuropathies.

Diagnosis of mononeuropathy rests on recognition of the patterns of weakness and sensory loss that occur when a specific nerve is damaged. With more severe or prolonged mononeuropathies, wasting may develop in the affected muscles. Most mononeuropathies are due to either compression of the nerve in question at a vulnerable anatomical location or trauma. However, mononeuropathy can also be due to systemic disease, eg because of microvascular injury in diabetes or one of the vasculitides.

16.6.1 Mononeuropathies

Below is a summary of the common clinical mononeuropathies.

Median nerve

Median neuropathy usually occurs due to compression at the carpal tunnel and causes:

- Weakness of Lumbricals (first and second), Opponens pollicis brevis, Abductor pollicis brevis and Flexor pollicis brevis (remember LOAF)
- Sensory loss in the thumb, forefinger, middle finger and half the ring finger.

Ulnar nerve

Ulnar neuropathy usually occurs due to compression around the elbow, particularly in the cubital tunnel, and causes:

- Weakness of flexor carpi ulnaris, dorsal interossei and palmar interossei. There is also weakness of the hypothenar muscles: flexor, abductor and opponens digiti minimi
- Sensory loss in the ulnar border of the hand, little finger and half the ring finger.

It should be noted that when the ulnar nerve is compressed more distally, eg at Guyon's canal in the wrist, the sensory loss involves only the fingers because the border of the hand is innervated by ulnar cutaneous branches that do not pass through this portion of the wrist.

Radial nerve

Radial neuropathy most commonly occurs due to compression of the nerve along the humerus, particularly in the spiral groove. It causes:

- Weakness of brachioradialis, extensor carpi radialis, extensor carpi ulnaris, extensor digitorum, extensor pollicis. This produces a characteristic wrist and finger drop
- Sensory loss over the dorsum of the hand, particularly the first web space.

Common peroneal nerve

Common peroneal neuropathy is the most common lower limb mononeuropathy and is usually due to compression of the nerve at the lateral border of the knee. Symptoms include:

- Weakness of tibialis anterior, extensor digitorum and hallucis, peroneus longus and brevis. This produces foot drop and weakness of foot eversion
- Sensory loss over the dorsum of the foot and the lateral border of the shin.

The sciatic nerve gives rise to both common peroneal and tibial nerves, so lesions of the sciatic nerve cause weakness in all of the above muscles but also in gastrocnemius, soleus and tibialis posterior, so there is complete weakness around the ankle, producing a 'flail' foot.

16.6.2 Mononeuropathy multiplex

When multiple individual nerves are clinically affected, there are a number of diagnostic possibilities. It is sometimes plausible that multiple compressions have occurred (bilateral carpal tunnel syndrome is common, for example), but more often a systemic condition has caused the nerve damage. Causes of mononeuropathy multiplex include:

- Diabetes mellitus
- ANCA-positive vasculitis
- Rheumatoid arthritis
- SLE
- Polyarteritis nodosa
- Haematological malignancy
- HNPP (hereditary neuropathy with liability to pressure palsy).

If the patient has developed rapid-onset, asymmetrical, painful mononeuropathies, the diagnosis is most likely to be a form of vasculitis and prompt investigation (for both the nerve disorder and other system involvement) is required.

16.6.3 Polyneuropathies

Polyneuropathy is a generalised process affecting the peripheral nerves. Most polyneuropathies involve both sensory and motor fibres, but pure motor and sensory neuropathy can occur. This distinction can be helpful because certain aetiologies will affect the peripheral nerves in a characteristic manner. In assessing patients with polyneuropathy, it is also useful to consider the time course of the symptoms. Acute polyneuropathies suggest inflammatory, vasculitic or toxic causes. Chronic neuropathic symptoms suggest a genetic or perhaps a metabolic cause. Discovering whether the neuropathy is axonal or demyelinating can provide further clues to the aetiological diagnosis (Table 16.9). In this regard, neurophysiological investigations, nerve conduction studies (NCS) and electromyography (EMG), are invaluable.

Symptoms and signs of polyneuropathy will vary according to the type and severity of neuropathic process in any given patient. However, some common patterns are seen. In typical mixed sensory and motor polyneuropathy, patients have distal, symmetrical weakness affecting lower limbs more than upper limbs. Patients have reduced sensation in the distal extremities, with the lower limbs affected more than the upper limbs. Patients will have reduced or absent reflexes; ankle jerks especially are usually lost. This typical pattern of distal extremity involvement, legs more than arms, reflects the 'length-dependent' nature of most neuropathies: the longest nerves are most vulnerable to damage. Most common neuropathies cause this pattern and findings of 'non-length dependency', where arms, face or trunk is affected earlier and more severely than the legs, is a strong clue that the neuropathy will be immune mediated.

Table 16.9 Causes of peripheral polyneuropathy

Group	Aetiology	Motor/ sensory/ mixed, plus helpful features
Metabolic	Diabetes	Typically chronic, sensory predominant, length dependent
	Uraemia	Mixed, may be acute
	Vitamins B_1, B_6, B_{12} deficiency	Mixed, may be acute
	Hypothyroidism	Mixed, relatively rare
Infective	HIV	Distal sensory, painful
	Lyme	Variable presentation, including cranial neuropathies
Toxic	Isoniazid	Mixed, usually subacute
	Pyridoxine	Sensory predominant
	Chemotherapeutics	Mixed, may start and worsen even after chemo has stopped ('coasting')
	Lead (and other metals)	May be acute, often motor predominant
Immune	Chronic inflammatory demyelinating polyneuropathy (CIDP)	Mixed, may have a relapsing course. Often non-length dependent
	Paraproteinaemic	Mixed, patients may have MGUS or myeloma
	Connective tissue disease	Mixed, consider RA, Sjögren syndrome, SLE, sarcoidosis – may be mononeuropathy multiplex
	Paraneoplastic	Mixed, may be acute/ subacute, lung carcinoma most commonly implicated
	Guillain–Barré syndrome	See section in the main text
Genetic	Charcot–Marie–Tooth (CMT) disease	Mixed, numerous types exist – CMT-1 is demyelinating, CMT-2 is axonal
	Acute intermittent porphyria (AIP)	Rare, acute, predominantly motor

MGUS, monoclonal gammopathy of unknown significance; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

The clinical picture guides investigation of polyneuropathy, eg acute mononeuropathy multiplex

requires urgent investigation for vasculitis, whereas chronic sensory predominant polyneuropathy will not. Neurophysiology can be very helpful in narrowing down the necessary investigations (demyelinating neuropathies will not be caused by common metabolic disturbances).

Suggested first-line investigations in typical mixed, length-dependent polyneuropathy include:

- Fasting glucose
- U&Es
- Liver enzymes
- FBC and vitamin B_{12}
- TFTs
- Serum immunoglobulins and electrophoresis.

Guillain–Barré syndrome

Guillain–Barré syndrome (GBS) is an acute dysimmune polyneuropathy presenting with rapidly evolving weakness (often 'ascending paralysis') and variable sensory loss. The neuropathy may be non-length dependent and weakness can be seen in facial muscles early in the disease course. Typical features include:

- Flaccid tone
- Areflexia
- Back pain
- Autonomic disturbance
- Neuromuscular ventilator failure (shortness of breath on exertion and lying flat, early morning headache, low forced vital capacity [FVC])
- Nadir of symptoms by day 14

Many patients report preceding infective symptoms (often upper respiratory tract infection [URTI]), but the most common identified antecedent infection is with *Campylobacter jejuni*, and this has been associated with a more severe disease course.

Investigations reveal CSF with raised protein and normal glucose and white cell count. Finding raised white cells in the CSF should lead to investigation for HIV, which can mimic GBS closely. Neurophysiology will show delayed conduction velocities suggestive of demyelination of peripheral nerves in most cases – these changes take up to 2 weeks to develop, so NCS performed too early may appear normal. There is a severe motor axonal form of GBS in addition to the classic demyelinating variety.

Patients who are non-ambulant due to their weakness are usually treated with either intravenous immunoglobulin or plasma exchange. Supportive care is critically important, with attention paid to venous thromboembolism prophylaxis, ventilatory function, feeding, pressure care and analgesia. 5–10% of patients fail to make a good recovery despite treatment. 5% of patients with GBS die as a result of the illness.

16.7 NEUROMUSCULAR JUNCTION AND MUSCLE DISORDERS

Neuromuscular transmission is dependent on cholinergic transmission between the terminals of motor nerves and the motor end-plate.

16.7.1 Myasthenia gravis

This is an autoimmune condition caused by autoantibodies against neuromuscular junction proteins, either the nicotinic acetylcholine receptor (AChR) or the muscle-specific tyrosine kinase (MuSK). The clinical hallmark is of painless *fatigable* skeletal muscle weakness because neuromuscular conduction is compromised with sustained effort. It is a relatively rare disorder with a prevalence of about 10 per 100 000 population. The pathogenesis is described in detail in Chapter 14. There is a bimodal onset with younger (<40 years) women and late onset in men being typical.

Most (but not all) patients have ptosis and weakness of eyelid closure, and may have ophthalmoplegia. Such patients may develop generalised myasthenia with limb, respiratory and bulbar dysfunction, and dysarthria and dysphagia, but any muscle may be affected. The pupil is never affected, which can be helpful in terms of differential diagnosis. Clinical evaluation should include manoeuvres to fatigue the patient, eg sustained upgaze, repetitive abduction/adduction of the shoulder or counting in the case of bulbar involvement. Quick lid retraction on refixation from downgaze is known as Cogan's sign.

Myasthenia gravis can mimic MND, mitochondrial myopathies, polymyositis, cranial nerve palsies or brainstem dysfunction, and can present with respiratory weakness.

Diagnosis of myasthenia gravis

- Single fibre EMG: gold standard (97% sensitive with evidence of jitter and blocking) for diagnosis, but time-consuming and available only in specialist centres
- ACh receptor antibodies: present in 85% of generalised and 50% of ocular cases

If AchR negative and ocular and bulbar involvement, check MuSK antibodies (present in 5–8% of generalised patients and rarely in ocular myasthenia)

- Electrophysiology: repetitive stimulation gives rise to diminution in the amplitude of the evoked EMG response
- Thyroid function tests: up to 10% have coexistent thyrotoxicosis
- CT of the thorax (thymoma present in 10–15% of cases)

Tensilon (Edrophonium) test: subject to false positives and negatives and risk of bradycardia/asthma attack; rarely used now (trial of pyridostigmine can be used instead as a "chronic Tensilon test")

Myasthenic crisis

This is a medical emergency that may progress to respiratory failure requiring ventilation.

It affects 10–15% of patients, usually within 2–3 years of diagnosis, occasionally at disease onset. It is more likely in MuSK antibody-positive patients. It may be triggered by:

- Infection: stress such as trauma and post-operative period
- Withdrawal of cholinesterase inhibitors
- Rapid introduction or increase of corticosteroids
- Electrolyte imbalance: hypokalaemia, hypophosphataemia
- Anaemia
- Medications, eg gentamicin, chloroquine, penicillamine, suxamethonimu, botulinum toxin.

Increasing muscle weakness and double vision may be harbingers of an impending crisis.

Quieter breath sounds, reduced chest expansion, tachycardia and rise in blood pressure indicate imminent deterioration. Note that oxygen saturation and arterial blood gases are normal until late in the crisis.

The FVC is a useful predictor for impending respiratory failure, with FVC <1 L or 15 mL/kg requiring intensive care treatment and respiratory support.

Treatment of myasthenia gravis

Primary treatment is with cholinesterase (ChE) inhibitors (eg pyridostigmine), and some patients will achieve control with these agents alone. The cause of the disease is usually modified with treatments directed at the immune system:

- Immunosuppression/immune modulation:
  - First-line corticosteroids
  - Second-line azathioprine, mycophenolate, cyclophosphamide, ciclosporin
- Acute rescue therapy:
  - Plasmapheresis (usually 2–3 L exchange daily for 5 days)
  - Intravenous immune globulin infusion (usually 0.4 g/kg daily for 5 days or equivalent).

In those with thymoma or hyperplasia of the thymus, up to 60% will improve or achieve remission after thymectomy. The benefits of surgery are greatest in patients aged <40 years, with AChR antibodies and generalised, rather than purely ocular, myasthenia.

16.7.2 Lambert–Eaton myasthenic syndrome

Lambert–Eaton myasthenic syndrome (LEMS) is 20 times less common than myasthenia gravis, is caused by presynaptic autoantibodies to P-/Q-type calcium channels and 50–60% of cases are paraneoplastic, most commonly associated with small-cell carcinoma of the lung (also breast, ovarian cancer and lymphoproliferative disorders). Nonparaneoplastic cases may be associated with endocrinopathies, such as type 1 diabetes mellitus and thyroid disease.

Clinical features of LEMS

- Proximal weakness of lower limbs
- Dry mouth

- Other autonomic symptoms (difficulty with micturition and impotence)
- Hyporeflexia or areflexia, which improves ('potentiates') after sustained muscle contraction (diagnostically useful)
- Ocular and bulbar muscles rarely affected
- Rapid progression strongly suggests an associated cancer (and dysarthria, impotence and early involvement of distal muscles also suggestive)
- Approximately 90% have voltage-gated calcium channel antibodies
- Neurophysiology shows reduced compound muscle potentials, which typically increase by 100% after repetitive nerve stimulation at 40 Hz or sustained voluntary contraction

Unlike myasthenia gravis, ophthalmoplegia, ptosis and facial weakness are less common. Reflexes are reduced or absent but return after exercise (potentiation). As with all potential paraneoplastic disorders, follow-up and repeat investigations including imaging are recommended for at least 5 years after diagnosis (compare myasthenia gravis).

Treatment

Diagnosis and treatment are of any underlying neoplasm, usually small-cell carcinoma of the lung.

Symptomatic treatment is with 3,4-diaminopyridine (3,4-DAP), a potassium channel blocker, typically 10–20 mg four times daily, sometimes combined with pyridostigmine.

- Immunosuppression with corticosteroids
- Secondary immunosuppression (eg azathioprine, mycophenolate, ciclosporin) in non-neoplastic cases
- Rescue therapy with plasma exchange and/or immunoglobulins as per myasthenia.

16.7.3 Muscle disorders

General principles

Disorders of muscle are known as myopathies. The cardinal clinical features of myopathies are:

- Weakness, usually proximal and symmetrical:
  - Unable to rise from sitting with arms folded
  - 'Climbing up legs' – Gower's sign, seen in Duchenne muscular dystrophy (see below)
  - Characteristic patterns of weakness seen in particular syndromes (see below)
- Muscle wasting
- Other muscle features, eg myotonia
- Associated systemic features, eg contractures, cardiac disease in some muscular dystrophies, diabetes/deafness/seizures in mitochondrial cytopathies, rash in myositis

Table 16.10 illustrates the aetiology of muscle disorders.

Investigations

- Serum creatine kinase (CK):
  - May be elevated after intramuscular injections, muscle trauma, denervation, eg MND
  - Markedly elevated in rhabdomyolysis, immune-mediated myositis, Duchenne/Becker muscular dystrophy, some other inherited dystrophies including acid maltase deficiency
  - Asymptomatic raised CK may be seen in endocrine disease (hypothyroidism), metabolic myopathies, drug-induced, idiopathic hyperCKaemia
- EMG:
  - Abnormalities including small amplitude, short duration and polyphasic motor action potentials can be seen
  - May be useful in guiding site of muscle biopsy
- Muscle biopsy:
  - May be necessary to determine type of myopathy, with characteristic changes in myositis, some drug-induced myopathies, metabolic myopathies
- Genetic testing:
  - Increasingly first-line investigation in inherited myopathies and may obviate need for muscle biopsy.

Table 16.10 Aetiology of muscle disorders

Immune/inflammatory	**Toxic**
Polymyositis	Statins
Dermatomyositis	Alcohol
Inclusion body myositis	Corticosteroids
Overlap syndromes, eg SLE, RA, scleroderma	Illicit drugs, eg cocaine
Vasculitis	Other drugs, eg colchicine, antimalarials
Infectious	**Endocrine**
Viral: influenza, HIV, CMV, Coxsackievirus	Hypothyroidism
Bacterial: Lyme disease	Hyperthyroidism
Parasitic: trichinosis, toxoplasmosis	Cushing syndrome
Inherited	
Muscular dystrophies, eg DMD, FSH, myotonic dystrophy	
Metabolic myopathies	
Mitochondrial cytopathies	
Periodic paralysis (channelopathies)	

CMV, cytomegalovirus; DMD, Duchenne muscular dystrophy; FSH, facioscapulohumeral muscular dystrophy; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Genetic myopathies

Muscular dystrophies are inherited genetic myopathies. A large number of genetic causes have been defined, and although onset is typically in childhood, a number of later-onset forms are now well recognised.

Duchenne/Becker muscular dystrophy

Duchenne muscular dystrophy is an X-linked myopathy with onset typically from age 3–5 years in boys. Symmetrical proximal limb weakness occurs with progressive disability:

- DMD is due to the absence of the sarcolemmal protein dystrophin, coded on chromosome Xp21
- Serum CK is elevated
- Complications include scoliosis, learning disability, respiratory failure and dilated cardiomyopathy
- Steroid treatment prolongs ability to walk
- Respiratory support prolongs survival to around 25 years.

Becker muscular dystrophy occurs with milder dystrophin mutations, leading to a reduction in dystrophin expression in muscles. Onset is typically age >7 years, with symmetrical proximal limb-girdle weakness. Cardiomyopathy remains a prominent issue and may occur before muscle weakness.

Facioscapulohumeral (FSH) dystrophy

- Third most common muscular dystrophy
- Mean onset in third decade
- Facial weakness often first sign
- Proximal upper limb weakness due to poor scapular fixation (clinical sign: scapular winging) with preserved deltoid power
- Progressive lower limb weakness with foot drop
- Most cases due to mutation in chromosome 4q35.

Myotonic dystrophy

Myotonic dystrophy type 1 (DM1) is caused by a CTG expansion repeat in the *DMPK* gene on chromosome 19q. This is the most common inherited myopathy in adults. Myotonia (delayed muscle relaxation after contraction) is a hallmark of this condition, although weakness is usually more disabling. Cardiorespiratory complications are the cause of death in >50% and need to be carefully screened for in the long-term management:

- Genetic anticipation: worse and earlier onset in successive generations
- Facial weakness and ptosis leading to ‘myopathic’ facies
- Distal weakness often seen: finger/wrist extensors, ankle dorsiflexors
- Frontal balding
- Endocrinopathy: hypogonadism, insulin resistance
- Cardiac conduction defects, cardiomyopathy
- Hypoventilation, obstructive sleep apnoea
- Gastrointestinal disturbance: oesophageal dysfunction, dysphagia, pseudo-obstruction.

Inflammatory muscle disorders

Polymyositis and dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are inflammatory myopathies characterised by gradual or subacute proximal muscle weakness and typically raised CK.

- Incidence estimated at 2/100 000, peak in fifth decade, more common in women
- Characteristic skin changes seen in DM include:
  - Gottron's papules: erythematous papules over dorsal aspects of finger joints
  - Heliotrope eruption on the upper eyelids ± oedema
  - Photosensitive facial erythema
  - Skin changes in light-exposed areas, eg shawl sign
  - Capillary nail-bed abnormalities
- Interstitial lung disease complicates >10% of DM and PM cases and is particularly associated with anti-Jo 1 antibodies
- May overlap with other connective tissue diseases, eg scleroderma, SLE
- Association with underlying malignancy (DM > PM): solid tumours, eg breast, lung, ovarian, pancreatic
- Muscle biopsy shows perifascicular and vessel inflammation in DM versus intrafascicular inflammation and fibre necrosis in PM
- Treatment: steroids, intravenous immunoglobulin, methotrexate, cyclophosphamide in refractory cases.

Inclusion body myositis

Inclusion body myositis is an inflammatory myopathy presenting with insidious weakness, with a mean age of onset of around 60 years:

- More common in men than women (compare PM/DM)
- Proximal lower limb weakness (quadriceps) and distal upper limb weakness (wrist/finger flexors may be selectively affected)
- Dysphagia due to upper oesophageal involvement
- CK mildly raised or may be normal
- Muscle biopsy: inflammatory changes, rimmed vacuoles (amyloid positive), abnormal aggregates and mitochondrial pathology
- Generally poor response to immunotherapy.

Mitochondrial cytopathies (Table 16.11)

Mitochondria are the principal source of adenosine triphosphate (ATP) which is essential for all active cellular processes. Nerve cells, muscle, endocrine organs and skeletal muscle are particularly dependent on ATP. The presentation of mitochondrial disease, prevalence about 1 in 5000, can be acute with stroke-like episodes, relapsing and remitting, eg an encephalopathy, or slow and progressive, mimicking neurodegenerative disorders. As mitochondrial genes are derived from both nuclear and mitochondrial (maternally inherited) DNA, mitochondrial disorders can be autosomal

recessive, autosomal dominant, X-linked or maternally inherited. Pathogenic mutations of mtDNA may occur as deletions (often involving multiple genes) and point mutations (affecting a single base pair). Nuclear DNA mutations can have secondary effects on mtDNA function. Within a cell and tissue type, there may be varying levels of normal (wild-type) and mutated mtDNA, which has implications both for phenotype and severity of symptoms and for diagnosis. Therefore, a negative genetic (blood) test must be interpreted with great caution, because the causative mutation may be present only in some tissues and not others, and in this case a muscle biopsy may be required.

Common extraneurological features include cardiomyopathy and cardiac conduction defects, endocrine dysfunction (particularly diabetes mellitus) and gastrointestinal symptoms, including vomiting, pseudo-obstruction and dysphagia.

In patients in whom one suspects a mitochondrial cytopathy, a family history of premature cardiac death, diabetes or CNS disease, eg attributed to MS, short stature or deafness, may be useful. General investigations such as an ECG, echocardiogram and blood glucose can screen for common non-neurological features. CSF and blood lactate may be normal. Muscle biopsy may show red ragged fibres, which are not specific for mitochondrial cytopathies but cyclo-oxygenase (COX) defects are more diagnostic, if present. Muscle biopsy can be normal, and molecular genetic tests on muscle can be pursued if clinical suspicion remains high.

Management is currently focused on appropriate genetic counselling and screening for and treating associated conditions such as diabetes and cardiac abnormalities. The results of a clinical trial of idebdenone in Leber's hereditary optic neuropathy were insufficient to obtain a licence.

16.8 INVESTIGATIONS IN NEUROLOGICAL DISEASE

16.8.1 Neuroimaging

The two main modalities used for neuroimaging are CT and MRI. CT has the advantage of being quick and readily available in most hospitals 24 hours a day. However, it involves ionising radiation and lacks the resolution to detect more subtle changes in CNS tissue. MRI has the advantages of excellent spatial resolution and no radiation, but takes longer to perform and is contraindicated in some circumstances due to metallic implants or devices.

CT is particularly useful in the following scenarios:

- Subarachnoid haemorrhage
- Acute stroke (to exclude haemorrhage)
- Head trauma.

This is due to the fact that acutely clotted blood appears bright white on CT.

MRI is particularly useful in the following scenarios:

- Acute stroke
- CNS tumours
- CNS infections
- Inflammation/demyelination of the CNS

- Neurodegenerative dementia
- Epilepsy (determining structural cause for focal seizures).

Different MRI sequences provide different information about the CNS, and the administration of gadolinium contrast can further enhance sensitivity to detect disease. Diffusion-weighted imaging (DWI) is a relatively recent advance in MRI that allows detection of acute cytotoxic oedema and has proven of great use in conditions as diverse as acute stroke, CJD and brain infection.

Table 16.11 Selected, typically adult-onset, mitochondrial cytopathies with neurological involvement

Syndrome	Selected features
Leber's hereditary optic neuropathy (LHON)	Subacute painless bilateral visual failure Males:females approximately 4:1, median age of onset 24 years, prevalence 1 in 14 000 males Diagnosed typically with blood genetics
Chronic progressive external ophthalmoplegia (CPEO)	External ophthalmoplegia, bilateral ptosis, proximal myopathy Usually requires muscle biopsy to diagnose
Kearns–Sayre syndrome	Progressive external ophthalmoplegia; onset before age 20 with pigmentary retinopathy plus one of the following: CSF protein >1 g/L, cerebellar ataxia, heart block Usually requires muscle biopsy to diagnose
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	Stroke-like episodes before age 40 years, seizures and/or dementia, ragged red fibres on muscle biopsy and/or lactic acidosis
Myoclonic epilepsy with ragged red fibres	Myoclonus, seizures, cerebellar ataxia, myopathy (MERRF) Initially blood, urine or buccal scraping initially, proceed to muscle biopsy if negative
Neurogenic weakness with ataxia	Late childhood or adult-onset peripheral
Retinitis pigmentosa	
Neuropathy with associated ataxia and pigmentary retinopathy retinitis pigmentosa (NARP)	Initially blood, urine or buccal scraping; proceed to muscle biopsy if negative

It is notable that, in many common neurological disorders, standard neuroimaging will be normal. In migraine, many cases of epilepsy, Parkinson's disease, early dementia and almost all neuromuscular diseases, the MRI will be unremarkable. Patients with raised ICP may have normal neuroimaging – availability of scans does not negate the need for fundoscopy in this situation!

This emphasises the importance of clinical diagnosis based on history and examination – increasingly sophisticated scanning is not a substitute for these core skills.

16.8.2 Neurophysiology

Neurophysiology encompasses a range of different tests, principally EEG and NCS/EMG.

EEG can be used in a number of different conditions to aid diagnosis, but is rarely diagnostic in its own right.

Interictal epileptiform discharges can support the diagnosis of epilepsy but must not be relied on to make the diagnosis. Up to 50% of patients with epilepsy have a normal EEG. In addition 0.5% of the healthy population have clear epileptiform changes on EEG, and many more have normal variations that can be misinterpreted as epileptiform. This undoubtedly leads to some people being misdiagnosed. As previously mentioned, the EEG should not be used indiscriminately to 'rule out' a seizure disorder.

In prion disease, particularly sporadic CJD, the EEG may show classic periodic sharp wave complexes to aid diagnosis.

NCS/EMG is principally used to investigate neuropathy and myopathy. It is considered a direct extension of the clinical examination and must be interpreted in light of this. Motor and sensory nerves are studied separately. The principle of NCS is to stimulate a nerve at one site and record the response at a second site. NCS measures the integrity of large fibre nerves only. The amplitude of response is measured and the conduction velocity of the nerve impulse can be calculated. Small fibre function can be assessed separately, eg by measuring temperature and pain thresholds. EMG measures spontaneous and volitional muscle activity and can be used to electrically assess muscle unit size and stability.

Axonal neuropathies

- Decreased amplitude of response on NCS
- Relative preservation of conduction velocity on NCS
- Denervation may be seen on EMG.

Demyelinating neuropathies

- Decreased conduction velocities or conduction 'block' on NCS
- Relative preservation of amplitudes on NCS
- No denervation typically seen on EMG.

Myopathic processes

Short duration, small amplitude, polyphasic motor unit action potentials on EMG.

Neuromuscular junction disorders

- Postsynaptic (myasthenia gravis): decrement in amplitude of compound muscle action potential after repetitive stimulation on NCS
- Presynaptic (Lambert–Eaton myasthenic syndrome): increment in compound muscle action potential on NCS after muscle exercise.

Remember, NCS/EMG will be normal in CNS disorders.

16.9 CEREBROSPINAL FLUID ANALYSIS

See Section 16.3.3 and under Section 16.3.1.

Examination of the CSF can prove useful in a variety of scenarios, from suspected subarachnoid haemorrhage to investigation of CNS infection or inflammation, neoplasia and inflammatory peripheral neuropathy.

It is important that the patient be relaxed if in the lateral decubitus position when the opening pressure is being taken, eg by slight extension of the lower limbs. If the patient coughs or strains it becomes immediately apparent what effect this has on intraspinal pressure! Ensure that enough CSF is taken for the tests that are required and, if the diagnosis is unclear, it can be helpful to take at least a millilitre of CSF into a couple of extra bottles, in the event that additional investigations become necessary. Ensure that a paired serum glucose sample is taken to compare with the CSF, and serum for electrophoresis if oligoclonal bands are being requested.

Normal CSF findings

- Pressure:
  - 10–20 cm CSF (patient recumbent); varies with BMI
- Protein:
  - 0.2–0.4 g/L
- Cell count:
  - Red cells 0, white cells <5/mm^3 (few monocytes or lymphocytes)
- Glucose: more than two-thirds of blood glucose
- Gram stain negative (no organisms)

Abnormal CSF findings

- Elevated protein
  - Very high: >2 g/L
    - Guillain–Barré syndrome
    - Spinal block (Froin syndrome)
    - TB meningitis
    - Fungal meningitis
  - High:
    - Bacterial meningitis
    - Viral encephalitis
    - Cerebral abscess
    - Neurosyphilis

    - Subdural haematoma
    - Cerebral malignancy
- Low CSF glucose:
    - Bacterial meningitis
    - TB meningitis
    - Fungal meningitis
    - Mumps meningitis (in 20% of cases)
    - Herpes simplex encephalitis (in 20%)
    - Subarachnoid haemorrhage (occasionally)
    - Malignancy
- Polymorphs:
    - Bacterial meningitis
    - Tuberculosis
- Lymphocytes:
    - Viral encephalitis/meningitis
    - Partially treated bacterial meningitis
    - Behçet syndrome
    - CNS vasculitides
    - HIV associated
    - Lymphoma
    - Leukaemia
    - MS (not typical)
    - Neuromyelitis optica
    - Lyme disease
    - SLE.

IgG oligoclonal bands in CSF

- Multiple sclerosis: 85–95%
    - Autoimmune
    - Neuro-SLE: 50%
    - Neuro-Behçet's disease: 20%
    - Neurosarcoidosis: 40%
    - Neuromyelitis optica: 20–40%
    - Infectious:
        - Subacute sclerosing panencephalitis (rare, late complication of measles): 100%
        - Progressive rubella panencephalitis: 100%
        - Neurosyphilis: 95%
        - Neuro-HIV: 80%

    - Neuroborreliosis: 80%
    - Tumour: <5%
- Hereditary:
    - Ataxia–telangiectasia: 60%
    - Adrenoleukodystrophy: 100%
- Subarachnoid haemorrhage (unusual).

Chapter 17
Ophthalmology

CONTENTS

Pupil and eye movement disorders, nystagmus and visual field defects are covered in the neuroophthalmology section of Chapter 16, Neurology.

17.1 BASIC ANATOMY OF THE EYE

17.1.1 Orbit

The orbit houses the globe, six extraocular muscles involved in eye movement, the levator palpebrae superioris, the lacrimal gland, orbital fat, and attendant blood vessels and nerves.

Extraocular muscles

The four rectus muscles and the superior oblique arise at the orbital apex and pass forwards to insert into the globe. The inferior oblique arises from the anteromedial orbital floor and runs across the inferior surface of the globe to insert into its posterolateral aspect.

The innervation and primary action of each muscle are shown in Table 17.1 – all other movements are composite, ie due to the action of two muscles acting together.

Table 17.1 The innervation and primary action of the extraocular muscles

Muscle	Nerve supply	Primary action
Superior rectus	III	Elevation in abduction
Inferior rectus	III	Depression in abduction
Medial Rectus	III	Adduction
Lateral rectus	VI	Abduction
Inferior oblique	III	Elevation in adduction
Superior oblique	IV	Depression in adduction

17.1.2 The globe

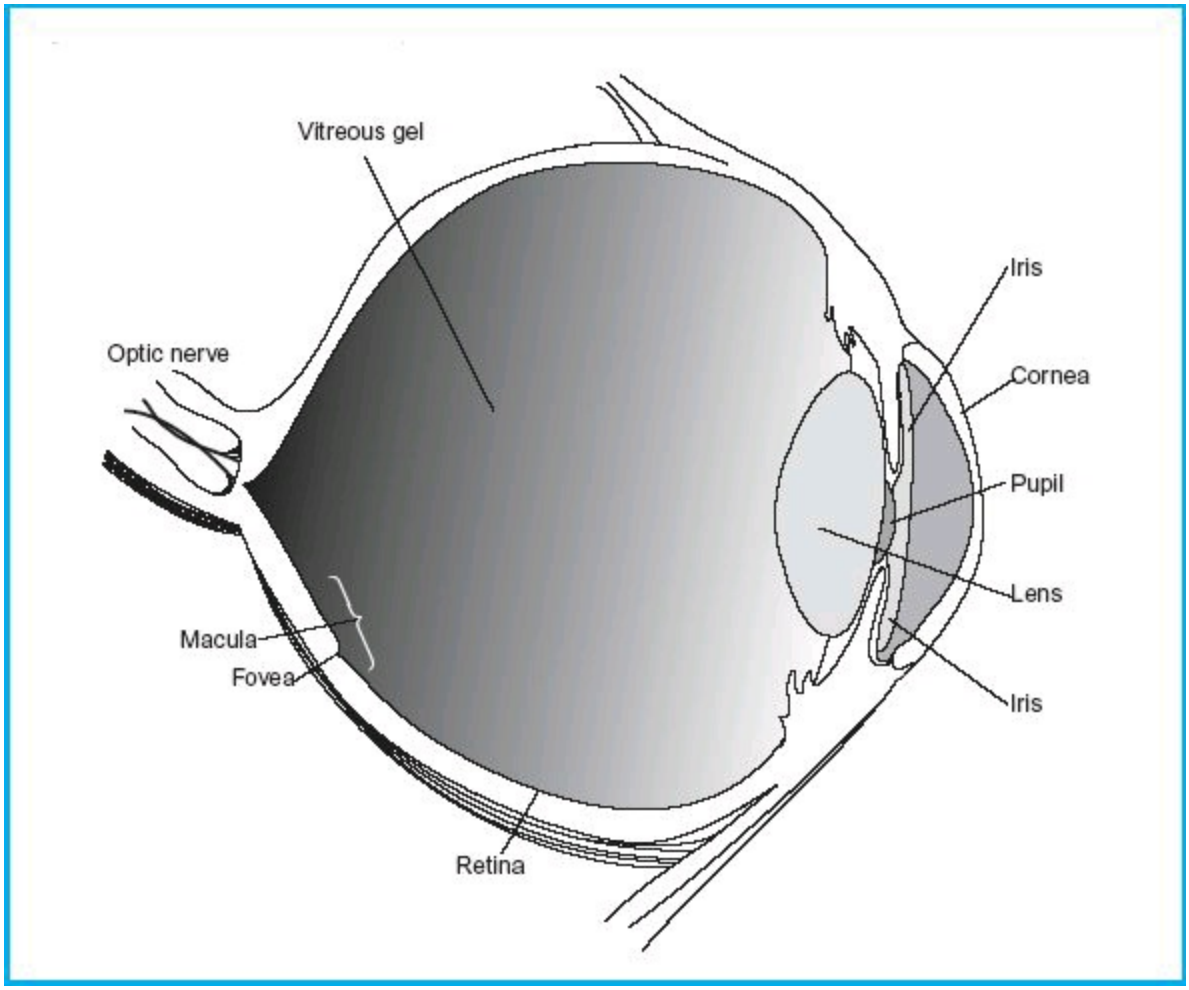
The following are the features (see Figure 17.1):

- **Cornea**: clarity is maintained in this avascular structure by regular structural array of component collagen fibrils and its relative dehydrated state, which is maintained by endothelial cell function. As a result of its curved surface, it acts as an important refractive structure
- **Conjunctiva**: thin mucous membrane that covers the anterior sclera and lines the eyelids

- **Sclera**: tough, opaque fibroelastic coat. Extends from the cornea to the optic nerve
- **Uveal tract**: anterior uvea comprises iris and ciliary body, and the posterior uvea is the choroid, a vascular layer lining the sclera, which nourishes the outer retinal layers
- **Retinal pigment epithelium**: cellular monolayer, the outermost layer of the retina. It is key to maintaining retinal health by acting as a selective barrier and regulator of transport of nutrients and waste products to and from the retina
- **Retina**: light-sensitive innermost layer of the globe that converts light energy to electrical energy. It comprises:
  - rods: more plentiful in peripheral retina and sensitive to low light and movement detection
  - cones: concentrated within the macular region, particularly at the fovea. This is where sharpest acuity and colour vision occurs. The macula is the central area of the retina, which is bordered by the optic nerve and the superior and inferior retinal arcades. The fovea is the central area of the macula.

Retinal vascular supply is from the central retinal artery. Capillaries have non-fenestrated endothelium and tight junctions preventing the passage of large molecules, analogous to the blood–brain barrier

Figure 17.1 Cross-section of the eye



- **Lens**: positioned behind the iris and anterior to the vitreous. It is enclosed in a capsule and anchored around its equator by the zonules. New lens fibres are continuously produced throughout life and the older fibres are compressed to form the lens nucleus. With increasing age

the lens becomes less deformable, and so accommodation – the ability to change focus – is lost

- **Vitreous**: translucent gel-like substance, which fills the posterior chamber of the eye.

17.2 RETINAL DISORDERS

17.2.1 Diabetic retinopathy

Until recently diabetic retinopathy was the most common cause of blindness in the working-age population in the UK. The introduction of improved disease control, screening programmes and timely treatment has resulted in a reduction of the incidence of visual loss in diabetic eye disease. Sight loss occurs due to either neovascularisation, which can lead to tractional retinal detachment or glaucoma, or macular disease. The development and progression of retinopathy are related to the type and duration of diabetes and its control, as well as associated factors such as hypertension, lipid levels and smoking. Conversely the risk of developing retinopathy can be reduced by early disease detection and optimal control of blood glucose, blood pressure and possibly lipids.

The precise mechanism of the biochemical pathways that causes hyperglycaemia to result in microvascular damage is unclear. Proposed mechanisms include the following:

- **Polyol pathway**: metabolises excess glucose into sorbitol using aldose reductase. Sorbitol accumulates and damages retinal cells partly by osmotic effects. Increased aldose reductase activity is known to occur in vascular pericytes, retinal pigment epithelium (RPE) cells, retinal endothelial cells, ganglion cells, Müllerian cells and neurons, and is associated with the destruction of retinal cells. The polyol pathway has also been implicated in increased thickness of the retinal capillary basement membrane, and leukocyte stasis and adhesion to vascular endothelium. Leukostasis leads to capillary occlusion and reactive oxygen stress (ROS)-mediated cell death, as well as amplifying the inflammatory response locally in the retinal tissue
- **Loss of vascular pericytes or endothelial cells**: increased concentrations of glucose results in reduced viability
- **Microthrombosis**: occludes retinal capillaries and leads to leakage and oedema
- **Growth factors**, eg VEGF (vascular endothelial growth factor), are produced secondary to hypoxia and promote neovascularisation.

Hypertension is thought to contribute to the progression of diabetic retinopathy by:

- Increased endothelial cell dysfunction via mechanical stretch, increased retinal perfusion and higher blood viscosity

Ethnic and genetic factors are also significant. Retinopathy is more common in patients with retinopathy affected first-degree relatives, and Black patients are more likely to develop retinopathy than White people.

Pregnancy may be associated with rapid progression of retinopathy.

Features of retinopathy

Background retinopathy

- Does not affect acuity
- Microaneurysms – first clinical change, saccular pouch, either leaks or resolves due to thrombosis
- Haemorrhages – blot (deep), flame (superficial)
- Exudates – leakage of lipid and lipoprotein

Diabetic maculopathy

- More common in type 2 diabetes
- Retinopathy within the macular region
- Most common cause of diabetic visual loss
- Treatment required if oedema close to the fovea

Preproliferative retinopathy

- Venous changes – dilatation, beading and reduplication
- Multiple large, deep haemorrhages
- Cotton-wool spots – axonal disruption due to ischaemia

Proliferative retinopathy

- More common in type 1 diabetes
- Retinal or iris neovascularisation may occur
- Treatment aims to abolish angiogenic factor production

Treatment of diabetic eye disease

Prevention is aimed at achieving tight diabetic control – usually maintaining HbA1c ≤53 mmol per l and controlling blood pressure. This may be limited by actual or fear of hypoglycaemic episodes.

Advice not to smoke and control of lipids may be helpful.

Macular oedema

The mainstay of treatment is focal laser therapy to areas of oedema. Resolution, probably due to stimulation of the pigment epithelium, occurs over 6–12 weeks. Several treatments may be required.

More recently VEGF inhibitors, eg ranibizumab, which are administered by repeated intravitreal injections, have been shown to be highly effective in promoting resolution of oedema and improving acuity, particularly when combined with focal laser therapy.

Intravitreal steroid has also been shown to successfully promote resolution of macular oedema, but repeated treatments are required because the effect is transient. As a result there is a high incidence of steroid-induced side-effects – particularly cataract and glaucoma, which can cause secondary ocular damage.

Proliferative retinopathy

Neovascularisation is seen at the disc or elsewhere in the retina, on the venous side of the retinal

circulation. The vessels have a chaotic appearance and loop back towards their base rather than tapering out. Laser burns scattered over the retina – panretinal photocoagulation – is standard treatment and is undertaken urgently, resulting in regression of neovascularisation. It is also indicated in selected patients with severe preproliferative disease. The aim of treatment is to reduce growth factor production and therefore the stimulus to neovascularisation.

Vitrectomy is a surgical treatment, in which the vitreous is removed. It is indicated in those patients with aggressive proliferative disease, which can lead to non-resolving vitreous haemorrhage, to prevent fibrovascular proliferation; this can result in traction on the retina and subsequent detachment.

Diabetic papillopathy

Diabetic papillopathy is a rare condition causing unilateral or bilateral disc oedema, classically in a young person with type 1 diabetes, usually with little impact on vision. It is probably due to a microangiopathic disease process

It is important to differentiate this from papilloedema and optic disc neovascularisation, but no specific treatment is required, and the condition is usually self-limiting with resolution within a few months.

17.2.2 Retinal venous occlusion

This is the second most common retinal vascular disease and may affect either a branch vessel, a hemi-central vein or the central retinal vein. Central venous occlusion is due to intraluminal thrombosis. When branches are affected the cause is thought to be compression of the retinal vein by an adjacent retinal artery in a common adventitial sheath whose wall has been thickened due to arteriosclerotic change, resulting in vascular stasis.

Risk factors

These should be sought and those that are modifiable treated:

- Age >50 years
- Systemic hypertension – prime risk factor, affects 64%
- Diabetes
- Glaucoma
- Hyperviscosity states
- Hyperlipidaemia – particularly in younger patients
- Thrombophilia – antiphospholipid antibody syndrome, hyperhomocysteinaemia, factor V Leiden, proteins S and C, and antithrombin 3 deficiency
- Oral contraceptive pill – in younger patients
- Inflammatory diseases associated with retinal vasculitis, eg Behçet's disease, polyarteritis nodosa (PAN)
- Chronic renal failure and other secondary causes of hypertension.

Clinical signs of retinal venous occlusion

- Reduced visual acuity – level depends on extent of macular involvement and degree of retinal ischaemia. May vary from normal acuity to less than 6/60
- Relative afferent pupillary defect – with retinal ischaemia
- Swollen optic disc
- Retinal haemorrhages in affected area:
  - Superficial in nerve fibre layer, flame shaped
  - Deep blots more common in ischaemia
- Dilated tortuous veins
- Cotton-wool spots
- Visual field defect – corresponds to area of retinal non-perfusion in BRVO (branch retinal vein occlusion)
- Neovascularisation develops in ischaemia – more common in CRVO (central retinal vein occlusion), affecting 16% of patients. Affects either the drainage angle and iris, resulting in glaucoma, which is frequently painful, or the retina

Treatment varies depending on whether the venous occlusion affects a central or branch retinal vein, and whether or not there is ischaemia or macular oedema.

Outcome is better in patients who present with better visual acuity.

Management is of the condition and identification and manipulation of any identified modifiable risk factors.

Ophthalmic intervention:

- Laser – macular oedema in BRVO can be treated with focal laser photocoagulation, leading to improved acuity. Patients with CRVO do not benefit from laser for macular oedema. Patients with both BRVO and CRVO may require laser for neovascular changes, reducing the risk of vitreous haemorrhage
- Intravitreal steroid implant – the National Institute for Health and Care Excellence (NICE) has approved the use of intravitreal dexamethasone implants in the UK (Ozurdex) for macular oedema in both CRVO and BRVO, although currently laser is the established firstline treatment in BRVO
- Anti-VEGF drugs have been shown to be beneficial for patients with macular oedema due to retinal venous occlusions.

17.2.3 Retinal arterial occlusion

The central retinal artery is an end-artery, arising from the ophthalmic artery. Occlusion of the central artery or one of its branches produces retinal infarction to the inner retinal layers and visual loss in the area supplied.

Aetiology

- Embolic, eg platelets, cholesterol. Carotid artery atherosclerosis is the most common underlying pathology. Cardiogenic emboli are more common in younger patients
- Rapid increase in intraocular pressure to above central arterial pressure, eg direct pressure on the globe from prone positioning, particularly surgical
- Arteritis/vasculitis: most commonly giant-cell arteritis (GCA), although visual loss in GCA is due to CRAO (central retinal artery occlusion) in only 10% of cases, the usual mode of visual loss being anterior ischaemic optic neuropathy, in which the circulation to the optic nerve head is damaged
- Profound hypotension
- Vasospasm
- Hypercoaguable states, eg antiphospholipid syndrome, protein S or C deficiency, factor V Leiden mutation
- Oral contraceptive pill

Symptoms and clinical signs of retinal artery occlusion

- **Sudden, profound, painless loss of vision** – corresponding sector field loss if branch occlusion. May be previous episodes of amaurosis
- **Pale oedematous retina with cherry-red spot at the fovea** – due to choroidal circulation being visible, as retina is thinner here and damaged retina is oedematous. Lasts approximately 48 h
- **Cilioretinal artery** in 15% patients may lead to small central island of preserved vision
- **'Cattle trucking'** – fragmentation of continuity of blood in the retinal arterioles. Emboli may sometimes be seen
- **Relative afferent pupillary defect**
- **Neovascular complications** – less frequent than in venous occlusions, probably due to retinal damage being so severe that angiogenic growth factors are not produced

Acute management

Spontaneous recovery in CRAO occurs in some patients.

The aim of treatment is to dislodge the obstruction or increase the perfusion pressure of the retinal artery. This can be achieved by:

- Ocular massage/intravenous acetazolamide/anterior segment paracentesis (removal of a small amount of aqueous from anterior chamber): all of these reduce the intraocular pressure
- Selective fibrinolysis: microcatheter administration into ophthalmic artery can be effective, but is rarely performed because of untimely presentation and risks of cerebrovascular events.

Underlying modifiable systemic risk factors should be sought and treated.

17.2.4 Hypertensive retinopathy

Hypertensive retinopathy is a manifestation of target organ damage.

There is no treatment except to manage the blood pressure and any underlying disorder. Vision is generally unaffected.

Retinal changes may be seen reflecting either acute hypertension, as in malignant hypertensive disease, or the chronic changes from systemic long-term hypertension.

Hypertensive vascular changes

Chronic hypertension causes arteriosclerotic changes, eg copper and silver wiring, due to hyalinisation of vessel walls and arteriovenous (AV) nipping, due to circulation changes resulting in venous dilatation around AV crossing.

Changes related to **more current** blood pressure changes include:

- **Focal or generalised arteriole narrowing**, due to muscle spasm in vessel wall, which can become permanent
- **Cotton-wool spots**, usually located around the disc, are due to precapillary occlusion causing retinal ischaemia
- **Haemorrhages**, which can be deep and blotchy or superficial and flame-shaped
- **Hard exudates**, which may radiate from the fovea in the form of a macular star and cause reduced acuity
- **Disc oedema** occurs in malignant or accelerated phase hypertension due to vasoconstriction and choroidal ischaemia. May be associated with transient visual obscurations.

Keith, Wagener and Barker Classification of Hypertensive Retinopathy:

Grade 1	– arteriolar attenuation
Grade 2	– focal arteriolar attenuation with AV nipping, sclerosis of retinal arterioles
Grade 3	– retinal haemorrhages, exudates and cotton-wool spots (due to infarction of retinal nerve fibre layer)
Grade 4	– optic disc swelling and severe Grade 3 changes

Grade 4 is associated with severe target organ damage and high mortality.

17.2.5 Macular degeneration

Macular degeneration is the most common cause of blindness in the population aged >65 years, and with increased longevity, is increasing in prevalence. It is thought that the retina may be susceptible to damage due to oxidative stress.

Risk factors

- Age

- Family history
- Cigarette smoking
- Nutritional factors
- Myopia

Early macular degeneration: irregularity of pigmentation, drusen (discrete yellow/white deposits). Changes may precede visual loss.

Late macular degeneration: subdivided into wet and geographic atrophy (dry) subtypes according to the presence or absence of macular oedema.

Geographic atrophy develops as areas of depigmentation, which increase in size and coalesce, leading to progressive visual loss.

Wet degeneration is associated with sudden central visual loss due to the development of a neovascular membrane in the choroid. The diagnosis can be confirmed using ocular coherence tomography (OCT), which images the retina non-invasively and can be used sequentially to assess response to treatment, and fluorescein angiography, when an intravenous injection of fluorescein dye demonstrates leakage.

Features

- Central visual loss: this occurs in both types of macular degeneration, leading to difficulty in activities that depend on acuity, eg reading and recognising faces, but preservation of peripheral vision, so navigation is generally preserved
- Distortion.

Treatment

Intravitreal injection of anti-VEGF has superseded other treatment modalities such as laser and photodynamic therapy. A course of intravitreal injections of ranibizumab, ideally started soon after onset of symptoms, has been shown to be safe and improve acuity. Sequential OCT scans demonstrate resolution of oedema and are used to monitor response to treatment.

Nutritional supplements are recommended for those patients who have lost vision in one eye due to wet macular degeneration.

17.2.6 Retinitis pigmentosa

Retinitis pigmentosa (RP) refers to a group of inherited diseases associated with degeneration of the photoreceptors and the RPE (retinal pigment epithelium), leading to progressive visual loss. This heterogenous group of disorders is now the commonest cause of blindness in the working-age population.

The disease primarily affects rods, but cones are also affected.

The term RP is used synonymously with rod–cone/photoreceptor/retinal dystrophy and pigmentary retinopathy.

The classic triad of findings is as follows:

1. Night blindness – due to loss of rod function
2. Tunnel vision – due to loss of peripheral visual field, also secondary to rod dysfunction. Central visual loss due to cone disease tends to be a late feature
3. Pigmented 'bony spicule', fundal appearance with associated waxy disc pallor and attenuation of retinal blood vessels.

The diagnosis is made clinically and confirmed using electrodiagnostic tests.

RP is genetically a complex group of disorders; numerous genes, expressed in either the photoreceptors or the RPE, have been implicated in RP.

There are three modes of inheritance:

1. Autosomal dominant 20–25% cases
2. Autosomal recessive 15–20%
3. X-linked recessive 10–15% – often symptomatic earlier in life and rapidly progressive. Approximately 30% cases are due to spontaneous mutations. Most cases are isolated, but it can also be associated with systemic conditions or part of a syndrome in approximately 20% of cases.

- **Usher syndrome**: untreatable autosomal recessive disorder. Association of RP with sensorineural deafness, the most common cause of deaf–blindness
- **Bardet–Biedl syndrome**: autosomal recessive association of RP with truncal obesity, polydactyly, cognitive impairment, renal abnormalities, male hypogonadotrophic hypogonadism and female genito-urinary malformations. Visual problems are usually evident by the age of 7 years
- **Refsum's disease**: autosomal recessive, earlyonset RP associated with anosmia, sensorimotor neuropathy, sensorineural deafness, ataxia and ichthyosis. It is unusual for an affected individual to manifest all features. Diagnosis is established by confirming elevated plasma phytanic acid levels due to genetic failure to metabolise this substance. Dietary restriction of phytanic acid can help neurological and cutaneous disease, and may stabilise RP. Siblings of an affected individual should have genetic testing so that early treatment can be instituted if indicated
- **Kearns–Sayre syndrome**: a mitochondrial deletion syndrome with onset at age <20 years, characterised by RP, progressive external ophthalmolplegia frequently associated with heart block, and cerebellar ataxia. Diagnosis is confirmed by the finding of ragged red fibres on muscle biopsy and myopathy on electromyography (EMG)
- **Alström syndrome**: autosomal recessive association of RP with sensorineural hearing impairment, obesity, insulin resistance, dilated cardiomyopathy and developmental delay.

17.3 LENS ABNORMALITIES

17.3.1 Cataract

Cataract, opacification of the lens of the eye, is the leading cause of worldwide blindness, affecting approximately 20 million people. The lens is a complex structure, with cells ordered in such a way as to allow transparency. Ageing and other insults lead to structural disarray and opacification.

Cataract surgery, with prosthetic lens implant, is the commonest surgical procedure performed in the UK. Intervention is indicated:

- When decreased visual function, uncorrectable by spectacles, has adverse affect on activities of daily living
- If the view of the fundus is impaired when monitoring or treating another condition, eg diabetic retinopathy
- To keep driving licence when vision below standard required to drive.

Causes of cataract

- **Congenital:**
  - Autosomal dominant (25%)
  - Maternal infection – rubella, cytomegalovirus (CMV), herpes simplex, varicella-zoster
  - Chromosomal abnormalities – Down syndrome, Turner syndrome
  - Metabolic – galactosaemia, hypocalcaemia, Lowe syndrome, hypoglycaemia
  - Maternal drug ingestion – corticosteroids, thalidomide
- **Age related**
- **Metabolic**, eg diabetes, hypoglycaemia, Lowe syndrome, Wilson's disease, hypoglycaemia, galactokinase deficiency
- **Secondary to ocular disease**, eg uveitis
- **Trauma**, eg blunt or penetrating, radiation, electric shock
- **Drugs**, eg steroids
- **Miscellaneous**, eg myotonic dystrophy, atopic dermatitis

17.3.2 Lens dislocation

The lens is anchored in position by the zonules, which attach the equator of the lens to the ciliary body. Zonular disruption results in dislocation of the lens.

Depending on the lens shift, this may produce myopia, hypermetropia or elevated intraocular pressure.

Causes of lens dislocation

- Marfan syndrome: up and out
- Homocystenuria: down and in
- Ehlers–Danlos syndrome

- Autosomal recessive ectopia lentis
- Trauma
- Uveal tumours.

17.4 OPTIC NERVE DISORDERS

The following are hallmarks of optic nerve disease:

- Reduced visual acuity
- Impaired colour vision
- Visual field defect – in particular central or centrocaecal scotoma, where the central field defect is contiguous with the blind spot.

17.4.1 Optic neuritis

Inflammatory demyelination of the optic nerve may affect the following:

- **Nerve head**: producing papillitis (30%) with optic disc swelling, hyperaemia and haemorrhages
- **Retrobulbar** portion of the nerve: producing retrobulbar neuritis, in which the nerve appears normal ('the patient sees nothing, the doctor sees nothing').

Optic neuritis is the presenting feature of multiple scelrosis (MS) in approximately 20% of patients, and up to 50% of patients with demyelinating disease will develop optic neuritis at some time during their lifetime.

The 15-year risk of developing MS from the Optic Neuritis Treatment Trial was found to be 25% with no lesions on cerebral MRI, but 75% with one or more lesions. The features of optic neuritis are shown in Table 17.2.

Spontaneous improvement in vision occurs within a few weeks and may continue for 12 months.

Patients may be treated with intravenous methylprednisolone, which accelerates visual recovery and may delay the onset of clinically definite MS.

Differential diagnosis optic neuritis/papillitis

- **Demyelination**
- **Ischaemic optic neuropathy**: arteritic and nonarteritic
- **Post-viral syndrome**: occurs 1–3 weeks postinfection or as post-immunisation event. Identified after infection with measles, mumps, chickenpox, influenza, and Epstein–Barr virus. More commonly bilateral, and generally prognosis good
- **Infections**: viral encephalitis (measles, mumps, chickenpox), infectious mononucleosis, cat scratch disease, toxoplasmosis, herpes zoster
- **Guillain–Barré-associated neuritis**
- **Inflammatory**: contiguous with orbital inflammation, sinusitis encephalitis or meningitis

- Secondary to **granulomatous optic nerve inflammation**, eg tuberculosis, sarcoid, syphilis
- **Systemic autoimmune disease**: systemic lupus erythematosus, Wegener's granulomatosis.

Table 17.2 Features of typical optic neuritis

M:F	1:2
Age	20–40 years
Reduced visual acuity	90% monocular with rapid progression over a few days, improves over 4–6 weeks; >90% regain 6/12 or better, although a RAPD often persists
Pain	Precedes visual loss, worsened by eye movement
Red colour desaturation	Red appears darker or brown
Relative afferent pupillary defect (RAPD)	Swinging flashlight test – see section 16.3.2, persists long term in approximately 25% of patients
Paracentral or central scotoma	Most common defect, although any type of scotoma may occur
Visual evoked potential prolonged	Reflects delayed conduction in optic pathway, frequently persists even with clinical recovery
Optic atrophy	Develops within weeks, may be seen in contralateral eye as sign of previous asymptomatic episode

Causes of optic atrophy

- **Congenital**: dominant or recessive, mitochondrial (Leber's optic atrophy)
- Secondary to **optic nerve compression**, eg pituitary mass, sphenoid wing meningioma, orbital cellulitis
- **Drugs**: ethambutol, isoniazid, chloramphenicol, digoxin, chlorpropamide, amiodarone, sidenafil
- **Radiation neuropathy**: progressive, usually bilateral visual loss classically within 6-12 months of local treatment. May respond to hyperbaric oxygen therapy
- **Carcinomatous**: due to microscopic infiltrates of nerve and sheath
- **Post-optic neuritis**
- **Post-trauma**: usually affecting portion of nerve within intraorbital or intracanalicular portion of the nerve
- **Toxic neuropathy**, eg tobacco, arsenic, lead, methanol
- **Nutritional**: vitamins B_1, B_2, B_6 and B_{12}, folic acid and niacin deficiencies

- **Tobacco–alcohol amblyopia** may be toxic or nutritional (mechanism not fully understood); may be good prognosis for recovery with cessation of tobacco and alcohol and vitamin B and folate supplementation, if atrophy not fully established
- **Infiltrative neuropathy**, eg sarcoid, lymphoma, leukaemia

17.4.2 The swollen optic nerve head

Papilloedema

This is a specific term relating to swelling of the optic nerve head due to **increased intracranial pressure**. It occurs as a result of the contiguity of the subarachnoid space with the optic nerve sheath. Investigation should be undertaken as an emergency because of the risk of serious underlying pathology, and because rapid visual loss occurs in some patients.

Visual acuity is maintained until late.

A swollen optic nerve head produces an enlarged blind spot on visual field testing. Peripheral visual field constriction, with the nasal field affected initially, then develops.

Transient obscurations or blacking out of vision, lasting a few seconds, occurring many times a day, particularly with positional changes are a common feature, probably due to transient reduction in perfusion of the optic nerve head.

Associated non-ocular symptoms include headache, classically with a diurnal variation, nausea or vomiting and pulsatile tinnitus.

Diplopia may result as a false localising sign due to compression of the sixth nerve as it traverses the apex of the petrous bone, or due to downwards displacement of the brainstem and traction of the nerve root.

Causes

- Space-occupying lesion
- Hydrocephalus
- Idiopathic intracranial hypertension
- Venous sinus thrombosis
- Cerebral oedema
- CO_2 retention

Papilloedema is usually bilateral, although may be asymmetrical. The following are features evident on disc assessment:

- Hyperaemia of the disc: due to capillary dilatation
- Splinter haemorrhages: around disc in nerve fibre layer, so flame-shaped

- Blurring and elevation of disc margins: due to nerve fibre layer swelling; also obscures vessels crossing the disc
- Exudates
- Cotton-wool spots
- Paton's lines: retinal folds concentric with disc
- Loss of spontaneous venous pulsation: absent in 10–20% of normal individuals
- Loss of cup: a late feature

Foster–Kennedy syndrome is unilateral papilloedema with contralateral optic atrophy. It occurs due to a space-occupying lesion, usually a frontal lobe mass or an olfactory groove meningioma, which directly compresses one optic nerve, causing ipsilateral optic atrophy, and simultaneously causing increased intracranial pressure and contralateral papilloedema.

Differential diagnosis of papilloedema

- Optic neuritis: papillitis
- Diabetic papillopathy
- Accelerated phase hypertension
- Anterior ischaemic optic neuropathy
- Infiltrative optic neuropathy: lymphoma, reticuloendothelial
- Intraocular inflammation
- Anomalous optic disc
- Disc tumours: haemangioma, glioma, metastatic
- Compressive optic neuropathy: optic nerve sheath meningioma, glioma, retrobulbar mass
- CRVO

17.5 OCULAR INFLAMMATION

17.5.1 Uveitis

Uveitis is inflammation of the uveal tract, which may affect the anterior (iris and/or ciliary body) and/or posterior uvea (choroid) and/or retina. A slit-lamp examination is required to make the diagnosis to establish the presence of inflammatory cells.

Anterior uveitis is the most common form of ocular inflammation and a common cause of a painful red eye. Typical presentation is with the following:

- Unilateral pain – often worse on attempted near gaze
- Photophobia
- Lacrimation
- Decreased vision

It is frequently idiopathic, but associations with systemic disease should be sought.

Posterior uveitis is more commonly painless and causes visual symptoms of floaters, due to inflammatory debris within the vitreous, and reduced acuity due to macular involvement.

Systemic associations of uveitis

Inflammatory diseases

- **Ankylosing spondylitis**: 30% of patients develop uveitis. The uveitis does not correlate with the severity of the systemic disease. Episodes are frequently recurrent, affecting either eye. Most patients with ankylosing spondyltitis and uveitis are HLA-B27-positive. Males are more commonly affected
- **Reactive arthritis**: 30% develop uveitis. Conjunctivitis and keratitis also occur; 90% of patients are HLA-B27-positive
- **Sarcoidosis**: uveitis may be unilateral or bilateral and affect the anterior or posterior uvea. Retinal vasculitis is common
- **Inflammatory bowel disease**: occurs in 5% of patients with Crohn's disease or colitis
- **Juvenile idiopathic arthritis**: ocular involvement typically occurs in patients who are ANA (antinuclear antibody)-positive with pauciarticular disease. Uveitis is usually asymptomatic and bilateral with no correlation to the severity of the joint disease. As a result of the high incidence of irreversible complications, cataract in up to 60%, glaucoma in 25% and band keratopathy in 60% (calcium deposit on the corneal surface), patients are regularly screened for uveitis
- **Behçet syndrome**: ocular involvement occurs in 70% of patients. Uveitis is typically bilateral and severe. Without treatment, blindness commonly occurs because the retina is frequently affected by vasculitis with infarction, secondary venous occlusion and retinal oedema.

Infections

- Tuberculosis (TB), syphilis, toxoplasmosis, herpes simplex and herpes zoster, toxocariasis, AIDS.

Malignancy

The following conditions can mimic uveitis:

- lymphoma
- leukaemia
- ocular melanoma
- retinoblastoma

Multiple sclerosis

Treatment

Underlying systemic disease should be sought and treated as appropriate.

Anterior uveitis is treated with topical steroids to reduce the inflammation and cycloplegia, which

results in a dilated pupil to break and reduce the formation of posterior synechiae, and reduces the pain caused by ciliary spasm.

Posterior uveitis is treated according to the threat to vision and varies with the different underlying disease processes. Steroids and immunosuppression are frequently required.

Scleritis

Scleritis causes a diffusely red eye associated with severe, deep, boring pain. Systemic associations are present in 50% of patients and include the following:

- herpes zoster
- sarcoidosis
- ankylosing spondylitis
- inflammatory bowel disease
- gout
- rheumatoid arthritis
- vasculitis, eg PAN, SLE, Wegener's granulomatosis
- post-ocular surgery.

17.6 OCULAR SIDE-EFFECTS OF SYSTEMIC MEDICATION

Blurred vision is a frequently reported side-effect of medication. The following are common or sight threatening complications (this is not an exhaustive list):

- **Steroids**: systemic, local (eg to eyelids) and topical steroids can all cause ocular side-effects. Cataract is common with systemic steroids and elevated intraocular pressure, leading to glaucoma, occurs in susceptible individuals with local/topical steroids. For this reason periocular steroid creams are best avoided and patients on topical steroid should have periodic intraocular pressure assessment
- **Drugs with anticholinergic side-effects**, eg tricyclic antidepressants, atropine, hyoscine and glycopyrolate: these can precipitate angle-closure glaucoma in susceptible individuals (usually long-sighted). They are not contraindicated in those with open drainage angles
- **Amiodarone**: causes vortex keratopathy in almost all patients. Epithelial deposits are reversible on cessation of drug and usually visually inconsequential. Amiodarone has also been linked with optic neuropathy, but the association has not been conclusively established
- **Chloroquine and hydroxychloroquine**: classically cause bull's eye maculopathy as a result of the drug binding to melanin in the RPE. Chloroquine is the far more toxic drug, but toxicity is rare with a cumulative dose of <300 g. Concentric rings of hypo- and hyperpigmentation surround a central hyperpigmented area at the fovea. Fundal changes occur after subjective visual loss and may be progressive after withdrawal of the drug. Baseline near and distance acuity, colour acuity and visual fields should be established and periodically monitored throughout treatment
- **Ethambutol**: causes optic neuropathy, more frequently when used in high doses or with renal

- impairment. Presents with subjective loss of acuity, usually reversible on drug cessation. Acuity and colour vision should be monitored pre-prescription and throughout course of treatment
- **Fingolimod**: a disease-modifying agent used in demyelinating disease linked with the development of macular oedema. Presentation is with blurred central vision, with onset usually in the first few months of treatment, although some patients are asymptomatic. Those patients with diabetes or a history of uveitis are more likely to be affected.
- **Sildenafil**: a blue tinge in vision with light sensitivity occurs in some patients, thought to be due to enzymatic effect in the retina. Nonarteritic anterior ischemic optic neuropathy (NAION) leading to visual loss has been reported
- **Tamoxifen**: causes maculopathy with refractile opacities associated with mild reduction in acuity
- **Vigabatrin**: anticonvulsant used in infantile spasms and partial seizures, causes severe restriction of peripheral visual field, initially predominantly nasal, affecting approximately 30% of patients. It is thought to be GABA (γaminobutyric acid)-mediated and cumulatively dose-dependent. Males are more frequently affected. Disc pallor, retinal arteriole narrowing and abnormal pigmentation at the retina have been described. The field defects persist on cessation of treatment.

17.7 GENITO-URINARY DISEASE

17.7.1 Chlamydial conjunctivitis

Features

- Acute conjunctivitis that persists for several weeks
- Associated preauricular lymphadenopathy
- Cause of ophthalmia neonatorum: affected neonates need systemic treatment to prevent pneumonitis.

17.7.2 Gonococcal conjunctivitis

Typically causes hyperacute conjunctivitis with chemosis and lid oedema, and profuse discharge. It may be associated with corneal ulceration and risk of ocular perforation. Swab and culture reveal Gram-negative diplococci.

17.7.3 Syphilis

The ophthalmic abnormalities are related to the stage of syphilis:

- **Congenital**: interstitial keratitis – leads to corneal clouding in second decade of life, iritis, chorioretinitis and optic atrophy
- **Primary**: chancre may occur on eyelid

- **Secondary**: iritis, usually bilateral, occurs in 4% of patients with secondary syphilis; optic neuritis chorioretinitis and scleritis are all associated
- **Tertiary**: associated with optic atrophy, chorioretinitis, iritis, interstitial keratitis and Argyll Robertson pupil (bilateral small irregular pupils that react to accommodation but not light).

All patients with genito-urinary disease affecting the eye should undergo systemic assessment and treatment.

17.7.4 Herpetic disease and the eye

Herpes simplex

Most herpes simplex virus (HSV) infections are subclinical and up to 90% of adults are seropositive.

- Primary infection with HSV: this usually occurs in children and causes conjunctivitis with lid swelling. Lesions heal without scarring
- HSV reactivation: this is associated with epithelial keratitis. The corneal ulceration has a branch-like appearance, termed a 'dendritic ulcer'. Lesions may become larger, particularly if treated erroneously with topical steroids, with an amoeboid shape – called a geographic ulcer. The corneal stroma may subsequently become involved. Treatment is with topical or long-term low-dose oral antiviral agents, dependent on severity.

Herpes zoster

As this painful acute vesicular rash follows a dermatomal pattern, disease affecting the second branch of the fifth cranial nerve can affect the eye. Hutchinson's sign indicates this, when the rash affects the tip of the nose, signalling involvement of the nasociliary nerve

The eye may be affected by conjunctivitis, corneal ulceration and uveitis – often with elevated intraocular pressure, scleritis, retinitis and oculomotility deficits due to cranial nerve involvement. Treatment is with oral antiviral agents, and associated complications are treated as appropriate.

17.8 TROPICAL EYE INFECTIONS

17.8.1 Trachoma

Chlamydia trachomatis is the most common infectious cause of blindness, and the second most common cause of blindness worldwide. Trachoma affects about 21 million people, of whom about 2.2 million are visually impaired and 1.2 million blind. The disease is prevalent in Africa, Asia, the Middle East, Central and South America, and parts of Aboriginal Australia. It is readily spread by close personal contact, flies and fomites.

Active trachoma generally occurs in preschool children as a mild self-limiting conjunctivitis. With severe and prolonged infections cicatricial disease develops.

Cicatricial disease is seen in adults, women more than men, probably reflecting the fact that women spend more time with small children. With repeated infections conjunctival scarring occurs, leading

to trichiasis, such that the eyelashes abrade the cornea, damaging the epithelium, and eventually leading to corneal opacification and blindness.

17.8.2 Onchocerciasis (river blindness)

Worldwide, onchocerciasis is the second leading infectious cause of preventable blindness, with 17 million people affected, of whom three-quarters of a million have sight impairment.

It is a parasitic disease caused by the filarial nematode *Onchocerca volvulus*, transmitted by infected blackflies, which spread the larval form of the worm from host to host. As the fly develops and breeds in flowing water, onchocerciasis is commonly found along rivers, hence the term 'river blindness'. The larvae form subcutaneous nodules where they mature to adult worms, and can live for approximately 15 years. The adults release microfilariae which produce an intense inflammatory reaction when they die.

The following are the ocular signs of this:

- Conjunctivitis: first reaction to the microfiliariae
- Corneal infections and opacification
- Iritis and chorioretinitis
- Glaucoma
- Optic neuritis or optic atrophy.

17.9 MISCELLANEOUS DISORDERS

17.9.1 Thyroid eye disease

The ocular manifestations of Graves' disease may predate, coincide with or follow the systemic disease. Most patients with thyroid disease do not develop, or experience only, mild eye problems.

The classic triad includes the association of ocular changes with thyroid acropachy (pseudoclubbing) and pretibial myxedema, both of which are rare.

Thyroid eye disease (TED) is an autoimmune disorder; most patients have positive antithyroglobulin antibodies. An inflammatory reaction occurs within the orbit, resulting initially in oedema and secondary fibrosis in orbital fat and the extraocular muscles.

Features include the following:

- Lid retraction: 'staring' appearance
- Redness and irritation: due to exposure
- Proptosis: orbital fat proliferation and muscle oedema, autodecompresses orbital contents
- Periocular swelling with lid oedema
- Extraocular muscle involvement: medial and inferior recti mainly affected, often pain with eye movements
- Sight loss: secondary to corneal disease or optic nerve compression.

The following are recognised stages of TED:

- **Active phase**: occurs early and lasts 3–12 months. This is the time of maximal symptoms. Treatment depends on the severity of the condition; steroids, immunosuppression, eg with azathioprine, or radiotherapy may be required. If optic nerve compression occurs or there is severe exposure a surgical orbital decompression may be required
- **Inactive stage**: at this time fibrosis of the tissues has occurred. Orbital decompression for proptosis may be performed at this time in addition to permanent treatment for diplopia and lid malposition.

Management

- Stop smoking: smoking associated with a more severe form of disease
- Control thyroid status
- Surface abnormalities: lubricants, tape lids at night, tarsorrhaphy
- Diplopia: prism, monocular occlusion with patch, surgery after 6-month period of stability
- Optic nerve compression: urgent treatment required to decompress, with systemic steroids, radiotherapy or surgery
- Proptosis: orbital decompression may be required
- Lid surgery: to improve lid position.

17.9.2 Myotonic dystrophy

This condition is characterised by failure of relaxation of voluntary muscle fibres. It is due to trinucleotide (CTG) repeat in the dystrophia myotonica protein kinase gene on chromosome 19q. The repeat expansion is transcribed into RNA but remains untranslated. Anticipation, a worsening of clinical features over successive generations, may be due to intergenerational instability of the size of the repeat expansion, with an increase in expansion size leading to increased symptoms. It is inherited in an autosomal dominant pattern, but inheritance is usually maternal due to the increased likelihood of anticipation in maternal transmissions.

Ophthalmic features

- Ptosis, poor lid closure, orbicularis weakness
- Retinal pigmentary changes
- Presenile cataract
- Miotic pupils

17.10 OCULAR FEATURES OF THE PHAKOMATOSES

The phakomatoses are a group of disorders affecting the nervous system, skin, eye and other organs, characterised by the presence of hamartomatous lesions.

17.10.1 Sturge–Weber syndrome

Fifty per cent of patients develop glaucoma on the side ipsilateral to the cutaneous angioma. Cavernous haemangioma may be seen in the choroid.

Vascular abnormalities, affecting the visual pathways, may be associated with visual field defects.

17.10.2 Neurofibromatosis type 1

Neurofibromatosis (NF) type 1 is an autosomal dominant condition, due to a mutation on chromosome 17. Fifty per cent of cases arise sporadically. Classic features include café-au-lait patches, axillary freckling and neuromas.

Ocular features include the following

- Lisch's nodules: hamartomatous lesions on the iris
- Optic pathway gliomas (15% of patients, usually by age 7)
- Sphenoid wing dysplasia
- Plexiform neuroma of the eyelid.

17.10.3 Von Hippel–Lindau syndrome

An autosomal dominant condition with incomplete penetrance and variable expressivity, the abnormality being on the short arm of chromosome 3.

Retinal haemangiomas, in the peripheral retina or at the disc, develop bilaterally in 25% of patients and may leak, leading to exudates or a serous retinal detachment, or rupture, leading to vitreous haemorrhage. These are histologically identical to the cerebellar haemangioblastomas, which are a feature of this condition.

17.10.4 Tuberous sclerosis

Autosomal dominant condition linked to several chromosomal abnormalities; 50% are new mutations. Ocular features include retinal hamartomas and, rarely, papilloedema or sixth nerve palsy, due to increased intracranial pressure secondary to central nervous system (CNS) lesions.

17.11 SARCOIDOSIS

Twenty-five per cent of patients with this multisystem granulomatous disease develop ocular manifestations, and they are the presenting feature in up to 20% of patients.

Ocular effects

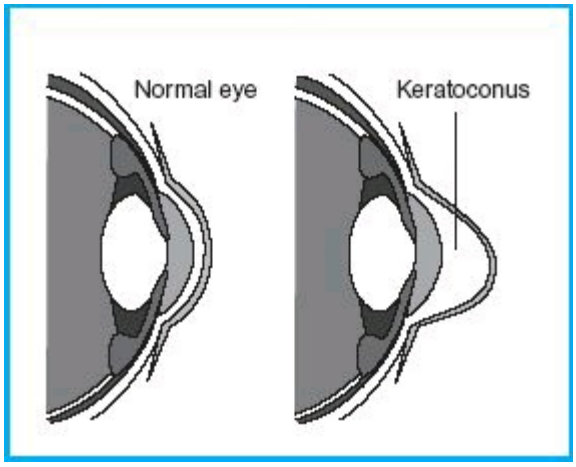
- Lids: lupus pernio, cutaneous granulomata
- Lacrimal glands: granulomatous infiltrate causes dry eye (Mikulicz syndrome when combined with parotid involvement)
- Uveitis: acute or granulomatous, frequently bilateral and complicated by glaucoma and cataract
- Posterior uveitis: chorioretinitis
- Retinal vasculitis: periphlebitis, 'candle wax exudates', haemorrhages, oedema and neovascularisation
- Optic neuropathy
- Cranial nerve palsies

17.12 KERATOCONUS

Keratoconus affects 1:2000 and causes a thinning and ectasia of the inferior paracentral cornea, producing a cone-shaped cornea (Figure 17.2) and resulting visual distortion. Onset is usually in the late teens with progressive myopic astigmatism, which initially is corrected with spectacles or hard contact lenses.

Patients with atopy and Down syndrome are predisposed to keratoconus.

Figure 17.2 Keratoconus



Corneal cross-linking, in which topical riboflavin is applied to the cornea and then activated by UV light, can be used to stabilise the condition.

In advanced disease, a corneal graft may be required, but this is only in a minority of patients.

17.13 GLAUCOMA

Glaucoma describes a group of conditions in which the intraocular pressure is sufficient to cause

visual damage with a characteristic optic neuropathy. The normal intraocular pressure is <22 mmHg, 2 standard deviations (SD) above the mean. Aqueous humour is formed by the ciliary body, behind the iris, passes through the pupil, and drains via the trabecular meshwork into the venous circulation through the episcleral venous system.

17.13.1 Acute glaucoma

- Acute glaucoma is more common in hypermetropes (long-sighted, glasses magnify the eyes to the observer)
- Presentation is usually monocular with rapid decrease in acuity, associated with severe pain and vomiting
- Mechanism is due to blockage of aqueous circulation and closure of the drainage angle, resulting in massive, rapid elevation in intraocular pressure
- Corneal oedema results in glassy appearance
- Mid-dilated fixed pupil
- Failure to reduce pressure rapidly may result in permanent visual loss.

17.13.2 Primary open-angle glaucoma

- This is the most common type of glaucoma, affecting 2% of population aged >40, with increasing incidence with advancing age. It is an insidious asymptomatic disease, more commonly seen in myopes, those with a positive family history in a first-degree relative, people with diabetes and African–Caribbean individuals
- The intraocular pressure tends to be only moderately elevated, resulting in loss of peripheral visual field; initially an arcuate scotoma progresses to generalised constriction and cupping of the optic nerve head, reflecting loss of retinal nerve fibres.

17.13.3 Secondary glaucoma

Glaucoma is a complication of almost any ocular disorder and may be classified as follows:

- **Pretrabecular**: eg fibrovascular membrane in drainage angle in rubeosis, as in diabetes or after retinal vascular occlusion
- **Trabecular**: blockage of the trabecular meshwork, eg by inflammatory cells in uveitis, blood in the anterior chamber as in traumatic hyphaema, or inflammatory meshwork oedema as in uveitis and scleritis
- **Post-trabecular**: raised episcleral venous pressure can prevent aqueous outflow, eg in caroticocavernous fistula or cavernous sinus thrombosis.

17.14 OCULAR TUMOURS

17.14.1 Primary tumours

- **Retinoblastoma**: childhood ocular tumour, inherited in 40% of cases. Prognosis is good if diagnosed and treated early
- **Choroidal melanoma** is the most common primary intraocular tumour. It presents as a unilateral lesion, which may be amelanotic or dark brown. It may be asymptomatic or affect the visual field or acuity, depending on location
- **Choroidal haemangioma** is a red–orange lesion, usually at the macula. In Sturge–Weber syndrome, the lesion may be more diffuse, resulting in a dark red fundal appearance, which may be appreciated only by comparison with the other eye.

17.14.2 Secondary tumours

The eye and orbit may be affected by metastases, and cerebral metastases may affect the eye by raising the intraocular pressure (IOP), affecting the visual pathway or causing oculomotility disorders.

Choroidal metastases: the most common primary sites are the breast, bronchus and kidney. Lesions, which are pale and minimally elevated, are frequently multiple and bilateral and associated with metastatic disease elsewhere. Symptoms are dependent on the site of the lesion, but macular lesions are most common and can cause marked visual loss. External beam radiation can result in successful palliation.

17.15 CERTIFICATE OF SIGHT IMPAIRMENT

Two levels of sight impairment are recognised. Registration as visually impaired can facilitate rehabilitation and social service support.

Monocular visual loss does not qualify the patient for registration.

- **Sight impairment**: acuity ≤6/24 in both eyes, or significant loss of visual field such as hemianopia
- **Severe sight impairment**: acuity <3/60 in both eyes

17.15.1 Visual standards for driving

The Department for Transport sets driving standards policy, and this policy is applied by the Driver and Vehicle Licensing Authority (DVLA). Drivers are legally obliged to inform the DVLA if they fail to reach the expected standards.

For a standard group 1 licence, for a car driver, the DVLA acuity requirement is to read a car number plate, with spectacles if worn, at 20 m, which equates to a binocular of 6/12. This is an absolute requirement.

The patient must have a visual field of 120° horizontally, with a minimum of 50° on either side of fixation and a vertical field of 20° above and below fixation.

If a driver develops a stable, barring field defect, he or she may be able to apply to be granted a

licence in exceptional circumstances. The defect must be one of the following:

- Present for 12 months
- Caused by an isolated event or non-progressive condition
- There must be no other condition or pathology present, which is regarded as progressive and likely to be affecting the visual field.

There must also be clinical confirmation of full functional adaptation.

Chapter 18
Psychiatry

CONTENTS

Psychiatry

18.1 SCHIZOPHRENIA

Schizophrenia is characterised by disturbances of thought, perception, mood and personality. These lead to 'positive' symptoms, such as delusions, hallucinations, and disorganisation of thoughts and speech, and 'negative' symptoms, including decreased motivation, poor self-care and social withdrawal. Patients do not have a 'split personality'. The lifetime risk is about 1% for men and women, although men consistently have an earlier age of onset. There is strong evidence of genetic predisposition, but not through a simple Mendelian model of inheritance (Table 18.1).

Schizophrenia is a heterogeneous condition; signs and symptoms vary greatly between individuals. Diagnostic criteria such as the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-V) and the *International Classification of Disease*, 10th revision (ICD-10) are based on core features.

18.1.1 First-rank symptoms

Originally described by Schneider, these represent an attempt to identify symptoms that occur exclusively in schizophrenia and tighten diagnostic practice. In clinical practice they occur in approximately 70% of people with schizophrenia and approximately 10% of people with mania. However, for the purpose of medical examinations, including the MRCP, they *should* be considered to be 'diagnostic of' or 'characteristic of' schizophrenia in the absence of obvious organic brain disease. A mnemonic for first-rank symptoms follows.

Table 18.1 Lifetime risk of schizophrenia in relatives of patients with schizophrenia

Relationship	Percentage with schizophrenia
Monozygotic twin	50
Children (both parents schizophrenic)	46
Children	13
Dizygotic twin	10
Sibling	10
Uncles/aunts	3
Unrelated	0.9

First-rank symptoms mnemonic: ATPD – aim to pass definitely

Auditory hallucinations of a specific type:

- Third person (ie two or more voices heard discussing the patient)
- Running commentary
- Thought echo

Thought disorder of a specific type (passivity of thought):

- Thought withdrawal
- Thought insertion
- Thought broadcasting

Passivity experiences (delusions of control):

- Actions/feelings/impulses under external control
- Bodily sensations being due to external influence

Delusional perception (two-stage process):

- Normal perception of commonplace object/sight, leads to:
- Sudden, intense, self-referential delusion (eg finding coin on the ground leads to belief of messianic role)

There are many other important clinical features of schizophrenia, including impaired insight, suspiciousness, flat/blunted or incongruous affect, decreased spontaneous speech, general lack of motivation and poor self-care, and abnormalities of motor activity such as dyskinesia and catatonia.

Auditory hallucinations that are not of the type covered by the first-rank symptoms may occur, as can other types of delusions, often bizarre and non-mood congruent. These symptoms can be divided into two categories, as follows.

Positive symptoms

These include delusions, hallucinations and disorder of the form of thought. Temporal lobe epilepsy is one important differential diagnosis that should be considered in individuals who experience positive symptoms and hence an EEG may be useful in certain patients.

Negative symptoms

These include flat/blunted affect, decreased motor activity and speech, and poor motivation and selfcare. Patients with schizophrenia who manifest predominantly negative symptoms often have frontal cognitive deficits in attention and executive function (planning, goal-directed behaviour and monitoring of performance). CT and/or MRI studies of the brain in such patients have shown ventricular enlargement and cortical sulcal prominence.

18.1.2 Medical co-morbidities

People with schizophrenia have standardised all-cause mortality rates two to three times that of the general population. Suicide accounts for the highest relative risk of mortality compared with the general population, but cardiovascular disease is the most common cause of death. The prevalence of smoking, dyslipidaemia, diabetes, hypertension, obesity and metabolic syndrome are all increased in schizophrenia, and these risk factors are present at a younger age. This risk is mediated by unhealthy lifestyle and medication. First-generation antipsychotics are associated with weight gain whereas second-generation antipsychotics or 'atypicals' increase the risk of metabolic syndrome, diabetes and dyslipidaemia.

18.1.3 Principles of treatment

Treatment of schizophrenia is based on the biopsychosocial model and compliance with medication is the best predictor of relapse.

Biological treatments

- **Second-generation 'atypical' antipsychotics** (eg clozapine, olanzapine, risperidone) are now considered to be first-line therapeutic agents. Use of **first-generation 'traditional' antipsychotics** (chlorpromazine, haloperidol, trifluoperazine, etc) is limited by extrapyramidal (tardive dyskinesia occurs in >30% of patients on longterm treatment) and cardiac side-effects (prolonged Q–T interval). Antipsychotics may be given orally, intramuscularly (im) or depot im; depot preparations aid compliance and are now available in atypical form (risperidone). 'Positive' symptoms respond better than 'negative' symptoms to antipsychotic therapy. There is no convincing evidence for clinical effectiveness of second- over first-generation antipsychotics. Second-generation antipsychotics have lower risk of extrapyramidal syndrome, may be better for negative symptoms, but have a greater propensity for metabolic side-effects. **Electroconvulsive therapy** (ECT) may be needed for catatonic stupor
- **Psychological treatments**: a number of trials have shown that cognitive–behavioural therapy (CBT) is a valuable adjunctive treatment for patients with persistent hallucinations and delusions; it can also aid compliance
- **Social interventions**: these should target accommodation, finances and daytime activities. Patients and relatives may both benefit from supportive psychotherapy, counselling and educational interventions such as problem-solving and crisis management. Intervention by specialist teams for young people with first-episode psychotic illness is vital in improving prognosis.

Predictors of long-term outcome

Lack of insight, long duration of untreated psychosis, substance misuse and poor response to early treatment predict poorer outcomes.

18.2 MOOD DISORDERS

Mood (affective) disorders are conditions in which a pathologically depressed or elated mood is the core feature. Depression is much more common than mania. Bipolar disorder has high heritability associated with multiple loci for genetic susceptibility.

18.2.1 Hypomania/mania (bipolar affective disorder)

Hypomania and mania are mood disorders characterised by pathologically elated or irritable mood. Lifetime prevalence is about 1% with a slight female predominance. Hypomania is a less severe form of mania – psychotic symptoms are absent. The majority of symptoms in both are 'mood congruent', ie understandable in the context of the pathological mood change. In mania there is usually a previous episode of depression or this is highly likely to occur in the future, hence hypomania/mania is part of a bipolar affective disorder. The main differential diagnoses are usually organic psychoses or schizophrenia. The clinical features of hypomania/mania are listed in the box.

Clinical features of hypomania/mania

- **Mood**
  - Predominantly elevated/elated or irritable
  - Expansive (but note transient depression common)
- **Speech and thoughts**
  - Pressured (fast)
  - Flight of ideas
  - Inflated self-esteem/grandiosity
  - Over-optimistic ideas
  - Poor attention, concentration
- **Behaviour**
  - Insomnia
  - Overactivity
  - Loss of normal social inhibitions: overfamiliar, sexual promiscuity, risk-taking, overspending
  - Increased libido, sexual disinhibition
  - Increased appetite, decreased weight
- **Psychotic symptoms (mania)**
  - Mood congruent (eg delusions of special ability or status, grandiose delusions or auditory hallucinations)

Perhaps the most crucial decision to make in the management of bipolar disorder is the timing of the introduction of long-term prophylactic, mood-stabilising medication (typically lithium or anticonvulsants). This is a matter of clinical judgement, but these drugs should be considered if there have been two or more acute episodes or if there has been a manic episode with significant risk.

Lithium is the most commonly prescribed mood stabiliser and it is particularly important to remember its therapeutic window. (See Chapter 2, Clinical pharmacology, toxicology and poisoning.)

Biological/physical treatments of hypomania/mania

- **Short-term, acute episode**
  - Stop antidepressants
  - Antipsychotics: if symptoms are severe and behaviour is disturbed (olanzapine is licensed for the treatment of acute mania)
  - Benzodiazepines (short course only)
  - Lithium (plasma level 1.0 mmol/L)
  - ECT: for prolonged or severe manic episode
- **Long-term, prophylaxis**
  - Lithium (plasma level 0.5 mmol/l): check levels after the first 5–7 days
  - Carbamazepine (in patients unresponsive to lithium, particularly 'rapid cyclers': more than four episodes per year)
  - Valproic acid, lamotrigine (effective where depressive episodes predominate)
  - Depot antipsychotics: if poor adherence
  - If frequent relapse or continuing severe functional impairment, consider combination of two of lithium, valproic acid and olanzapine

18.2.2 Depression

Depression occurs with a wide range of severity and has a multifactorial aetiology. Lifetime incidence of depression varies from 1% to 20% according to severity. Evidence for a genetic contribution is most compelling in the most severe illness, whereas mild and moderate depression are usually best explained by psychosocial models. These latter disorders are rarely treated by psychiatrists unless they are complicated by co-morbidity with substance misuse or personality disorder. The variation in severity and symptomatology of depression has led to a number of classification systems:

- Endogenous versus reactive (more closely related to precipitating life events)
- Melancholic versus neurotic
- Unipolar (depression only) versus bipolar (depression with mania).

Clinical features of depression

Most diagnostic criteria require at least 2 weeks of symptoms. 'Biological' symptoms (shown in italics) are especially important because their presence predicts response to physical treatments. They are also known as 'somatic', 'endogenous' or 'melancholic' symptoms:

- **Mood**
  - Loss of reactivity
  - *Diurnal variation (worse in am)*
  - Pervasively lowered
  - Variable anxiety (common)/irritability
- **Speech and thoughts**
  - Slowed speech, low volume
  - Reduced attention/concentration
  - Reduced self-esteem
  - Reduced confidence
  - Ideas of guilt, worthlessness, hopelessness
  - Bleak, pessimistic outlook
  - Ideas and acts of self-harm
- **Behaviour**
  - *Insomnia (early morning wakening)*
  - *Psychomotor agitation or retardation*
  - *Reduced libido*
  - *Loss of enjoyment (anhedonia)*
  - *Decreased appetite*
  - *Weight loss*
  - Decreased social interactions
  - Reduced energy/increased fatigue
  - Decreased activity
- **Psychotic symptoms**
  - Occur in severe depression
  - Mood congruent
  - Delusions of guilt, physical illness
  - Auditory hallucinations with derogatory content

18.2.3 Depression in older people

Depression is common in later life but often missed. This is in part due to the prejudice that depression is an inevitable consequence of increasing age, but also because older patients tend to present less with depressed mood and more with physical complaints. It is likely to be associated with social isolation, bereavement, financial problems or being in a care home. Prevalence is increased by disorders such as dementia, Parkinson's disease, stroke, diabetes, pain and disability. Physical symptoms appear to be more common in older people, including hypochondriasis, insomnia and psychomotor disturbances. Agitation is frequent but stupor may occur. Cognitive deficits

secondary to depression may mimic dementia (see below).

18.2.4 Differentiation of depression from dementia

The cognitive impairment seen in severe depression, sometimes called depressive pseudodementia, can lead to a misdiagnosis of primary dementia, particularly in older people. Conversely, it is important to recognise that organic dementia often presents with depressive symptoms in the early stages.

Table 18.2 details differentiating clinical features of depression and dementia

18.2.5 Principles of treatment

Treatments in depression target the biological, psychological and social aetiologies. If biological symptoms are present then physical treatments are indicated, whatever the apparent psychosocial precipitants. (See also Section 18.11, Treatments in psychiatry.)

Table 18.2 Clinical features of depression and dementia

Clinical features	Depression	Dementia
Family history	Affective disorder	Alzheimer's disease (in some)
Illness duration	Short	Long
Progression	Rapid	Slow
History of previous depression	Yes	No
Biological symptoms of depression	Present	Absent
With poor memory	No	Yes
History given	Detailed	Vague
Effort at testing	Poor	Good
Response at test results	Picks on faults	Pleased
Other behaviour	Contrary	Compatible
Examination of concentration/attention	Variable	Consistently poor
Orientation tests	'Don't know'	Poor
Memory loss	Global	Recent
Primitive reflexes	Absent	Present
Apraxias	Absent	Present
Word intrusions	Corrects	Unaware
Neuropsychological tests:		
Test performance	Variable	Always poor
Pattern	Nil-specific	Verbal IQ > performance IQ

Treatment of depression

- **Biological treatments**
  - Antidepressants: for moderate-to-severe depression. Selective serotonin reuptake inhibitors (SSRIs such as citalopram or sertraline) should be considered first line (safer in overdose and better tolerated than other classes). Second-line choices include mirtazapine and venlafaxine
  - Lithium (for augmentation of antidepressant effect, long-term prophylaxis or in treatment-resistant illness)
  - ECT (for severe or resistant depression)
  - Antipsychotics (if psychotic symptoms present)
  - Thyroid hormone (triiodothyronine or T_3; augmentation therapy in resistant depression)
- **Psychological treatments**
  - Computerised cognitive–behavioural therapy (CBT) and guided self-help in mild cases
  - Cognitive therapy: for mild-to-moderate depression
  - Supportive psychotherapy/counselling
- **Social interventions**
  - Accommodation, finances, daytime activities

Additional considerations for treatment of depression in older people

Again, a biopsychosocial model is used:

- **Biological**: **SSRIs** are used first line and are better tolerated than tricyclic antidepressants but increase the risk of gastrointestinal (GI) bleeds and hyponatraemia. Sertraline inhibits cytochrome P450 less; citalopram may prolong the Q–T interval. **ECT** may be used in severe illness
- **Psychological**: CBT, problem-solving therapy
- **Social**: decrease isolation, befriending, structured activities, exercise, day centres

18.3 ANXIETY DISORDERS

18.3.1 Generalised anxiety disorder

The clinical features of generalised anxiety disorder are persistent and generalised, occurring across a range of daily circumstances. Patients never completely return to a baseline level of zero anxiety. Anxiety affects 1–5% of the population (more common in females) and commonly coexists with other psychiatric problems, particularly mood disorders. Organic causes of anxiety disorder include drugs (eg caffeine) and thyrotoxicosis.

Cognitive symptoms

- Apprehension
- Fear of death, losing control or going mad
- Hypervigilance.

Somatic symptoms (associated with autonomic hyperarousal)

- Palpitations
- Shortness of breath and hyperventilation
- Butterflies in the stomach, nausea, loose bowel motions
- Urinary frequency
- Muscle tension
- Headaches, dizziness, light-headedness, tingling in fingers and around mouth.

Treatment of anxiety disorders

- **Psychological**: should be first-line treatment; CBT (challenges dysfunctional thoughts and processes) and anxiety management (structured education, relaxation training), guided self-help and computerised therapy in mild cases

  Biological: specific SSRI antidepressants have been shown to be especially useful.
- Benzodiazepines (with care), β blockers, buspirone (5-HT_{1A} partial agonist) and tricyclic antidepressants are also used in the short term.

18.3.2 Panic disorder

These patients have paroxysms of intense unpredictable recurring anxiety (panic) interspersed with periods of complete remission. Typical attacks last several minutes and occur without situational cues. Somatic symptoms are prominent. Patients may develop an anticipatory fear of the next attack.

CBT should be the first-line treatment, then SSRIs or, if ineffective, imipramine or clomipramine. Benzodiazepines should be used short term and with care.

18.3.3 Phobic disorders

These patients have intense anxiety which is reliably precipitated by a situational cue. The fear that they experience is out of proportion to the situation and cannot be reasoned or explained away. This results in the avoidance of the feared situation and related situations and this, in turn, further reinforces the phobia.

Specific/simple phobias include fear of flying, heights, animals, etc. Agoraphobia is anxiety about being in places or situations from which escape may be difficult, eg in crowds, on public transport, on a bridge. Social phobia is a persistent fear of humiliation or embarrassment in social situations.

Treatment of specific phobias

- For specific phobias, behavioural therapy, ie graded exposure treatments, systematic desensitisation (controlled exposure to the feared situation), flooding and modelling are the most effective and should be used first line
- Appropriate physical treatments include SSRIs, β blockers and occasionally short-term use of benzodiazepines 'with care'
- Psychotherapy: supportive or psychodynamic may be useful in a minority of cases (see Section 18.11.5, The psychotherapies).

18.3.4 Post-traumatic stress disorder

This develops following a stressful or exceptionally traumatic event. Often symptoms appear immediately but these may be delayed by years in up to 15% of people. The following symptoms are typically associated with post-traumatic stress disorder (PTSD):

- Re-experiencing: flashbacks, nightmares, repetitive and intrusive memories and thoughts
- Avoidance: of people or situations associated with the event
- Hyperarousal: hypervigilance, sleep problems, irritability, difficulty concentrating, exaggerated startle response
- Emotional numbing: feeling detached from others, unable to experience feelings.

PTSD is commonly associated with depression, anger, substance misuse and higher risk of suicide. Those particularly at risk include children, staff involved in major disasters and refugees.

Treatment of PTSD

Routine debriefing straight after the event is not effective.

- **Psychological**: CBT and supportive counselling are first-line treatments
- **Biological**: paroxetine or mirtazapine if CBT is not desired or effective. Hypnotics should be used only short term.

18.4 OBSESSIVE COMPULSIVE DISORDER

Obsessive–compulsive disorder may also be called obsessional illness, or obsessional neurosis. Mild obsessional symptoms are very common and may actually be helpful for certain occupations (eg accountancy and medicine). Pathologically severe symptoms may be secondary to other psychiatric or neuropsychiatric disorders (see below). The lifetime prevalence of primary obsessive–compulsive disorder is between 2% and 3%, with a slight excess of females affected. It is widely considered to be a neurobiological disorder associated with inadequate serotonin regulation.

Obsessions are the following ideas, thoughts (ruminations) or images:

- Recurrent
- Persistent and intrusive
- Occurring against the patient's will

- Regarded as absurd, but insight is maintained
- Recognised as a product of the patient's own mind (in contrast to psychosis, the patient recognises that thoughts are abnormal)
- Resisted → anxiety.

Compulsions are:

- Irresistible impulses to carry out a particular activity
- Usually triggered by an obsessional thought (with the belief that the compulsion will 'neutralise' the thought and thus lower anxiety levels).

OBSESSION → COMPULSION → RITUAL

hands dirty must wash hands washing

Compulsions and ritualised behaviours are sometimes referred to together as 'compulsions'. There is a large overlap with depressive disorder, and the two conditions often coexist:

- 30% of patients with obsessive–compulsive disorder have associated depression
- 25% of patients with depression develop obsessions.

Other associations include:

- Schizophrenia (3–5%)
- Anorexia nervosa
- Organic brain disease: frontal lobe syndromes, Sydenham's chorea, Gilles de la Tourette syndrome (obsessional symptoms in 11–80%).

Treatment of obsessive–compulsive disorders

- **Psychological**: used first line and in mild cases, CBT, which includes habituation training and thought stopping (for obsessions), and exposure with response prevention (for compulsions)
- **Biological**: in moderate disease, SSRIs or clomipramine (to increase 5HT neurotransmission) combined with CBT. Antipsychotic augmentation can be used if the patient is resistant to SSRIs alone. Very rarely psychosurgery may be effective for the extremely disabled patient.

18.5 UNEXPLAINED PHYSICAL SYMPTOMS

Within a general hospital or general practice setting psychiatric referral may occur because no organic cause is found for physical symptoms. Somatic symptoms may be a manifestation of depression, anxiety or schizophrenia (rare), and these diagnoses should be excluded before a diagnosis of somatoform, conversion or factitious disorder is made.

18.5.1 Somatoform disorders

In this group of disorders there is repeated presentation of physical symptoms accompanied by persistent requests for medical investigations. If physical disorders are present, they do not explain

the nature or extent of symptoms. Repeated negative findings and reassurance have little effect and patients usually refute the possibility of psychological causation. In somatisation disorder the emphasis is on particular **symptoms** (eg back pain); in hypochondriacal disorder, patients believe they have a specific **disease** (eg cancer).

Somatisation disorder

- More than 2 years of **multiple physical** *symptoms* without adequate explanation
- Persistent refusal to accept advice or reassurance that there is no physical explanation
- Functional impairment due to the nature of symptoms and resultant behaviour
- Affects women much more often than men
- Is accompanied by a tendency to excessive drug use.

Particularly common symptoms include gastrointestinal symptoms (pain, belching, vomiting, nausea), abnormal skin sensations (itching, burning, tingling), and sexual and menstrual complaints.

Hypochondriacal disorder

- Persistent belief in presence of at least one **specific serious physical** *disease* despite repeated negative investigations
- Typical illnesses include cancer, AIDS
- Persistent refusal to accept advice or reassurance
- Fear of drugs and side-effects.

The principles of treatment for somatoform disorders are to be empathetic, encourage the person to take an active role in his or her own care, exclude an organic basis for the complaint, acknowledge that the symptoms exist, educate the patient about basic physiology, and elicit and challenge the assumptions arising from the symptoms. Self-monitoring (by keeping a diary) can assist with the reattribution of physical experiences.

Treatment of somatoform disorders

- CBT: first-line treatment
- Psychotherapy: detection of the underlying conflict (may require hypnosis/abreaction)
- Antidepressants.

18.5.2 Conversion disorder

This is a **rare** cause of unexplained physical symptoms, often resembling serious neurological disorder. The theory is that intolerable psychic anxiety is **unconsciously** 'converted' to physical symptoms. The extent of 'motivation' or voluntary control is usually hard to assess, but there is a clear alteration or loss in physical function which is usually acute, but may be chronic.

Such 'psychogenic' symptoms usually follow an unresolved stressful event and their existence may lead to a reduction in psychological distress ('primary gain') and a resolution of the stressful event. Although some patients experience the 'secondary gain' of attention from others, others may be

indifferent to their loss of function ('la belle indifference'). Isolated conversion symptoms may be associated with schizophrenia or depression.

Convincing evidence of psychological causation may be difficult to find. It is vital to exercise caution in making a diagnosis of conversion disorder, especially in the presence of a known central nervous system (CNS) or peripheral nervous system disorder.

18.5.3 Factitious disorder

Also known as Munchausen syndrome, this is the **intentional** production of physical or psychological symptoms. It is usually associated with severe personality disorder and treatment is extremely difficult.

18.6 EATING DISORDERS

Anorexia nervosa and bulimia nervosa share many clinical features (Figure 18.1 and Table 18.3) and patients may satisfy criteria for anorexia or bulimia at different stages of their illness. Eating disorders are much more common in women, but 5–10% of cases of anorexia are male. They are frequently undiagnosed and many such patients are not known to the health-care system.

Anorexia nervosa is largely restricted to social groups in which thinness is coveted. Presentation is usually in adolescence and associated with childhood negative self-evaluation and perfectionism. The long-term outcome is poor, with only 20% making a full recovery, and the long-term mortality rate is around 15–20%; it has the highest mortality of any psychiatric disorder.

Figure 18.1 A schematic representation of the relationship between anorexia nervosa and bulimia nervosa. In clinical practice a diagnosis of bulimia is restricted to those with greater than average body weight. Those in the overlap are considered to have anorexia, bulimic subtype

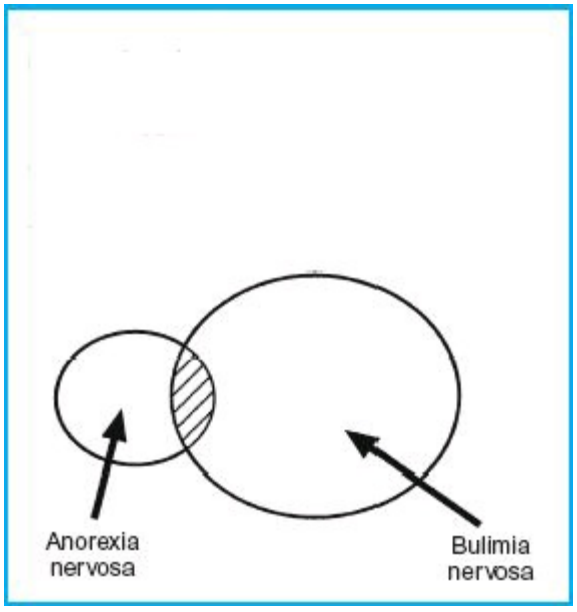


Table 18.3 Differentiation of eating disorders

	Anorexia nervosa	Anorexia nervosa	Bulimia nervosa

	(restricting subtype)	(bulimic subtype)	
'Nervosa' psychopathology	Yes	Yes	Yes
Behaviour to control weight	Yes	Yes	Yes
Bulimic episodes	No	Yes	Yes
Low weight (<15% average body weight)	Yes	Yes	No
Amenorrhoea	Yes	Yes	Possible

Bulimia nervosa has a prevalence in young women of 1–2% and usually presents in the 20s. About a third of patients have a previous history of anorexia. The outcome is highly variable but is worse if there is preceding anorexia or the bulimia is part of a multi-impulsive personality disorder. People with bulimia are more likely to die from suicide.

18.6.1 Anorexia nervosa and bulimia nervosa: diagnostic criteria

The diagnostic criteria of anorexia nervosa are shown in Table 18.4.

Table 18.4 Diagnostic criteria of anorexia nervosa

Loss of (>15%) normal body weight (BMI <17.5 kg/m^2) which is self-induced:	Extreme avoidance of foods considered 'fattening' Aggravated by self-induced vomiting, purging or exercise
A specific psychopathology ('nervosa'):	Overvalued idea that fatness is a dreadful state Extremely harsh definition of fatness Will not let weight rise above very low threshold
Specific endocrine associations: Female	Amenorrhoea Delayed puberty if very young (primary amenorrhoea)
Male	Loss of sexual interest and potency Delayed puberty if very young; arrest of secondary sexual characteristics

Bulimia nervosa: diagnostic criteria

Key features:

- Episodes of binge eating
- Persistent preoccupation with eating
- Irresistible craving for food.

Attempts to counteract the 'fattening' effects of food

- Self-induced vomiting
- Periods of starvation
- Purgative and diuretic abuse
- Abuse of appetite suppressants
- Abuse of thyroid hormones
- Neglect to use insulin (diabetics)

Specific psychopathology ('nervosa')

- Morbid fear of fatness
- Sharply defined weight threshold
- Earlier episode of anorexia nervosa

18.6.2 Medical complications of anorexia nervosa

The medical complications of anorexia nervosa are mostly physiological adaptations to starvation and usually regress with refeeding (Table 18.5).

Table 18.5 Medical complications of anorexia nervosa

Cardiovascular	Bradycardia (87%) Hypotension (85%) Ventricular arrhythmias ECG abnormalities (including increased QT/RR slope) Congestive cardiac failure and cardiomyopathy
Gastroenterological	Eroded dental enamel/caries (secondary to vomiting) Enlarged salivary glands (secondary to vomiting) Oesophagitis, erosions, ulcers Oesophageal rupture Acute gastric dilatation with refeeding Decreased gastric emptying Constipation Duodenal dilatation Irritable bowel syndrome Melanosis coli (secondary to laxatives)
Renal	Decreased glomerular filtration rate Decreased concentration ability Hypokalaemic nephropathy Prerenal uraemia

Haematological	Pancytopenia Hypoplastic marrow Low plasma proteins
Musculoskeletal and skin	Early onset leads to shorter stature Osteoporosis and pathological fractures Muscle weakness and proximal myopathy Cramps Tetany Xerosis (dry scaly skin) Lanugo hair Hair loss Acne Carotinoderma: yellow–orange skin discoloration caused by increased serum carotenoids Acrocyanosis Russell's sign: calluses on the dorsum of the hand, caused by using the fingers and hands to induce vomiting
Metabolic	Hypothermia and dehydration Electrolyte disturbance (especially hypokalaemia, hyponatraemia, hypomagnesaemia) Hypercholesterolaemia and carotinaemia Hypoglycaemia and raised liver enzymes
Neurological	Reversible brain atrophy (on CT scan) Abnormal EEG and seizures
Endocrine	Low follicle-stimulating hormone (FSH), luteinising hormone (LH), oestrogens, testosterone Low triiodothyronine (T_3) Raised cortisol and positive dexamethasone suppression test Raised growth hormone (GH)

18.6.3 Principles of treatment

The principles of treatment for anorexia nervosa and bulimia nervosa are given in Table 18.6.

18.7 SELF-HARM AND SUICIDE

A good deal is known about the epidemiology of, and risk factors for, deliberate self-harm, both fatal and non-fatal. These are presented in Table 18.7. Suicide is a leading cause of life-years lost, and a decrease in the rate of suicide, particularly in patients with mental illness, has been the target of many government policies.

The incidence of completed suicide is reduced during wartime and in certain religious groups (eg

Roman Catholics). It is associated with mental illness (although most people who commit suicide have **not** had prior contact with mental health services), chronic painful illness and substance misuse. Social factors include job loss, debt, imprisonment, divorce and family breakdown. The incidence is increased in springtime among those working in high-risk occupations, such as farmers and doctors, and among those who are unemployed, and those who have a family history of suicide and have the means available to carry it out (ie weapons/drugs). People aged 35–49 have the highest suicide rate, followed by males aged >75 years.

Table 18.6 Principles of treatment for anorexia nervosa and bulimia nervosa

Biological/physical treatments	Psychological treatments
Anorexia nervosa	**Anorexia nervosa**
• Restoration of weight as an inpatient, ideally in a specialist eating disorder unit	• Supportive psychotherapy
• Drugs have a limited place in management	• Family therapy
• Enteral/parenteral nutrition is rarely indicated	• Cognitive–behavioural therapy
• Selective serotonin reuptake inhibitor (SSRI) may be useful in relapse prevention	
Bulimia nervosa	**Bulimia nervosa**
• SSRI may be useful	• Cognitive–behavioural therapy
• Reduce bingeing and self-induced vomiting	• Cognitive–analytic therapy
• Effect not related to the presence of depressive symptoms	• Self-help manuals

Table 18.7 Features of suicide and non-fatal self-harm

	Suicide	Non-fatal self-harm
Annual incidence in UK	1/10 000 (5000 total)	20–30/10 000
Sex	M:F = 3:1	F > M
Age	Young and old males	Young <35 years
Socio-economic class	I, V	IV, V
Childhood	Parental death	Broken home
Physical health	Chronic or terminal illness, handicapped, pain	Nil specific
Mental illness	Depression ~ 60% Alcoholism ~ 20%	Depression ~ 10%

	Schizophrenia 10%	
Premorbid personality	Usually well adjusted	Antisocial and borderline personality disorder
Precipitants	Guilt, hopelessness	Situational
Setting	Premeditated, alone, warnings	Impulsive, others present
Method	Drug overdose. Males use more 'violent' methods, ie hanging	Drug overdose and cutting

- Non-fatal deliberate self-harm is a strong risk factor for eventual completed suicide
- Approximately 20% of non-fatal deliberate self-harm cases repeat within 1 year
- 1–2% per year of non-fatal deliberate self-harm cases will lead to suicide within 1 year
- 10–20% eventually commit suicide.

Prevention of the above involves the identification and treatment of mental illness, increased awareness among GPs and hospital staff, and the removal of the means to commit suicide (firearms restrictions, limit sales of paracetamol, catalytic converters).

18.8 ORGANIC PSYCHIATRY

Organic brain disorders can mimic any other functional mental disorder. Features that raise the possibility of an organic disorder include acute onset, visual perceptual abnormalities (illusions or hallucinations), cognitive deficit clearly preceding other symptoms, neurological signs and fluctuating symptoms.

18.8.1 Delirium

This is also known as acute confusional state, or acute organic brain syndrome. Young and elderly people are especially vulnerable. A breakdown of the blood–brain barrier is implicated. There are multiple possible aetiologies, both intra- and extra cranial. Many of these converge in a final common pathway of profound cholinergic deficit. It occurs in 20–30% of medical inpatients and 10–50% of people who have had surgery.

Causes of acute organic brain syndrome

- **Extracranial**
  - Hypoxia (cardiac, respiratory)
  - Infection (respiratory, urinary, septicaemia)
  - Metabolic (dehydration, electrolyte imbalance, uraemia, hepatic encephalopathy, porphyria, hypoglycaemia)

- Hypovitaminosis (thiamine, B_{12})
- Endocrine (hypo/hyperthyroid, hypo/hyperparathyroid, diabetes, Addison/Cushing, hypopituitarism)
- Toxic (alcohol intoxication, alcohol withdrawal, all other illicit drugs, prescribed drugs (many), heavy metals)
- Pain
- Sensory impairment
- Sleep deprivation

- **Intracranial**
  - Trauma (head injury)
  - Infection (meningitis, encephalitis)
  - Vascular disease (transient ischaemic attack/stroke), hypersensitive encephalopathy, subarachnoid haemorrhage
  - Space-occupying lesion (tumour, abscess, subdural haemorrhage)
  - Epilepsy

Characteristic clinical features of acute organic brain syndrome

- Fluctuating disturbance of consciousness
- Disorientation
- Poor attention (can be tested with digit span)
- Memory deficits
- Disturbed behaviour, particularly agitation and wandering (especially at night)
- Mood abnormalities
- Disordered speech and thinking
- Abnormal perceptions (especially visual misperceptions and hallucinations)
- Abnormal beliefs
- Patients may be severely agitated (hyperactive delirium) or withdrawn and stuporose (hypoactive delirium)

EEG in this condition is sensitive but not specific; results may be abnormal (slowing of rhythm, low voltage trace) in the absence of clear cognitive abnormalities.

Outcomes associated with delirium are increased admission length, an increased risk of developing dementia, and complications such as falls, pressure sores and increased mortality.

Principles of treatment are:

- **Specific**: to treat cause of confusional state
- **General**: to optimise immediate environment and reduce disorientation

  Symptomatic: careful use of sedatives (haloperidol or olanzapine, started at low dose and

- increased slowly, for short time – <1 week) if necessary.

18.8.2 Dementia

Dementia is the global deterioration of higher mental functioning secondary to progressive neurodegenerative disease. Characteristic clinical features of dementia include episodic memory loss, apraxia, deterioration in self-care skills, temporal and topographical disorientation, and personality changes in the presence of clear consciousness (compare acute confusional state). Delusions, hallucinations (particularly visual hallucinations in Lewy body dementia), and agitation and aggression occur, particularly in the moderate stages before the dementia becomes severe.

Aetiology

- Alzheimer's disease approximately 50%
- Lewy body dementia approximately 20%
- Vascular dementia (multi-infarct dementia) approximately 20%
- Often, *post-mortem*, mixed pathology is found.

For differentiation of dementia from depression, see Section 18.2.4.

Table 18.8 lists the features of Alzheimer's disease and vascular dementia.

Table 18.8 Features of Alzheimer's disease and vascular dementia

Clinical feature	Alzheimer's disease	Vascular dementia
Age of onset (years)	70–90	60–80
Sex	F > M	M > F
Family history	FAD <1%	–
Aetiology	Genetic + environmental	Embolic or ischaemic
Onset	Insidious	Acute
Presenting symptoms	Cognitive	Emotional
Cognitive impairment	Diffuse	Patchy
Insight	Early loss	Preserved
Personality	Early loss	Preserved
Course of progression	Relentless	Stepwise
Focal neurological signs	Unusual	Common
Previous CVA or TIA	–	+++
Hypertension	–	+++
Associated ischaemic heart disease	–	+++
Seizures	+	+++
Most common cause of death	Infection	Ischaemic heart disease
Time to death from diagnosis (years)	2–5	4–5

CVA, cerebrovascular accident; FAD, familial Alzheimer's disease; TIA, transient ischaemic attack.

18.8.3 Physical illnesses particularly associated with mental disorders

Physical illnesses particularly associated with mental disorders

- **Neurological**
  - Parkinson's disease (depression, dementia)
  - Huntington's disease (personality change, depression, suicide, dementia)
  - Neurosyphilis (dementia, depression, grandiosity)
  - Epilepsy (depression, psychosis)
  - Multiple sclerosis (depression, elation, dementia)
  - Wilson's disease (affective disorder, aggression, cognitive impairment)
  - Prion diseases (depression, personality changes, dementia)
  - Brain tumour (location determines early symptoms)
  - Myasthenia gravis (depression)
  - Motor neuron disease (depression, dementia)
  - Cerebrovascular disease (depression, emotional lability)
  - Subdural haematoma (confusion, personality change)
- **Endocrine**
  - **Cushing syndrome**: psychiatric disturbance in about 50% of hospital cases; depression, euphoria, confusion, paranoid psychoses, cognitive dysfunction in 66%
  - **Addison's disease**: psychiatric features in virtually 100%; depression, withdrawal, apathy, memory difficulties in up to 75%
  - **Hyperthyroidism**: psychological disturbance in 100%; restlessness, agitation, confusional state (rare), psychosis (very rare)
  - **Hypothyroidism**: mental symptoms universal at presentation, lethargy, cognitive slowing, apathy > depression, irritability, confusional state, dementia, affective or schizophreniform psychosis (very rare)
  - **Phaeochromocytoma**: paroxysmal anxiety
- **Other systemic causes**
  - Systemic lupus erythematosus (SLE) (acute confusional state, affective or schizophreniform psychosis) may be further complicated by the effect of steroids
  - Vitamin deficiency (vitamin B_1: Wernicke–Korsakoff syndrome; vitamin B_{12}: acute confusional state, depression)
  - Porphyria (especially AIP): acute confusional state, depression, paranoid psychosis
  - Paraneoplastic syndrome: depression, psychosis

18.8.4 Drug-induced mental disorders

Many drugs can lead to psychiatric conditions (Table 18.9).

18.9 ALCOHOL ABUSE

The complications of alcohol are wide-ranging and cross social, psychological and neuropsychiatric domains. General medical problems are not covered here.

Alcohol dependence syndrome – seven key features

1. Sense of compulsion to drink
2. Stereotyped pattern of drinking
3. Prominent drink-seeking behaviour
4. Increased tolerance to alcohol
5. Repeated withdrawal symptoms
6. Relief drinking to avoid withdrawal symptoms
7. Reinstatement after abstinence

18.9.1 Acute withdrawal

Acute withdrawal causes a wide spectrum of symptoms. The fully developed syndrome is known as delirium tremens.

Delirium tremens

- **Definition of full syndrome**
  - Vivid hallucinations (often visual)
  - Delusions
  - Profound confusional state
  - Tremor
  - Agitation
  - Sleeplessness
  - Autonomic overactivity (including pyrexia)
- **Other clinical features**
  - Associated trauma or infection in 50%
  - Prodromal features may occur

- Onset usually after 72 hours of abstinence
- Visual illusions/hallucinations prominent
- Duration ≤3 days in majority
- Hypokalaemia common ± hypomagnesaemia
- Mortality rate up to 5%

Treatment of alcohol withdrawal

- Inpatient
- Rehydration, antibiotics, parenteral highpotency B-complex vitamins, sedation
- Sedative drugs that facilitate GABA-ergic (GABA is γ-aminobutyric acid) neurotransmission are cross-tolerant with alcohol and have anticonvulsant properties (eg a reducing dose of chlordiazepoxide is the first-line treatment (oxazepam in alcoholic liver disease) or chlormethiazole oral/intravenous (only when patient in hospital)). Phenothiazine should be avoided because of the risk of seizure. If an antipsychotic drug is required, then haloperidol should be used.

Table 18.9 Mental disorders induced by drugs

Anxiety	Depression	Psychotic symptoms
Amphetamines	Reserpine	Amphetamines (including MDMA, 'Ecstasy')
Cocaine	β blockers	Lysergic acid diethylamide (LSD)
Alcohol	Calcium antagonists	Cocaine
Phencyclidine (PCP)	Oral contraceptive pill	Marijuana
Caffeine	Corticosteroids	L-Dopa
	Alcohol	Anticholinergic drugs
	Furosemide	Anabolic steroids
		PCP
		Mefloquine

Relapse prevention and maintaining abstinence (outpatient)

- **Pharmacological**: disulfiram, acamprosate
- **Psychosocial**: essential to maintain abstinence, group therapy and support, ie Alcoholics Anonymous, '12-step programme' (specific principles guiding action for recovery from addiction).

18.9.2 Social consequences of alcohol abuse

- Family/marital problems (including incest)
- Absenteeism from work
- Accidents (major factor in ≥10% of road traffic accidents)
- Crime (associated with acute abuse)
- Vagrancy.

18.9.3 Psychological consequences of alcohol abuse

Alcohol abuse commonly occurs secondary to other psychiatric illnesses, particularly bipolar disorder, depression, anxiety and PTSD; this may be 'selfmedication'. Other consequences of alcohol abuse include dysphoric mood, pathological jealousy (Othello's syndrome) and sexual problems (impotence, decreased libido). Other symptoms are alcoholic hallucinosis and alcohol dependence syndrome.

Suicide is more common amongst this group (16% with full dependence syndrome) as is parasuicide (alcohol is used acutely in 35% of suicide attempts).

18.9.4 Neuropsychiatric consequences of alcohol abuse

The most likely neuropsychiatric consequences of alcohol abuse are Wernicke's encephalopathy and Korsakoff syndrome/psychosis. This group is also more likely to have seizures, head injury and dementia.

Rarer conditions associated with alcohol abuse include cerebellar degeneration, central pontine myelinosis and Marchiafava–Bignami disease (demyelination of the corpus callosum, optic tracts and cerebral peduncles).

Wernicke's encephalopathy (WE)

A disorder of acute onset featuring the following:

- Nystagmus
- Abducens and conjugate gaze palsies (96%)
- Ataxia of gait (87%)
- Global confusional state (90%)
- Hypothermia and hypotension.

Note: the 'classic triad' (ocular signs, ataxia and confusional state) of symptoms is not always present.

It is caused by thiamine deficiency, most commonly secondary to alcoholism, but more rarely due to one of the following:

- Carcinoma of the stomach
- Toxaemia
- Pregnancy

- Persistent vomiting
- Dietary deficiency.

Pathology

- **Macroscopic**: petechial haemorrhages
- **Microscopic**: dilatation and proliferation of capillaries, small haemorrhages, pale staining parenchyma, reactive change in astrocytes and microglia, neurones relatively spared.

Structures affected

- Mammillary bodies
- Walls of third ventricle
- Floor of fourth ventricle
- Periaqueductal grey matter
- Certain thalamic nuclei: medial dorsal, anteromedial, pulvinar
- Brainstem
- Cerebellum anterior lobe/vermis
- Cortical lesions rarely seen.

Treatment
Parenteral thiamine. Up to 80% of sufferers go on to develop Korsakoff syndrome.

Korsakoff syndrome

A marked memory disorder with good preservation of other cognitive functions.

Clinical features

- Chronic disorder usually following Wernicke's encephalopathy
- Inability to consolidate new information
- Retrograde amnesia of days/years
- Patchy preservation of long-term memory
- Confabulation: not complaints of poor memory
- Apathy
- Lack of insight

Pathology
As for Wernicke's encephalopathy.

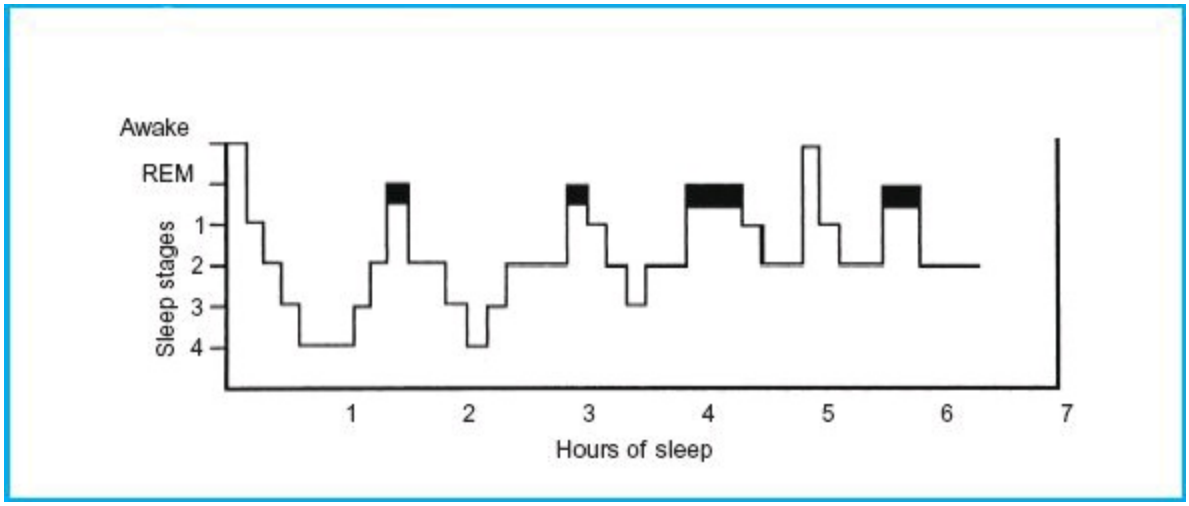
Treatment
Thiamine. There may be a response in only 20% of sufferers.

18.10 SLEEP DISORDERS

18.10.1 Normal sleep

In normal sleep, drowsiness first gives way to increasingly deep non-REM (rapid eye movement) sleep. The first REM period occurs after 50–90 minutes and lasts for 5–10 minutes. The cycle repeats at approximately 90-minute intervals so that there are four to six REM periods each night. In total, REM occupies 20–25% of a night's sleep (Figure 18.2).

Figure 18.2 Pictorial representation of the adult sleep cycle. Shaded areas indicate rapid eye movement (REM) sleep



- **REM sleep**
  - Asynchronous, mixed-frequency EEG
  - Bursts of rapid conjugate eye movements
  - Prominent autonomic changes – increased heart rate, blood pressure – penile tumescence
  - Decreased muscle tone
  - Extensor plantar responses may occur
- **Non-REM sleep**
  - EEG synchronous, with sleep spindles, K-complexes, generalised slowing with delta waves
  - Four stages recognised: stages 3 and 4 characterised as 'slow-wave' sleep

18.10.2 Insomnia

Insomnia is seen in a wide range of psychiatric and medical disorders. Psychiatric disorders may account for up to 36% of patients with insomnia. Paradoxically, sleep deprivation may be used to treat depression and may precipitate mania.

Table 18.10 describes the pattern of insomnia in various disorders.

18.10.3 Narcolepsy

Narcolepsy is a condition that is often undiagnosed. Typically, onset is between the ages of 10 and 20, and the increased risk in a first-degree relative is × 40. The syndrome of narcolepsy comprises **excessive daytime somnolence** and **cataplexy** (sudden loss of muscle tone leading to collapse); cataplexy occurs in response to an emotional stimulus (eg laughing, crying) and is pathognomonic of the disease.

- Hypersomnolence 100%
- Cataplexy 90%
- HLA-DR2 positive 99%
- Major affective disorder or personality problems 50%
- Sleep paralysis 40%
- Hypnagogic hallucinations (auditory hallucinations while dropping off to sleep) 30%
- Physical associations: obesity, insulin-resistant diabetes, hypotension, reduced food intake

In narcolepsy, REM sleep occurs at the **onset** of nocturnal sleep. Daytime attacks also consist of periods of REM sleep occurring out of context.

18.11 TREATMENTS IN PSYCHIATRY

18.11.1 Antipsychotics

Antipsychotics are indicated in schizophrenia, mania, other paranoid psychoses and psychotic depression. Atypical 'second-generation' antipsychotics have preferable side-effect profiles, are now used as first-line treatment in schizophrenia and are more effective in treating negative symptoms.

Antipsychotics are most effective against the 'positive' symptoms of schizophrenia. They have an immediate sedative action but the antipsychotic action may be delayed for 3 weeks. They play an important role in preventing relapse. Antipsychotics are sometimes used as sedatives in other conditions but should be used with caution, especially in older people or those with dementia, particularly Lewy body disease, because they increase the risk of transient ischaemic attacks (TIAs), stroke and mortality.

Table 18.10 Mental disorders and sleep disturbance

Disorder	Pattern of insomnia
Major depression	Initial (early morning waking) and late insomnia in up to 80%
Mania	Globally reduced sleep
Generalised anxiety disorder	Initial and middle insomnia
Post-traumatic stress disorder	Intrusive nightmares about trauma

Acute confusional state	Disturbed sleep cycle

Clozapine is effective in treatment-resistant schizophrenia and severe tardive dyskinesia. However, there is increasing evidence that the atypical antipsychotics clozapine, olanzapine and, to a lesser extent, risperidone are linked to hyperglycaemia, impaired glucose tolerance and occasionally to fatal diabetic ketoacidosis.

Table 18.11 gives examples of the different classes of antipsychotic drugs and their side-effects.

Table 18.11 Side-effects of antipsychotic drugs

Class	Example	Side-effects
Atypical antipsychotics (highly selective blockade of mesolimbic D_2 receptors and serotonin ($5HT_{2A}$) receptors)	Sulpiride/ amisulpride Olanzapine	Hyperprolactinaemia Weight gain, impaired glucose tolerance, dyslipidemia
	Risperidone	Nausea, dyspepsia, hyperprolactinaemia Blood dyscrasias: eosinophilia, neutropenia (3%), agranulocytosis (1%); tachycardia, fatal myocarditis and cardiomyopathy, Hypersalivation, impaired glucose tolerance
	Clozapine (also α_1 receptor antagonist)	
Typical antipsychotics (D_2 receptor antagonists of the mesolimbic, tuberoinfundibular and nigrostriatal systems)		All of the following side-effects can be seen with each of the three classes of typical antipsychotic drugs:
Phenothiazines	Chlorpromazine, thioridazine	**Extrapyramidal:** acute dystonia, parkinsonism, akathisia, tardive dyskinesia **Anticholinergic:** dry mouth, constipation, etc **Antiadrenergic:** postural hypotension **Antihistaminergic:** sedation **Endocrine:** Hyperprolactinaemia, photosen
Butyrophenones Thioxanthenes	Haloperidol, droperidol Flupentixol, zuclopenthixol	

		sitivity (especially phenothiazines) **Other:** Lowered seizure threshold Neuroleptic malignant syndrome (sympathetic hyperactivity: fever, sweating, rigidity, confusion, raised serum creatine kinase) Prolonged Q–T_C interval

18.11.2 Antidepressants

Antidepressants are indicated in depressive illness, anxiety disorders (especially panic disorder and phobic disorders) and obsessional illness.

In depressive illness, antidepressants have a response rate of around 65%, with a delay in action of between 10 days and 6 weeks. The presence of 'biological' symptoms can help in the prediction of response. Antidepressants also play a prophylactic role in recurrent depressive disorders.

Drugs that inhibit 5HT reuptake are particularly useful in obsessional illness. Most antidepressants (particularly SSRIs) are associated with hyponatraemia, which is mediated via the syndrome of inappropriate antidiuretic hormone secretion (SIADH); elderly women are particularly vulnerable to developing this. Abrupt cessation of paroxetine can cause a discontinuation syndrome with flu-like symptoms, dizziness and insomnia.

Table 18.12 gives examples of the different classes of antidepressants and their side-effects.

The side effects and toxicity of lithium are described in detail in Chapter 2, Clinical Pharmacology, Toxicology and Poisoning.

Table 18.12 Examples of the different classes of antidepressants and their side-effects

Class	Example	Side-effects
SSRI	Citalopram	Nausea, sexual dysfunction, headache, sleep disturbance (early), increased anxiety (early)
	Fluoxetine Fluvoxamine Paroxetine Sertraline	
Tricyclic	Amitriptyline	**Anticholinergic:** dry mouth, urinary retention, acute glaucoma, constipation, etc **Antiadrenergic:** postural hypotension

	Imipramine Clomipramine	**Antihistaminergic:** sedation Weight gain Lower seizure threshold Cardiac arrhythmias (prolonged Q–T interval)
SNRI	Venlafaxine	Nausea Hypertension
MAOI	Phenelzine	Anticholinergic Antiadrenergic Hypertensive reaction with tyramine-containing foods (the cheese effect) Important drug interactions
RIMA	Moclobemide	Potential tyramine interaction
Presynaptic α_2 receptor antagonist	Mirtazapine	Agranulocytosis

MAOI, monoamine oxidase inhibitor; RIMA, reversible inhibitor of monoamine oxidase A; SNRI, selective noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

18.11.3 Benzodiazepines

Benzodiazepines are indicated only for the shortterm relief of severe, disabling anxiety. The *British National Formulary* recommends only 2–4 weeks of use. They are not indicated for 'mild' anxiety but can be used as adjunctive treatment for anxiety, agitation and behavioural disturbance in acute psychosis or mania. They are indicated for insomnia only if the condition is severe, disabling or subjecting the patient to extreme distress. Table 18.13 shows the pharmacokinetics of some benzodiazepines.

Benzodiazepine withdrawal syndrome may not develop for up to 3 weeks, but can occur within a few hours for short-acting drugs. Symptoms include insomnia, perspiration, anxiety, tinnitus, decreased appetite, decreased weight, perceptual disturbances and tremor.

The recommended withdrawal regimen involves transferring the patient to an equivalent dose of diazepam, preferably taken at night. Ideally the dose should be decreased by approximately an eighth of the daily dose every 2 weeks. If withdrawal symptoms occur, the dose is maintained until symptoms improve.

18.11.4 Electroconvulsive therapy

ECT is indicated in severe or treatment-resistant depression or where there are psychotic symptoms, life-threatening lack of food and fluid intake, or for stupor and elderly (especially agitated) patients. 'Biological' features help predict the likely response. It is also indicated to treat catatonia associated with schizophrenia and in treatment-resistant cases of mania. The mechanism through which ECT works is not well understood. The most commonly used hypothesis is that it enhances the postsynaptic

response to neurotransmitters.

Side-effects of ECT

- **Early**
  - Headache
  - Temporary confusion
  - Impaired short-term memory (bilateral ECT worse than unilateral)
  - (Rare) fractures, dislocation, fat embolism
- **Late (6–9 months)**
  - No memory impairment detected
  - Subjective impairment

Contraindications to ECT

Raised intracranial pressure is the **only** absolute contraindication, cardiac arrest <2 years previously, other cardiac disease, pulmonary disease, history of cerebrovascular accident.

ECT has a mortality rate of 3 deaths per 100 000 (compare general anaesthesia in healthy adults 1 per 100 000). The mortality rate of untreated major depression is 10%.

Table 18.13 Pharmacokinetics of benzodiazepines

Longer half-life	Diazepam equivalent (mg)[a]	Half-life (hours)	Shorter half-life	Diazepam equivalent (mg)	Half-life (hours)
Diazepam	5	20–90	Lorazepam	0.5	8–24
Chlordiazepoxide	15	20–90[b]	Oxazepam	15	6–28
Nitrazepam	5	16–40	Temazepam	10	6–10
Clorazepate	–	50–100	Alprazolam	–	6–16
Flurazepam	–	50–100			

[a]Approximate equivalent doses to diazepam 5 mg.

[b]Includes active metabolites.

18.11.5 The psychotherapies

Table 18.14 lists the different forms of psychotherapy available, their indications and delivery.

Table 18.14 The psychotherapies

Type	Frequency	No. of sessions	Indications
			Mild depression Anxiety

Counselling	Weekly to monthly	6–12	Berea vement
Cognitive– behavioural	Weekly	8–12	Depression Anxiety Somat oform disorder Eating disorders
Behavioural	Weekly	6–12	Phobias Anxiety Obses sional illness Sexual dysfunction Dementia
Psychoanalytic	1–5/ week	50– indef inite	Neurosis Personality disorders Psycho sexual
Group	Weekly	6–12	Anxiety Substance misuse Eating disorders

Chapter 19
Respiratory Medicine

CONTENTS

Respiratory Medicine

19.1 LUNG ANATOMY AND PHYSIOLOGY

The human lung is composed of approximately 300 million alveoli, each around 0.3 mm in diameter. Gas exchange takes place in the alveoli, and air is transported to these via a series of conducting airways. It is warmed and humidified in the upper airways and transported through the trachea, main bronchi, and lobar and segmental bronchi to the terminal bronchioles, the smallest of the conducting tubes. These airways take no part in gas exchange and constitute the anatomical dead space (approximately 150 mL). The terminal bronchioles lead to the respiratory bronchioles, which have alveoli budding from their walls. Lung tissue distal to the terminal bronchiole forms the primary lobule.

19.1.1 Ventilation

The most important muscle of inspiration is the diaphragm, a muscular dome that moves downwards on inspiration. The external intercostal muscles assist inspiration by moving the ribs upwards and forwards in a 'bucket-handle' movement.

- The accessory muscles of respiration include the scalene muscles, which elevate the first two ribs, and sternocleidomastoids, which elevate the sternum; these are not used during quiet breathing
- Expiration is passive during quiet breathing
- During exercise, expiration becomes active and the internal intercostal muscles and the muscles of the anterior abdominal wall are utilised
- The greatest ventilation is achieved at the lung bases and this is matched by increased perfusion in these areas.

Normal lung is very compliant. Compliance is reduced by pulmonary venous engorgement and alveolar oedema, and in areas of atelectasis. Surfactant, secreted by type 2 alveolar epithelial cells, substantially lowers the surface tension of the alveolar lining fluid, increasing lung compliance and promoting alveolar stability. Lack of surfactant leads to respiratory distress syndrome.

Resistance to airflow is related to the radius of the airway, but the greatest overall resistance to flow occurs in medium-sized bronchi. Airway calibre is influenced by lung volume; at low lung volumes, small airways may close completely, leading to areas of atelectasis, particularly at the lung bases.

19.1.2 Perfusion

The pulmonary vessels form a low-pressure system conducting deoxygenated blood from the pulmonary arteries to the alveoli where they form a dense capillary network. The pulmonary arteries have thin walls with very little smooth muscle; the mean pulmonary artery pressure is 15 mmHg and the upper limit of normal pressure is 30 mmHg.

- Pulmonary vascular resistance is one-tenth systemic vascular resistance
- Hypoxic vasoconstriction refers to contraction of smooth muscle in the walls of the small arterioles in a hypoxic region of lung; this helps to divert blood away from areas with poor ventilation, so maintaining ventilation and perfusion matching.

19.1.3 Control of respiration

The respiratory centre comprises a poorly defined collection of neurons in the pons and medulla; to a certain extent, the cortex can override the function of the respiratory centre. Chemoreceptors are crucial to the control of respiration, and these may be central or peripheral:

- Central chemoreceptors are located on the ventral surface of the medulla. They respond to increased hydrogen ion concentration in the cerebrospinal fluid (CSF), generated by increased carbon dioxide partial pressure (*P*CO2) in the blood
- Peripheral chemoreceptors are located in the carotid bodies (at the bifurcation of the common carotid arteries) and the aortic bodies (near the aortic arch); they respond to hypoxaemia, hypercapnia and pH changes.

In people with normal respiratory function, the most important factor for control of ventilation is the *P*CO2, which is maintained to within 0.4 kPa of baseline (normal range 4.7–6.0 kPa). However, in patients with severe lung disease, chronic CO_2 retention develops and the hypoxic drive to ventilation becomes very important.

- Ventilation may increase by 15 times the resting level during extreme exercise
- Cheyne–Stokes respiration is characterised by periods of apnoea separated by periods of hyperventilation; it occurs in severe heart failure or brain damage and at altitude.

19.1.4 Pulmonary function tests

Peak expiratory flow rate

The peak expiratory flow rate (PEFR) is measured in litres per minute and is a useful guide to airway obstruction. Attention to technique is important to obtain accurate, repeatable readings:

- It is most useful in asthma because it reflects central airway obstruction
- It may underestimate disease severity in chronic obstructive pulmonary disease (COPD).

Spirometry

- The forced expiratory volume in 1 s or FEV_1 refers to the volume of gas expired in the first second of a forced expiration

- The forced vital capacity (FVC) refers to the total volume of gas expired on forced expiration
- The normal ratio FEV_1:FVC is 70–80%

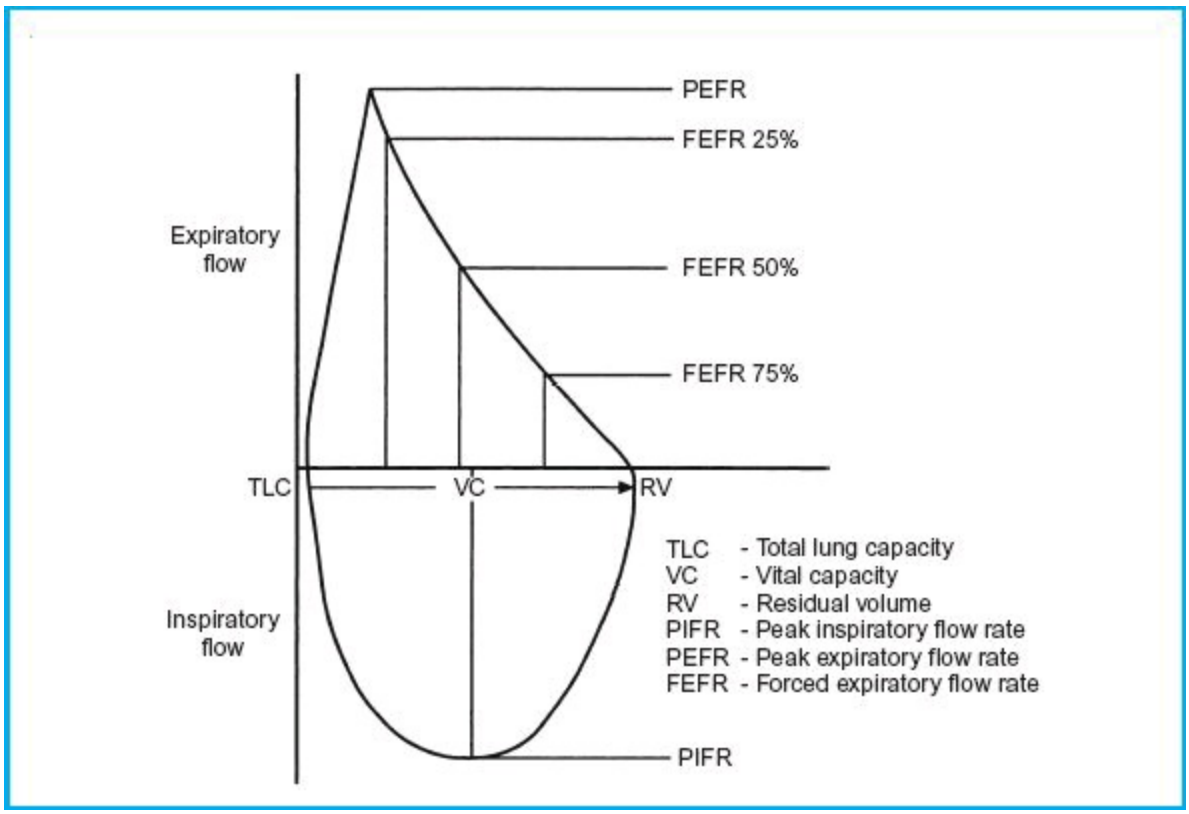
  A reduction in FEV_1 with a preserved FVC occurs in airway obstruction (eg asthma or COPD).
- In patients with severe COPD a slow vital capacity is a more accurate measurement, because it allows time for the lungs to empty fully and hence a true FEV_1:FVC ratio can be determined
- Restriction refers to a reduction in FVC with a preserved FEV_1:FVC ratio, and occurs in conditions such as pulmonary fibrosis, neuromuscular disorders, obesity and pleural disease.

Flow–volume loops

A flow–volume loop (Figure 19.1) is produced by plotting flow on the *y* axis against volume on the *x* axis.

If an individual inspires rapidly from residual volume (RV) to total lung capacity (TLC), and then exhales as hard as possible back to RV, a record can be made of the maximum flow–volume loop. This loop shows that expiratory flow rises very rapidly to a maximum value, but then declines over the rest of expiration. During the early part of a forced expiration the maximum effort-dependent flow rate is achieved within 0.1 s, but the rise in transmural pressure leads to the airways being compressed and therefore to the flow rate being reduced. The flow rate is then said to be effort independent.

Figure 19.1 Typical flow–volume loop



A great deal can be learned by comparing the form of the loop to that which is normally seen ('triangle sitting on a semi-circle'). Several patterns can be recognised, reflecting various disorders (Figure 19.2).

Lung volumes

- Tidal volume, inspiratory and expiratory reserve volumes and vital capacity can all be measured by the use of a spirometer (Figure 19.3)
- TLC, RV and functional residual capacity (FRC) can be measured using a helium dilution method, nitrogen washout or body box.

19.1.5 Gas transfer

Transfer of carbon monoxide is solely limited by diffusion and is used to measure gas transfer. Either a single breath-hold or a steady-state method can be used. Results are expressed both as total gas transfer (*D*LCO) or gas transfer corrected for lung volume (*K*CO, ie *K*CO = *D*LCO/*V*A where *V*A is alveolar volume).

Figure 19.2 Flow–volume loops in different disorders

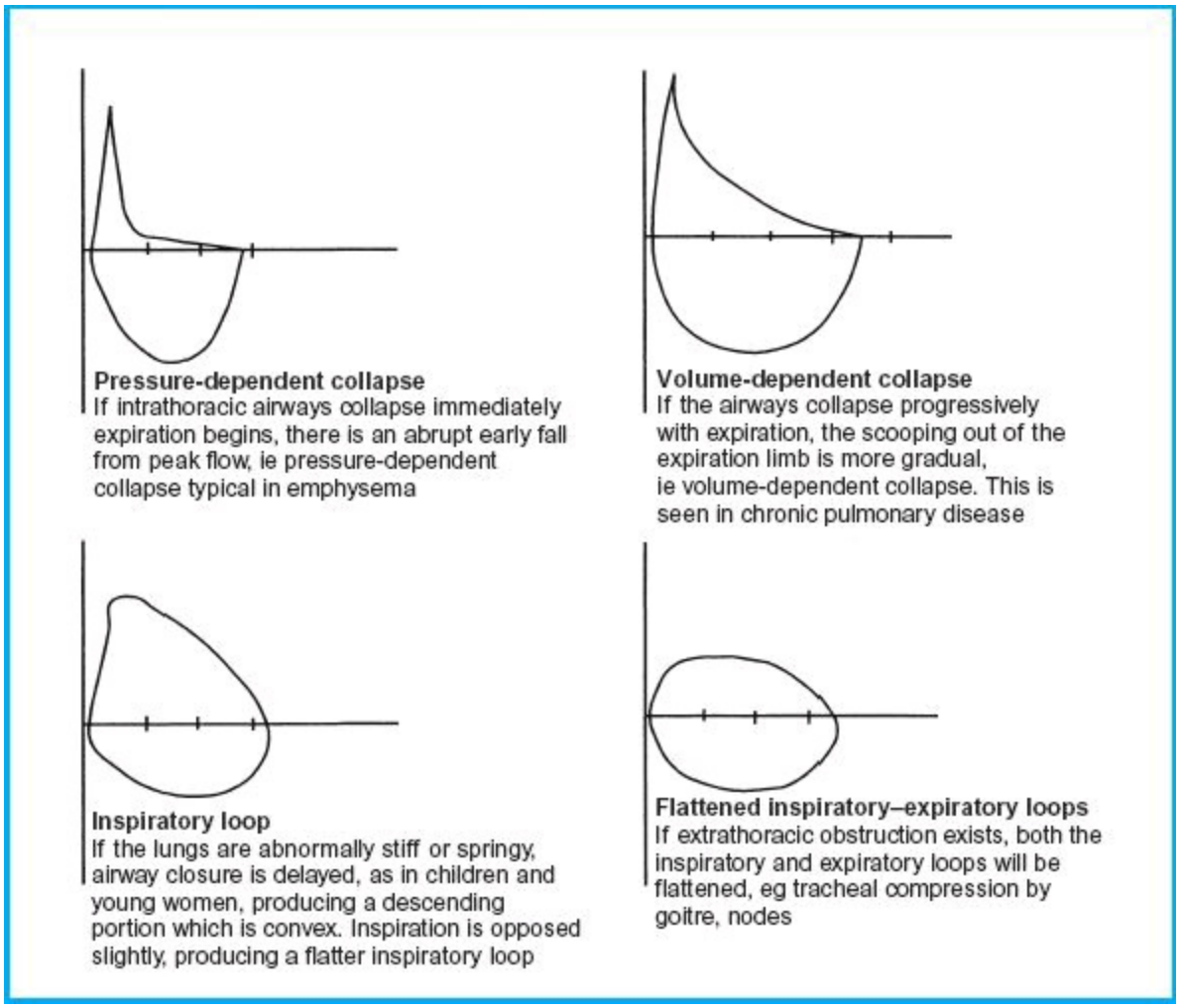
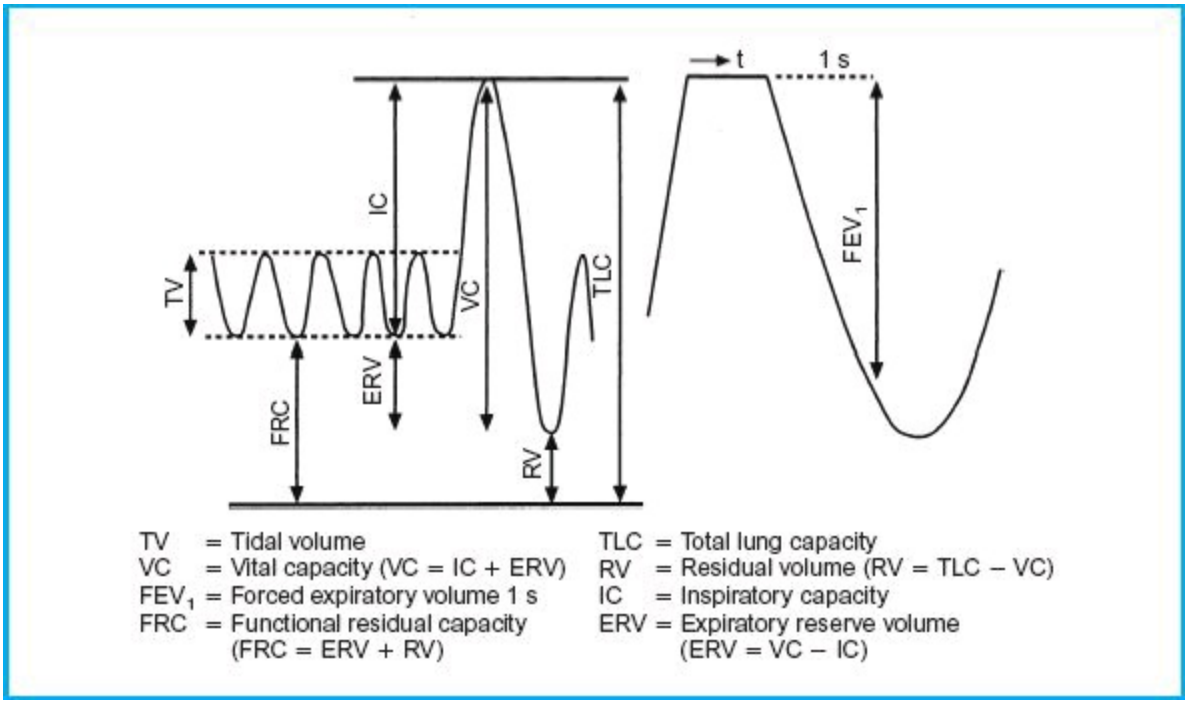


Figure 19.3 Subdivision of lung volume



Causes of hypoxaemia

- **Hypoventilation**
  - Opiate overdose
  - Paralysis of respiratory muscles
- $\dot{V}/\dot{Q}$ **mismatch**
  - Pulmonary embolus
- **Low-inspired partial pressure of oxygen**
  - High altitude
- **Breathing a hypoxic mixture**
- **Diffusion impairment**
  - Pulmonary oedema
  - Interstitial lung disease
- **Bronchiolar–alveolar cell carcinoma**
- **Shunt**[a]
  - Pulmonary arteriovenous (AV) malformations
  - Cardiac right-to-left shunts

[a] Hypoxaemia caused by shunt cannot be abolished by administering 100% oxygen.

Oxygen and carbon dioxide transport

Oxygen is transported in the blood by combination with the haemoglobin (Hb) in red cells. A tiny amount is dissolved (0.3 mL/100 mL blood, assuming PO_2 100 mmHg). The oxyhaemoglobin dissociation curve is sigmoid in shape. Once oxygen saturation falls below 90%, the amount of

oxygen carried to the tissues falls rapidly. The P_{50} (the partial pressure at which haemoglobin is 50% saturated) is 26 mmHg.

- The curve is **shifted to the right** by high temperature, acidosis, increased *P*CO2 and increased levels of 2,3-diphosphoglycerate (2,3-DPG); this encourages offloading of oxygen to the tissues
- The curve is **shifted to the left** by changes opposite to those above, and by carboxyhaemoglobin and fetal haemoglobin.

Carbon dioxide is transported in the blood as bicarbonate, in combination with proteins as carbamino compounds, and it is also dissolved in plasma. Carbon dioxide is 20 times more soluble than oxygen and about 10% of all CO_2 is dissolved. CO_2 diffuses into red blood cells where carbonic anhydrase facilitates the formation of carbonic acid, which dissociates into bicarbonate and hydrogen ions. Bicarbonate diffuses out of the cell and chloride moves in to maintain electrical neutrality.

Acid–base control

The normal pH of arterial blood is 7.35–7.45. Blood pH is closely regulated and variation outside this pH range results in compensation by either the lung or the kidney to return the pH to normal. Failure to excrete CO_2 normally results in a respiratory acidosis; this is usually due to hypoventilation. Hyperventilation causes lowering of the *P*CO2 and alkalosis.

The pH can also be altered by metabolic disturbance. Metabolic acidosis and alkalosis are considered in Chapter 13, Metabolic Diseases. Mixed respiratory and metabolic acid–base disturbances are common.

Arterial blood gases

Normal values are:

- pH 7.35–7.45
  PO_2 while breathing room air:
- >11.3 kPa (85 mHg) or
  >10.7 kPa (80 mmHg) if aged >70 years
- *P*CO2 4.7–6.0 kPa (35–45 mmHg)
- HCO_3^- (bicarbonate) 22–28 mmol/l.

When recording blood gases, the percentage of inspired oxygen should always be stated. The value in kilopascals (kPa) should be multiplied by 7.6 to convert to millimetres of mercury (mmHg).

19.1.6 Adaptation to high altitude

The barometric pressure decreases with altitude: at 18 000 feet (5460 m) it is half the normal 760 mmHg. Hyperventilation, due to hypoxic stimulation of peripheral chemoreceptors, is an early response to altitude.

The respiratory alkalosis produced is corrected by the renal excretion of bicarbonate.

Hypoxaemia stimulates the release of erythropoietin from the kidney, and the resultant

- polycythaemia allows increased carriage of oxygen by arterial blood
- There is an increased production of 2,3-DPG, which shifts the oxygen dissociation curve to the right, allowing better offloading of oxygen to the tissues
- Hypoxic vasoconstriction increases pulmonary artery pressure causing right ventricular hypertrophy. Pulmonary hypertension is sometimes associated with pulmonary oedema – altitude sickness.

19.2 DISEASES OF LARGE AIRWAYS

19.2.1 Asthma

Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals this inflammation causes symptoms that are associated with widespread but variable airflow obstruction, which is reversible either spontaneously or with treatment. There is an increase in airway sensitivity to a variety of stimuli.

The prevalence of asthma has been increasing in recent years, principally among children. Approximately 5.4 million people are receiving treatment for asthma in the UK – 1.1 million of these are children.

There were over 1100 deaths due to asthma in the UK in 2010. It is estimated that as many as 90% of asthma deaths are preventable.

The development of asthma is almost certainly due to a combination of genetic predisposition and environmental factors. Atopy is strongly associated with asthma. The most important allergens are the house dust mite (*Dermatophagoides pteronyssinus*), dog allergen (found in pelt, dander and saliva), cat allergen (predominantly in sebaceous glands), pollen, grasses and moulds.

Factors provoking asthma attacks

- Exposure to sensitising agents
- Exercise
- Infection
- Gastro-oesophageal reflux
- Drugs, including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β blockers
- Cigarette smoke, fumes, sprays, perfumes, etc
- Failure to comply with medication

In patients with asthma the airways are narrowed by a combination of contraction of bronchiolar smooth muscle, mucosal oedema and mucus plugging. In the early stages changes are reversible, but, in chronic asthma, structural changes (including thickening of the basement membrane, goblet cell hyperplasia and hypertrophy of smooth muscle) develop and ultimately lead to irreversible fibrosis of the airways. Asthma is regarded as a complex inflammatory condition and mast cells, eosinophils,

macrophages, T lymphocytes and neutrophils are all involved in the pathogenesis. A variety of inflammatory mediators are released, including histamine, leukotrienes, prostaglandins, bradykinin and platelet-activating factor (PAF).

Chronic asthma

The hallmark of chronic asthma is variable and reversible airflow obstruction, which causes the following:

- Shortness of breath
- Chest tightness
- Wheeze
- Cough

At times the cough may be productive of sputum which may be clear, or yellow/green, due to the presence of eosinophils. The normal diurnal variation in airway calibre is accentuated in people with asthma and symptoms may be worse early in the morning and at night.

Physical signs of asthma

- Tachypnoea
- Wheezing, most marked in expiration
- Hyperinflation of the chest
- Nasal polyps (particularly in people with aspirin-sensitive asthma)
- Atopic eczema

Diagnosis of asthma

The diagnosis of asthma is clinical and is often confirmed by diary recordings of the PEFR. The pattern of lung function tests may be very helpful (see box). Challenge tests with histamine or methacholine, or with exercise, can be used to assess airway responsiveness where the diagnosis is unclear. Responsiveness is expressed as the concentration of provoking agent required to decrease the FEV_1 by 20% (PC_{20}).

Lung function tests that support diagnosis of asthma

- Significant (>20% difference) diurnal PEFR variability on at least 3 days per week for a minimum of 2 weeks
- Significant improvement in PEFR (>15%) and FEV_1 (at least 400 mL) after bronchodilator or a trial of oral or inhaled steroids
- Increased lung volumes
- Reduced FEV_1
- FEV_1:FVC ratio <70%

- Gas trapping
- Metacholine or histamine airway provocation testing (PC_{20}) value of <8 mg/ml
- Exhaled nitric oxide concentration (FE_{NO}) >25 parts per billion
- Sputum eosinophils >2%

Other clinical features that are helpful in making a diagnosis of asthma are:

- A history of asthma in childhood, or of eczema or hay fever
- A family history of asthma
- Symptoms of perennial rhinitis, nasal polyps or chronic sinusitis
- History of wheezing associated with aspirin, NSAIDs or β blockers
- Otherwise unexplained peripheral eosinophilia.

Skin-prick tests

Skin-prick tests can be used to assess atopy. Many individuals with asthma make IgE in response to common allergens. A tiny quantity of allergen is introduced into the superficial layers of the dermis and tests are read at 20 minutes. The diameter of the weal is measured in millimetres, the size of the weal correlating well with bronchial challenge testing. Serum total IgE is commonly raised in people with asthma. Specific IgE may be measured by radioallergosorbent testing (RAST).

Treatment

The aims of prophylactic treatment in patients with asthma are to do the following:

- Minimise symptoms during day and night
- Minimise the need for 'reliever' (eg bronchodilator) medication
- Avoid exacerbations
- Prevent limitation of physical activity
- Maintain normal lung function (FEV_1 and PEFR >80%).

The mainstay of treatment is inhaled corticosteroid with short-acting β agonists to relieve symptoms. Treatment is altered in a stepwise fashion as recommended in the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) national guidelines. The initial dose of inhaled steroid prescribed should be appropriate to the severity of symptoms.

- Long-acting β agonists (eg salmeterol or eformoterol) should be added in patients who are inadequately controlled on beclometasone dipropionate (200 mg/day) or an equivalent steroid inhaler
- Oral theophylline preparations or β_2 agonist tablets are of benefit in some patients
- Leukotriene receptor antagonists (see also Chapter 2, Clinical pharmacology, toxicology and poisoning) may be particularly useful for exercise-induced asthma, and in patients with aspirin sensitivity
- Long-term oral corticosteroids are reserved for patients with very severe asthma

- Markers of steroid responsiveness include sputum eosinophil levels of >2% and exhaled nitric oxide levels of >50 parts per billion. These tests may be helpful in patients with poor asthma control despite high doses of inhaled ± oral corticosteroids
- Allergen avoidance may be helpful in reducing the severity of existing disease in patients exposed and sensitised
- Smoking cessation is essential and should be advised. Smoking decreases the effectiveness of inhaled steroids
- Omalizumab, a monoclonal antibody that binds to IgE, is a possible add-on therapy for patients with severe persistent allergic asthma
- All inhalers are now required to be CFC free.

Acute severe asthma

Asthma symptoms may worsen acutely, necessitating prompt treatment to relieve the attack. An immediate assessment is essential, looking for signs of severity, which include the following:

- Speech impairment
- Respiratory rate >25 breaths/min
- Tachycardia (pulse >110 beats/min)
- PEFR 33–50% of predicted.

Life-threatening asthma is associated with any one of the following:

- Hypoxaemia
- PEFR <33% of predicted
- Exhaustion
- Bradycardia (pulse <60 beats/min) or arrhythmmia
- Hypotension
- A silent chest
- Altered consciousness
- Poor respiratory effort
- Cyanosis
- A normal or raised *P*CO2.

Arterial blood gases should be performed if the patient is hypoxic on air (saturations <92%), and a chest radiograph is necessary to exclude pneumothorax.

Management consists of high-flow oxygen therapy, nebulised bronchodilators (β agonists, ipratropium) and steroids. If infection is considered likely, antibiotics should be precribed. PEFR should be measured regularly to assess the response to treatment.

- If there is no improvement with nebulisers, then intravenous infusions of either salbutamol or aminophylline should be used
- A single dose of intravenous magnesium, which causes smooth muscle relaxation and bronchodilation, may improve outcome in patients with acute severe asthma who have not had a good response to bronchodilators, or to those with life-threatening asthma.

Patients should be referred to intensive care if they have one of the following:

- A deteriorating PEFR
- Persistent or worsening hypoxia
- A rising CO_2
- A decreasing blood pH
- Exhaustion
- Altered consciousness
- Respiratory arrest.

Before discharging a patient with asthma the following criteria should be met:

- PEFR should be at least 75% of the patient's best or predicted value
- PEFR diurnal variability on monitoring should be <25%
- The patient should have required no nebulised bronchodilators for at least 24 hours
- The patient should have a written asthma action plan
- The patient should have follow-up in primary or secondary care within 30 days of discharge

Allergic bronchopulmonary aspergillosis

Most patients with allergic bronchopulmonary aspergillosis have asthma, but the condition may occur in those without asthma. This condition is considered in detail in Section 19.3.6.

19.2.2 Chronic obstructive pulmonary disease

COPD is defined as a chronic, slowly progressive disease characterised by airflow obstruction that does not markedly change over several months. Most of the lung function impairment is fixed, although some reversibility can be produced by bronchodilator therapy. Long-term prognosis is determined by post-bronchodilator FEV_1. COPD is an inflammatory condition that progresses even if the patient has stopped smoking.

It is estimated that 3 million people in the UK have COPD, although fewer than 1 million people have been diagnosed with the condition. COPD currently accounts for 5% of all deaths worldwide. However, the incidence of COPD is increasing and it is likely to become the third most common cause of death worldwide (it is currently fourth) by 2020. It is the only one of the 'top 10' worldwide causes of death that is increasing.

The diagnosis is made as follows:

- History of cough with sputum production, wheeze and shortness of breath
- History of frequent winter bronchitis and delayed recovery from viral infections
- Reduced FEV_1:FVC ratio without reversibility.

Causes of COPD

- Smoking (usually a history of at least 20 pack-years)
- Air pollution
- Low birthweight and low socio economic status
- Dust exposure
- α_1-Antitrypsin deficiency

COPD is now the preferred term for the conditions in patients with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema – each of which are described below.

Chronic bronchitis is defined as chronic cough and sputum production for at least 3 months of 2 consecutive years in the absence of other diseases recognised to cause sputum production.

Emphysema is characterised by abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls without obvious fibrosis. Emphysema may be centriacinar (predominantly affecting the upper lobes and associated with smoking), panacinar, paraseptal or predominantly localised around scars (scar emphysema).

Signs of COPD

Many patients with COPD will have no abnormal physical signs until the disease is advanced:

- Hyperinflation
- Central cyanosis
- Weight loss
- Cor pulmonale: raised jugular venous pressure (JVP), right ventricular heave, loud P2, tricuspid regurgitation, peripheral oedema, hepatomegaly
- Flapping tremor
- Pursed-lip breathing
- Wheeze
- Reduced breath sounds

Investigations

- **Pulmonary function tests** (PFTs): FEV_1:FVC <70%; FEV_1 is classically <80% predicted, but COPD may be diagnosed in patients with an obstructive FEV_1:FVC ratio and an FEV_1 ≥80% if they have typical symptoms of COPD – patients have large lung volumes (TLC) and reduced *D*LCO in emphysema. Degrees of airflow obstruction in COPD may be graded by the FEV_1:
  - **Mild**: FEV_1 ≥80% predicted
  - **Moderate**: FEV_1 50–79% predicted
  - **Severe**: FEV_1 30–49% predicted

- **Very severe**: FEV_1 <30% predicted

- **Chest radiograph**: may be normal or show evidence of hyperinflation, bullae or prominent vasculature due to pulmonary hypertension
- **CT of the thorax**: may be helpful if symptoms are disproportionate to spirometric impairment or to assess suitability of patients for lung volume reduction surgery
- **Arterial blood gases**: may indicate type 1 or 2 respiratory failure
- **Full blood count** (FBC): possible polycythaemia
- **α_1-Antritypsin levels**: should be measured in younger patients or patients with a minimal smoking history or a family history of COPD
- **ECG**: may show P-pulmonale, right axis deviation, right bundle-branch block
- **Sputum culture**: *Haemophilus influenzae*, *Streptococcus pneumoniae* or less commonly staphylococci, *Moraxella catarrhalis* or Gram-negative organisms.

COPD severity and prognostic factors

FEV_1 considered in isolation is a poor guide to a patient's symptom burden and prognosis. A combination of factors should be considered when assessing the severity of a patient's COPD and prognosis:

- FEV1
- Exacerbation frequency
- Body mass index (BMI)
- Degree of dyspnoea (which can be objectively measured using the Medical Research Council's dyspnoea scale)
- Exercise capacity (which can be measured objectively by a 6-minute walk test)
- Degree of hypoxia
- Degree of hypercapnia
- Presence of cor pulmonale.

The BODE (**B**MI, airflow **o**bstruction, **d**yspnoea, **e**xercise) index can be used for an objective assessment of COPD prognosis (a score is calculated based on the patient's BMI, degree of airflow obstruction, level of dyspnoea and exercise capacity). A BODE score ≥7 predicts a 31% 2-year mortality rate.

Treatment of COPD

Several recent clinical trials have shown no impact of inhaled steroids in addition to long-acting bronchodilators on disease progression in COPD. However, combination therapy with inhaled steroids and long-acting β agonists do reduce exacerbation frequency and improve quality of life in those patients with severe or very severe airflow obstruction (ie FEV1 <50% of predicted) who remain breathless when stable or have have at least two exacerbations each year. Pulmonary rehabilitation is increasingly recognised as an important part of disease management.

Treatments available for COPD

- Smoking cessation
- Lung volume reduction surgery (for patients with severe emphysema) or bullectomy
- Inhaled anticholinergic drugs
- Inhaled short- or long-acting β_2 agonists
- Inhaled steroids[a]
- Theophyllines
- Oral mucolytics
- Diuretics
- Long-term oxygen therapy (LTOT) – see Section 19.2.4
- Ambulatory oxygen therapy: for patients who desaturate on exercise and who are shown to have an improvement in their exercise capacity and/or dyspnoea with supplemental oxygen therapy
- Pulmonary rehabilitation
- Domicilary non-invasive ventilation may be considered in patients who have persistent hypercapnic respiratory failure that has required previous acute invasive or noninvasive ventilation. It may also be considered in patients who become acidotic or significantly hypercapnic on supplemental oxygen
- Transplantation may be considered in patients under 65 years with a FEV1 and *D*LCO <20% predicted, a history of hospitalisation with an exacerbation associated with acute hypercapnea or pulmonary hypertension, and/or cor pulmonale despite oxygen therapy

[a]Maintenance oral corticosteroids are reserved for very severe cases.

Pulmonary rehabilitation

This plays a key role in the management of respiratory diseases causing breathlessness, particularly COPD. A multidisciplinary team, usually comprising a physiotherapist, occupational therapist, respiratory nurse, dietician and sometimes a psychologist, is needed. Patients usually participate two to three times per week over 6–8 weeks. Aerobic exercise, including specific upper and lower limb strengthening, is followed by educational and relaxation sessions. Pulmonary rehabilitation has been shown to be effective for all patients with COPD regardless of severity. It has been shown to increase exercise tolerance (and this effect lasts approximately 6 months) and improve quality of life. All motivated patients should be referred for this treatment.

Treatment of acute exacerbations

Antibiotics are indicated for acute exacerbations if two of the following are present:

- Increased breathlessness
- Increased sputum volume
- Increased sputum purulence.

Regular bronchodilators (nebulised or inhaled) are given in addition to short courses of oral steroids (30 mg prednisolone for 7–14 days) and controlled oxygen therapy.

If initial blood gases show hypercapnia and acidosis:

- Patients should be treated along conventional lines for an hour and arterial blood gases then repeated
- If significant acidosis (pH <7.35) with hypercapnia persists, then non-invasive positive-pressure ventilation (NIPPV) should be instituted via a face mask.

19.2.3 α_1-Antitrypsin deficiency

Many different phenotypes of α_1-antitrypsin are known, the common ones being designated M, S and Z. MM confers 100% protease inhibitor activity, whereas the most severe deficiency is produced by ZZ. Panlobular emphysema develops, which is most marked in the basal areas of the lungs. Emphysema is thought to result from an imbalance in the lung between neutrophil elastase (which destroys elastin) and the elastase inhibitor α_1-antitrypsin (which protects against the proteolytic degradation by elastin). The decline in lung function is accelerated in smokers.

- PFTs show airflow obstruction, large lung volumes and reduced *K*CO
- Cirrhosis of the liver is more common, particularly in those of ZZ phenotype
- Smoking cessation is imperative
- Replacement therapy with α_1-antitrypsin is not routinely given
- Lung transplantation may be an option for some patients
- Genetic counselling should be offered, and siblings of index cases should be genetically tested.

19.2.4 Long-term oxygen therapy

Two trials have established the benefit of LTOT. In the Medical Research Council (MRC) trial, oxygen via nasal cannulae was given to raise the PO_2 to 8 kPa (60 mmHg) for at least 15 hours per day compared with patients with COPD receiving conventional therapy. After 3 years of treatment, survival was 50% better in the group receiving oxygen.

The NOTT trial compared 12 and 24 hours of continuous oxygen therapy and was terminated prematurely due to better survival in the group receiving 24-hour therapy. Patients are eligible for LTOT if they **exhibit all of the following**:

- PO_2 on air <7.3 kPa (55 mmHg)
- Normal or elevated *P*CO2
- FEV_1 <1.5 L/<40% of predicted
- PO_2 7.3–8 kPa (55–60 mmHg) with evidence of pulmonary hypertension, polycythaemia, peripheral oedema or nocturnal hypoxaemia.

Arterial blood gases must be measured when the patient is clinically stable (at least 6 weeks post-

exacerbation), and on two occasions that are at least 3 weeks apart. The PO_2 on oxygen should be >8 kPa (60 mmHg) without an unacceptable rise in *P*CO2. Oxygen should be given via a concentrator for at least 15 h/day. The patient should have stopped smoking before LTOT is considered.

19.2.5 Respiratory failure

Respiratory failure is an inability to maintain adequate oxygenation and carbon dioxide excretion. There are two recognised types of respiratory failure:

1. Type 1 respiratory failure is present when there is hypoxaemia with normal or low levels of carbon dioxide
2. Type 2 respiratory failure is hypoxaemia with high *P*CO2.

Causes of respiratory failure

- **Reduced ventilatory drive**
  - Sedatives including opiates and alcohol
- **Brainstem disorders such as encephalitis, tumour or cerebrovascular accident**
- **Metabolic alkalosis**
- **Mechanical problems**
  - Chest trauma causing flail chest
  - Severe kyphoscoliosis
  - Obesity
- **Neurological conditions (affecting chest wall muscles)**
  - Guillain–Barré syndrome
  - Polio
  - Motor neuron disease
  - Spinal muscular atrophy
- **Myopathies**
  - Muscular dystrophy
  - Myotonic dystrophy
  - Acid maltase deficiency (Pompe's disease)
  - Hypothyroidism
- **Alveolar problems**
  - Barriers to diffusion:
    - Pulmonary oedema
    - Pulmonary fibrosis
- $\dot{V}/\dot{Q}$ **mismatch**
  - Pulmonary embolus

- Shunt (cardiac or pulmonary)
- **Reduced inspired partial pressure of oxygen**
  - High altitude
- **Upper airway obstruction**
  - Laryngeal tumour
  - Obstructive sleep apnoea
- **Lower airway obstruction**
  - Bronchospasm
  - Sputum retention
- **Type 1 respiratory failure** may be corrected by increasing the inspired oxygen concentration
- **Type 2 respiratory failure** may require mechanical ventilatory support. Respiratory stimulants such as doxapram may be useful for those with reduced respiratory drive when non-invasive ventilation is either unavailable or considered inappropriate

19.2.6 Ventilatory support

This may be invasive or non-invasive.

Non-invasive positive-pressure ventilation

This involves the use of a securely fitting nasal or full face mask. The technique has been used to provide long-term respiratory support in the community for patients with respiratory failure due to conditions such as severe chest wall deformity, neuromuscular disorders or obesity hypoventilation syndrome.

- It is used increasingly to manage episodes of acute respiratory failure due, for example, to exacerbations of COPD – as an alternative to (and often more appropriate than) ventilation on the intensive care unit (ICU)
- Non-invasive positive-pressure ventilation (NIPPV) can be carried out on general wards using portable bilevel pressure support ventilators. Supplementary oxygen can be given via the port on the face mask. Regular monitoring of blood gases is necessary and the ventilator settings are altered in response. As the patient improves, time spent off the ventilator is lengthened until the patient has been weaned
- When NIPPV treatment is instituted, a decision as to whether ICU referral would be appropriate if the patient were to deteriorate should be clearly stated in the case notes.

Invasive positive-pressure ventilation

Conventional ventilation requires access to the airway, by means of either an endotracheal tube or a tracheostomy. Indications for invasive positive-pressure ventilation are:

- Type 2 respiratory failure from any cause
- Paralysis of respiratory muscles (eg Guillain–Barré syndrome)

- Multiple organ failure
- Trauma cases, including injury to the chest or cervical spine
- Inability to maintain a clear airway
- Reduced conscious level – Glasgow Coma Scale (GCS) score <5
- During and after certain surgical procedures.

Ventilation should be considered when there is failure to maintain oxygenation (PO_2 >8 kPa (60 mmHg)) despite high-inspired oxygen concentrations (usually associated with hypercapnia and acidosis). It is often necessary in patients with multiple organ dysfunction associated with sepsis or trauma.

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is delivered through a tightly fitting face mask, or it may be used together with conventional ventilation. It provides a pneumatic splint to the airway and is the treatment of choice for obstructive sleep apnoea. CPAP improves oxygenation in patients requiring high concentrations of oxygen by the recruitment of collapsed airways. High levels may, however, cause hypotension, the rise in mean intrathoracic pressure inhibiting venous return and reducing cardiac output.

19.3 LUNG INFECTIONS

HIV-/AIDS-associated respiratory disease is covered in Chapter 8, Genitourinary medicine and AIDS.

19.3.1 Pneumonia

Pneumonia is an acute inflammatory condition of the lung usually caused by bacteria, viruses or, rarely, fungi. The chest radiograph will show consolidation, the hallmark of which is an air bronchogram. Pneumonia continues to be an important cause of mortality across all age groups, with 50% of pneumonia deaths occurring in those aged 15–64 years. The UK mortality rate for all patients admitted to hospital with community-acquired pneumonia ranges from 5.7% to 14%, and for those patients admitted to intensive care is >30%.

Community-acquired pneumonia

The incidence is 5/1000 to 11/1000 adult population per year, and this is much more common in elderly people. Causal organisms are given in the following box.

Causes of pneumonia

- *Streptococcus pneumoniae* (60–70%)
- *Haemophilus influenzae*

- *Staphylococcus aureus*
- Gram-negative organisms
- Atypical organisms, including *Mycoplasma pneumoniae* (5–15%), *Legionella pneumophila*, *Chlamydia psittaci*, *Chlamydia pneumoniae* and *Coxiella burnetii* (Q fever)
- Viruses, including influenza, varicella-zoster, cytomegalovirus (CMV)

General investigations for patients admitted to hospital with pneumonia

These include FBC, biochemical profile (including liver function tests), C-reactive protein (CRP), arterial blood gases, chest radiograph, and blood and sputum cultures.

Paired serological tests for atypical organisms and viruses, and urinary antigen tests for *Legionella* spp. and pneumococci should be used in selected cases.

Signs of severe pneumonia (CURB-65 criteria)

- **C**onfusion (<8/10 score on abbreviated mental test [AMT])
- **U**rea >7 mmol/L
- **R**espiratory rate >30 breaths/min
- **B**P systolic <90 mmHg and/or diastolic <60 mmHg
- Age >**65**.

Patients with three or more CURB criteria are at high risk of death and are regarded as having severe community-acquired pneumonia.

Other markers of increased pneumonia severity (and therefore prognosis) include:

- Hypoxaemia (PO_2 <8 kPa despite oxygen therapy)
- Multilobar involvement
- White cell count $<4 \times 10^9$/L or $>20 \times 10^9$/L
- Hypoalbuminaemia
- Positive blood cultures.

The presence of coexisting disease is also a bad prognostic factor.

Specific pneumonias

Streptococcus pneumoniae There is an abrupt onset of illness, with high fever and rigors. Examination reveals crackles or bronchial breathing, and herpetic cold sores may be present in more than a third of cases.

- Elderly patients may present with general deterioration or confusion
- Capsular polysaccharide antigen may be detected in serum, sputum, pleural fluid or urine
- Increasing incidence of penicillin resistance, particularly in countries such as Spain
- Vaccine available.

Mycoplasma pneumoniae

Mycoplasma pneumoniae tends to affect young adults; it occurs in epidemics every 3–4 years. There is typically a longer prodrome, usually of ≥2 weeks, and the white cell count (WCC) may be normal. Cold agglutinins occur in 50%; the mortality is low.

- Extrapulmonary complications include: peri-/myocarditis, erythema multiforme, erythema nodosum, Stevens–Johnson syndrome, haemolytic anaemia, disseminated intravascular coagulation (DIC), thrombocytopenia, meningoencephalitis, cranial and peripheral neuropathies, bullous myringitis, hepatitis and pancreatitis.

Legionella pneumophila

Outbreaks are usually related to contaminated water-cooling systems, showers or air-conditioning systems, but sporadic cases do occur. Legionnaires' disease usually affects middle-aged and elderly patients, often with underlying lung disease. Males are affected more than females (3 : 1). Diagnosis is by direct fluorescent antibody staining or serological tests; antigen may be detected in the urine.

Clinical and laboratory features

- Gastrointestinal upset common; diarrhoea, jaundice, ileus and pancreatitis may occur
- WCC often not elevated with lymphopenia; thrombocytopenia/pancytopenia may occur
- Hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Headache, confusion and delirium are prominent, and focal neurological signs may develop
- Abnormal liver and renal function in approximately 50%
- Acute renal failure, interstitial nephritis and glomerulonephritis may develop

Staphylococcus aureus

Staphylococcus aureus pneumonia may follow a viral illness; it has a high mortality rate (30–70%). The disease is more common in intravenous drug users.

Specific features include the following:

- There is toxin production with extensive tissue necrosis
- Staphylococcal skin lesions may develop
- Chest radiograph shows patchy infiltrates with abscess formation in 25%, and this organism is responsible for around 10% of parapneumonic effusions
- Of patients >25% have positive blood cultures.

Treatment of pneumonia

All patients should be given appropriate concentrations of oxygen and they may require intravenous fluids if circulating volume is depleted. Treatment is with oral amoxicillin and a macrolide (eg clarithromycin) for non-severe cases requiring hospitalisation. A broad-spectrum, β-lactamase, stable antibiotic, such as co-amoxiclav, given intravenously, coupled with a macrolide, is indicated in

severe cases.

- A single antibiotic can be used for community patients or those admitted to hospital for non-medical reasons
- Newer fluoroquinolones (eg moxifloxacin) provide an alternative for patients who are allergic to penicillin or macrolides
- Intravenous treatment should be stepped down to oral treatment after 48 hours provided that the patient is improving
- If a specific organism is isolated, the appropriate antibiotic is given.

Treatment should continue for 7–10 days depending on response. Up to 21 days of treatment is recommended for legionella pneumonia.

Nosocomial (hospital-acquired) pneumonia

This is defined as pneumonia that develops 2 days or more after admission to hospital (0.5–5% of hospitalised patients). It has a higher mortality rate than community-acquired pneumonia at >30%. The organisms usually involved include:

- *S. aureus*
- Gram-negative bacteria: *Klebsiella* spp, *Pseudomonas* spp, *Escherichia coli*, *Proteus* spp, *Serratia* spp, *Acinetobacter* spp
- Anaerobes
- Fungi
- *S. pneumoniae* (and other streptococci) are less common

Treatment is with broad-spectrum agents (eg coamoxiclav, pipericillin/tazobactam or levofloxcacin), and choice of therapy should be guided by local hospital policy.

Aspiration pneumonia

Aspiration pneumonia may complicate impaired consciousness and dysphagia. Particulate matter may obstruct the airway, but also chemical pneumonitis may develop from aspiration of acid gastric contents, leading to pulmonary oedema.

- Anaerobes are the principal pathogens, arising from the oropharynx
- There are typically 2–3 separate isolates in each case
- Multiple pulmonary abscesses or empyema may result
- Treat with metronidazole in combination with broad-spectrum agent (eg third-generation cephalosporin).

Cavitation may develop in certain lung infections (see box).

Cavitation associated with lung infections

- *S. aureus*
- *Klebsiella pneumoniae*

- *Legionella pneumophila* (rare)
- Anaerobic infections
- *Pseudomonas aeruginosa*
- *Mycobacterium tuberculosis* and nontuberculous mycobacterial infections

Lung abscess

Lung abscesses are normally due to mixed anaerobic infection and are commonly caused by bacteria found in the oral cavity. A lung abscess may be suspected when the patient is slow to improve from pneumonia. The mortality rate is high at 20–30%. A chest radiograph will show single or multiple fluid-filled cavities.

Risk factors include the following:

- Immunocompromise
- Bronchial carcinoma
- Dental disease
- Pneumonia
- Septic emboli (eg from right heart infective endocarditis).

Prolonged courses of antibiotics are needed, sometimes with percutaneous drainage.

19.3.2 Empyema

A collection of pus in the pleural space may complicate up to 15% of community-acquired pneumonias and is more common when there is a history of excess alcohol consumption, poor dentition, aspiration or general anaesthesia. *Streptococcus* species, including *Streptococcus milleri*, *Streptococcus pneumonia*, accounts for approximately 50% of community-acquired pleural infections. Other causative organisms include *Staphylococcus aureus*, Gram-negative aerobes and anaerobes. Hospital-acquired pleural infections are most commonly caused by staphylococci, but other organisms such as the Gram-negative aerobes *Escherichia coli* and *Pseudomonas aeruginosa* are also known causes.

- A diagnosis of empyema is suspected if a patient is slow to improve, has a persistent fever or elevation of the WCC or CRP, and has radiological evidence of a pleural fluid collection. The pH of pleural fluid is <7.2
- Untreated, extensive fibrosis occurs in the pleural cavity, weight loss and clubbing develop, and the mortality rate is high at 10–20%
- The mainstay of treatment is drainage of the pleural space combined with continuous high-dose intravenous antibiotic treatment. Daily intrapleural administration of tissue plasminogen activator, alongside DNAse, for 3 days has been shown to improve percutaneous drainage and may decrease the length of hospital stay and need for thoracic surgery
- For those who fail to resolve with medical therapy, thoracotomy and decortication of the lung may be necessary.

19.3.3 Tuberculosis

Unlike community-acquired pneumonia, the number of new cases of tuberculosis (TB) declined in the UK throughout the twentieth century, mainly due to the improvement in living standards. In recent years, however, the incidence of TB has begun to increase again. Those at risk include the following:

- Those on low incomes
- Homeless people
- People with alcohol problems
- HIV-positive individuals
- Immigrants from countries with a high incidence of TB.

The most commonly involved site is the lung – with lymph node, bone, renal tract and gastrointestinal (GI) tract being less common. Tuberculous meningitis is the most serious complication.

Primary TB

Primary infection occurs in those without immunity. A small lung lesion known as the Ghon focus develops in the mid- or lower zones of the lung, and is composed of tubercle-laden macrophages. Bacilli are transported through the lymphatics to the draining lymph nodes, which enlarge considerably and caseate. Infection is often arrested at this stage and the bacteria may remain dormant for many years. The peripheral lung lesion and the nodes heal and may calcify. The entire process is often asymptomatic. However, specific immunity begins to develop and tuberculin skin tests become positive.

Post-primary TB

Organisms disseminated by the blood at the time of primary infection may reactivate many years later. The most common site for post-primary TB is the lungs, with bone and lymph node sites being less common. Reactivation may be precipitated by a waning of host immunity, eg due to malignancy or immunosuppressive drugs (including steroids).

Clinical picture

Primary infection is often asymptomatic, but may cause mild cough and wheeze or erythema nodosum. Clinical features of reactivation or reinfection are described in the box.

Features of TB reactivation or reinfection

- Persistent cough
- Weight loss
- Night sweats
- Haemoptysis
- Pleural effusion
- Pneumonia

- Meningitis
- Lymphadenopathy

Miliary TB

This is caused by widespread dissemination of infection via the bloodstream. It may present with non-specific symptoms of malaise, pyrexia and weight loss. Eventually hepatosplenomegaly develops and choroidal tubercles may be visible on fundoscopy. The chest radiogaph shows multiple rounded shadows a few millimetres in diameter. It is universally fatal if left untreated.

Diagnosis of TB

- **Chest radiograph**: may show patchy shadowing in the upper zones with volume loss and cavitation, and ultimately fibrosis
- **Sputum collections**: at least three including one early morning sample – for acid- and alcohol-fast bacilli smear and culture
- **Pleural fluid aspiration and biopsy**
- **Bronchoscopy and lavage**: used for those unable to expectorate; transbronchial biopsy if miliary disease is a possibility
- **Early morning urine specimens**: for renal tract disease
- **Liver biopsy**
- **Lymph node biopsy**
- **Bone marrow aspirate**
- **CSF culture**

Specimens are examined for acid- and alcohol-fast bacilli (AAFB) using Ziehl–Neelsen or auramine stain and then cultured on Löwenstein–Jensen medium. Cultures are continued for at least 6 weeks, as the organism is slow growing. Polymerase chain reaction (PCR) for tuberculous DNA can be used to provide a rapid diagnosis whilst awaiting a culture result. This may be helpful in confirming diagnosis and allowing earlier initiation of anti-tuberculous chemotherapy in acutely unwell patients with smear-negative samples, particularly if immunocompromised. This allows early differentiation from non-tuberculous mycobacterial infection (which would be important before embarking on an extensive screening programme of contacts) and can also be used to detect multidrug-resistant disease.

Treatment

(See also Section 11.6.1 in Chapter 11, Infectious Diseases and Tropical Medicine.)

This is with a combination of four drugs:

1. Rifampicin
2. Isoniazid

3. Pyrazinamide
4. Ethambutol.

Short courses of treatment for 6 months are now standard. All drugs are given for 2 months and isoniazid and rifampicin are continued for a further 4 months.

- Sensitivity testing will identify drug resistance and all four drugs are continued until sensitivities are known
- If pyrazinamide has to be discontinued due to side-effects, a 9-month regimen is necessary
- Second-line agents (eg ethionamide, propionamide, streptomycin, cycloserine) may be needed
- Compliance can pose major problems and directly observed therapy (DOT – larger doses of drugs administered three times per week) is used when poor compliance is anticipated
- Meningeal TB requires 12 months of anti-tuberculous therapy with quadruple therapy for the first 2 months, then rifampicin and isoniazid continue for a further 10 months. Steroids are also indicated in meningeal TB for at least 3 weeks before being weaned down gradually.

Once 2 weeks of anti-tuberculous chemotherapy has been completed, a smear-positive patient is considered to be non-infectious.

Multidrug-resistant TB (MDR-TB) signifies resistance to rifampicin and isoniazid and currently accounts for 1.6% of tuberculous infections. It is mainly concentrated in the London area.

Extremely drug-resistant TB (XDR-TB) signifies resistance to rifampicin, isoniazid, a quinolone and a second-line injectable agent (eg amikacin, capreomycin, kanamycin). A total of 26 cases of XDR-TB in the UK have been reported since 1995.

Side-effects of anti-tuberculous treatment

Side-effects are common:

- **Hepatitis**: may be caused by rifampicin, isoniazid and pyrazinamide
- **Optic neuritis**: may be caused by ethambutol; visual acuity should be checked before treatment is initiated
- **Peripheral neuropathy**: may be due to isoniazid; 10 mg pyridoxine daily is given in those at particular risk of this complication (eg people with alcohol problems, diabetes and patients with renal failure).

Prevention

The school BCG (Bacille Calmette–Guérin) programme has now been withdrawn. Neonatal BCG immunisation is recommended for babies at high risk of tuberculosis infection. Unimmunised children between 4 weeks and 16 years of age, who would have qualified for neonatal immunisation, should be opportunistically screened with Mantoux testing and offered BCG immunisation if Mantoux testing is negative. The efficacy of BCG varies greatly in different communities but usually helps prevent disseminated disease.

All immigrants to the UK from high-risk countries who are aged <35 years old are screened for latent disease. This is by a combination of history, Mantoux and/or interferon-γ testing ± chest radiograph. Mantoux testing may be offered to all those without a definite BCG scar. If the Mantoux test is

negative, a BCG immunisation is offered.

If there is evidence of prior BCG immunisation and Mantoux is positive, an interferon-γ test is also performed. If both screening tests are positive and there is no evidence of active TB on history, examination and a chest radiograph, then chemoprophylaxis is offered. Some centres use interferon-γ only as a screening test to guide the need for treatment of latent TB.

Patients aged ≥35 are not routinely screened/treated for latent TB due to increasing risk of hepatotoxicity from anti-tuberculous chemotherapy with age.

Chemoprophylaxis comprises isoniazid for 6 months or rifampicin and isoniazid for 3 months.

- Patients with pulmonary TB (particularly those who are sputum smear-positive for AAFB) are potentially infectious and close contacts should be screened for active disease by examination and chest radiograph. Once active TB has been ruled out, latent disease is screened for as outlined above. In contacts aged <35 who are previously unimmunised AND are household contacts of a person with smear-positive TB AND are Mantoux-negative, an interferon-γ test is also performed 6 weeks after Mantoux testing. The result will determine need for BCG immunisaiton or treatment for latent TB (once active TB infection has been ruled out). Patients aged >35 years are screened for active TB with a chest radiograph
- The use of anti-tumour necrosis factor-α (TNF-α) therapy can be associated with reactivation of latent TB. Patients due to start such treatment should be screened for active/latent/past TB. Those who have had adequately treated past TB should be monitored closely. Where past TB has not been treated fully or latent TB is identified, a course of chemoprophylaxis is given.

TB is a notifiable disease.

Opportunistic mycobacterial infections

These account for 10% of all mycobacterial infections. Causative organisms include the following:

- *Mycobacterium kansasii* (most common)
- *M. xenopi*
- *M. malmoense*
- *M. avium intracellulare*.

These organisms cause disease that is clinically and radiologically identical to TB, and indistinguishable from TB on sputum smear. Pulmonary disease, lymphadenitis (in children) and disseminated infection are the most common clinical problems. Most patients are middle-aged/elderly with significant underlying COPD, bronchiectasis or previous TB. A minimum of two positive cultures taken a week apart in a patient with an appropriate clinical picture is necessary to make the diagnosis. The organisms are ubiquitous in the environment and are low-grade pathogens. Opportunistic mycobacterial infections constitute a relatively higher proportion of mycobacterial infections in patients with acquired immune deficiency syndrome (AIDS).

- The onset of symptoms is usually gradual
- Treatment programmes are generally longer than for TB, and are continued for at least 9 months and often for 2 years
- Rifampicin and ethambutol are the mainstay of treatment; clarithromycin or ciprofloxacin may be

added

- Opportunistic infections do not need to be notified
- Contact tracing is unnecessary as person-to-person infection is very rare.

19.3.4 Bronchiectasis

This is the permanent dilatation of subsegmental airways, which are inflamed, tortuous, flabby and partially/totally obstructed by secretions. Bronchiectasis may be cystic, cylindrical or varicose, with the cystic pattern being the most severe. The obstruction often leads to post-obstructive pneumonitis so that the lung parenchyma may be temporarily or permanently damaged.

Causes of bronchiectasis

- Idiopathic – 60%
- Congenital (eg Marfan and Williams–Campbell syndromes)
- Post-infective (eg after episodes of measles, pneumonia, tuberculosis or pertussis)
- Immune deficiency (eg HIV, haematological malignancy or post transplantation)
- Allergic bronchopulmonary aspergillosis (ABPA) – proximal
- Cystic fibrosis
- Complicating sarcoidosis or pulmonary fibrosis (traction bronchiectasis)
- Distal to an obstructed bronchus (or a bronchus severely compressed from encroaching lymph nodes)
- Secondary to bronchial damage resulting from a chemical pneumonitis (eg inhalation of caustic chemicals)
- Mucociliary clearance defects: primary ciliary dyskinesis or associated with situs inversus (Kartagener syndrome) or associated with azoospermia and sinusitis in males (Young syndrome)
- α_1-Antitrypsin deficiency

Clinical features

There is a history of chronic sputum production, which is often mucopurulent and accompanied by episodes of haemoptysis. Occasionally bronchiectasis can be 'dry' with no sputum production but with episodic haemoptysis. Exertional dyspnoea and wheeze may be associated. Patients complain of malaise and fatigue; a third have symptoms of chronic sinusitis. There may be few abnormal clinical findings other than occasional basal crackles or wheeze on chest examination; clubbing may be present. In more advanced disease, weight loss and cachexia are prominent.

Investigations

- **Sputum microbiology**: most commonly shows *Haemophilus influenzae*, *S. pneumoniae* or *Pseudomonas aeruginosa*; mycobacteria and fungi may also be seen

  Chest radiograph: may be normal or may show thickening of bronchial walls and in cystic

- bronchiectasis, ring shadows ± fluid levels. The upper lobes are most frequently affected in ABPA, cystic fibrosis, sarcoidosis and TB
- **Pulmonary function tests**: usually obstructive but may be normal or show a restrictive or mixed pattern
- **High-resolution CT**: diagnostic in >90% of cases
- All patients should have blood taken for immunoglobulin levels, functional antibodies and aspergillus serology
- If indicated, based on the clinical history, patients may require tests of ciliary function, cystic fibrosis genotyping or sweat testing, α_1-antitrypsin levels or neutrophil function testing
- Bronchoscopy should be considered in localised disease.

Conditions associated with bronchiectasis

- Rheumatoid arthritis (30% of patients have coexisting bronchiectasis)
- Malignancy (childhood acute lymphoblastic leukaemia, adult chronic lymphocytic leukaemia)
- Sjögren syndrome
- Yellow nail syndrome and primary lymphoedema
- Inflammatory bowel disease (usually ulcerative colitis)
- Infertility
- Ankylosing spondylitis

Treatment

As far as possible the aetiology of the bronchiectasis should be established in every case. If there is an underlying immune deficiency state, treatment with intravenous γ-globulin replacement therapy is beneficial. Regular physiotherapy with postural drainage and using 'the active cycle of breathing' helps to clear the airways.

- Inhaled bronchodilators may be used if there is evidence of reversibility and improvement of lung function or sypmtoms
- There is no evidence for the routine use of inhaled steroids
- **Antibiotics** are used to treat acute exacerbations and the choice of antibiotics should be pathogen-guided where possible
- Antibiotic prophylaxis should be considered in patients who have three or more exacerbations per year
- Long-term antibiotic prophlaxis choice should be guided by sputum culture. Rotating antibiotics are not routinely recommended
- Azithromycin given three times a week to patients chronically colonised with *Pseudomonas* spp. (when all other treatment is optimised but patient still having frequent exacerabtions or copious sputum) can decrease exacerbation rate and intravenous antibiotic requirements
- Nebulised antibiotics can be used to reduce the microbial load and they are particularly useful

- when a patient is colonised with *Pseudomonas* spp. or more than three exacerbations per year

- Adequate hydration is important but mucolytics are generally not helpful
- Nebulised hypertonic saline can increase sputum yield, decrease sputum viscosity and aid expectoration
- Surgery is reserved for those with localised severe disease; lung transplantation has been successful.

Complications

Infective exacerbations are the principal problem. Haemoptysis usually settles with treatment of the infection ± tranexamic acid, but occasionally embolisation of the bleeding vessel is required. Chest pain over an area of bronchiectatic lung is not uncommon. In the long term, systemic amyloid may result.

19.3.5 Cystic fibrosis

Cystic fibrosis (CF) is the most common fatal autosomal recessive condition in the White population, affecting 1 in 2500 live births; 1 in 25 adults is a carrier of the gene. There are over 10,000 people in the UK diagnosed with CF. The cystic fibrosis gene has been localised to the long arm of chromosome 7 and codes for the cystic fibrosis transmembrane conductance regulator protein (CFTR), which functions as a chloride channel (see also Chapter 7, Genetics). Over 1900 mutations have been identified, the most common being F508del. The basic defect involves abnormal transport of chloride across the cell membrane; in the sweat gland there is a failure to reabsorb chloride and in the airway there is failure of chloride secretion. Diagnosis is made by detection of an abnormally high sweat chloride (>60 mmol/L) and by genetic analysis (initial screen is for the 24 most common genotypes). Neonatal screening for CF is now performed via Guthrie's (heel-prick) test in newborn babies.

Pulmonary disease

A significant inflammatory infiltrate may be identified in the lungs at a very early age. The airways become obstructed by thick mucus due to decreased chloride secretion and increased sodium reabsorption, and so bacterial infection becomes established in early life.

Infection occurs in an age-related fashion: infants and young children become colonised with *S. aureus* and subsequently *H. influenzae*. In the teenage years, infection with *Pseudomonas aeruginosa* usually occurs.

The other major pathogens involved are:

- *S. pneumoniae*
- *Burkholderia cepacia* complex
- *Mycobacterium tuberculosis*
- Non-tuberculous mycobacteria
- *Aspergillus fumigatus*

- Viruses.

Chronic infection and inflammation cause lung damage, with bronchiectasis affecting predominantly the upper lobes. Patients experience breathlessness and reduced exercise tolerance, cough with chronic purulent sputum production and occasional haemoptysis. Physical signs include clubbing, cyanosis, scattered coarse crackles and occasional wheeze. Small volume haemoptysis is often associated with infection but major haemoptysis may occasionally necessitate pulmonary arterial embolisation.

- Pulmonary function tests show airflow obstruction; chest radiograph may show hyperinflation, atelectasis, visibly thickened bronchial walls, fibrosis and apical bullae; pneumothorax occurs in up to 10% of patients
- In the terminal stages of disease, respiratory failure develops; 90% of deaths are attributable to respiratory failure as a consequence of lung infection. The average life expectancy has increased into the fourth decade of life.

Gastrointestinal tract

Pancreatic exocrine insufficiency due to secretions blocking pancreatic ducts is present in >90% of patients. Malabsorption causes steatorrhoea, with weight loss and deficiency of fat-soluble vitamins (A, D, E and K). Of adults with CF, 30% have pancreatic endocrine insufficiency, causing frank diabetes due to gradual loss of pancreatic islet cells and pancreatic fibrosis. This is associated with respiratory deterioration due to increased vulnerability to acute and chronic pulmonary infection, increased lung stiffness and decreased gas diffusion, and requires treatment with insulin.

Babies may present with meconium ileus and adults may develop an equivalent syndrome (distal intestinal obstruction syndrome) with small bowel obstruction, due to poorly digested intestinal contents, causing abdominal pain, distension, vomiting and severe constipation. This is usully treated with rehydration, Gastrografin and laxatives.

- Obstruction of the biliary ductules in the liver may eventually lead to cirrhosis with portal hypertension, splenomegaly and oesophageal varices
- Gallstones (in 15% of patients), peptic ulcer and reflux oesophagitis are all more prevalent
- Pancreatitis may develop in older patients.

Involvement of other systems

- **Upper airway disease**: nasal polyps occur frequently (up to a third of patients); chronic purulent sinusitis may develop
- **Fertility**: virtually all males are infertile due to abnormal development of the vas deferens and seminiferous tubules, but fertility in women is only slightly reduced. Although many women with CF have had successful pregnancies, pregnancy may lead to life-threatening respiratory complications
- **Osteoporosis**: is more common with an increased risk of fractures
- **Renal disease**: renal calculi (oxalate stones) are more common in people with CF. Renal tubular dysfunction may occur secondary to long-term or frequent antibiotic use – in particular aminoglycoside therapy

- Female urinary incontinence is common.

Treatment of cystic fibrosis

Care for patients with cystic fibrosis is best given in a specialist unit, which can provide extensive multidisciplinary input.

Antibiotics and respiratory treatments

In the UK most centres give antibiotics when sputum becomes increasingly purulent, PFTs are deteriorating or the patient is generally unwell with weight loss. Most patients become chronically colonised with *P. aeruginosa*, and so two antibiotics from different classes (eg ceftazidime and tobramycin) are used in combination to prevent resistance developing. Some patients are infected with a transmissible strain of *Pseudomonas* and these patients are segregated in specific outpatient clinics.

- Up to 10% of patients become colonised with a group of bacteria called *Burkholderia cepacia* complex, some of which are highly transmissible from one individual to another and associated with a worse prognosis (particularly *Burkholderia cenocepacia*). These patients are therefore segregated from other patients in the hospital, at outpatient clinics and also socially. This group of organisms is usually multiresistant to antibiotics and a combination of three intravenous antibiotics is used to treat exacerbations
- Continuous anti-staphylococcal treatment with flucloxacillin is currently routinely recommended in the UK for the first 3 years of life
- Azithromycin 250 mg once daily has immunomodulatory effects and may marginally increase lung function and decrease the frequency of admissions and intravenous antibiotic requirements; it is usually prescribed on a long-term basis
- Nebulised antibiotics reduce the microbial load and are useful in those who need frequent courses of intravenous antibiotics; colistin or tobramycin is used continuously in a twice-daily regimen
- Colistin and tobramycin administered via inhaler devices are now also available and licensed for use in patients chronically colonized with *P. aeruginosa*. These newer devices may improve adherence to long-term antibiotic therapy due to their portability, ease of use and speed of drug delivery
- DNase helps to liquefy viscous sputum and is helpful in some patients. Bronchodilators and inhaled steroid are given to treat airflow obstruction
- Hypertonic saline may help aid sputum expectoration and is of benefit in some patients
- Physiotherapy, using the active cycle of breathing technique, should be tailored to individual needs
- NIPPV may be used as an adjunct to airway clearance tecniques in acute exacerbations or on a more long-term basis in patients with chronic type 2 respiratory failure

Pancreatic enzyme supplements

These are given with main meals and snacks to those with pancreatic insufficiency. Meconium ileus equivalent (distal intestinal obstruction syndrome) is treated with vigorous rehydration and regular oral Gastrografin. Good nutritional status is associated with improved prognosis; supplementary

overnight feeding with nasogastric tube or via gastroenterostomy can help to maintain body weight.

Transplantation

Double-lung transplantation (if only single-lung transplantation performed, the new lung would be vulnerable to infection from the remaining damaged lung) may be appropriate for some patients with terminal respiratory failure. NIPPV may be utilised to support a patient before transplantation. The optimal timing of lung transplantation must be assessed in each individual case. Liver and occasionally pancreas transplantations are also carried out in some patients.

Future developments in cystic fibrosis

Recent years have seen the development of new therapies targeted at the underlying protein defect that causes CF. Ivacaftor represents the first licensed medication targeted at correcting the CFTR protein dysfunction. Phase III studies suggest that it significantly increases lung function and weight, and also reduces sweat chloride to normal levels in a number of individuals. Currently ivacaftor is licensed only for patients carrying the *G551D* mutation, which is the most common class III mutation, being present in 4% of patients worldwide (6% in the UK). Ivacaftor increases the probability that the CFTR chloride channel remains open. Due to advances in care over the past 10–20 years, median survival has steadily increased and median life expectancy for those diagnosed with CF is now 43.5 years.

Clinical trials are ongoing to develop medications that will be beneficial for individuals with the more common genetic mutation F508del. Current strategies involve combining a novel molecule with ivacaftor, with the hope of assisting in the transport of the CFTR protein from the nucleus to the cell surface, and increasing the probability of keeping this channel open when at the cell surface. This combination is currently being tested in phase II and III trials. Trials for gene therapy in CF are ongoing and results are awaited.

19.3.6 *Aspergillus spp. and the lung*

There are four distinct forms of pulmonary disease caused by aspergillus infection: allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, invasive aspergillosis and aspergilloma.

Allergic bronchopulmonary aspergillosis

Most patients with allergic bronchopulmonary aspergillosis (ABPA) have asthma, but the condition may occur in those who do not have asthma.

The disease is due to sensitivity to *Aspergillus fumigatus* spores mediated by specific IgE and IgG antibodies. The allergic response results in airways becoming obstructed by rubbery plugs of mucus containing aspergillus hyphae, mucus and eosinophils. Plugs may be expectorated. The following changes may be found on investigation:

- Lobar or segmental collapse of airways
- Fleeting chest radiograph shadows due to intermittent obstruction of airways
- Positive skin-prick tests and RAST to *Aspergillus* spp.

- Positive precipitins to *A. fumigatus*
- Raised serum IgE >1000 ng/mL
- Peripheral blood and sputum eosinophilia
- May result in proximal bronchiectasis.

Treatment is with oral corticosteroids which may be required long term; itraconazole is also useful and may allow the dose of steroid to be reduced.

Chronic pulmonary aspergillosis

This condition represents a low-grade chronic invasion of *Aspergillus* spp. into the airway walls and surrounding lung. Patients affected are typically mildly immunocompromised, eg chronic lung disease, diabetes, malnutrition and long-term oral steroid. This condition covers a spectrum of severity, ranging from relatively minor consolidation to severe multi-cavitatory disease.

Appropriate investigations include sputum fungal culture ± aspergillus PCR testing. Radiological imaging may show a 'tree-in-bud' pattern or cavitatory disease.

Treatment is usually with oral antifungals and minimisation of any pre-existing iatrogenic immunosuppression.

Invasive aspergillosis

Fungal infection spreads rapidly through the lung causing granulomas, necrosis of tissue and suppuration. It occurs most commonly in the significantly immunosuppressed host and may be rapidly fatal. Progressive chest radiograph shadowing (which may cavitate), associated with fever, chest pain and haemoptysis that does not settle promptly with antibacterial agents, suggests invasive aspergillosis.

Infection can spread to any site in the body and sinuses, brain, heart, eyes and skin are commonly involved.

- Cough with copious sputum production, often with haemoptysis, is usual. Patients may be febrile and experience chest pain
- Galactomannan, a polysaccharide, which is part of the aspergillus cell wall and released during its growth, can be tested for in the blood of patients with suspected invasive aspergillosis
- Examination of sputum or bronchoalveolar lavage fluid may demonstrate fungal hyphae, and PCR testing for aspergillus may be helpful. Transbronchial biopsies may be required in patients who are fit for the procedure where there is diagnostic uncertainty
- High-resolution CT shows pulmonary infiltrates with the 'halo' sign. Treatment is with intravenous antifungal agents.

Aspergilloma

A mass or ball of fungus may develop within a lung cavity or pleural space in patients infected with *Aspergillus* spp. known as an aspergilloma. *A. fumigatus* is usually responsible, but occasionally *A. niger*, *A. flavus* or *A. nidulans* may be implicated. Cavities due to TB, sarcoidosis, CF or pulmonary neoplasms are typical sites for aspergillomas to develop within.

Cough and sputum production often occur and are features of the underlying disease. Haemoptysis is a common complication, and this may be massive and require bronchial artery embolisation.

- An aspergilloma is usually suspected by chest radiograph, which demonstrates a cystic space containing a rounded opacity. An airspace is visible between the fungal mass and the cavity wall – the 'halo' sign
- Precipitating antibodies are nearly always present but response to skin testing is variable
- Sputum examination may reveal fungal hyphae.

Many aspergillomas require no specific treatment. Treatment is indicated for recurrent haemoptysis, systemic symptoms and where there is evidence of fungal invasion of surrounding tissue. Intracavitary instillation of amphotericin paste is sometimes useful, and systemic treatment with the newer azoles (eg voriconazole) may be helpful in some cases. Surgical resection of the affected area of lung may be curative but surgery can be technically difficult.

19.4 OCCUPATIONAL LUNG DISEASE

19.4.1 Asbestos-related disease

Exposure to asbestos was previously commonplace in many occupations including those who worked as shipbuilders, laggers, builders, dockers and workers in factories engaged in the manufacture of asbestos products.

Effects of asbestos on the lung

Pleural plaques

These appear 20 years or more after low-density exposure. They develop on the parietal pleura of the chest wall, diaphragm, pericardium and mediastinum, and commonly calcify. Pleural plaques are usually asymptomatic but they may cause mild restriction.

Diffuse pleural thickening

This can extend continuously over a variable proportion of the thoracic cavity, but is most marked at the lung bases. It causes exertional dyspnoea ± chest pain; PFTs show restriction, decreased compliance and reduced TLC, but the *K*CO is normal.

Pleural effusions

These may occur in asbestos-related disease, usually within 15 years of exposure. They are usually small and unilateral. They often resolve spontaneously, leaving thickening of the visceral pleura. Pleural fluid is usually exudative and may be blood-stained, so patients are usually investigated for more sinister causes of the effusion such as malignancy before the diagnosis of asbestos-related pleural effusion is made.

Asbestosis

The onset of asbestosis is usually >20 years after exposure (but with higher levels of exposure fibrosis occurs earlier). Fibrotic changes are more pronounced in the lower lobes; patients present with slowly worsening exertional dyspnoea and clinical examination reveals fine inspiratory crackles

in the lower zones. Clubbing may occur.

- Chest radiograph shows reticulonodular shadowing primarily affecting the lower lobes and, in more advanced disease, honeycomb shadowing can be seen
- High-resolution CT (HRCT) confirms fibrosis, and associated pleural plaques and/or thickening may be seen
- PFTs show a restrictive defect with reduced *K*CO
- There is an increased risk of lung cancer (see below)
- Lung biopsy may show asbestos bodies but is only rarely indicated.

The disease is untreatable and death is usually due to respiratory failure or malignancy

Lung cancer

Mesothelioma is the most common malignancy associated with asbestos exposure. The risk of lung cancer is also substantially increased, particularly in those who smoke (see below).

Compensation claims for occupational lung disease

Patients with all of the above asbestos-related diseases (except pleural plaques and effusions) are entitled to state compensation and a disability pension. Patients can also claim against their employers for negligently exposing them to asbestos for any of the above asbestos-related conditions (including pleural effusions but not pleural plaques). They should be advised to begin legal action within 3 years of being told that they have an asbestos-related condition.

- The same applies for patients with **coal-workers' pneumoconiosis** and **occupational asthma**, and a small number of other industrial diseases.

19.4.2 Coal-workers' pneumoconiosis

The incidence of this pneumoconiosis is related to total dust exposure. Dust particles 2–5 μm in diameter are retained in the respiratory bronchioles and alveoli. Simple coal-workers' pneumoconiosis (CWP) is characterised by small, rounded opacities (<1 cm in diameter), usually seen in the upper zones of the lungs on chest radiograph, and is associated with focal emphysema. The lesions are asymptomatic.

Progressive massive fibrosis

Progressive massive fibrosis (PMF) involves the aggregation of nodules to form larger opacities (of at least 1 cm in diameter) on a background of simple CWP.

- PMF lesions are usually in the upper zones and may cavitate
- Cough, sputum production and dyspnoea occur with reduced life expectancy; deaths occurring from progressive respiratory failure
- PFTs show a mixed obstructive/restrictive pattern with reduced *K*CO.

Coal mining is recognised as a cause of COPD.

Caplan syndrome is the development of multiple round pulmonary nodules in patients with seropositive rheumatoid arthritis and a background of CWP. Nodules may develop before the joint disease, and occur in crops in the periphery of the lung. They may be associated with pleural effusion and may ultimately calcify.

19.4.3 Silicosis

This is caused by inhaling silicon dioxide, a highly fibrogenic dust; those commonly affected are quarry workers, hard-rock miners and civil engineers. Silicosis was commonly associated with TB in the first half of the twentieth century.

- Acute silicosis is characterised by dry cough, and breathlessness occurs within 12 months of exposure to very high levels of dust, eg from sandblasting. Patients rapidly deteriorate over 1–2 years and there is no effective treatment to slow disease progression
- With more chronic exposure silicotic nodules form, which are 3–5 mm in diameter and predominantly affect the upper lobes. These nodules can coalesce and lead to progressive massive fibrosis
- Eggshell calcification occurs around enlarged hilar glands
- Gradually worsening breathlessness is associated with restrictive lung physiology and a fall in gas transfer
- There is no effective treatment (other than lung transplantation in patients with respiratory failure), but the disease is compensable
- Silicosis is associated with an increased incidence of TB.

19.4.4 Berylliosis

The inhalation of fumes from molten beryllium causes an acute alveolitis. However, most cases of berylliosis are due to chronic low-level exposure, causing a tissue reaction similar to sarcoidosis. Non-caseating granulomas form in the lungs and lymph nodes surrounded by fibrous tissue; the chest radiograph shows fine nodulation evenly distributed throughout the lung fields with bilateral hilar lymphadenopathy.

- A positive beryllium lymphocyte proliferation assay in blood and on bronchoalveolar lavage (BAL) is strongly associated with the presence of chronic beryllium disease
- Interstitial fibrosis develops, with shrinking of the lungs
- Patients develop progressive breathlessness, with death ultimately occurring due to respiratory and right heart failure.

19.4.5 Byssinosis

This is caused by exposure to cotton dust, flax and hemp. Acute exposure causes airways narrowing in a third of affected individuals. However, chronic byssinosis develops after years of heavy exposure to cotton dust; symptoms are worse on the first day back after a break from work, and include chest tightness, cough, dyspnoea and wheeze.

- There is a progressive decline in FEV_1 during the working shift, most marked on the first day of the week
- Prevention is by reducing the levels of cotton dust to which employees are exposed
- Bronchodilators may provide some relief of symptoms.

19.4.6 Occupational asthma

Occupational asthma is now the most common industrial lung disease in developed countries. A large number of agents encountered at work cause asthma and are officially recognised for industrial compensation, as listed in the box.

Causes of occupational asthma

- Isocyanates
- Acid anhydride and amine-hardening agents
- Platinum salts
- Stainless steel welding
- Resin used in soldering flux
- Epoxy resins
- Proteolytic enzymes
- Azodicarbonamide (PVC, plastics)
- Pharmaceuticals
- Glutaraldehyde
- Many other chemicals
- Wood dust
- Any known sensitising agent in the workplace
- Laboratory animals and insects
- Dyes
- Flour/grains

Occupational asthma develops after a period of asymptomatic exposure to the allergen, but usually within 2 years of first exposure. Detection depends on a careful history, and 2-hourly PEFR monitoring both at work and at home. Once occupational asthma has developed, bronchospasm may be precipitated by other non-specific triggers such as cold air and exercise. Occupational asthma may develop in workers with previously diagnosed asthma. To identify the substance involved, specific IgE levels may be measured or occasionally bronchial provocation testing may be performed. Early diagnosis and removal of the individual from exposure to the allergen are essential if the person is to make a full recovery. Asthma symptoms may persist despite termination of exposure.

19.4.7 Reactive airway dysfunction syndrome

This reactive airway dysfunction syndrome (RADS) refers to bronchial hyperresponsiveness following the inhalation of high concentrations of irritant gas, aerosols or particles. Asthma-like symptoms usually develop within minutes to hours after exposure and airway hyperreactivity persists over a prolonged period of time. 'Irritant asthma' occurs after multiple exposures to lower concentrations of irritants.

19.4.8 Extrinsic allergic alveolitis (hypersensitivity pneumonitis)

This is a hypersensitivity pneumonitis caused by a specific immunological response (usually IgG mediated) to inhaled organic dusts. It is more common in people who don't smoke.

- **Farmers' lung** is due to the inhalation of thermophilic actinomycetes (usually *Micropolyspora faeni* and *Thermoactinomyces vulgaris*), when workers are exposed to mouldy hay
- **Bird fancier's lung** is caused by inhaled avian serum proteins, present in excreta, and in the bloom from feathers; it primarily affects those who keep racing pigeons and those who have pet budgerigars
- **Ventilation pneumonitis** occurs in inhabitants of air-conditioned buildings where thermophilic actinomycetes grow in the humidification system
- **Bagassosis** is due to exposure to *Thermoactinomyces sacchari* in sugar cane processors
- **Malt workers' lung** is due to the inhalation of *Aspergillus clavatus*
- **Mushroom workers' lung** is due to the inhalation of thermophilic actinomycetes.

Clinical features of extrinsic allergic alveolitis

The clinical features depend on the pattern of exposure. An acute allergic alveolitis develops several hours after exposure to high concentrations of dust. Breathlessness and 'flu-like' symptoms occur, sometimes associated with fever, headaches and myalgia. The symptoms are short-lived and usually resolve completely within 48 hours.

- Inspiratory crackles may be heard on chest auscultation
- The disease may present in a subacute or chronic form characterised by cough, breathlessness, fatigue and weight loss
- Clubbing may occur in association with irreversible pulmonary fibrosis.

Investigation and treatment

The diagnosis of extrinsic allergic alveolitis (EAA) is made by establishing a history of exposure to antigen and the demonstration of precipitating antibodies in the patient's serum.

- **Chest radiograph** may show a generalised haze, sometimes associated with diffuse small nodules. In chronic cases, progressive upper zone fibrosis and loss of lung volume occur
- **Spirometry** becomes restrictive and gas transfer is reduced

Histology of lung biopsy tissue shows a mononuclear cell infiltrate with the formation of non-

- caseating granulomas

- Fluid obtained from **BAL** has a high lymphocyte count (typically >40%)

Precipitins: the demonstration of specific IgG antibodies in serum against the identified antigen.

- The vast majority of patients with hypersensitivity pneumonitis will have positive precipitins to the antigenic stimulus however; precipitins may be present in the absence of clinical disease.

Once the diagnosis has been established, the patient should be isolated from the antigen; if this is impossible, respiratory protection should be worn. Corticosteroids accelerate the rate of recovery from an acute attack but are generally not helpful once established fibrosis has developed.

Pulmonary fibrosis in extrinsic allergic alveolitis

Multiple episodes of acute exposure to agents causing EAA, or long-term, low-grade exposure, as occurs in budgerigar owners, can lead to irreversible lung fibrosis. These chronic cases present with progressive dyspnoea, weight loss and fatigue. The chest radiograph will show lung shrinkage but calcification or cavitation does not develop. HRCT demonstrates reticular, nodular and ground-glass opacities. Prompt diagnosis of extrinsic allergic alveolitis is important because the disease is reversible when diagnosed early.

19.5 TUMOURS

19.5.1 Lung cancer

Lung cancer is the most prevalent cancer worldwide and accounts for 1 in 3 cancer deaths in men and 1 in 6.5 cancer deaths in women. Female mortality from lung cancer now exceeds that from breast cancer. There are over 40 000 new cases of lung cancer diagnosed in the UK every year. Twenty per cent of people who smoke will develop lung cancer. The prognosis is poor, with a 1-year survival rate of around 30%. The 5-year survival rate is <10%. Lung cancer is rare under the age of 40 but the incidence rises steeply with age, peaking in the 80- to 84-year age group.

Causes of lung cancer

- **Smoking**
  - Nearly 90% of lung cancers occur in those who are current or ex-smokers. Those currently smoking are almost 15 times more likely to die from lung cancer than those who have never smoked in their lives
- **Atmospheric pollution**
  - Persistently higher lung cancer rates in urban populations; passive smoking
  - Industrial exposures
  - Asbestos fibre, aluminium industry, arsenic compounds, benzoyl chloride, silica, beryllium
  - Increased incidence in patients with idiopathic pulmonary fibrosis and systemic sclerosis

Smoking is the leading cause of lung cancer. Although smoking rates have declined among adult men and to a lesser extent among women, there is an increasing number of teenage smokers, particularly girls.

Histological types of lung cancer

- **Squamous cell** (35%): usually arises from a central airway. It has a doubling time of 90 days and the best survival of all the different histological types of lung cancer due its potential operability
- **Small-cell** (20%): arises in central airways and grows rapidly. It has a doubling time of 29 days. and is usually metastatic at diagnosis, so surgery is usually inappropriate. This histological subtype is very sensitive to chemotherapy and radiotherapy, and active treatment options are therefore considered in patients with poor performance statuses
- **Adenocarcinoma** (30%): often peripheral. It is slow growing with a doubling time of 160 days
- **Undifferentiated large cell** (10%)
- **Bronchiolar–alveolar** cell carcinoma (5%).

Clinical features of lung cancer

Patients commonly present with cough, breathlessness, haemoptysis, chest pain, hoarse voice or weight loss. Lung cancer should be suspected if a pneumonia fails to resolve radiologically. Occasionally an asymptomatic lesion will be noted on a routine chest radiograph.

Intrathoracic complications of lung cancer

- Collapse of lung distal to obstructing tumour
- Recurrent laryngeal nerve palsy causing hoarseness
- Dysphagia due to compression of the oesophagus by enlarged metastatic lymph nodes or tumour invasion
- Pericarditis with effusion
- Phrenic nerve palsy with raised hemidiaphragm
- Pleural effusion
- Superior vena caval obstruction causing headache, distension of the veins in the upper body, fixed elevation of the JVP, facial suffusion with conjunctival oedema
- Rib metastases
- Spontaneous pneumothorax

Metastases can occur throughout the body but the most commonly involved sites are supraclavicular and anterior cervical lymph nodes, adrenals, bones, liver, brain and skin.

Haemoptysis is one of the common presenting symptoms of lung cancer.

Causes of haemoptysis

- **Common causes**
  - Carcinoma of the bronchus
  - Pneumonia/acute bronchitis
  - Bronchiectasis
  - Pulmonary TB
  - Pulmonary embolus
  - Mitral valve disease
  - Infective exacerbation of COPD
- **Rarer causes**
  - Vascular malformations
  - Mycetoma
  - Connective tissue disorders
  - Vasculitis
  - Goodpasture syndrome
  - Cystic fibrosis
  - Bleeding diathesis
  - Idiopathic pulmonary haemosiderosis

Paraneoplastic syndromes

- **SIADH**: chiefly associated with small-cell lung cancer. May resolve with chemotherapy but recurs with tumour progression. Treatment involves fluid restriction initially and demeclocycline for resistant cases
- **Ectopic adrenocorticotrophic hormone** (ACTH): mainly associated with small-cell lung cancer
- **Hypercalcaemia**: usually associated with multiple bony metastases from squamous cell carcinoma; ectopic parathyroid hormone (PTH) secretion occurs in a few squamous cancers
- **Gynaecomastia**: associated with large-cell carcinoma and adenocarcinoma; may be painful
- **Hyperthyroidism**: rare (due to ectopic thyroid-stimulating hormone (TSH)) – squamous cell lung cancer
- **Lambert–Eaton syndrome**: almost exclusively associated with small-cell lung cancer; produces a proximal myopathy, reduced tendon reflexes and autonomic features
- **Clubbing**: occurs in 10–30% of lung cancers; may resolve after resection (see box below)
- **Hypertrophic pulmonary osteoarthropathy** (HPOA): produces periostitis, arthritis and gross finger clubbing. HPOA is most commonly associated with adenocarcinoma and least frequently with small-cell carcinoma. It involves the long bones (tibia/fibula, radius/ulna or femur/humerus). It is associated with subperiosteal new bone formation visible on plain radiograph and is often painful.

Pulmonary causes of clubbing

- Carcinoma of the bronchus
- Asbestosis
- Lung abscess
- Cystic fibrosis
- Tuberculosis
- Idiopathic pulmonary fibrosis
- Bronchiectasis
- Empyema
- Mesothelioma

Pancoast syndrome

This is due to a tumour of the superior sulcus. The most common presenting complaint is pain (due to involvement of the eighth cervical and first thoracic nerve roots) extending down the medial side of the upper arm to the forearm and hand. The small muscles of the hand may atrophy. Horner syndrome may develop. Chest radiograph demonstrates a shadow at the extreme apex, and there may be destruction of the first and second ribs.

Diagnosis of lung cancer

Wherever possible, the histological type of lung cancer should be confirmed and the patient should be staged, usually by CT. All lung cancers are now staged using the 2009 TNM classification. An assessment of performance status is important prognostically and when considering suitability for treatments such as chemotherapy. Positron emission tomography (PET) is used to to complete staging before surgery or radical radiotherapy, and is also used to assess solitary pulmonary nodules >7 mm in diameter

Diagnosis of lung cancer

- CT of the thorax
- Percutaneous CT-guided biopsy of peripheral nodules
- Bronchoscopy and endobronchial ultrasonography
- Biopsy of metastatic deposit (including lymph nodes)
- Resection of peripheral nodules
- Sputum cytology: occasionally useful if the patient is unfit for bronchoscopy and the tumour is proximally situated.

Treatment of lung cancer

The management of all cases of lung cancer should be discussed at a multidisciplinary team meeting. Surgery offers the best chance of cure. At the time of presentation, only 10–20% of patients with non-small-cell lung cancer will be operable. The 5-year survival rate of all lung cancers depends on the

clinical stage at diagnosis. In small-cell lung cancer, the 5-year survival is 60% for stage I tumours but only 7% for stage IIIb tumours, when disease is locally advanced. Patients whose tumour is technically operable, but who are unfit for surgery due to coexisting medical conditions or poor lung function, may be treated with radical radiotherapy.

- **Palliative radiotherapy** is very effective in relieving pain from bony metastases, controlling haemoptysis and cough. Dysphagia due to oesophageal compression by lymph nodes responds well to radiotherapy
- **Superior vena caval obstruction** can also be treated with radiotherapy, although stenting provides more immediate relief of symptoms
- **Chemotherapy** for unresectable non-small-cell lung cancer offers a small survival benefit but has been shown to provide effective palliation
- **Unresectable tumours** that compromise the trachea or large airways may be palliated by local techniques to maintain airway patency. These include brachytherapy (intraluminal radiotherapy), laser therapy, airway stents and/or photodynamic therapy.

More recently, gene mutations have been identified, particularly in adenocarcinomas, that have become molecular targets for treatment. Epidermal growth factor receptor tyrosine kinase (EGFR-TK) and anaplastic lymphoma tyrosine kinase ALK-TK mutations, if present, can respond to newer therapies such as erlotinib or crizotinib. These mutations are more common in patients who have never smoked. Typically 70–80% patients suitable for this therapy will respond and their prognosis is significantly better than those with adenocarcinomas who do not carry the mutation.

Small-cell lung cancer is associated with an extremely poor prognosis if left untreated, with a median survival of only 6 weeks in advanced disease. The tumour is, however, much more sensitive than other types of lung cancer to chemotherapeutic agents, and cycles of combination chemotherapy can result in remission in up to 80% of cases.

- Median survival is now 16–24 months for limited disease and 6–12 months for extensive disease
- Once the disease has relapsed, mean survival is 4 months.

Prophylactic cranial irradiation increases survival when given in limited disease or extensive disease that has responded to chemotherapy and should be considered.

19.5.2 Mesothelioma

This is most common in men between the ages of 50 and 70 years. The lesion arises from mesothelial cells of pleura or, less commonly, the peritoneum. Asbestos exposure is responsible for at least 85% of malignant mesotheliomas, and the risk of mesothelioma increases with the dose of asbestos received. Crocidolite (blue asbestos) is more potent than amosite (brown asbestos), and both are more potent than chrysotile (white asbestos) in causing mesothelioma.

There is usually a latent period of >30 years between asbestos exposure and development of mesothelioma. The tumour arises from the visceral or parietal pleura, and expands to encase the lung. Pleural mesothelioma presents with chest pain, weight loss and dyspnoea, and may cause pleural effusion.

- Annual incidence of mesothelioma in the UK exceeds 1300 cases. Controls over asbestos exposure came into force only in the 1970s, and the incidence of mesothelioma is rising and expected to peak around 2015. A detailed occupational history is essential
- Chest radiograph and CT of the thorax usually show an effusion with underlying lobulated pleural thickening and contraction of the hemithorax
- Diagnosis is made by pleural biopsy, often done as a video-assisted thoracic surgery (VATS) procedure (see Section 19.6.4); the main differential diagnosis is adenocarcinoma of the pleura or benign pleural thickening
- Treatment is unsatisfactory; radical surgical procedures such as extrapleural pneumonectomy (EPP) should be performed only within the setting of a randomised trial, and current evidence suggests that EPP together with chemotherapy and radiotherapy does not improve survival but may lower quality of life. A further trial looking at less radical surgery in mesothelioma is under way. Radiotherapy is helpful for pain relief. Prophylactic irradiation of tracts (PIT) after invasive chest wall intervention such as pleural biopsy is usually performed, and a multicentre trial assessing the effect of PIT on the development of chest wall metastasis is currently under way. Randomised trials of chemotherapy for mesothelioma are currently ongoing. Pleural effusions should be drained and talc pleurodesis considered once a tissue diagnosis has been made. Involvement of the palliative care team is often helpful
- Median survival from presentation is 9–12 months for pleural mesothelioma and 7 months for peritoneal mesothelioma
- Patients with mesothelioma may be eligible for industrial compensation.

19.5.3 Mediastinal tumours

Mediastinal tumours are often asymptomatic and they may be an incidental finding on a routine chest radiograph. In adults, 90% are benign. Clinical presentation is with stridor, superior vena caval obstruction, dysphagia, Horner syndrome, hoarseness or pericardial effusion. The causes of mediastinal masses can be divided according to situation in the mediastinum:

- **Anterior mediastinum**: thymoma, retrosternal thyroid, lymphoma, teratoma, fibroma, lipoma, seminoma and choriocarcinoma
- **Middle mediastinum**: aortic arch aneurysm, left ventricular aneurysm and pericardial cysts
- **Posterior mediastinum**: neurogenic tumours (neurofibroma, neuroblastoma, neurolemoma, chemodectoma and phaeochromocytoma), oesophageal tumours and diaphragmatic hernia.

The initial investigation is usually chest radiograph, which will be followed by CT. Occasionally radionuclide scans are needed to confirm the presence of functioning thyroid tissue. Magnetic resonance imaging (MRI) may be used to define tissue planes and operability.

19.6 INTERSTITIAL LUNG DISEASE INCLUDING GRANULOMATOUS DISEASE

19.6.1 Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder primarily affecting young adults. The aetiology is unknown. The prevalence varies among different populations, but in the UK it is 20/100 000 to 30/100 000, being highest among West Indian and Asian immigrants. The characteristic histological lesion is the granuloma composed of macrophages, lymphocytes and epithelioid histiocytes, which fuse to form multinucleate giant cells. The disease may present acutely with erythema nodosum and bilateral hilar lymphadenopathy on the chest radiograph (good prognosis with most patients showing radiological resolution within a year) or insidiously with multiorgan involvement. Of patients, 90% have intrathoracic involvement.

Chest radiograph changes are graded as:

- **Stage 0**: clear chest radiograph
- **Stage 1**: bilateral hilar lymphadenopathy (BHL)
- **Stage 2**: BHL and pulmonary infiltration
- **Stage 3**: diffuse pulmonary infiltration
- **Stage 4**: pulmonary fibrosis.

Patients may have no respiratory symptoms or complain of dyspnoea, dry cough, fever, malaise and weight loss. Chest examination is frequently normal; finger clubbing is rare.

Diffuse parenchymal lung involvement may progress to irreversible fibrosis; the mid- and upper zones of the lungs are most frequently affected. Calcification of the hilar nodes or the lung parenchyma may occur with chronic disease. Lung function tests may show a restrictive pattern with a decreased transfer factor. Pleural effusion is rare.

Upper airway involvement is infrequent; the nasal mucosa may become hypertrophied and cause obstruction, crusting and discharge; perforation of the nasal septum and bony erosion are rare.

Extrapulmonary disease

- **Lymphadenopathy**: painless, rubbery lymph node enlargement is more common in Black patients; the cervical and scalene lymph nodes are most frequently affected
- **Splenomegaly** (25%)
- **Liver involvement**: this is common but, apart from liver enlargement, is often subclinical (derangement of liver function tests). Liver biopsy is of diagnostic value in 90% (typical sarcoid granulomas)
- **Skin**: erythema nodosum (most commonly in White females) in disease with BHL; skin plaques, subcutaneous nodules and lupus pernio (violaceous lesions on the nose, cheeks and ears) seen in chronic disease
- **Acute anterior uveitis** (25%): chronic iridocyclitis affects older patients and responds poorly to treatment
- **Heerfordt–Waldenström syndrome**: consists of parotid gland enlargement, uveitis, fever and cranial nerve palsies
- **Neurological manifestations** (uncommon): cranial nerve palsies (facial nerve most often affected), meningitis, hydrocephalus, space-occupying lesions and spinal cord involvement; granulomas infiltrating the posterior pituitary may produce diabetes insipidus, hypothalamic

hypothyroidism or hypopituitarism

- **Cardiac sarcoid**: may result in cardiac muscle dysfunction or involve the conducting system, producing arrhythmias, bundle-branch block or complete heart block
- **Renal involvement**: renal impairment may be associated with hypercalcaemia. Acute renal failure can be due to granulomatous interstitial nephritis. Glomerulonephritis is a rare complication (see also Chapter 15, Nephrology)
- **Bone cysts**: with overlying soft-tissue swelling, bone cysts occur most often in the phalanges, metacarpals, metatarsals and nasal bones; arthritis is common
- **Hypercalcaemia**: this occurs in at least 11% of cases of sarcoidosis and is due to excess production of vitamin D and gut activity (calcium reabsorption). Hypercalciuria is found in 40% of patients and 10% of patients with sarcoidoisis will develop renal calculi.

Diagnosis

The combination of BHL with erythema nodosum (EN) in a young adult is virtually diagnostic of acute sarcoidosis. The combination of BHL and EN in association with fever and arthralgia is known as Löfgren syndrome. The main differential diagnoses are TB and lymphoma, and every effort should be made to confirm the diagnosis of sarcoidosis histologically.

- **Thoracic CT** appearances are often characteristic, showing hilar and mediastinal lymphadenopathy, nodules along bronchi, vessels and, in subpleural regions, ground-glass shadowing, parenchymal bands, cysts and fibrosis
- **Tissue biopsy** (transbronchial and endobronchial biopsy) can demonstrate non-caseating granulomas in 85–90% of cases with respiratory involvement
- Elevated serum angiotensin-converting enzyme (ACE) and calcium are consistent with the diagnosis but are non-specific. The 24-hour urinary calcium excretion is often raised
- The **Kveim–Siltzbach test** (intradermal injection of extract of spleen from a patient with active sarcoidosis with skin biopsy at 4–6 weeks demonstrating a granulomatous response) is **no longer used**
- Anergy to Heaf testing favours a diagnosis of sarcoid, but patients who are HIV positive or who have overwhelming TB may also be anergic.

Treatment of sarcoidosis

The best prognosis is associated with acute sarcoidosis which frequently undergoes complete remission without specific therapy.

- Stage 0 and 1 disease usually resolves spontaneously
- With stage 2 disease, lung function tests should be performed serially and treatment instituted if there is evidence of progressive deterioration
- Steroids are the mainstay of therapy for chronic disease but response is unpredictable.

Steroid therapy is definitely indicated for hypercalcaemia and hypercalciuria which persist despite dietary calcium restriction, and also for ophthalmological and neurological complications. Prednisolone, where indicated, should be prescribed at 0.5 mg/kg per day for the first 4 weeks of

treatment and subsequently gradually down-titrated to the lowest maintenance dose that controls the disease and its symptoms. Withdrawal of treatment should be considered after 6–24 months. Other immunosuppressive agents (eg azathioprine or methotrexate) may be used as steroid-sparing agents.

19.6.2 Histiocytosis X

Three clinical entities are recognised:

- **Eosinophilic granuloma**: solitary bone lesions occurring in children and young adults. Lung disease is known as Langerhans' cell histiocytosis
- **Letterer–Siwe disease**: a diffuse multisystem disorder of infancy which is rapidly lethal
- **Hand–Schüller–Christian disease**: characterised by exophthalmos, bony defects and diabetes insipidus (in children and teenagers). Diffuse nodular shadows occur in the lung with hilar lymphadenopathy

In adults, histiocytosis is often confined to the lung. It is rare and most likely in young adults.

Patients present with non-productive cough and breathlessness. The chest examination is usually normal.

- Strongly associated with smoking
- Chest radiograph shows multiple ring shadows on a background of diffuse reticulonodular opacities, mainly in the upper and mid-zones; the lung bases are spared
- With disease progression, larger cysts and bullae form and interstitial fibrosis develops. Spontaneous pneumothorax occurs in 25%. Lung volumes are preserved
- Diagnosis is by HRCT and occasionally lung biopsy
- Treatment includes smoking cessation and steroids; spontaneous remission occurs in 25% of patients, but in a further 25% the disease may be rapidly fatal. Patients may progress to end-stage fibrotic lung disease.

19.6.3 Interstitial lung disease

Interstitial lung disease is associated with many conditions, including the connective tissue diseases (particularly systemic lupus erythematosus [SLE] and systemic sclerosis), rheumatoid arthritis and sarcoidosis. When pulmonary fibrosis develops without obvious cause, it is known as idiopathic pulmonary fibrosis. Extrinsic allergic alveolitis also causes diffuse interstitial fibrosis.

19.6.4 Idiopathic pulmonary fibrosis ('usual interstitial pneumonia')

This is a specific form of lung fibrosis characterised by usual interstitial pneumonia (UIP) on lung biopsy. UIP is the term given to the histopathological pattern of honeycombing, minimal cellular inflammation and regions of proliferating myofibroblasts (fibroblastic foci) occurring in a patchy distribution. This pattern of disease can also be seen radiologically via HRCT. It accounts for around 80% of patients with interstitial lung disease. The prevalence is increasing (currently 20–30/100 000 in some areas). It is a disease of middle-aged and elderly people, more common in men, and is

possibly the result of an inhaled environmental antigen; metal and wood dusts have been implicated but no causal relationship has been identified. There may be an association with Epstein–Barr virus (EBV). Patients present with a dry cough and breathlessness, and signs include cyanosis, finger clubbing and fine, late inspiratory crackles. Prognosis is poor and median survival is 3 years from diagnosis.

- **Lung function tests**: small static lung volumes, with reduction in gas transfer and restrictive spirometry
- **Blood gas analysis**: typically shows type 1 respiratory failure with hypoxaemia and a normal or low *P*CO2
- **Chest radiograph**: reveals small lung volumes and interstitial shadowing most marked at the bases and peripheries. HRCT is useful to determine radiological pattern of disease (typically UIP) and, within an appropriate clinical setting, it may be enough to diagnose IPF without proceeding to more invasive diagnostic tests.
- **VATS** (or open lung biopsy): should be used in patients who are fit enough to undergo the procedure when there is any diagnostic doubt
- **Histology**: shows variable degrees of established fibrosis and acute inflammation.

Treatment of idiopathic pulmonary fibrosis

Treatment options are limited. Until 2011 'triple therapy' with a combination of azathioprine, prednisolone and *N*-acetylcysteine was commonly prescribed. After interim data analysis of a large clinical trial of treatments for idiopahtic pulmonary fibrosis (IPF), this regimen is no longer recommended because it may cause harm. *N*-Acetylcysteine as montherapy for IPF is currently being evaluated via this trial. Pirfenidone, an immunosuppressant with anti-inflammatory and anti-fibrotic effects, may be used in patients who have a FVC of 50–80% of their predicted values, and has been shown to slow the rate of FVC decline and disease progression. Single-lung transplantation should be considered in patients below the age of 65 years. Patients may benefit from pulmonary rehabilitation, oxygen therapy and, in terminal cases, morphine/lorazepam to palliate symptoms.

Other forms of interstitial lung disease

The following conditions are recognised subtypes of interstitial lung disease:

- Non-specific interstitial pneumonia (NSIP)
- Desquamative interstitial pneumonia (DIP)
- Acute interstitial pneumonia (AIP)
- Respiratory bronchiolitis-associated interstitial lung disease (RBILD)
- Lymphocytic interstitial pneumonitis (LIP).

Of these, NSIP, DIP and RBILD are more steroid responsive and carry a better prognosis. AIP carries the same poor prognosis as adult respiratory distress syndrome (ARDS).

Drugs causing pulmonary fibrosis

- Amiodarone – Causes an alveolitis (which may be reversible on drug cessation), progressing to diffuse fibrosis; more common when higher doses are used
- Sulfasalazine
- Methotrexate
- Busulfan
- Bleomycin
- Cyclophosphamide
- Nitrofurantoin
- Gold
- Melphalan

Extrinsic allergic alveolitis (or hypersensitivity pneumonitis)

(This is covered in Section 19.4.8)

Causes of reticular–nodular shadowing on chest radiograph

- Upper zone
- Extrinsic allergic alveolitis
- Sarcoidosis
- Coal-workers' pneumoconiosis
- Silicosis
- Basal zone
- Idiopathic pulmonary fibrosis
- Lymphangitis carcinomatosis
- Drugs
- Connective tissue disorders

Causes of calcification on chest radiograph

- Lymph node calcification
- Sarcoidosis
- Silicosis
- TB
- Parenchymal calcification
- Healed tuberculous lesions
- Healed fungal infections
- Previous varicella pneumonia
- Mitral stenosis*

- Chronic left ventricular failure*
- Hyperparathyroidism
- Chronic renal failure
- Vitamin D intoxication
- Benign tumours
- Busulfan lung
- Caplan syndrome
- Alveolar microlithiasis
- Pleural calcification
- Calcified pleural plaques following asbestos exposure, and pleural calcification due to previous haemothorax or TB

*Results in secondary pulmonary haemosiderosis.

19.7 PULMONARY VASCULITIS AND EOSINOPHILIA

19.7.1 Granulomatosis with polyangiitis (previously known as Wegener's granulomatosis)

Small/medium-sized arteries, veins and capillaries are involved with a granulomatous inflammation. Of cases, 90% present with upper or lower respiratory tract symptoms. Upper airway involvement includes crusting and granulation tissue on the nasal turbinates, producing nasal obstruction and a bloody discharge; collapse of the nasal bridge produces a saddle-shaped nose; cANCA (antineutrophilic cytoplasmic autoantibody, cytoplasmic) is present in 90% of cases (see also Chapter 10, Immunology, Chapter 15, Nephrology and Chapter 20, Rheumatology).

- **Respiratory symptoms**: cough, haemoptysis, breathlessness and pleurisy. Stenosis of a main airway may cause severe breathlessness and stridor
- Large, rounded shadows may be visible on the chest radiograph and these often cavitate. Pleural effusions and infiltrates may develop
- Seventy-five per cent develop glomerulonephritis, and eye and joint involvement are common. Patients may have a typical vasculitic skin rash and mononeuritis multiplex may also develop
- **Prognosis**: untreated, the median survival is 5 months. Treatment with cyclophosphamide and steroids has now reduced the mortality rate to around 10%.

19.7.2 Eosinophilic granulomatosis with polyangiitis

As a syndrome of necrotising vasculitis, eosinophilic infiltrates and granuloma formation, there is often a prior history of asthma and sometimes allergic rhinitis. The mean age of onset is about 38 years. Peripheral blood eosinophilia occurs with eosinophilic infiltrates of the lungs and often the GI tract. GI symptoms can include, pain, diarrhoea and bleeding. Vasculitic lesions may appear on the

skin (purpura, erythema or nodules) and mono- or polyneuropathy may occur. Approximately half of all patients will have renal involvement.

Diagnosis

Tissue biopsy of the an involved site is the gold standard for diagnosis:

- The perinuclear ANCA (pANCA) is positive in 50%
- High peripheral blood and BAL eosinophil cell counts are usually present
- Serum total IgE levels are usually significantly raised
- Chest radiograph shows pulmonary infiltraes and/or nodules without cavitation.

Untreated, 50% patients will die within 3 months of diagnosis. Treatment is with steroids and/or cyclophosphamide, and mean survival with treatment is 9 years.

19.7.3 Polyarteritis and Henoch–Schönlein vasculitis

- Microscopic polyangiitis (MPA) may involve the lungs to produce pulmonary haemorrhage, haemoptysis and occasionally pleurisy; granulomas are not a feature
- Lung involvement is uncommon in polyarteritis nodosa; it consists of pulmonary infiltrates (composed mainly of neutrophils) without granuloma formation
- Pulmonary involvement is a rare feature in Henoch–Schönlein purpura (HSP). The disorder can be associated with streptococcal or hepatitis B (less often with viral or fungal) infections.

19.7.4 Connective tissue disorders

- **Rheumatoid disease**: has many pulmonary associations including bronchiectasis, obliterative bronchiolitis, bronchiolitis obliterans organising pneumonia (BOOP), pulmonary fibrosis, nodules, Caplan syndrome and pleurisy with effusion
- **SLE**: pulmonary fibrosis, BOOP, pleural effusion and shrinking lung syndrome can all occur
- **Systemic sclerosis**: associated with bronchiectasis, pulmonary fibrosis and aspiration pneumonia (due to dysphagia).

All may cause pulmonary hypertension, but this occurs most frequently in systemic sclerosis patients.

Pulmonary vasculitis occurs in association with

- Ulcerative colitis
- Giant-cell arteritis
- Takayasu's arteritis
- Behçt syndrome
- Multiple pulmonary emboli
- Infection
- Polyarteritis nodosa

- Microscopic polyangiitis
- Granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis
- Idiopathic pauci-immune cappilaritis
- Systemic lupus erythematosus

19.7.5 Pulmonary eosinophilia

This describes a group of disorders characterised by peripheral blood eosinophilia and eosinophilic infiltrates in the lungs.

Causes of pulmonary eosinophilia

- Eosinophilic granulomatosis with polyangiitis
- Löffler syndrome
- Drug induced (eg nitrofurantoin, sulfasalazine, imipramine, phenytoin)
- ABPA
- Chronic eosinophilic pneumonia
- Hypereosinophilic syndrome
- Acute eosinophilic pneumonia
- Tropical pulmonary eosinophilia (associated with parasite infection, eg *Strongyloides stercoralis*, *Toxacara canis*)

Löffler syndrome (simple pulmonary eosinophilia)

Transient radiographic shadows and peripheral blood eosinophilia are seen in association with the passage of parasites (commonly *Ascaris lumbricoides* or *strongyloides*) through the lungs. The illness usually lasts <2 weeks and the eosinophilia is moderate (usually 5–20% of the total white blood cell differential). Symptoms are mild and include cough, rhinitis, night sweats, breathlessness, wheeze and fever. It usually takes 2–3 months after initial infection before parasites can be detected in stool specimens. The condition usually resolves spontaneously but may be treated with an anthelmintic agent such as mebendazole.

Chronic eosinophilic pneumonia

Peripheral blood eosinophilia and persistent pulmonary infiltrates occur without any obvious cause. Onset is insidious, with symptoms such as cough, fever, breathlessness and weight loss, usually occuring over approximately 8 months.

- The chest radiograph shows peripheral infiltrates and is often described as a ‘reverse batwing’, being the photonegative appearance of pulmonary oedema
- Lung biopsy shows airspace consolidation with an eosinophilic inflammatory infiltrate

- Symptoms are more severe than in simple pulmonary eosinophilia. The condition responds to steroids.

Hypereosinophilic syndrome

Characterised by very high eosinophil counts (mean 20 × 10^9/L), the syndrome has clinical manifestations (weight loss, fever, night sweats, hepatomegaly and lymphadenopathy) similar to chronic eosinophilic pneumonia. Cardiac involvement occurs in 60% (producing arrhythmias and cardiac failure).

- Thromboembolism occurs in two-thirds of patients
- Other organ involvement: the central nervous system (intellectual deterioration and peripheral neuropathies), GI tract and kidney (proteinuria and hypertension)
- Steroids are usually effective but cyclophosphamide, hydroxyurea, azathioprine or interferon-α may be required.

Acute eosinophilic pneumonia

Patients present with an acute illness with fever, myalgia, pleurisy and respiratory failure. The chest radiograph shows diffuse infiltrates, but these are not usually peripheral. The blood eosinophil count is usually normal, although the eosinophil count in fluid obtained from BAL is very high. Parasitic infection should be excluded. Treatment is with high-dose steroids and ventilatory support.

19.8 MISCELLANEOUS RESPIRATORY DISORDERS

19.8.1 Pleural effusion

A pleural effusion is a collection of fluid within the pleural space and can result from pleural, pulmonary and extrapulmonary diseases. They can be grouped into two main categories: transudates and exudates.

Diagnostic pleural aspiration of effusions, preferably ultrasound-guided, should be performed to help ascertain the underlying aetiology (with the exception of bilateral effusions in which the clinical setting is strongly in keeping with a transudative cause). Fluid should be sent for pH, protein and lactate dehydrogenase (LDH) concentrations, cytological examination, Gram stain, AAFB stain and microbiological culture. Raised pleural fluid protein and/or LDH concentrations are found in exudative pleural effusions. The diagnostic yield from microbiological culture is higher if some of the fluid sampled is sent for analysis in blood culture bottles. Paired peripheral blood samples for serum protein and LDH concentrations should be sent.

Causes of pleural effusion

- **Transudates**
  - **Common**
    - Left ventricualr failure (LVF)

    - Cirrhosis of the liver
    - Nephrotic syndrome
    - Other causes of hypoproteinaemia
- **Uncommon**
    - Myxoedema
    - Pulmonary emboli
    - Sarcoidosis
    - Peritoneal dialysis
- **Exudates**
    - **Common**
        - *Infections*: Bacterial pneumonia TB
        - *Malignancy*: Primary carcinoma of bronchus Metastatic carcinoma
        - Pulmonary embolism
        - *Connective tissue disorders*: Rheumatoid arthritis SLE
        - *Subdiaphragmatic*: pancreatitis subphrenic abscess
        - *Trauma*: Haemothorax Chylothorax
    - **Uncommon**
        - *Infections*: fungal viral parasitic
        - *Malignancy*: lymphoma, pleural tumours
        - *Connective tissue disorders* Wegener's granulomatosis Sjögren syndrome Immunoblastic lymphadenopathy
        - *Subdiaphragmatic*: Hepatic abscesses
        - *Trauma*: Ruptured oesophagus

Other rare causes

- Meigs syndrome
- Asbestos exposure
- Familial Mediterranean fever
- Yellow nail syndrome
- Post-thoracotomy syndrome
- Dressler syndrome

To determine whether fluid is a transudate or an exudate, fluid protein content should be examined: protein levels <25 g/L are consistent with a transudate, protein levels >35 g/L are consistent with an exudate. For fluid that has a protein concentration between 25 and 35, Light's criteria should be applied. Light's criteria state that pleural fluid is exudative if one of the following applies:

- Pleural fluid:serum protein ratio is >0.5

- Pleural fluid:serum LDH ratio is >0.6
- Pleural fluid LDH is more than two-thirds limit of normal serum
- A pH <7.1 also suggests an exudate.

If clinically indicated, other assays may be requested to help ascertain the underlying aetiology of an effusion:

- Low concentrations of glucose in the pleural fluid compared with serum glucose are found in infection, malignancy and oesophageal rupture. Particularly low glucose levels (<1.6 mmol/L) are seen in effusions due to rheumatoid arthritis
- In pancreatitis, the amylase level may be higher in pleural fluid than in blood.

Pleural fluid cell content should be examined:

- Transudates contain <1000 white cells per cubic millimetre, made up of a mixture of polymorphs, lymphocytes and mesothelial cells. Exudates usually have a much higher WCC. In bacterial infection, this is usually polymorphs, but in TB and malignancy, lymphocytis is common
- Malignant cells from a primary bronchial carcinoma or metastatic disease may be found in approximately 60% of malignant pleural effusions.

Pleural fluid pH and microbiological culture are particularly important in deciding appropriate management of effusions associated with infection.

Tube drainage is indicated if:

- The pleural fluid pH is <7.2 (suggesting a developing empyema)
- Pleural fluid Gram stain and/or culture is positive
- Frank pus is aspirated

If the cause of an exudative effusion is not apparent, the patient should have further investigation with contrast-enhanced CT of the thorax and pleural biopsy. Medical thoracoscopy is increasingly performed and allows direct visualisation of the pleura. Biopsies can be taken and, if the appearances are of malignancy, talc pleurodesis can be performed.

19.8.2 Pneumothorax

Pneumothorax may be classified as either primary or secondary, the latter complicating underlying lung disease. Presenting symptoms are of pleuritic chest pain and breathlessness, and the degree of dyspnoea relates to the size of the pneumothorax.

Primary spontaneous pneumothorax usually occurs at rest, and the peak age of presentation is in patients in their early 20s. Pneumothorax is much more common in people who smoke.

Clinical signs of pneumothorax

- Diminished breath sounds
- Decreased chest excursion on the affected side
- Hyperresonance of percussion note
- Auscultatory 'clicks'

Signs of tension

- Severe breathlessness
- Hypotension
- Mediastinal shift
- Cardiac arrest (often electromechanical dissociation)

Diagnosis

This is made when a visceral pleural line is seen on chest radigraph. In patients with emphysema it must be differentiated from large, thin-walled bullae. In general, the pleural line is convex towards the lateral chest wall in pneumothorax, whereas a large bulla tends to be concave towards the lateral chest wall. A CT scan can be used to differentiate between these two conditions.

Treatment

- In a patient who has no underlying lung disease and with no clinical distress accompanying a small (≤2 cm) pneumothorax, no specific therapy is required, but a follow-up chest radiograph should be arranged to ensure lung re-expansion. In patients aged >50 years with significant smoking history or underlying lung disease and no clinical distress accompanying a particularly small (<1 cm) pneumothorax, no intervention is immediately required other than oxygen therapy. These patients should be admitted and observed for 24 hours
- In most other patients, aspiration of the pneumothorax should be attempted first. The exceptions to this rule are summarised in the box below.

Indications for intercostal drain insertion as initial pneumothorax management

- Patients aged >50 years with large pneumothoraces (>2 cm) with either:
  - A significant smoking history
  - Underlying lung disease
- Signs of a tension pneumothorax

- If the pneumothorax recurs despite aspiration, a small-bore chest drain should be inserted. This may be removed when the lung has fully reexpanded and no air leak (bubbling) has occurred for at least 24 hours

Patients with chest drains should be managed by a specialist respiratory team. Chest drains

- should not be clamped. Once the lung has been fully reinflated and bubbling has ceased for 24 hours, the drain can then be removed. Removal of the drain too early is likely to result in recurrence of the pneumothorax
- If the lung does not re-expand with chest drain insertion, high-volume, low-pressure suction may be applied to the drain, although this is not recommended as routine and should be done under the supervision of a respiratory team. A patient should be referred for thoracic surgical opinion if the pneumothorax has not resolved within 48 hours of chest drain insertion
- Patients with recurrent pneumothorax on the same side will also need thoracic surgical intervention.

19.8.3 Obstructive sleep apnoea/hypopnoea syndrome

It is estimated that approximately 4% of middle-aged men and up to 2% of middle-aged women have symptomatic obstructive sleep apnoea (OSA). The cardinal symptom is daytime somnolence due to the disruption of the normal sleep pattern. This leads to poor concentration, irritability and personality changes, and a tendency to fall asleep during the day. Road traffic accidents are more frequent in this group of patients. The problem is exacerbated by night-time alcohol intake and sedative medication.

Pathogenesis

During sleep, muscle tone is reduced and the airway narrows so that airway obstruction develops between the level of the soft palate and the base of the tongue. Respiratory effort continues but airflow ceases due to the obstructed airway; eventually the patient arouses briefly and ventilation is resumed. The cycle is repeated several hundred times throughout the night.

- Over 80% of men with OSA/hypopnoea syndrome (OSAHS) are obese (BMI >30 kg/m^2). Hypothyroidism and acromegaly are also recognised causes. Retrognathia can cause OSAHS, and large tonsils may obstruct the airway. Patients with OSAHS have higher blood pressure than matched controls
- Patients (or their partners) give a history of loud snoring interrupted by episodes of apnoea. There may be a sensation of waking up due to choking. Sleep is generally unrefreshing
- Patients suspected of having OSAHS have some measure of daytime somnolence made (eg using the Epworth scoring system). Mental concentration is impaired
- Diagnosis is made by demonstration of desaturation (SaO_2 <90%) associated with a rise in heart rate and arousal from sleep, together with cessation of airflow. The frequency of apnoeic/hypopnoeic episodes per hour is used to assess disease severity. The diagnosis can be made in most patients by home pulse oximetry recordings or by limited sleep studies, but, where the diagnosis is in doubt, full polysomnography (sleep studies) may be needed.

Treatment of sleep apnoea

- Nocturnal CPAP administered via a nasal mask
- Tonsillectomy if enlarged tonsils are thought to be the cause

- Correction of underlying medical disorders (eg hypothyroidism)
- Weight loss for individuals who are obese
- Anterior mandibular positioning devices – useful in some patients
- Tracheostomy (only as a last resort)

Uvulopalatopharyngoplasty is not generally of benefit.

Once a patient has been diagnosed as having OSAHS, and if he has excessive daytime somnolence, then the DVLA (Driver and Vehicle Licensing Agency) should be informed and the patient should refrain from driving. Patients may resume driving once their OSAHS has been satisfactorily treated. Holders of large goods vehicle (LGV) licences may also have their licence reinstated once they have been adequately treated.

19.8.4 Adult respiratory distress syndrome

This syndrome comprises the following:

- Arterial hypoxaemia
- Bilateral, fluffy pulmonary infiltrates on chest radiograph
- Non-cardiogenic pulmonary oedema (pulmonary capillary wedge pressure <18 cmH_2O)
- Reduced lung compliance.

Causes of ARDS

- Sepsis
- Burns
- DIC
- Pneumonia
- Aspiration of gastric contents
- Near-drowning
- Drug overdoses (eg diamorphine, methadone, barbiturates, paraquat)
- Trauma
- Pancreatitis, uraemia
- Cardiopulmonary bypass
- Pulmonary contusion
- Smoke inhalation
- Oxygen toxicity

Management

No specific treatment is available and management is essentially supportive. Supplemental oxygen is

given and patients frequently require mechanical ventilation. Pressure-controlled, inverse-ratio ventilation is used because this lowers peak airway pressure, reduces barotrauma and creates better distribution of gas in the lungs. With the addition of positive end-expiratory pressure (PEEP), there is greater alveolar recruitment, increased FRC, better lung compliance and reduced shunt. Turning the patient into the prone position intermittently allows those dependent parts of the lung that are susceptible to atelectasis to re-expand and improves blood flow to the ventilated parts of the lung.

- Inhaled nitric oxide (NO) is a potent vasodilator which causes selective vasodilatation of the ventilated areas of the lung when inhaled at low concentrations
- Use of exogenous surfactant in adult patients has no proven value
- Corticosteroids have been shown to be beneficial in the latter stages of ARDS (characterised by progressive pulmonary interstitial fibroproliferation).

19.8.5 Rare lung disorders

Lymphangioleiomyomatosis

This affects young/middle-aged women and is characterised by non-neoplastic proliferation of atypical smooth muscle, resulting in airway and vascular obstruction, cyst formation and progressive decline in lung function. It may occur spontaneously or as part of the tuberous sclerosis complex. Of patients, 50% have renal angiomyolipomas.

- Patients present with progressive breathlessness, pneumothorax or chylous effusions
- The chest radiograph may appear normal initially but HRCT shows thin-walled cysts. The condition must be differentiated from histiocytosis X
- Pregnancy and oestrogen replacement are associated with more rapid disease progression
- The only known cure is lung transplantation. Hormonal therapy with progesterone is used to slow disease progression
- Average survival is 10–20 years.

Alveolar proteinosis

A disorder characterised by the accumulation of phospholipid and proteinaceous material in the alveoli and distal airways. The male:female ratio is 3 : 1, with age of onset 30–50 years. Patients present with dyspnoea of effort and cough; occasionally constitutional symptoms (fever, weight loss and malaise) develop. Haemoptysis and chest pain may occur.

- Chest radiograph shows bilateral infiltrates with air bronchograms in a butterfly pattern. CT classically shows a ‘crazy-paving’ pattern of airspace shadowing
- BAL establishes the diagnosis, yielding milky fluid
- Treatment consists of interval whole-lung lavage under general anaesthesia.

Pulmonary amyloidosis

The lungs are frequently involved in systemic amyloidosis (most often in primary amyloidosis); either

the lung parenchyma or the tracheobronchial tree may be predominantly affected. The diagnosis is usually confirmed by biopsy. (See also Chapter 15, Nephrology.)

- **Bronchial tree**: plaques visible on bronchoscopy; leads to breathlessness, wheezing, stridor and haemoptysis
- **Nodules**: may develop throughout the lung parenchyma or a solitary nodule may occur
- **Diffuse parenchymal amyloidosis**: may develop with amyloid deposited along the alveolar septa and around blood vessels; this form is extremely rare.

Idiopathic pulmonary haemosiderosis

This condition is of unknown cause and is characterised by recurrent episodes of alveolar haemorrhage, haemoptysis and secondary iron-deficiency anaemia. It may present in childhood with chronic cough, pallor and failure to thrive. Generalised lymphadenopathy and hepatosplenomegaly may occur. It is associated with autoimmune disorders.

- In the early stages the chest radiograph shows transient blotchy shadows
- Eventually pulmonary fibrosis develops, and this is associated with chronic dyspnoea and finger clubbing. Steroids are unhelpful and patients die of cor pulmonale or massive bleeding.

Chapter 20
Rheumatology

CONTENTS

Rheumatology

20.1 SEROLOGY IN RHEUMATOID ARTHRITIS

20.1.1 Rheumatoid factors

Rheumatoid factors are antibodies directed against the Fc fragment of IgG. They can be of any isotype (IgM/IgG/IgA) but routine tests are for IgM rheumatoid factors. They were originally detected by agglutination tests (latex beads/sheep cell agglutination), but radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) are now the more common methods.

Rheumatoid factors

- Present in 75% of cases of rheumatoid arthritis
- 100% of cases of rheumatoid arthritis with extra-articular disease
- 5% of the normal population
- Associated with more severe arthritis
- Predict persistence of inflammatory arthritis.

Other conditions with rheumatoid factors

- normal population
  - 5% RF-positive
  - 15% aged >65
- other rheumatological disorders
  - systemic lupus erythematosus (SLE) 20%
  - Sjögren syndrome >75%
  - systemic sclerosis 30%
  - dermatomyositis 10%
- hypergammaglobulinaemic states
- chronic liver disease
- paraproteinaemia
- cryogolulinaemia (often very high titre)
- chronic infection
- bacterial endocarditis
- leprosy

- hepatitis C >50%
- miscellaneous
- sarcoidosis
- malignancy
- acute infections.

Anti-cyclic citrullinated protein (anti-CCP) or anti-citrullinated protein antibodies (ACPAs)

- Present in 70% of patients with rheumatoid arthritis (RA)
- More specific than rheumatoid factor for RA
- Measured by ELISA
- May be present years before the onset of disease
- Associated with more severe disease course.

Other conditions with anti-CCP antibodies

- SLE and Sjögren syndrome (<15%, usually with erosive arthritis)
- Autoimmune hepatitis type 1 (found in <10%, but associated with progression to cirrhosis).

20.2 RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic, symmetrical inflammatory polyarthritis, characteristically involving small joints. Soft tissues and extra-articular structures may also be involved in the disease process.

- Prevalence 1–3%
- Female:male ratio of 3:1
- Peak onset in middle age.

The cause is not known, but both genetic and environmental factors play a part. Genetic factors account for 10–30% of the risk of developing RA. There is an association with HLA-DR4. The strongest environmental risk factor is smoking. Both HLA-DR4 and smoking are associated with more severe disease.

Prognosis is variable and difficult to predict in individual cases:

- 50% are too disabled to work 10 years after diagnosis
- 25% have relatively mild disease
- There is excess mortality (mostly cardiovascular).

The following are associated with a worse prognosis:

- rheumatoid factor
- anti-CCP antibodies
- smoking
- extra-articular features

- HLA-DR4
- female sex
- early erosions
- insidious onset
- severe disability at presentation.

20.2.1 Clinical features

The onset of disease may take several forms:

- Insidious (weeks/months) 55–70%
- Intermediate 15–20%
- Acute (days) 8–15%.

Other rare patterns of onset

- **Palindromic**: episodic with complete resolution between attacks
- **Systemic**: presentation with systemic/extra-articular features
- **Polymyalgic**: symptoms initially similar to polymyalgia rheumatica

Diagnosis

Undifferentiated inflammatory arthritis

Undifferentiated inflammatory arthritis (UIA) is an inflammatory arthritis that cannot yet be categorised as a specific form of arthritis (the clinical features do not fulfil the diagnostic criteria). The inflammation may be evident clinically or with imaging (ultrasonography or magnetic resonance imaging [MRI]).

Outcome of UIA

- 30% remit
- 30% evolve into rheumatoid arthritis
- 20% remain undifferentiated.

Conditions that may present as UIA

- Rheumatoid arthritis
- Self-limiting inflammatory arthritis
- Crystal-induced arthritis
- Psoriatic arthritis
- Spondyloarthropathies

- Reactive arthritis
- Polymyalgia rheumatica
- SLE

The American College of Rheumatology classification criteria for rheumatoid arthritis (1988) require four of the following:

- Arthritis of hand joints for >6 weeks
- Symmetrical arthritis for >6 weeks
- Morning stiffness >1 hour for >6 weeks
- Arthritis of three or more joint areas for >6 weeks
- Rheumatoid factor
- Subcutaneous nodules
- Characteristic radiological findings.

But these criteria cannot identify those patients with UIA that will evolve into RA. For patients with UIA, therefore, the likelihood of developing RA must be estimated, to allow appropriate treatment to be given. This is sometimes referred to as predictive testing.

Factors predictive of progression from UIA to RA

- Number and pattern of joints involved
- Positive RF or ACPA
- Duration of disease
- Raised inflammatory markers

These features have been combined in the ACR/ EULAR 2011 classification criteria for RA. Patients receive management as for RA if they score ≥6 points.

Joint involvement

1 large joint (0 points)
2–10 large joints (1 point)
1–3 small joints (2 points)
4–10 small joints (3 points)
>10 joints (including at least 1 small joint) (5 points)

Serology

Not positive for either RF or ACPA (0 points)
At least one of these tests are positive at low titre (2 points)
At least one test is positive at high titre (3 points)

Duration of synovitis

<6 weeks (0 points)
≥6 weeks (1 point)

Acute phase reactants

Neither CRP nor ESR is abnormal (0 points)
Abnormal CRP or abnormal ESR (1 point)

Note that patients receive the highest point score they fulfil within each domain. For example, a patient with five small joints involved and four large joints involved, scores 3 points.

Low titre serology means more than the upper limit of normal, but not higher than three times the upper limit of normal. High titre serology is more than three times the upper limit of normal.

20.2.2 Musculoskeletal features

Joints

Symmetrical metacarpophalangeal (MCP), proximal interphalangeal (PIP) and wrist joint synovitis is characteristic but any synovial joint may be involved. There is involvement of the cervical spine in 30%. Hip and distal interphalangeal (DIP) joint involvement is rare in early disease.

Characteristic deformities

- Ulnar deviation of MCP joints
- Boutonniére deformities of fingers
- Swan-neck deformities of fingers
- Z-deformity of thumbs

Soft tissue involvement in RA

- **Tenosynovitis**
  - Tendon rupture (extensor more frequently than flexor)
  - Carpal tunnel syndrome (common)
- **Ligament laxity**
  - Atlanto-axial subluxation (most are asymptomatic)
  - Subaxial subluxation
- **Lymphoedema**
  - Rare

20.2.3 Extra-articular manifestations

Extra-articular features may arise in several ways:

- True extra-articular manifestations of the rheumatoid process
- Non-articular manifestations of joint/tendon disease (not specific to RA)
- Systemic effects of inflammation (not specific to RA) (eg amyloidosis)
- Adverse drug effects.

True extra-articular manifestations of rheumatoid disease:

- Present in approximately 30% of patients with RA
- Rheumatoid factor is always positive
- Arthritis tends to be more severe.

Rheumatoid nodules are the most characteristic extra-articular feature.

Rheumatoid nodules

- 5% of cases in early disease
- 20–30% of cases long term
- Rheumatoid factor always positive
- Any site (subcutaneous or visceral)
- Associated with more severe arthritis
- Methotrexate may produce accelerated nodule formation
- Rheumatoid nodule histology:
  - Central fibrinoid necrosis
  - Surrounding pallisading macrophages
  - Fibrous capsule

Eye involvement is common: 20%–30% of patients have keratoconjunctivitis sicca (Sjögren syndrome). Episcleritis (painless reddening of the eye lasting about a week) is likely to be as common but usually goes unnoticed. Scleritis (reddening and pain) is a manifestation of vasculitis and is uncommon. Repeated attacks of scleritis produce scleromalacia (blue sclera) and the eye may perforate (scleromalacia perforans). This is very rare. In contrast to the spondyloarthropathies, iritis is not a feature.

Vasculitis is usually benign, manifesting as nail fold infarcts and mild sensory neuropathy in association with active joint disease. The much rarer systemic rheumatoid vasculitis carries a significant mortality. Its features include cutaneous ulceration, mononeuritis multiplex and involvement of the mesenteric, cerebral and coronary arteries. Renal vasculitis is unusual.

Cardiorespiratory manifestations: pleural and pericardial disease are common (30%) but

asymptomatic in all but a few cases. Less common features include interstitial lung disease and the very rare, and often rapidly fatal, obliterative bronchiolitis. Caplan syndrome (massive lung fibrosis in RA patients with pneumoconiosis) is very rare.

Felty syndrome (splenomegaly, neutropenia and RA) is rare. Patients with Felty syndrome usually have a positive ANA and may have associated leg ulcers, lymphadenopathy and anaemia.

Systemic effects of inflammation

- Malaise, fever, weight loss, myalgia
- Anaemia of chronic disease
- Increased incidence of coronary heart disease
- Osteoporosis (immobility also contributes)
- Lymphadenopathy
- Amyloidosis (now rare)

Non-articular manifestations of joint/tendon disease:

- Entrapment neuropathy, most commonly carpal tunnel syndrome, may occur in up to 30% of patients, but is usually mild. It may be the first symptom of RA
- Cervical myelopathy due to atlanto-axial subluxation (rare, but high mortality)
- Hoarseness and stridor due to cricoarytenoid arthritis (rare, but dangerous).

Adverse drug effects:

- **Skin rashes**: may be due to non-steroidal anti-inflammatory drugs (NSAIDs) or disease-modifying drugs. Rashes occur in about 10% of patients treated with gold or penicillamine
- **Renal impairment**: due to prostaglandin inhibition, or the much rarer acute interstitial nephritis, may be due to NSAIDs. Proteinuria occurs in 10% of patients treated with gold or penicillamine, but these are now rarely used
- **Gastrointestinal**: NSAIDs commonly cause peptic and intestinal ulceration. Gold may cause stomatitis (common) and enterocolitis (rare). Diarrhoea is common with leflunomide
- **Hypertension**: this can occur with NSAIDs, ciclosporin A and leflunomide
- **Respiratory**: acute pneumonitis may occur with methotrexate or leflunomide
- **Infection**: methotrexate, leflunomide and the biologic agents are associated with increased infection rates and may reactivate latent tuberculosis.

Other extra-articular features/ associations of RA

- Palmar erythema (common)
- Recurrent respiratory infections
- Pyoderma gangrenosum

- Depression (30%)

20.2.4 Investigations

The diagnosis of RA is based primarily on the history and examination. Laboratory tests and X-rays may be helpful but are rarely diagnostic in early disease.

Radiology

- Early changes:
  - Soft tissue swelling
  - Juxta-articular osteoporosis
- Intermediate changes:
  - Joint space narrowing (due to cartilage loss)
- Late changes:
  - Bone and joint destruction
  - Subluxation
  - Ankylosis (rare nowadays).

Laboratory studies

- Rheumatoid factor is positive in 70%
- Antibodies to cyclic citrullinated peptide (anti-CCP) have a high specificity for RA and can be particularly useful in RF-negative patients
- Most laboratory abnormalities are secondary to active inflammation or drug effects and are not specific to RA. They are used to monitor disease activity and screen for adverse drug effects
- Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and plasma viscosity reflect disease activity
- Alkaline phosphatase is often mildly raised in active disease
- Anaemia is common and may be:
  - Iron-deficiency: gastric blood loss from NSAIDs
  - Normochromic: with active disease (often with thrombocytosis)
  - Aplastic: rare drug effect (eg aurothiomalate, NSAIDs)
  - Haemolytic: rare as a manifestation of RA, but mild forms common with sulfasalazine
- Immunoglobulin levels may be raised, particularly in active disease
- Complement levels are usually normal, or elevated as an acute phase response
- Ferritin may be elevated in an acute phase response and cannot be used to assess iron status
- Synovial fluid examination is rarely helpful in diagnosis but is often done to exclude other diagnoses (eg sepsis, gout). Rheumatoid effusions, like those of most other inflammatory arthropathies, contain large numbers of polymorphs.

Assessment

Patients are evaluated with regard to disease activity, joint damage and function.

Disease activity is assessed using composite scores, which include the number of swollen joints, tender joints, inflammatory markers and a global assessment. The most commonly used is the DAS28 (**d**isease **a**ctivity **s**core using **28** joints).

This is based on the number of swollen joints, tender joints, ESR and the patient's self assessment:

- DAS28 >5.1: high disease activity
- DAS28 3.2 – 5.1: moderate disease activity
- DAS28 <3.2: low disease activity
- DAS28 <2.6: remission.

20.2.5 Drug therapy

Treatment

- Early recognition and treatment of RA produces better long-term outcomes
- Regular monitoring of disease activity and treating to target, aiming for remission, improve outcomes

Drugs used in the treatment of RA fall into two categories: **symptom-modifying** and **disease-modifying**. The disease-modifying drugs are also referred to as slow-acting antirheumatic drugs or second-line drugs; **biologic agents** also fall into this category. **Corticosteroids** produce rapid improvement in symptoms and may have disease-modifying actions.

- **Symptom-modifying drugs**: reduce pain, stiffness and swelling (eg NSAIDs)
- **Disease-modifying antirheumatic drugs (DMARDs)** have additional actions and will:
  - Reduce pain, swelling and stiffness
  - Reduce ESR and CRP
  - Correct the anaemia of chronic disease
  - Slow disease progression.

Other extra-articular features may not respond to disease-modifying drugs, though nodules may regress. Methotrexate is unusual in that it can increase the formation of rheumatoid nodules.

Methotrexate is the DMARD of choice in RA. The aim is to begin treatment with DMARDs as soon as RA is diagnosed and achieve control of inflammation as quickly and completely as possible, the aim being to reduce disease activity to remission or low disease activity levels. Achieving and maintaining a target of low disease activity are associated with better outcomes. Methotrexate may be used alone or in combination with other disease-modifying agents. Since DMARDs take several weeks to become effective, corticosteroids are employed during this period. Corticosteroids may be given intraarticularly, parenterally or orally.

DMARDs in common use are listed in Table 20.1, together with the necessary parameters for monitoring.

Other agents with DMARD activity include sodium aurothiomalate (gold), azathioprine, ciclosporin and D-penicillamine.

Effects of DMARDs

- Improve symptoms (pain and stiffness)
- Reduce numbers of swollen and tender joints
- Reduce inflammatory markers
- Slow radiological damage
- Slow onset (2–6 months)

Biologic disease-modifying agents

These agents are very effective at controlling the symptoms of RA and reducing joint damage. Their effectiveness is enhanced when used in combination with methotrexate.

Table 20.1 Disease-modifying drugs in common use

Drug	Monitoring
Methotrexate	Full blood count (FBC), liver function tests (LFTs)
Sulfasalazine	FBC, LFTs
Leflunomide	FBC, LFTs, blood pressure (BP)
Hydroxychloroquine	Ophthalmological

Table 20.2 Biologic disease-modifying drugs licensed for rheumatoid arthritis

Drug	Target	Administration
Infliximab	TNF-α	iv
Etanercept	TNF-α	sc
Adalimumab	TNF-α	sc
Certulizumab pegol	TNF-α	sc
Golimumab	TNF-α	sc
Rituximab	CD20 (B cell)	iv
Tocilizumab	Interleukin-6	iv or sc
Abatacept	CTLA4-Ig (T cell)	iv or sc
Anakinra	Interleukin-1	sc

iv, intravenous; sc, subcutaneous; TNF, tumour necrosis factor.

Adverse effects of biologic DMARDs

- Infusion or injection reactions
- Immunosuppression
  - Risk of infection
  - Reactivation of latent mycobacterial infection
  - Reactivation of viral hepatitis
  - Progressive multifocal leukoencephalopathy (anti-CD20)
  - Live vaccines should not be used
- Malignancy (small risk)
- Multiple sclerosis (may be exacerbated by anti-TNF-α)
- Autoantibody formation (antinuclear antibodies can occur with anti-TNF-α, but clinical SLE is very rare)

The biologic agents are used in severe active rheumatoid arthritis (DAS28 >5.1) when standard disease-modifying therapy has failed. The onset of clinical effects can be rapid compared with traditional disease-modifying drugs (usually apparent within weeks). A fall in DAS28 of 1.2 is regarded as a good response to treatment.

TNF-α blockers

- **Infliximab**: chimeric (human/mouse) monoclonal antibody against TNF-α – administered intravenously
- **Adalimumab, certulizumab pegol, golimumab**: human monoclonal antibody against TNF-α – administered subcutaneously
- **Etanercept**: TNF-α receptor fusion protein consisting of a dimer of the extracellular portion of two p75 receptors fused to the Fc portion of human IgG1 – administered subcutaneously.

Adverse effects:

- Immunosuppression: severe infections (mostly respiratory, but disseminated tuberculosis can occur). Live vaccines are contraindicated in patients receiving these agents
- Injection site reactions (common but rarely significant)
- Worsening of heart failure
- Antinuclear antibodies develop in about 10% of patients, but clinical lupus is rare
- Demyelination (rare).

Rituximab

- A chimeric mouse/human monoclonal antibody directed against CD20, a cell surface marker found on B lymphocytes. The effect is to deplete B lymphocytes. The time to clinical effect is slower than that for the TNF-α blockers, taking up to 16 weeks to become maximal.

Adverse effects:

- Infusion reactions
- Immunosuppression.

Infliximab and rituximab are usually given in combination with methotrexate. Adalimumab, certulizumab pegol, golimumab and etanercept can be used with methotrexate or as monotherapy. Biologic disease-modifying agents are also effective in psoriatic arthritis, ankylosing spondylitis and juvenile arthritis.

20.3 SPONDYLOARTHROPATHIES (HLA-B27-ASSOCIATED DISORDERS)

This group of disorders is characterised by seronegative (ie rheumatoid factor-negative) inflammatory arthritis and/or spondylitis. The peripheral arthritis is typically asymmetric, involving larger joints, especially the knees and ankles. Characteristic musculoskeletal features include enthesitis (inflammation at sites of tendon insertion), sacroiliitis and dactylitis. These arthropathies should not be confused with seronegative RA, which is a symmetric small-joint arthritis.

Features of spondyloarthropathies

- **Musculoskeletal features**
  - Inflammatory spondylitis
  - Peripheral inflammatory arthritis
  - Enthesitis
- **Extra-articular features**
  - Uveitis
  - Psoriasis
  - Inflammatory bowel disease
  - Aortitis/Endocarditis
- **Genetic features**
  - Family history
  - HLA-B27

Table 20.3 Associations with HLA-B27

Prevalence of HLA-B27 in spondyloarthropathies	(%)
Normal Caucasian population	8
Ankylosing spondylitis	90
Reiter syndrome	70

Enteropathic spondylitis	50
Psoriatic arthritis	20
Psoriatic arthritis with sacroiliitis	50

20.3.1 Ankylosing spondylitis

Typically begins with the insidious onset of low back pain and stiffness in a young man. The back pain has inflammatory characteristics and is often accompanied by anterior chest pain.

The age of onset is usually between 15 and 40 years and the male:female ratio is about 5:1. It is less common than RA, with a prevalence of about 0.1%. The prognosis is good.

Clinical features of ankylosing spondylitis

- **Articular**
  - Sacroiliitis is the characteristic feature, but radiological changes may not be evident for several years
  - Spondylitis (100%)
  - Peripheral arthritis (35%)
  - Intervertebral discitis (rare)
- **Extra-articular**
  - Anterior uveitis (25%)
  - Aortic incompetence (4%)
  - Apical lung fibrosis (rare)
  - Aortitis (rare)
  - Amyloidosis (rare)
  - Heart block (rare)

Inflammatory back pain

- Onset before age 40
- Insidious onset
- Improvement with exercise
- No improvement with rest
- Pain at night with improvement on getting up

Diagnosis

Definitive diagnosis requires radiological evidence of sacroiliitis, inflammatory spinal pain and limited spinal movement or chest expansion. Since sacroiliitis may take many years to become

evident on X-rays, these criteria have a poor sensitivity in early disease and magnetic resonance imaging (MRI) evidence of sacroiliitis may be diagnostically useful in the early stages.

Investigations

- ESR/CRP may be elevated
- Normochromic anaemia
- Alkaline phosphatase often mildly elevated
- Radiology (see box below).

Radiology

- **Sacroiliac joints**
  - Irregular/blurred joint margins
  - Subchondral erosion
  - Sclerosis
  - Fusion
- **Spine**
  - Loss of lumbar lordosis
  - Squaring of vertebrae
  - Romanus lesion (erosion at the corner of vertebral bodies)
  - Bamboo spine (calcification in anterior and posterior spinal ligaments)
  - Enthesitis (calcification at tendon/ ligament insertions into bone)

HLA-B27 in diagnosis

Testing for HLA-B27 is not a reliable way of diagnosing ankylosing spondylitis, but it can sometimes be useful in cases of undifferentiated axial spondyloarthropathy without sacroiliitis.

Assessment

A number of indices and scores are used in the assessment of patients, both in clinical practice and research. The BAS-DAI is used to identify patients suitable for treatment with anti-TNF-α therapies and to assess their response to treatment.

- **BAS-DAI** (Bath Ankylosing Spondylitis Disease Activity Index)
  - Fatigue
  - Spinal pain
  - Joint pain
  - Localised tenderness
  - Morning stiffness
- **BAS-FI** (Bath Ankylosing Spondylitis Functional Index)

    - Activities of daily living
- **BAS-G** (Bath Ankylosing Spondylitis Patient Global Score)
    - General wellbeing in the last week
    - General wellbeing in the last 6 months
- **BAS-MI** (Bath Ankylosing Spondylitis Metrology Index)
    - Cervical rotation
    - Tragus to wall distance (a measure of thoracic kyphosis, measured as the distance between the tragus of the ear and the wall with the patient standing with their back to the wall)
    - Lumbar lateral flexion
    - Lumbar flexion (modified Schober's test)
    - Intermalleolar distance

Treatment

- Physiotherapy and regular home exercise
- NSAIDs
- Sulfasalazine or methotrexate help peripheral arthritis but are not effective for spinal disease
- Anti-TNF-α therapy is very effective. Used when the BAS-DAI score is above 4 despite NSAIDs
- Surgery (joint replacement, spinal straightening) in end-stage disease.

20.3.2 Reactive arthritis

Reactive arthritis usually begins 1–3 weeks after an initiating infection at a distant site. Antigenic material from the infecting organism may be identified in affected joints, but complete organisms cannot be identified or grown, and the arthritis does not respond to treatment with antibiotics. Reiter syndrome is a form of reactive arthritis characterised by a triad of arthritis, conjunctivitis and urethritis.

Reactive arthritis is said to be 20 times more frequent in men than in women. This is likely to be an overestimate because cervicitis may go unrecognised. The true male:female ratio is more likely to be 5:1. Post-dysenteric reactive arthritis has an equal sex distribution. The age of onset is 15–40 years.

Infections that may cause reactive arthritis:

- **Enteric**:
    - *Yersinia* spp.
    - *Salmonella* spp.
    - *Shigella* spp.
    - *Campylobacter* spp.
    - *Clostridium difficile*
    - *Escherichia coli* O157
    - Urethritis: *Chlamydia trachomatis*

- **Upper respiratory tract**:
  - Group A streptococci
  - *Chlamydia pneumoniae*.

Clinical features of reactive arthritis

- **Classic triad**
  - Arthritis
  - Conjunctivitis
  - Urethritis
- **Rare features**
  - Heart: pericarditis, aortitis, conduction defects
  - Lung: pleurisy, pulmonary infiltrates
  - CNS: meningoencephalitis, peripheral neuropathy
- **Other features**
  - Circinate balanitis (25%)
  - Buccal/lingual ulcers (10%)
  - Keratoderma blenorrhagica (10%)
  - Iritis (chronic cases only – 30%)
  - Plantar fasciitis/Achilles tendonitis
  - Fever/weight loss

Prognosis

- Complete resolution 50%
- Initial resolution then recurrence 35%
- Chronic persistent disease 15%.

The arthritis is more likely to recur or be persistent in those with HLA-B27 or when urethritis is the triggering infection.

Treatment

- Mild disease: NSAIDs
- Chronic disease may need disease-modifying drugs
- Prominent systemic symptoms may need corticosteroids.

20.3.3 Psoriatic arthritis

Chronic synovitis occurs in about 8% of patients with psoriasis. The arthritis may precede the diagnosis of psoriasis in 1 in 6 of these patients. Males and females are equally affected.

Diagnosis

The Classification Criteria for Psoriatic Arthritis (CASPAR):

- Psoriasis or a family history of psoriasis: 2 points
- Typical psoriatic nail dystrophy: 1 point
- Negative rheumatoid factor: 1 point
- Dactylitis: 1 point
- Radiographic evidence of new bone formation: 1 point.

A score of ≥3 in a patient with inflammatory arthritis or spondylitis confirms a diagnosis of psoriatic arthritis.

Patterns of psoriatic arthritis

- Polyarthritis similar to RA (most common type)
- Distal interphalangeal joints (5–10%)
- Sacroiliitis and spondylitis (20–40%)
- Asymmetric oligoarthritis (20–40%)
- Arthritis mutilans (<5%)

Characteristic features of psoriatic arthritis

- Nail pitting and onycholysis
- DIP joint arthritis
- Telescoping fingers in arthritis mutilans
- Paravertebral calcification
- Dactylitis

Drug treatment

- Symptom-modifying drugs (analgesics, NSAIDs)
- Disease-modifying drugs
- Anti-TNF-α therapy for disease refractory to DMARDs.

Disease-modifying drugs used in psoriatic arthritis:

- leflunomide
- sulfasalazine
- methotrexate
- ciclosporin.

20.4 INFLAMMATORY CONNECTIVE TISSUE DISORDERS

20.4.1 Markers in inflammatory connective tissue disorders

Antinuclear antibodies

Antinuclear antibodies (ANAs) are directed against a variety of nuclear antigens and may be induced by certain drugs (hydralazine). Like rheumatoid factors, ANAs can be of any immunoglobulin class (remember that IgG can cross the placenta).

Indirect immunofluorescence is the routine method for detecting ANA. It is highly sensitive and the fluorescence staining pattern can give some indication of the type of ANA/disease present:

- **Homogeneous staining** suggests lupus
- **Speckled staining** suggests mixed connective tissue disease
- **Nucleolar staining** suggests scleroderma
- **Centromere staining** suggests CREST syndrome (ie calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasia).

ANAs are found in

- Drug-induced lupus (100%)
- Systemic lupus erythematosus (SLE) (95%)
- Scleroderma (90%)
- Sjögren syndrome (80%)
- Mixed connective tissue disease (93%)
- Polymyositis (40%)
- Normal population (5%, titres usually below 1:320)

ANA in rheumatoid arthritis suggests Felty syndrome or Sjögren syndrome. ANA against double-stranded DNA (anti-dsDNA) in high titre is virtually diagnostic of SLE. The ANA in drug-induced lupus is usually against single-stranded DNA (anti-ssDNA).

Anti-dsDNA

High titres are specific for SLE; anti-dsDNA is present in approximately 80% of patients with SLE.

Methods of detection

- Radioimmunoassay (Farr assay)
- *Crithidia lucillae* immunofluorescence
- Enzyme-linked immunosorbent assay (ELISA)

Extractable nuclear antigens

These are specific nuclear antigens and therefore are usually associated with positive ANA tests. They are useful in defining the type of connective tissue disease present. Method of detection: counter immunoelectrophoresis or ELISA.

Extractable nuclear antigens

- **Anti-Ro** – Sjögren syndrome, congenital heart block, neonatal lupus syndrome, ANA-negative SLE
- **Anti-La** – primary Sjögren syndrome
- **Anti-Sm** – SLE (20%, very specific: conferring a high risk of renal lupus)
- **Anti-RNP** – mixed connective tissue disease (100%), SLE
- **Anti-Jo 1** – seen in a specific variant of polymyositis
- **Anti-Scl70** – progressive systemic sclerosis (20%)
- **Anti-centromere** – CREST syndrome

Antiphospholipid antibodies

Antiphospholipid antibodies are associated with arterial or venous thrombosis, transient neurological deficits, fetal loss, livido reticularis and thrombocytopenia (Hughes syndrome; see Section 20.4.2). Different antibody isotypes exist: IgG and, to a lesser extent, IgM isotypes of anticardiolipin antibodies (ACLA) are associated with clinical features.

Antiphospholipid antibodies have activity against a variety of cell membrane phospholipids, and the most commonly measured are those against cardiolipin. Protein complexes such as β2-glycoprotein-1, which have anticoagulant properties, are found on cell membranes, and it is the interaction between antiphospholipid antibodies and these proteins that is likely to explain the development of thrombosis. About 10% of patients with anticardiolipin-associated thrombosis have antibodies to β2-glycoprotein-1 itself. Antiphospholipid antibodies are found in 2% of the normal population.

Antibody levels are measured by ELISA. The presence of antiphospholipid antibodies can also be reflected in false-positive VDRL tests and a prolonged activated partial thromboplastin time which is not corrected by the addition of normal plasma (lupus anticoagulant test). This is known as a lupus anticoagulant (LA). LA and ELISA show 80% concordance but LA detects some antibodies not picked up by ELISA.

20.4.2 Systemic lupus erythematosus (SLE)

A multisystem inflammatory connective tissue disorder with small-vessel vasculitis and non-organ-specific autoantibodies. It is characterised by skin rashes, arthralgia and antibodies against dsDNA. Young women are predominantly affected, with a female:male ratio of 10:1. It is more common in West Indian populations. Ten-year survival exceeds 90%.

Clinical features of SLE

- **Common** (>80% of cases)
  - Arthralgia or non-erosive arthritis
  - Rash (malar, discoid or photosensitive)
  - Fever
- **Others**
  - Serositis (30–60%): pericarditis, pleurisy, effusions
  - Renal: proteinuria (30–60%), nephrotic syndrome less common, glomerulonephritis (15–20%)
  - Neuropsychiatric (10–60%): psychosis, seizures
  - Haematological (up to 50%): leukopenia, thrombocytopenia, haemolysis
  - Alopecia (up to 50%)
  - Raynaud's phenomenon (10–40%)
  - Oral or nasal ulcers (10–40%)
  - Respiratory (10%): pneumonitis, shrinking lung syndrome
  - Cardiac (10%): myocarditis, endocarditis (Libman–Sacks)

Investigations for SLE

The FBC may show the abnormalities listed in the box below.

Abnormalities of FBC in SLE

- Anaemia of chronic disease (normal mean cell volume (MCV))
- Neutropenia
- Thrombocytopenia
- Haemolytic anaemia (high MCV, reticulocytosis)
- Lymphopenia
- Aplastic anaemia (rare)

ESR reflects disease activity. CRP usually rises with active disease of the joints or serositis (pericarditis, pleurisy), but in active lupus of other organ systems it may not rise. This discrepancy can be used to differentiate between a flare of SLE and intercurrent infection.

Low C3 and C4 suggest lupus nephritis.

Lupus variants

Drug-induced lupus is more common in men than in women. It is usually mild and always resolves on stopping the drug. CNS and renal disease are rare. ANA is positive but antibodies to dsDNA are

not usually present. The pathogenesis is not known, and antibodies to the drug do not occur. The drugs commonly implicated (procainamide, isoniazid and hydralazine) all have active amido groups.

Antiphospholipid antibody syndrome (Hughes syndrome): recurrent venous or arterial thromboses, fetal loss and thrombocytopenia. Libman–Sacks endocarditis and focal neurological lesions (such as cerebrovascular accident (CVA) or transient ischaemic attack (TIA)) in lupus are usually due to antiphospholipid antibodies.

Treatment of lupus depends on severity and organ involvement.

Treatment of SLE

- Sunscreens (sunburn can provoke a generalised flare in disease)
- NSAIDs for arthritis
- Hydroxychloroquine: will suppress inflammatory arthritis but also reduces the risk of flares and can reduce steroid requirements
- Corticosteroids and immunosuppressive drugs: used for vital organ involvement
- Plasma exchange or biological agents (rituximab, belimumab) are used in disease refractory to standard treatment

There is significant morbidity associated with cardiovascular disease in SLE, so risk factor reduction (blood pressure, smoking, obesity, lipids, exercise) is an important aspect of treatment.

Prognosis

Mortality and morbidity in SLE have improved dramatically with improved treatment of SLE itself, reduction in drug-associated problems by limiting corticosteroid use, and treatment of co-morbidities such as cardiovascular disease. Ten-year survival now approaches 90%. The main causes of death in the first 5 years of disease are active SLE and infection, with thrombotic diseases becoming the predominant causes in later disease.

20.4.3 Dermatomyositis and polymyositis

Polymyositis is an idiopathic inflammatory disorder of skeletal muscle. When associated with cutaneous lesions it is called dermatomyositis. These conditions are rare (5 cases per million). Five-year survival is 80% with treatment. Myositis may also occur with other connective tissue disorders.

Clinical features of dermatomyositis and polymyositis

- **Muscle disease**
  - Proximal weakness
  - Swelling and tenderness of muscles
- **Others**

- Pulmonary muscle weakness
- Interstitial lung disease
- Oesophageal dysfunction
- Arthralgia
- Weight loss
- Fever

- **Skin rash**
  - Heliotrope discoloration of the eyelids
  - Gottron's papules (scaly papules over MCP/PIP joints)
  - Periungual telangiectasia
  - Erythematous macules

Juvenile dermatomyositis differs from the adult form. Vasculitis, ectopic calcification and lipodystrophy are commonly present.

Malignancy

The elderly with dermatomyositis and polymyositis have a higher prevalence of malignancy than would be expected by chance, and this is most pronounced in dermatomyositis. There is no association between dermatomyositis/polymyositis and malignancy in children or adults of young and middle age.

Laboratory tests in dermatomyositis/ polymyositis

- **Muscle**
  - Elevated muscle enzymes: creatine kinase (CK), aspartate transaminase (AST), lactate dehydrogenase (LDH)
  - Abnormal EMG
  - Biopsy showing inflammation, muscle fibre necrosis and regeneration
- **Autoantibodies**
  - Antinuclear antibodies may be present
  - Anti-Jo 1 is associated with a specific syndrome of: acute-onset myositis; interstitial lung disease; fever; arthritis; Raynaud's phenomenon; mechanic's hands (fissuring of the digital pads without ulceration and periungual infarcts)

Treatment

- Corticosteroids: CK falls rapidly but muscle power takes many weeks to improve
- Immunosuppressives: methotrexate or cyclophosphamide are used in resistant cases

20.4.4 Systemic sclerosis

Systemic sclerosis is a connective tissue disorder characterised by thickening and fibrosis of the skin (scleroderma) with distinctive involvement of internal organs. It is a rare condition, occurring in all racial groups, with an incidence of 4–12/million per year. It is more common in women (female:male ratio 4:1) and may start at any age.

Some cases may be due to exposure to substances such as vinyl chloride.

Clinical features of systemic sclerosis

- **Raynaud's phenomenon**
  - Initial complaint in 70%
  - Associated digital ulcers and calcinosis (very unusual in primary Raynaud's phenomenon)
- **Musculoskeletal**
  - Arthralgia
  - Erosive arthritis in about 30%
  - Myositis (usually mild, often asymptomatic with raised CK)
  - Flexion deformities of fingers due to skin fibrosis
- **Pulmonary**
  - Fibrotic interstitial lung disease
  - Pulmonary hypertension
- **Renal**
  - Scleroderma renal crisis (malignant hypertension, rapid renal impairment with 'onion skin' intrarenal vasculature)
- **Scleroderma**
  - Early oedematous phase
  - Later indurated and hidebound
  - Affected areas may become pigmented and lose hair
- **Gastrointestinal**
  - Motility can be impaired at any level (smooth muscle atrophy and fibrosis)
  - Oesophagus (reflux, dysphagia, peptic strictures)
  - Gastric dilatation
  - Intestine (bacterial overgrowth, malabsorption, steatorrhoea, pseudo-obstruction
  - Colon (constipation)

Investigations

Laboratory tests include:

- Elevated ESR or CRP

- Autoantibodies
  - Rheumatoid factor-positive in 30%
  - Antinuclear factor-positive in 90% (homogeneous, speckled or nucleolar staining)
  - Anti-centromere and anti-Scl70 are quite specific
  - Anti-centromere-positive in 50–90% of limited and 10% of diffuse scleroderma
  - Anti-Scl70 (anti-topoisomerase-l)-positive in 20–40%.

Disease patterns

- **Limited scleroderma with systemic involvement – CREST**
  - Scleroderma limited to the face, neck and limbs distal to the elbow and knee
  - Usually begins with Raynaud's phenomenon
  - CREST (calcinosis, Raynaud's, oesophageal dysmotility, sclerodactyly, telangiectasia)
  - Anti-centromere antibody-positive in most
  - Renal crisis rare, pulmonary hypertension more common
  - Better prognosis (>70% 10-year survival)
- **Diffuse scleroderma with limited involvement**
  - Scleroderma involving trunk and proximal limbs as well as face and distal limbs
  - Usually begins with swelling of fingers and arthritis
  - Anti-Scl70 antibodies 20–40%
  - Pulmonary hypertension rare, renal crisis more common
  - Worse prognosis (50% 10-year survival)
- **Scleroderma without internal organ disease**
  - Plaques: morphoea
  - Linear: coup de sabre.

Management of systemic sclerosis

- Screening for pulmonary hypertension and pulmonary fibrosis (annual echocardiography and pulmonary function tests)
- Monitoring for renal involvement (blood pressure and creatinine)
- Corticosteroids: increase the risk of renal crisis and are avoided except where essential (eg pulmonary fibrosis, myositis)
- **Supportive treatment**
  - Proton pump inhibitors for reflux
  - Intermittent antibiotics for small-bowel bacterial overgrowth
  - Vasodilators for Raynaud's phenomenon
  - Iloprost infusions for severe digital ischaemia
- **Specific**

  Immunosuppressants (mycophenolate, cyclophosphamide) for rapidly progressive skin

- disease
- Cyclophosphamide and corticosteroids for pulmonary fibrosis
- Angiotensin-converting enzyme (ACE) inhibitors for sclerodermal renal crisis
- Iloprost, bosentan, sildenafil for pulmonary hypertension

Prognosis

Both diffuse and limited forms of the disease are associated with an increased mortality, 5–8 times higher than the general population. Diffuse disease has a worse outcome.

20.4.5 Sjögren syndrome

A connective tissue disorder characterised by lymphocytic infiltration of exocrine glands, especially the lacrimal and salivary glands. The reduced secretions lead to the dry eyes and dry mouth of the sicca syndrome. Secondary Sjögren syndrome describes the presence of sicca syndrome and either RA or a connective tissue disorder. About 30% of rheumatoid patients have secondary Sjögren syndrome.

Clinical features of Sjögren syndrome

- **Dryness from atrophy of exocrine glands**
  - Eyes (xerophthalmia), which may lead to corneal ulceration
  - Mouth (xerostomia), with increased dental caries
  - Respiratory, with hoarseness, dysphagia, respiratory infections
  - Vaginal, causing dyspareunia
- **Arthralgia or arthritis**
  - Can be erosive
- **Raynaud's phenomenon**
- **Lymphadenopathy**
- **Gland swelling**
  - In the early stages (eg parotid)
- **Vasculitic purpura**
- **Neuropathies**
- **Renal tubular acidosis** (30%)
- **Pancreatitis**

Laboratory tests

- Anaemia and leukopenia are common

- ANA frequently present
- Anti-Ro or anti-La present in primary Sjögren syndrome
- ESR and CRP reflect disease activity
- Rheumatoid factor-positive in most cases
- Polyclonal hypergammaglobulinaemia

Treatment

- **Artificial tears**: plugging of lacrimal punctae in severe cases
- **Moistening sprays** for the mouth
- **NSAIDs** and sometimes hydroxychloroquine for arthritis.

20.4.6 Mixed connective tissue disease/overlap syndromes

Some patients have features of more than one connective tissue disorder and are said to have 'overlap syndromes'. One specific overlap syndrome, mixed connective tissue disease, is associated with anti-RNP antibodies. The clinical features are Raynaud's phenomenon, swollen hands and other features from at least two connective tissue disorders (SLE, scleroderma or polymyositis).

Prognosis

The 10-year survival is 80%. Patients who have features mainly of scleroderma and polymyositis fare much worse, with a 10-year survival as low as 30%.

20.5 VASCULITIS

20.5.1 Overview of vasculitis

Systemic vasculitis usually presents with constitutional symptoms such as general malaise, fever and weight loss, combined with more specific signs and symptoms arising from the specific organs involved. The diagnosis is based on a combination of clinical and laboratory findings, and is usually confirmed by biopsy and/or angiography.

Aetiology

Infections, malignancy and drugs may all lead to vasculitic illness but, in many cases, the trigger for endothelial injury is unknown. The following mechanisms of endothelial cell injury have been proposed in the pathogenesis of vasculitis:

- **Immune complex deposition**: hepatitis B-associated polyarteritis nodosa
- **Direct endothelial cell infection**: HIV
- **Anti-endothelial cell antibodies**: Kawasaki disease, Behçet syndrome
- **ANCA-mediated neutrophil activation**: Wegener's granulomatosis, microscopic polyangiitis
- **T cell-dependent injury**: giant-cell arteritis.

Clinical features of vasculitis

- **General**
  - Constitutional (fever, weight loss, fatigue, anorexia)
  - Musculoskeletal (arthralgia, arthritis, myalgia)
- **Related to specific organ involvement**
  - Kidney (glomerulonephritis – manifests by acute renal failure, proteinuria/ haematuria); *see* Chapter 15, Nephrology
  - Respiratory (alveolitis, infiltrates, haemorrhage, sinusitis)
  - Neuropathy (mononeuritis multiplex, sensory neuropathy)
  - Gastrointestinal (diarrhoea, abdominal pain, perforation, haemorrhage)
  - Cardiovascular (jaw or extremity claudication, angina, myocardial infarction)
  - Central nervous system (headache, visual loss, stroke, seizures)
  - Skin (livedo reticularis, urticaria, vasculitic lesions including purpura and erythema multiforme)

20.5.2 Classification of vasculitis

The Chapel Hill Classification for Vasculitis (2012) classifies vasculitis according to the predominant vessel involved:

- Large-vessel vasculitis
- Medium-vessel vasculitis
- Small-vessel vasculitis
- Variable-vessel vasculitis
- Single-organ vasculitis
- Vasculitis associated with systemic disease.

Clinical features are usually a combination of constitutional symptoms (weight loss, malaise) and specific features arising from the organs involved.

- **Large-vessel vasculitis**
  - Takayasu's arteritis
  - Giant-cell arteritis
- **Medium-vessel vasculitis**
  - Polyarteritis nodosa (PAN)
  - Kawasaki's disease
- **Small-vessel vasculitis**

    - *ANCA-associated vasculitis:*
        - Microscopic polyangiitis
        - Granulomatosis with polyangiitis (previously Wegener's granulomatosis)
        - Eosinophilic granulomatosis with polyangiitis (previously Churg–Strauss syndrome)
    - *Immune complex vasculitis:*
        - Anti-glomerular basement membrane (GBM) disease (previously Goodpasture's disease)
        - Cryoglobulinaemic vasculitis
        - IgA vasculitis (Henoch–Schönlein purpura)
        - Hypocomplementaemic urticarial vasculitis
    - Variable vessel vasculitis
    - Behçet's disease
    - Cogan syndrome
- **Single-organ vasculitis**
    - Cutaneous leukocytoclastic angiitis
    - Cutaneous arteritis
    - Primary CNS vasculitis
    - Isolated aortitis
- **Vasculitis associated with systemic disease**
    - Lupus vasculitis
    - Rheumatoid vasculitis
    - Sarcoid vasculitis
- **Vasculitis associated with probable aetiology**
    - Hepatitis C virus-associated cryoglobulinaemic vasculitis
    - Hepatitis B virus-associated vasculitis
    - Drug-associated immune complex vasculitis
    - Drug-associated ANCA-associated vasculitis
    - Cancer-associated vasculitis
- **Single-organ vasculitis** (eg primary CNS vasculitis)
- **Vasculitis associated with systemic disease** (eg rheumatoid vasculitis)
- **Vasculitis with other aetiology** (eg hepatitis virus-associated vasculitis)

Anti-neutrophil cytoplasmic antibodies

Anti-neutrophil cytoplasmic antibodies (ANCAs) are found in a number of inflammatory disorders including vasculitides, ulcerative colitis, autoimmune hepatitis and connective tissue disorders, and as drug reactions.

Immunofluorescence reveals two major staining patterns:

1. Cytoplasmic (cANCA): associated with anti-PR3 antibodies

2. Perinuclear (pANCA): associated with anti-MPO antibodies.

Anti-PR3 and anti-MPO titres can reflect disease activity, so are helpful in monitoring responses to treatment and recognising relapse. In non-vasculitic conditions there may be ANCA positivity, with perinuclear or cytoplasmic staining, but without positive results for anti-PR3 or anti-MPO.

Although ANCAs can be found in a variety of vasculitides the predominant associations are with:

- Microscopic polyangiitis: 70% ANCA-positive, usually anti-MPO
- Granulomatosis with polyangiitis: 90% ANCA-positive, usually anti-PR3
- Eosinophilic granulomatosis with polyangiitis: 50% ANCA-positive, anti-MPO (75% anti-MPO, 25% anti-PR3).

Treatment of ANCA-positive vasculitides

- Induction with cyclophosphamide and corticosteroids
- Maintenance with azathioprine or mycophenolate and reducing doses of corticosteroid. Plasma exchange or biologic agents such as rituximab are used in resistant cases.

Prognosis

Despite treatment with immunosuppressants and corticosteroids, up to 20% of patients with ANCA-associated vasculitis or PAN will die within 5 years.

20.5.3 Polymyalgia rheumatica, giant-cell and other large-vessel arteritides

Giant-cell arteritis

- Mean age of onset 70 years
- Rare before age 50 years
- More common in White people
- Female:male 3:1.

Symptoms

- Abrupt-onset headache (usually unilateral)
- Scalp pain, difficulty in combing hair
- Jaw or tongue claudication
- Visual symptoms (amaurosis fugax/diplopia)
- Constitutional symptoms (fever, weight loss, anorexia)
- Polymyalgia rheumatica.

Examination

- Temporal artery tender, thickened or beaded with reduced pulsation
- Scalp tenderness
- Reduction in visual acuity

- Visual field defect
- Afferent pupillary defect
- Pale, swollen optic disc with haemorrhages
- Unilateral or bilateral central retinal artery occlusion
- Upper cranial nerve palsies
- Large-vessel giant-cell arteritis (GCA): asymmetrical pulses and bruits.

Diagnosis

The American College of Rheumatology (ACR) classification criteria for GCA require three of the following to be present:

- Age at disease onset >50 years
- New headache
- Temporal artery abnormality: tenderness or decreased pulsation
- Elevated erythrocyte sedimentation rate (ESR)
- Positive temporal artery biopsy.

Complications

- Early (visual loss, stroke)
- Late (aortic aneurysm, dissection)
- Treatment-related (corticosteroid side-effects).

Treatment

- Early high-dose corticosteroids and gradual taper
- Methotrexate as adjunctive therapy for relapsing disease
- Low-dose aspirin (to reduce risk of stroke).

Polymyalgia rheumatica

Core features

- Age >50 years, duration >2 weeks
- Bilateral shoulder or pelvic girdle aching, or both
- Morning stiffness duration of >45 min
- Evidence of an acute phase response.

In diagnosing polymyalgia rheumatica (PMR), it is important to consider and exclude infection, malignancy and other rheumatic diseases. Both rheumatoid arthritis and pyrophosphate arthropathy can produce polymyalgic features, and polymyalgia itself can produce inflammatory arthritis.

Treatment is with corticosteroids which are tapered according to symptoms. Most patients will require steroids for 1–3 years, with up to 25% requiring more long-term treatment.

Relationship between PMR and GCA

- 50% of patients with GCA will have PMR
- 15% of PMR patients will develop GCA.

Takayasu's arteritis (pulseless disease)

This rare condition presents with systemic illness such as malaise, weight loss and fever. The main vasculitic involvement is of the aorta and its main branches, producing arm claudication, absent pulses and bruits. Thirty per cent of patients have visual disturbance. Diagnosis is by angiography, and treatment involves corticosteroids.

Treatment

Corticosteroids are used to control both PMR and GCA. Immunosuppressants such as methotrexate and azathioprine are used as steroid-sparers if the corticosteroid dose cannot be tapered.

Low-dose aspirin is recommended in GCA because there is an increased risk of stroke.

Takayasu's arteritis is usually treated with combined corticosteroids and immunosuppressants. Arterial reconstruction or bypass is needed in up to 70%.

20.5.4 Granulomatosis with polyangiitis

- Previously known as Wegener's granulomatosis
- Necrotising granulomatous inflammation involves the upper and lower respiratory tracts
- Necrotising glomerulonephritis is common
- ANCA-positive in 90%; usually anti-PR3.

20.5.5 Eosinophilic granulomatosis with polyangiitis

- Previously known as Churg–Strauss syndrome
- Eosinophil-rich, necrotising granulomatous inflammation
- Respiratory tract, renal, skin, peripheral nerves
- Associated with asthma and eosinophilia
- 50% ANCA-positive
- ANCA is more frequent with glomerulonephritis.

20.5.6 Microscopic polyangiitis

- Necrotising vasculitis
- Granulomatous inflammation absent
- Few or no immune deposits
- Necrotising glomerulonephritis very common
- Pulmonary capillaritis: causes pulmonary infiltrates and haemorrhage

- Skin involvement can produce palpable nodules
- Gut, eye and peripheral nerves can be involved
- 70% ANCA-positive, usually anti-MPO.

20.5.7 Polyarteritis nodosa

- Necrotising arteritis of medium or small arteries
- Not associated with ANCA
- Hepatitis B-associated PAN, which accounts for 30% of cases worldwide, is now classified separately
- Eosinophilia, if present, is mild
- May involve skin, gut, renal, lung, peripheral nerves and joints.

20.5.8 Kawasaki's disease

An acute febrile illness with systemic vasculitis which mainly affects children under the age of 5 years. The peak onset is at 1.5 years, and it has an incidence of about 6/100 000 in the under-5s. It is more common and more severe in males. The cause is not known, but its occasional occurrence in mini-epidemics suggests an infectious agent. (Rickettsia has been implicated.)

Clinical features of Kawasaki's disease

- **Fever**
  - (Followed by thrombocytosis)
- **Mucocutaneous**
  - Rashes, red cracked lips, strawberry tongue, conjunctivitis
- **Vasculitis**
  - With coronary aneurysm formation
  - Myocardial infarctions in 2.5%
- **Lymphadenopathy**
  - (Especially cervical)

Treatment differs from most other vasculitides. Corticosteroids are contraindicated since they increase coronary aneurysms. Anti-inflammatory doses of aspirin are used during the acute febrile phase and antiplatelet doses are given once the fever resolves and thrombocytosis occurs. Intravenous immunoglobulin is also effective.

20.5.9 Behçet syndrome

Behçet syndrome is a rare condition most commonly found in Turkey and the eastern Mediterranean,

where there is a strong association with HLA-B5. There is an equal sex ratio but the disease is more severe in males. The pathological findings are of immune-mediated occlusive vasculitis and venulitis. The diagnosis is based on clinical features.

Main clinical features

- Recurrent oral ulceration (100%)
- Recurrent painful genital ulceration (80%)
- Recurrent iritis (60–70%)
- Skin lesions (60–80%)

Other features

- Cutaneous vasculitis
- Thrombophlebitis
- Pathergy reaction (red papules >2 mm at sites of needle pricks after 48 hours)
- Erythema nodosum
- Arthritis (usually non-erosive, asymmetric, lower limb)
- Neurological involvement (aseptic meningitis, ataxia, pseudobulbar palsy)
- Gastrointestinal involvement

20.6 CRYSTAL ARTHROPATHIES AND OSTEOARTHRITIS

20.6.1 Gout

Hyperuricaemia is common and usually asymptomatic, but in some individuals uric acid crystals form within joints or soft tissues, leading to a variety of diseases.

Gout is now the most common inflammatory arthritis in men and in women aged >60. The incidence is rising probably as a consequence of increasing obesity.

Clinical features of gout

- **Acute crystal arthritis**
  - Particularly affecting the small joints of the feet (eg first MTP, usually recurrent)
- **Gouty nephropathy**
  - Tubulointerstitial disease due to parenchymal crystal deposition
  - Acute intratubular precipitation resulting in acute renal failure
  - Urate stone formation (radiolucent)

- **Chronic tophaceous arthritis**
  - These are aggregations of urate crystals affecting articular, periarticular and nonarticular cartilage (eg ears)

Aetiology

Uric acid is a breakdown product of purine nucleotides. Purines can be synthesised from precursors, but significant amounts are ingested in normal diets and released at cell death. Hyperuricaemia arises because of an imbalance in uric acid production/ ingestion and excretion.

Causes of gout

- **Primary** (innate)
  - Idiopathic (90% of these are due to under-excretion of uric acid)
  - Rare enzyme deficiencies: eg hypoxanthine–guanine phosphoribosyltransferase (HGPRT) deficiency (Lesch–Nyhan syndrome)
- **Secondary hyperuricaemia**
  - *Increased uric acid production/intake*
    - Myeloproliferative and lymphoproliferative disorders
    - High purine diet, eg purines in beer (even non-alcoholic)
    - Cytolytic therapy
    - Acidosis, eg the ketosis of starvation or diabetes
    - Extreme exercise, status epilepticus
    - Psoriasis
  - *Decreased uric acid excretion*
    - Renal failure
    - Drugs (diuretics, low-dose aspirin, ciclosporin, pyrazinamide)
    - Alcohol
    - Lead intoxication (saturnine gout)
    - Down syndrome

Diagnosis

- Negatively birefringent needle-shaped crystals must be identified in joint fluid or other tissues for a definitive diagnosis
- In chronic tophaceous gout, the X-ray appearances (large punched-out erosions distant from the joint margin) are characteristic and may allow diagnosis
- In clinical practice, a characteristic history with hyperuricaemia is often thought sufficient, but there are pitfalls: uric acid may fall by up to 30% during an acute attack; hyperuricaemia is common and may be coincidental.

Treatment of gout

- **Acute attacks**: NSAIDs, colchicine or prednisolone
- **Canakinumab**, a monoclonal antibody against Il-1β is licensed for treatment of acute gout but is not in general use
- **Prophylaxis** against acute attacks
  - Avoid dehydration
  - Aim for an ideal body weight
  - Reduce alcohol intake
  - Stop diuretics
- **Urate-lowering drugs**
  - Allopurinol (xanthine oxidase inhibitor)
  - Febuxostat (xanthine oxidase inhibitor)
- Benzbromarone, probenicid and sulphinpyrazone are **uricosuric agents**, but are less effective than xanthine oxidase inhibitors at reducing uric acid
- **Losartan and fenofibrate** have a modest urate-lowering effect
- **Uricase agents** (pegloticase, raspuricase) rapidly reduce serum urate and produce rapid regression of tophi. Their main use is in tumour lysis syndrome, but they may have a place in gout resistant to other treatments

Other management issues:

- Lose weight if obese
- Reduce alcohol intake
- Reduce excessive dietary purine intake
- Identify and treat associated factors (hyperlipidaemia, hypertension, hyperglycaemia)
- Withdraw drugs which cause hyperuricaemia, such as diuretics.

Indications for urate-lowering therapy

Introduce urate-lowering drugs if:

- attacks recur within a year of the first attack
- Or after the first attack if:
  - visible tophi
  - renal impairment
  - uric acid stones
  - cannot stop diuretics.

The aim is to reduce the serum urate to <0.30 mmol/L. The reduction in serum urate, whether by lifestyle changes, stopping diuretics or potent urate-lowering agents such as the xanthine oxidase inhibitors, can precipitate acute attacks. These can be prevented by using colchicine during the first

few months of urate lowering.

Conditions associated with gout:

- hypertension
- glucose intolerance
- hyperlipidaemia
- obesity.

20.6.2 Calcium pyrophosphate deposition disease (CPDD)

This is a spectrum of disorders ranging from asymptomatic radiological abnormalities to disabling polyarthritis. The underlying problem is the deposition of calcium pyrophosphate crystals in and around joints. This is most commonly idiopathic and age-related, but may occur in metabolic disorders, especially those with hypercalcaemia or hypomagnesaemia. Calcium pyrophosphate forms positively birefringent brick-shaped crystals.

Variants:

- **Asymptomatic**: radiological chondrocalcinosis (30% of over-80s)
- **Acute monoarthritis**: pseudogout (usually knee, elbow or shoulder)
- **Inflammatory polyarthritis**: mimicking RA (10% of CPDD)
- **Osteoarthritis**: often of hips and knees but with involvement of the index and middle MCP joints (rarely seen in primary osteoarthritis).

Causes of CPDD

- Hyperparathyroidism
- Wilson's disease
- Bartter syndrome
- Hypomagnesaemia
- Haemochromatosis
- Hypophosphatasia
- Ochronosis

Treatment

- Asymptomatic CPDD does not require treatment
- Underlying metabolic disorders should be treated
- Acute attacks: NSAIDs, colchicine or corticosteroids
- Prophylaxis against frequent acute attacks: colchicine or NSAIDs
- Chronic inflammatory arthritis: methotrexate or hydroxychloroquine

20.6.3 Osteoarthritis

Osteoarthritis (OA) is the most common joint disease. It is characterised by softening and degradation of articular cartilage, with secondary changes in adjacent bone. The prevalence of OA on X-ray rises with age and affects 70% of 70-year-olds. Many individuals with radiological OA, however, are asymptomatic. Obesity is the most common modifiable risk factor for developing osteoarthritis.

Common joints involved are:

- Distal interphalangeal joints (Heberden's nodes)
- Proximal interphalangeal joints (Bouchard's nodes)
- Base of thumb (first carpometacarpal joint)
- Hips
- Knees
- Spine.

Metacarpophalangeal joint OA suggests a secondary cause (eg CPDD).

OA subsets

- **Primary**
  - Localised (one principal site, eg hip)
  - Generalised (eg hands, knees, spine)
- **Secondary**
  - Inherited dysplastic disorders
  - Mechanical damage (eg osteonecrosis, post-meniscectomy)
  - Metabolic (eg ochronosis, acromegaly)
  - Previous inflammation (eg sepsis, gout, RA)

Diagnosis

Osteoarthritis can be diagnosed clinically without investigations if a person:

- is aged >45 years
- has activity-related joint pain
- has morning joint stiffness that lasts <30 minutes (or no stiffness).

Treatment

Core treatment

- **Education**: advice and access to information

- **Exercise**: muscle strengthening and aerobic fitness
- **Weight loss** if overweight.

Other treatments

- Analgesics: topical or oral (eg NSAID)
- Non-pharmacological pain relief (eg transcutaneous electrical nerve stimulation or TENS)
- Surgery (joint replacement)

20.7 ARTHRITIS IN CHILDREN

Juvenile idiopathic arthritis (JIA) is a persistent arthritis of more than 6 weeks' duration beginning before the age of 16. It is one of the most common physically disabling conditions of childhood with a prevalence of 1 in a 1000. At least seven clinical subtypes are seen.

Subtypes of JIA

- Systemic disease (Still's disease)
- Oligoarthritis (or pauciarthritis)
- Extended oligoarthritis
- Rheumatoid factor-negative polyarthritis
- Rheumatoid factor-positive polyarthritis
- Psoriatic arthritis
- Enthesitis-related arthritis

20.7.1 Systemic onset juvenile arthritis

- 10% of JIA
- Onset usually early childhood (but adult cases do occur)
- Variable pattern of joint involvement
- 50% develop destructive arthritis
- Systemic features (fever, myalgia, weight loss)
- Characteristic salmon-pink rash
- Difficult to control, often need immunosuppression.

20.7.2 Oligoarthritis

- 50% of JIA
- Mainly preschool girls (sex ratio 5:1)

- Four or fewer joints
- Knee, ankle and wrist most common joints involved
- High risk of uveitis if ANA-positive
- Regular slit-lamp examinations required to detect asymptomatic uveitis
- Leg-length discrepancies can occur if one knee inflamed.

20.7.3 Extended oligoarthritis

- A third of children who have oligoarthritis in the first 6 months will develop arthritis in more than four joints
- Asymptomatic uveitis is common
- Prognosis worse than oligoarthritis.

20.7.4 Rheumatoid factor-negative polyarthritis

- 25–30% of JIA
- Preschool girls
- Symmetrical arthritis of upper and lower limbs
- Uveitis rare.

20.7.5 Rheumatoid factor-positive polyarthritis

- <5% of JIA
- Late childhood or adolescence
- Similar features and prognosis as adult RA.

20.7.6 Psoriatic arthritis

- Similar to adult psoriatic arthritis
- Asymptomatic uveitis common and slit-lamp examinations required.

20.7.7 Enthesitis-related arthritis

- Usually starts after the age of 6, more common in boys
- Lower limb arthritis and enthesitis
- Probably a variant of adult ankylosing spondylitis
- Sacroiliitis rare at presentation
- Uveitis usually symptomatic
- Remission is rare (<20%)
- Associated with worse function and quality of life than other forms of JIA.

Treatment of juvenile arthritis

- Analgesics and NSAIDs for pain relief
- Disease-modifying agents (eg methotrexate, sulfasalazine)
- Biologic agents (anti-TNF, tocilizumab)
- Corticosteroids are avoided where possible, but are sometimes needed for severe disease

Complications of JIA

- Macrophage activation syndrome (occurs in 7% of systemic JIA)
- Chronic anterior uveitis (especially in ANA-positive JIA)
- Growth disturbance
- Cardiac disease can occur in systemic JIA
- Amyloidosis is now less common
- Osteoporosis
- Interference with schooling

Chapter 21
Statistics

CONTENTS

Statistics

21.1 RESEARCH QUESTIONS

A research study should always be designed to answer a particular research question. The question usually relates to a specific population. For example:

- Question 1: Does taking folic acid early in pregnancy prevent neural tube defects?
- Question 2: Is a new inhaled steroid better than standard treatment for improving lung function among cystic fibrosis patients?
- Question 3: Are those who smoke more likely to develop cancer?

An acronym that is sometimes used to help make sure that a question is specific enough is PICO. This stands for **p**atient, **i**ntervention, **c**omparison and **o**ut-come. Although this cannot be applied to all research questions, it is a useful breakdown that may sometimes assist in the definition of a research question. The following is an explanation of each part:

- **P:** What is the **p**opulation/**p**atient or **p**roblem? Describe the group(s) to which the question applies.
- **I:** What is the **i**ntervention or exposure or test being considered?
- **C:** Is there a **c**omparative intervention/group? Or perhaps comparison is with healthy individuals?
- **O:** What is the **o**utcome measure? Differences in what feature of the population are being explored?

The PICO of the three questions presented above can be defined as shown in Table 21.1.

Table 21.1 Application of the acronym PICO to the three questions

	Question 1	**Question 2**	**Question 3**
P	Pregnant women	Cystic fibrosis patients	General population
I	Early folic acid	New inhaled steroid	Smokers
C	(Late folic acid)	Current treatment	Non-smokers
O	Neural tube defects	Lung function	Cancer

Note, that there is not a unique PICO definition for some questions. Different ways of defining PICO will usually correspond to different types of studies employed to answer the same research question (or a slightly altered one due to different study design).

For example, the following question could have two slightly different PICO definitions:

- Question: Are children who develop epilepsy between 5 and 15 years of age more likely to have been prescribed antibiotics in the first year of life?

The answer is given in Table 21.2

The first way requires a cohort study (with duration of at least 5 years, ie very long), whereas the second requires a case-control study. Depending on the resources available the most appropriate type of study should be decided.

To answer the three research questions at the start of this chapter, random samples from the relevant groups are taken, eg pregnant and non-pregnant women, cystic fibrosis patients and those without the condition, smokers and non-smokers.

Based on the observed outcome in the sample(s), inferences are made about the population from which the sample(s) were randomly taken. Statistical inference enables us to determine what inferences can be made about the population from the sample patients/subjects (Figure 21.1).

21.2 DATA

21.2.1 Types of data

Information collected from a sample can be either quantitative or qualitative. In this chapter, ways of analysing only the first type are covered. Quantitative information can be of two types, numerical or categorical.

- **Numerical** data are measured on a numerical scale, eg weight, head circumference
- **Categorical** data are measured on categories, i.e. on a which-category-one-lies scale, eg, smokers/non-smokers, healthy/diseased.

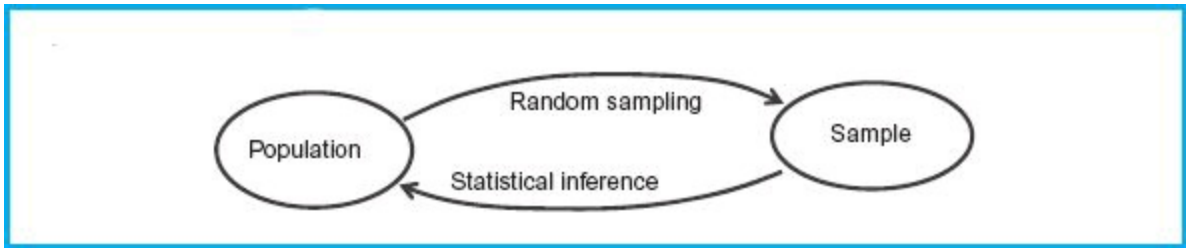
Numerical data can be either discrete – distinct values within a range (eg number of fits) – or continuous – any values within a range (eg body length).

Categorical data have three subcategories: binary – two levels only (eg gender); ordinal – more than two levels with specific order (eg pain severity as low/medium/high); and nominal – more than two levels with no order (eg ethnicity).

Table 21.2 Answer to question re antibiotics

	First way	**Second way**
P	Babies	5- to 15-year-old children
I	Antibiotics in first year of life	Epileptic
C	No antibiotics in first year of life	Non-epileptic
O	Epilepsy between ages 5 and 15years	Use of antibiotics in first year of life

Figure 21.1 From populations to samples – statistical inference



All methods employed to analyse observations depend on the type of data that are being analysed, hence it is very important to be clear on the different types. For a summary see Figure 21.2.

21.2.2 Summaries of numerical data

The two main features of interest for numerical variables are the centre (the point around which most observations lie) and the spread (how variable the data are around the centre).

The shape of the histogram of a numerical variable, ie its distribution, will determine the type of descriptive measures that should be used to summarise this variable.

The centre and spread of symmetrical, bell-shaped curves (also known as normally distributed – Figure 21.3) are well described via the mean and standard deviation (SD). The mean is the arithmetic average of the observations (dotted vertical line in Figure 21.4). The SD is the average of the squared distances of each point from the mean (ie average of the squared values of the length of the solid horizontal lines in Figure 21.4). The smaller the SD, the more tightly grouped the values are around the mean (Figure 21.5). Sometimes, the term 'variance' is used instead of SD. The two terms can be used interchangeably, ie variance = SD^2 or SD = √variance. Most statistical properties/rules use SD rather than variance in their formulae.

Figure 21.2 Types of variables – flowchart

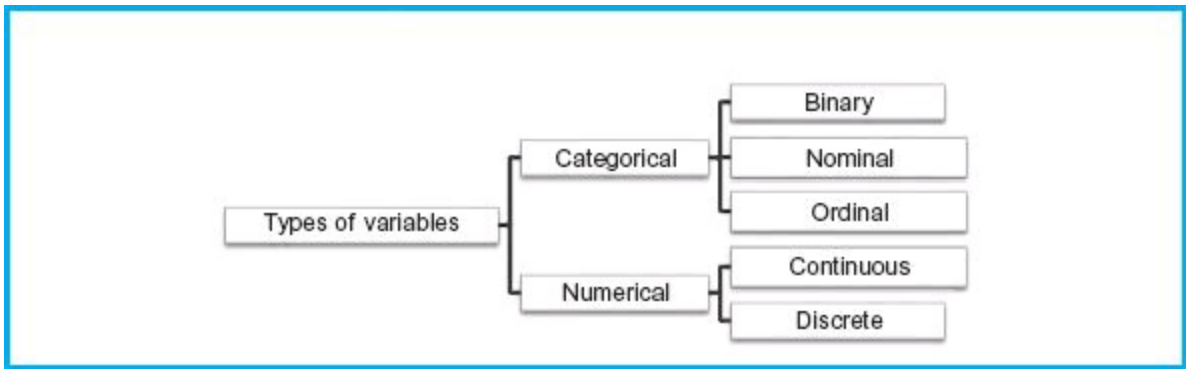


Figure 21.3 Normal distribution

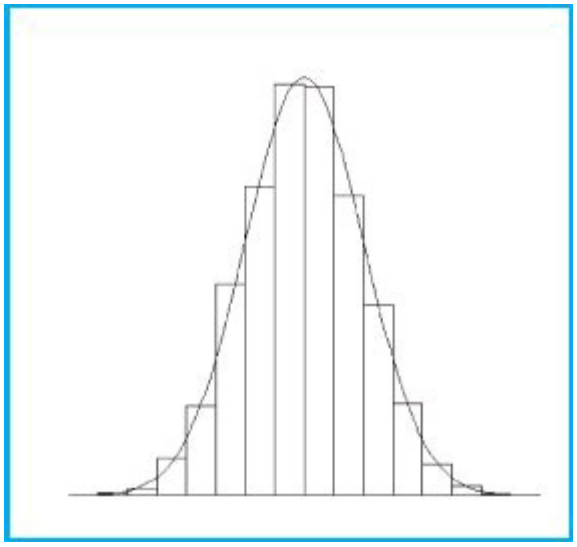


Figure 21.4 Mean and standard deviation (SD)

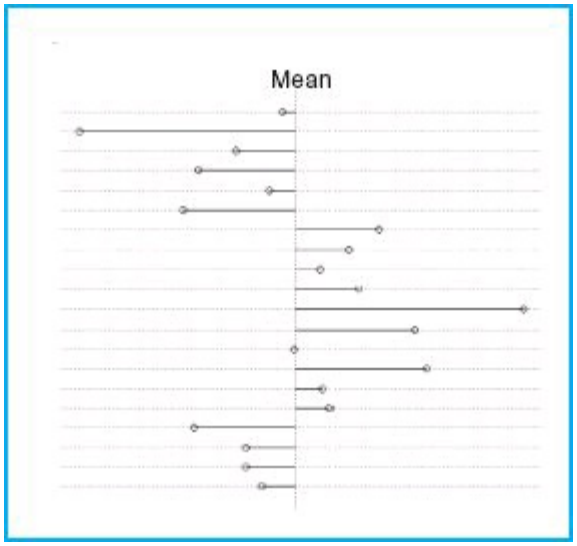
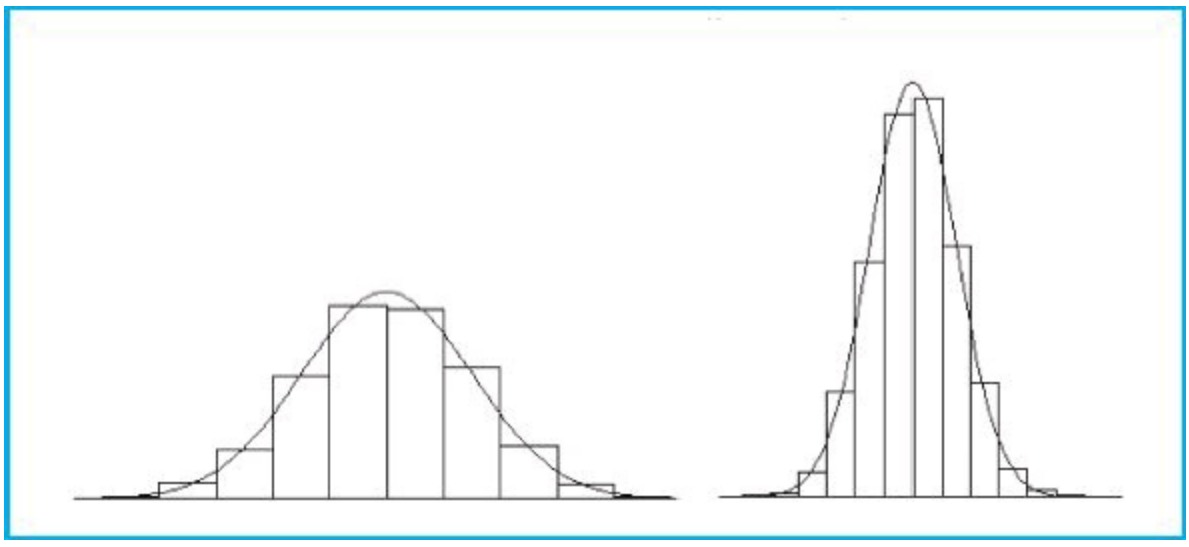


Figure 21.5 Distributions with different spread (large and small respectively)



The centre and spread of numerical data that are not normally distributed should be summarised via the median and interquartile range (IQR), respectively.

The median is the middle value or the average of the two middle values (of the ordered observations) if there is an odd or even number of observations, respectively. For a sample of six observations, the

median is calculated as follows:

7, −3.5, 2, −5, 0, 2.2 → in order of magnitude → 5, −3.5, 0, 2, 2.2, 7 → median = (0 + 2)/2 = 1

Similarly, for a sample of nine values:

9, −4, 5, −1, −0.4, 3, 18, 1.5, −2, → in order → 4, −2, −1, −0.4, 1.5, 3, 5, 9, 18 → median = 1.5

The IQR splits the data into four sections, quarters. Each section contains 25% of the ordered data. The IQR is the difference between the datapoints that define the end of the first and the third quarters, also known as the first and third quartiles, respectively, ie IQR = 3rd quartile − 1st quartile.

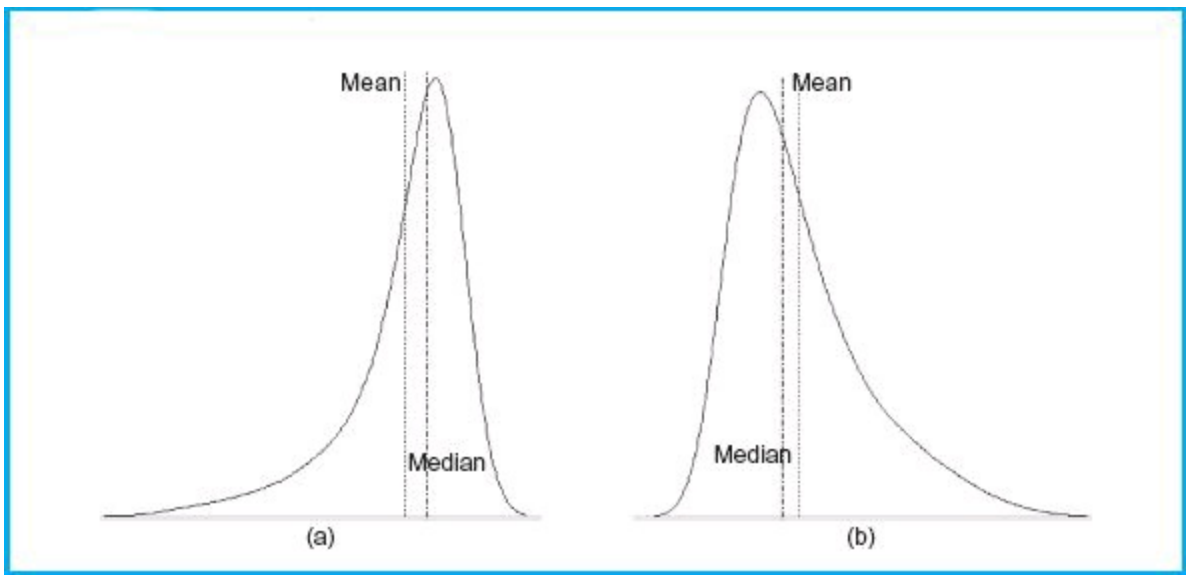
For a sample of 12 (already ordered) values, this is what the IQR would look like/be calculated as:

−7, −1, 0.5	1, 2, 3.2	4, 5.1, 6	7, 8.1, 10
Quarters: 1st	2nd	3rd	4th
Quartiles: 0.5	3.2	6	10
IQR = 6 – 0.5 = 5.5			

It is essential that the right descriptive measures are used, depending on the distribution of the data. When the sample data form a skewed distribution (Figure 21.6a or b), the mean is 'pulled towards' the values in the outlying tail of the histogram. Hence it is an unrepresentative measure (either over- or under-estimate) of the centre of the bulk of the data. The same applies to the SD, which uses the mean in its calculation; it will not be a representative measure of spread.

Note that skewed distributions take their name after the direction of the skewedness. Figure 21.6a is called left/downward/negative skewed and Figure 21.6b is called right/upward/positive skewed.

Figure 21.6 Skewed distributions



Normal distribution or not?

The histogram of the data is the best tool that helps determine whether the data are normally distributed. However, very often there is need to evaluate the distribution of a variable while not being able to see/draw its histogram. Sometimes the similarity between the mean and median can be helpful, because, the closer the two are, the closer the histogram of a variable resembles a

symmetrical distribution. However, there are no universal measures of how close the two should be. There is a very useful property of the normal distribution that comes very handy in this exploration of normality.

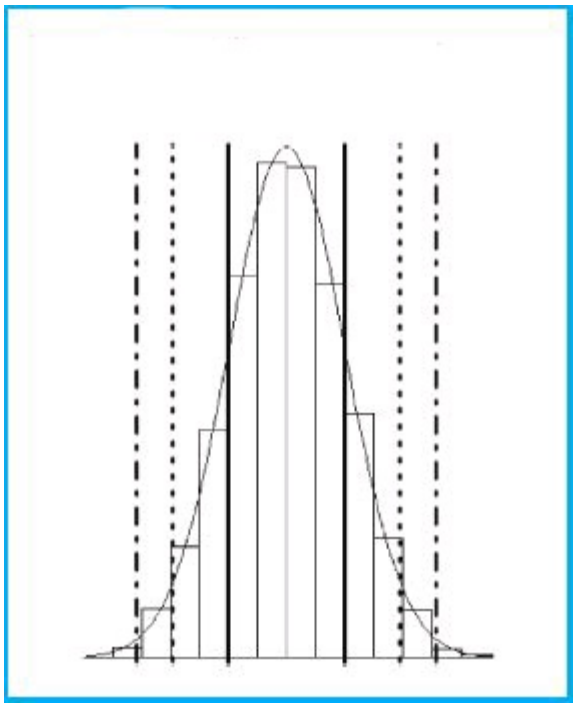
If a variable is normally distributed, then a certain percentage of its values are within a certain number of SDs away from the mean. More specifically:

- **Approximately 68%** of the values lie within **±1 SD** of the mean
- **Approximately 95%** of the values lie within **±2 SDs** of the mean
- **Exactly 95%** of the values lie within **±1.96 SDs** of the mean
- **Exactly 99%** of the values lie within **±2.58 SDs** of the mean.

Most commonly the 95% range of the data is used because it contains a satisfyingly (by convention) large enough amount of the data and also leaves out a satisfying number of extreme values (5%), ie not too large (eg 10%) and not too small (eg 1%).

Figure 21.7 illustrates the 68%, 95% and 99% ranges.

Figure 21.7 Normal distribution ranges: solid, dotted and dashed lines represent 68%, 95% and 99% ranges, respectively



This property will give meaningful results only if the data are normally distributed. If, for example, the 95% range (either lower or upper ends of the range) leads to non-possible values, eg negative weight or biologically impossible blood pressure, then this is an indication that the variable of interest is not normally distributed. Hence the median and IQR should be used as summary measures.

21.2.3 Summaries of categorical data

All types of categorical data are summarised via counts/frequencies, proportions/percentages and odds. Table 21.3 shows an example of a binary categorical variable. This example can extend to nominal and ordinal variables.

Note that there are no distribution assumptions when dealing with categorical data and the notions of

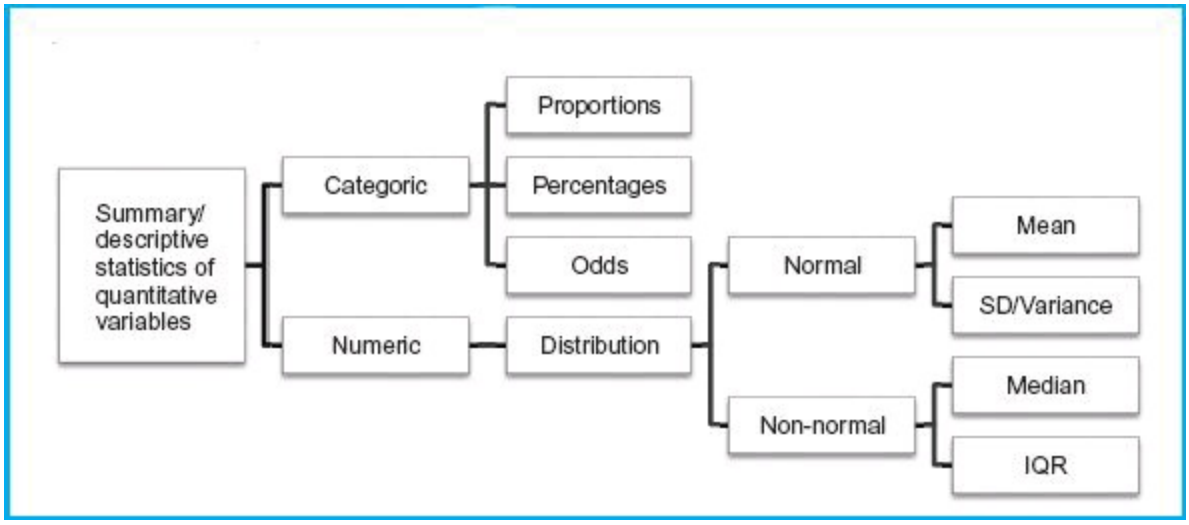
centre and variability are not applicable any more. As a result of this, some argue that the analysis of categorical data is easier, so they decide to chop numerical variables into categories. This is very wasteful of the data and should be avoided. If a variable is numerical and its original data exist, then it should be kept in this format, because it is the most informative 'version' of the variable. Analysis of numerical variables is more powerful and often simpler.

(For more measures relating to comparisons of categorical data, ie relative risks, odds ratios, etc, see Chapter 5, Epidemiology.) For a summary see Figure 21.8.

Table 21.3 An example of a binary categorical variable

	Observed count/Frequency	Total	Proportion	Percentage	Odds
Level 1	r_1	n_1	r_1/n_1	$(r_1/n_1) \times 100$	$r_1/(n_1 - r_1)$
Level 2	r_2	n_2	r_2/n_2	$(r_2/n_2) \times 100$	$r_2/(n_2 - r_2)$

Figure 21.8 Summary measures – flowchart



21.3 CONFIDENCE INTERVALS

Data are collected to answer a pre-specified research question that relates to a large population. This answer most commonly takes the form of sample estimates of means, percentages, odds ratios (ORs), etc. The sample value is the best estimate of what is happening in the population. For example, the mean birthweight of a random representative sample of children in Manchester is the best estimate from our study of the average birthweight of all children in Manchester. Nevertheless, it is not 100% precise. Other samples (possibly collected from a similar research facility somewhere else in Manchester) would lead to different estimates because there is random variation in everything being measured.

The standard error (SE) measures how precisely the sample value approximates the unknown population value, eg how precisely the birthweight of our Manchester-sampled infants estimate the birth-weight of all infants in Manchester (population). The SE can take any positive value but there is no universal scale that defines small and large SEs. When the SE is put in context with the sample estimate itself, then confidence intervals (CIs) are created.

CIs provide a range of population values with which the sample is compatible. In other words, a CI is a range of values for a variable of interest that has a specified confidence of including the true value of the variable. The specified confidence is the confidence level, and the end points of the confidence interval are the confidence limits. The narrower the CI, the more precise the sample estimate is in comparison to a wider CI. CIs can be calculated for all summary statistics seen earlier and for many other quantities, such as ORs, relative ratios (RRs), etc. For these calculations, the SE of the estimate is required. The following formula gives the **exact 95% CI**:

Sample estimate ± (1.96 × SE)

The 95% CI can be interpreted as: 'With 95% confidence, it can be stated that the true mean lies inside this interval.' Hence, there is a 5%, or 0.05 or 1 in 20, chance that the true mean lies outside the 95% CI.

How good an estimate is will depend on the sample size, ie bigger samples will give smaller error, hence better estimates, hence narrower CIs, ie the more observations in the sample, the more precise the sample estimate of the population quantity will be.

For the simplest case of the single mean, the SE is given by $SD/\sqrt{n}$, where n is the size of the sample. Notice how the error is inversely related to the sample size. In fact, this is the case for all SE formulae that exist.

For example, the forced expiratory volume in 1 s (FEV_1) is measured in 100 students. The mean value for this group is 4.5 L with an SD of 0.5 L. If the values are normally distributed, then approximately 95% of the values lie in the range $(4.5 \pm 2 \times 0.5) \rightarrow (3.5, 5.5)$ L. The SE for the sample mean is $0.5/\sqrt{100} = 0.05$. An approximate 95% CI for the population mean FEV_1 is given by $(4.5 \pm 2 \times SE) \rightarrow (4.5 \pm 2 \times 0.05) \rightarrow (4.4, 4.6)$ L.

This means that the true population mean FEV_1 of students lies in the range 4.4–4.6 L with 95% confidence.

Note the difference between the SD and the SE:

- SD gives a measure of the spread of the data values
- SE is a measure of how precisely the sample mean approximates the population mean.

21.4 STATISTICAL SIGNIFICANCE TESTS

21.4.1 Null hypothesis and *p* values

Statistical significance tests, or hypothesis tests, use the sample data to assess how likely the data were to have occurred if some specified statement is correct. This statement is known as the null hypothesis, because it always assumes there is no (null) change/improvement/difference between the groups. The measure of 'how likely' is given by a probability (p) value.

Recall the research questions from the first section. The null hypotheses for each could be phrased as follows:

- There is no difference in the incidence of fetuses with neural tube defects between the groups of

pregnant women who do and do not take folic acid supplements

- Lung function is similar in cystic fibrosis patients who receive the new inhaled steroid when compared with the patients on standard treatment
- Smokers and non-smokers have equal chances of contracting cancer.

Even if these null hypotheses were true, it would not be expected that the averages or proportions in our sample groups would be identical. As a result of random variation there will be some difference between the groups. The *p* value is the probability of observing a difference of the observed magnitude if the null hypothesis is true, in other words it measures compatibility of the data with the null hypothesis. As the *p* value is a probability, it takes values between 0 and 1.

Values near to zero suggest that the data are unlikely to have occurred if the null hypothesis was true or the data have low compatibility with the null hypothesis (loosely speaking, because the truth will almost never be known, the null hypothesis could then be 'rejected'). Values close to 1 indicate that the data are very likely to have occurred if the null hypothesis was true or that the data have high compatibility with the null hypothesis ('accept' it). The terms 'accept'/'reject' should never be used as we will almost never know the truth about the null hypothesis. Instead, we are only making probabilistic statements about the compatibility of the sample with the null hypothesis. The smaller the *p* value the more significant the result:

- $p < 0.05$, the result is significant at 5%: the sample difference had a 1 in 20 chance of occurring if the null hypothesis was true
- $p < 0.01$, the result is significant at 1%: the sample difference had a 1 in 100 chance of occurring if the null hypothesis was true.

Statistical significance is not the same as clinical significance. Although a study may show that the results from drug A are statistically significantly better than those for drug B, the magnitude of the improvement has to be considered, the costs, ease of administration and potential side-effects of the two drugs, etc before deciding that the result is clinically significant and that drug A should be introduced in preference to drug B.

Depending on the type of the data and the number of groups that are being compared, different tests should be used to explore compatibility with the null hypothesis (these are discussed in section 21.4.4). The principle of all tests is the same as that described above and the result of all tests is a *p* value. Note that **exact *p* values** should always be reported along with the **actual estimate** and the **CI of the estimate**.

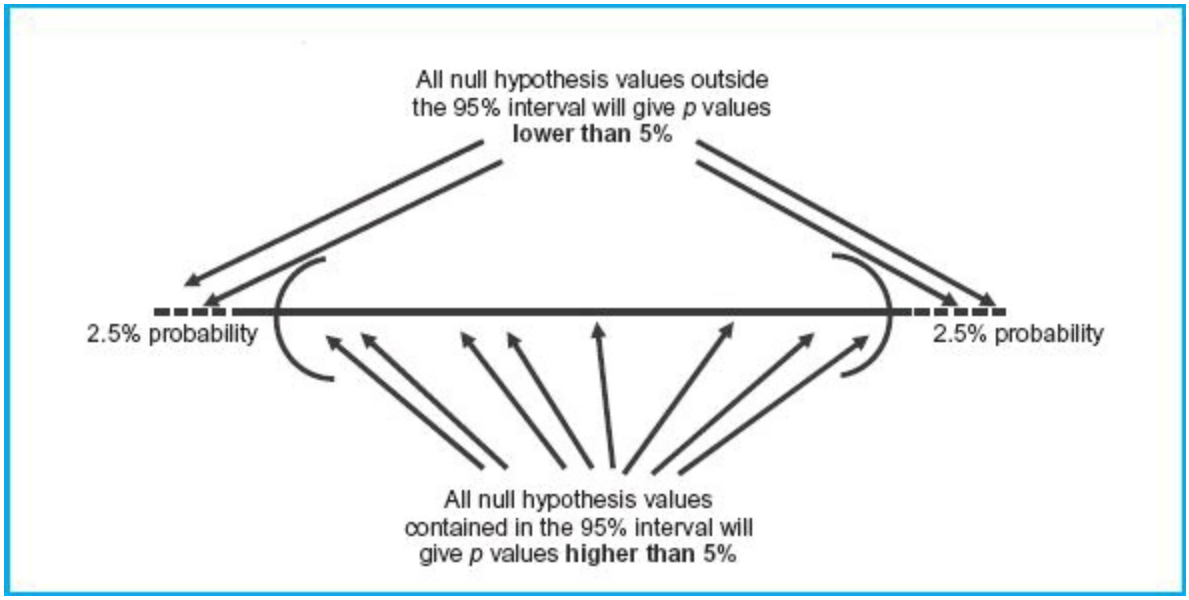
21.4.2 Significance and confidence intervals

The result from a CI and the corresponding significance test should always agree. Both give a measure of compatibility of the sample with a/some population value(s). The CI gives a range of values with which the sample is compatible and the p value tests compatibility of a sample against a specific value. If this specific (null hypothesis) value is included in the CI then the *p* value will reflect this, with a high probability (strong compatibility). If the value is not included, the *p* value will be small (low compatibility). More specifically:

A test will give lower than 5% probability (hence significant result) for all hypothesised values

- outside the 95% CI range, since the probability ascribed to these values is 100 − 95 = 5, remaining 5%
- A test will give higher than 5% probability (hence non-significant result) for all values inside the 95% CI range, since the probability ascribed to these values is higher than 5%
- A test will give higher than 1% probability for all values inside the 99% range
- A test will give lower than 1% probability for all values outside the 99% range.

Figure 21.9 95% CI and *p* values



For example, the difference in weight change between two groups of patients following an exercise regimen and food counselling sessions is 0.8 kg, ie the exercise group lost 0.8 kg more. The 95% CI goes from −0.2 kg to 1.8 kg, ie with 95% confidence, there is compatibility with 0.2 kg more loss for the counselling group and up to 1.8 kg more loss for the exercise group. Zero is also included in this interval; hence the sample is compatible with 0, ie no significant weight change between the two groups. The *p* value will be non-significant, >0.05, ie agree with the CI.

21.4.3 Significance, power and sample size

Based on the data collected from the sample, the *p* value will lead researchers to either 'accept' or 'reject' the null hypothesis. But, will this decision be the correct one? In real life, if data from the entire population could be collected, the null hypothesis would be either true or false. So, in actual fact, the researcher could be experiencing one of the four occurrences in Table 21.4. In more detail, the researcher might:

- 'accept' the null hypothesis, when it is indeed correct (OK - good result)

- 'accept' the null hypothesis, when it is actually incorrect (bad result – error: Type II error)

- 'reject' the null hypothesis, when it is indeed incorrect (OK - good result)

- 'reject' the null hypothesis, when it is actually correct (bad result – error: Type I error).

Let's recall what a significance level of 0.05 (which is very commonly used in published research) means. It means that researchers allow themselves to say that there is a significant difference ('reject'

the null hypothesis) 5% of the time when actually there might be no difference at all. This is in fact the type I error seen in Table 21.4.

Table 21.4 Null hypothesis

	Real life	
Study result	True	False
'Accept'	OK	Error II
'Reject'	Error I	OK

It is not possible to calculate the two types of errors as it will never be known if the null hypothesis is wrong or right. But, type I error is used as indication to define statistically significant results and type II error is used for power.

However, the study may lead to the wrong conclusions. To recap:

- A low (significant) *p* value may lead us to 'reject' the null hypothesis when it is actually true: error I in Table 21.4. This is known as a type I error
- The *p* value may be high (non-significant) when the null hypothesis is false: error II in Table 21.4. This is known as a type II error.

The power of a study is the probability (usually expressed as a percentage) of correctly rejecting the null hypothesis when it is false – in other words, concluding that there is a significant difference when indeed there is one. The power to identify correctly a difference of a certain size can be increased by increasing the sample size. Larger differences between the groups can be detected more easily, in other words with greater power, for the same sample size. Small samples often lead to type II errors, ie there is not sufficient power to detect differences of clinical importance.

In practice there is a grey area between 'accepting' and 'rejecting' the null hypothesis. The decision will be made in the light of the *p* value obtained. The same conclusions should be drawn based on a *p* value of 0.051 compared with a value of 0.049. The *p* value is a probability. As it gets smaller the less compatible the data are with the null hypothesis. Despite common practice in the medical field (and beyond) of dichotomisation of the significance of results (below and above 0.05 or 0.01), best practice is to always report exact *p* values along with the actual estimate and the CI of this estimate.

21.4.4 Parametric and non-parametric tests

Each significance test corresponds to a specific null hypothesis, eg equality of means, equality of percentages. Statistical hypothesis tests are either parametric or non-parametric. Choosing the appropriate statistical test depends on the following:

- The type of variable being compared/mentioned in the null hypothesis
- If it is numerical, on its distribution
- If it is categorical, on the counts in the cells of the frequency table
- Whether or not the data are paired.

Parametric tests usually assume that the data are normally distributed (if numerical) or that there are sufficient counts in the frequency table (>5, if categorical). Examples are:

- The *t*-test (sometimes called the 'Student's *t*-test' or 'Student's paired *t*-test')
- The chi-squared (χ^2) test
- Pearson's coefficient of linear correlation.

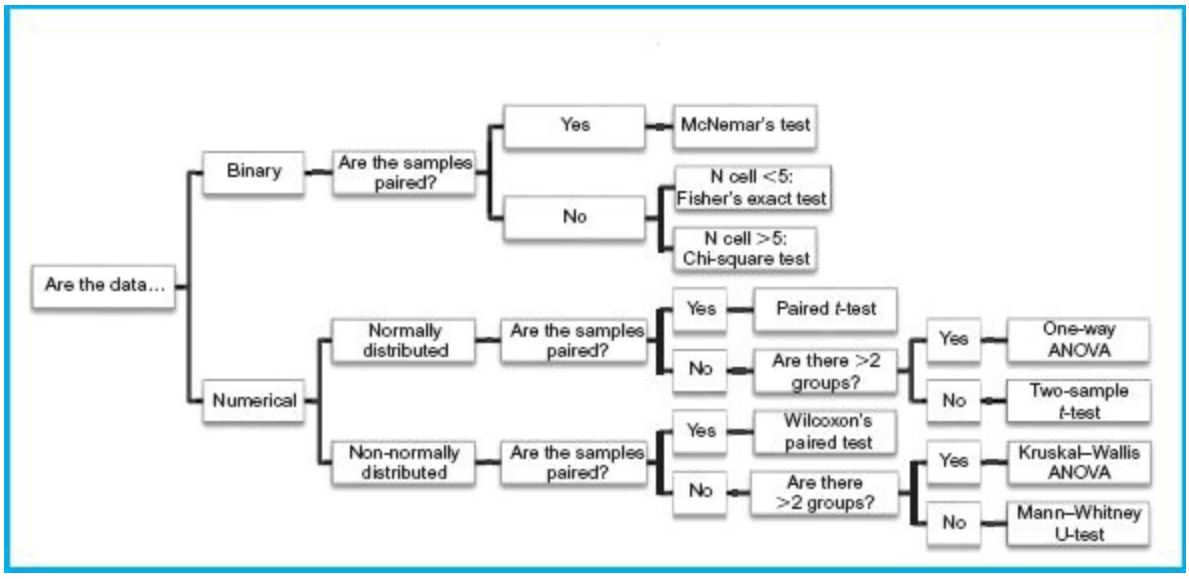
An unpaired (or two-sample) *t*-test is used to compare the average values of two independent groups (eg patients with and without disease, treated versus placebo, etc). A paired *t*-test is used if the members of the groups are paired, eg each individual with disease is matched with a healthy individual of the same age and sex; in a crossover trial the measurements made on two treatments/conditions are paired within individuals (eg pre and post-surgery measurements).

Non-parametric tests make no distribution assumptions for the data (eg can be used with non-normally distributed values) and have no required minimum sample size/observed counts. Examples are:

- Wilcoxon's tests
- Mann–Whitney U test
- Fisher's test
- Spearman's rank correlation.

Figure 21.10 summarises the most commonly used parametric and non-parametric significance tests. As the sample size becomes greater than 20, deviations from the normal distribution become less important, hence parametric tests can be used.

Figure 21.10 Most commonly used parametric and non-parametric significance tests. N cell: count in the cell of a frequency table, ANOVA: analysis of variance

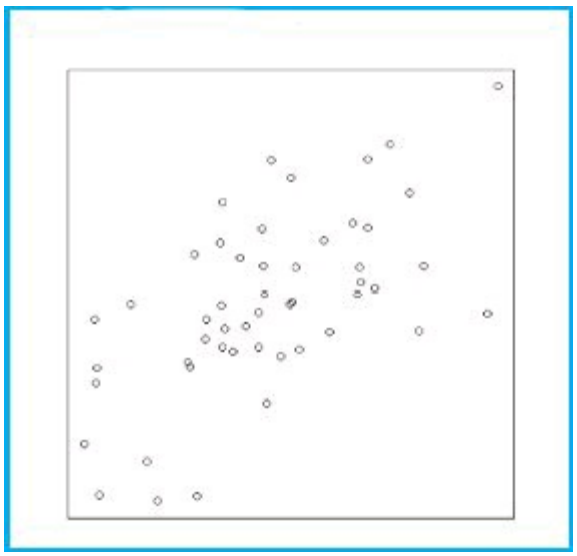


21.5 REGRESSIONS AND CORRELATIONS

Sometimes measurements are made on two continuous variables for each study participant, eg CD4 count and age, blood pressure and weight, functional residual capacity (FRC) and height. Interest lies in the association between these two variables. The scatter plot of the data, as in Figure 21.11, is the

first step for the exploration of this association.

Figure 21.11 Scatter plot



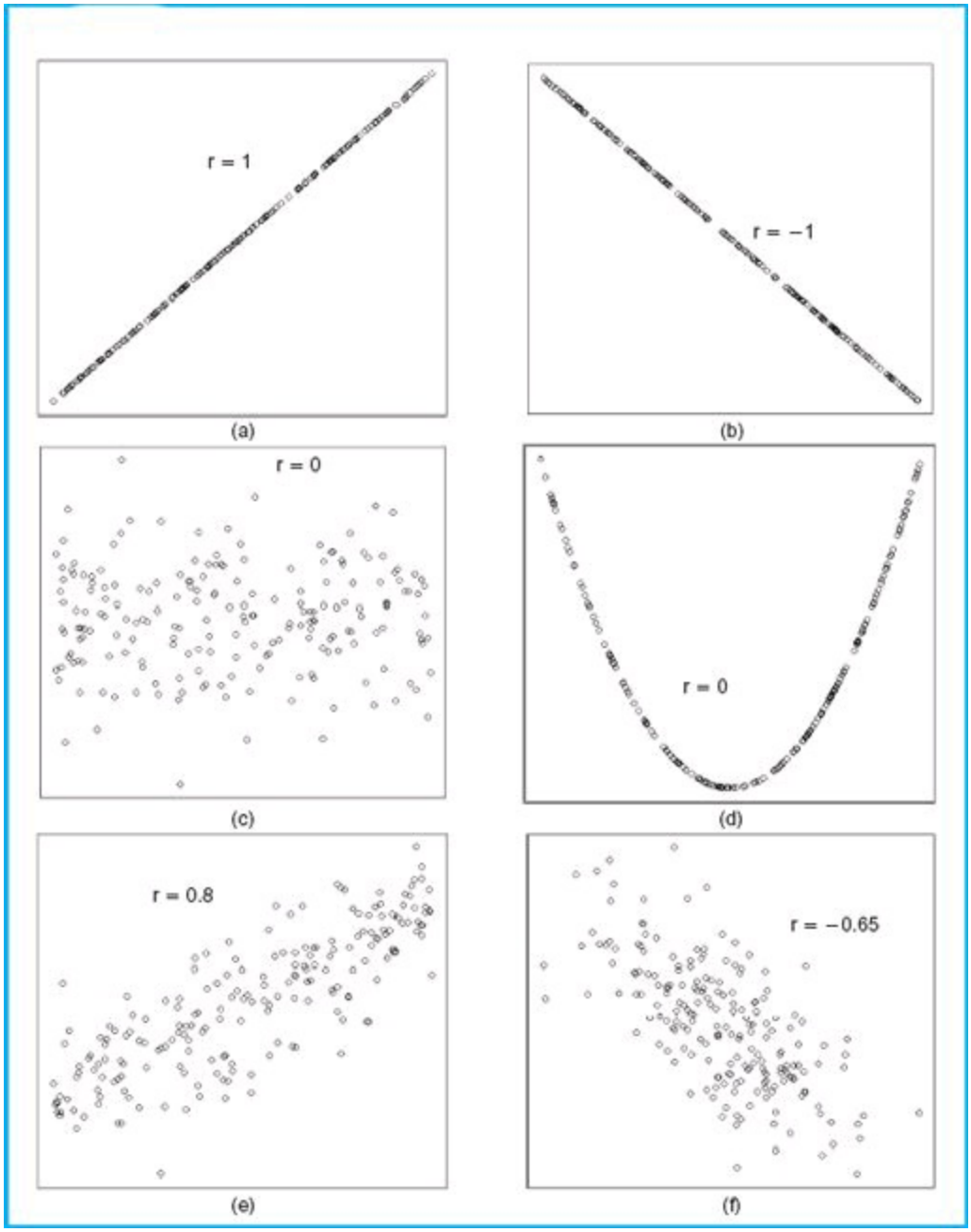
21.5.1 Correlation coefficients

The linear association between the two variables is measured via the correlation coefficient (sometimes called Pearson's coefficient of linear correlation) and is denoted by r. It indicates how closely the points lie to a line, and takes values between −1 and +1; the closer it is to zero, the less the linear association between the two variables. (Note that the variables may be strongly associated but not linearly.)

Negative values of r indicate that one variable decreases as the other increases (eg CD4 count falls with age). Values of −1 or +1 show that the variables are perfectly linearly related, ie the points on the scatter plot lie on a straight line. As things get closer to 1 or −1, they become more correlated, but there is no such thing as a universally accepted threshold of correlation. Correlation coefficients (several examples of which are shown in Figure 21.12) do the following:

- Show how one variable increases or decreases as the other variable increases
- Do not give information about the size of the increase or decrease
- Do not give a measure of agreement.

Figure 21.12 Correlation coefficients



Pearson's *r* is a parametric correlation coefficient, ie the variables that are being correlated should be normally distributed. Spearman's rank correlation and Kendall's tests are non-parametric correlation coefficients.

- Parametric correlation coefficients quantify the extent of any linear increase or decrease
- Non-parametric correlation coefficients quantify the extent of any tendency for one variable to increase or decrease as the other increases (for example, exponential increase or decline, increasing in steps, etc). Hence they would be more appropriate for the U-shaped graph of Figure 21.12(d).

A value of 1 or −1 for Pearson's correlation indicates very strong positive/negative linear association, respectively, whereas a value of 1 or −1 for the non-parametric coefficients indicate a very strong positive and negative association, respectively, of any shape (not necessarily linear).

21.5.2 Regression

Regression models quantify explicitly the association measured by the correlation coefficients. They are built for the purpose of **understanding relationships** between one or more outcome variables and one or more explanatory variables. The outcome/ dependent variables are those whose behaviour is being explored while some 'conditions' change in our 'experiment'/sample. These other 'conditions' are expressed via the so-called explanatory/independent/predictor variables. For example, for the following research question 'How does age affect CD4 values?' there is one outcome variable, CD4, and one explanatory variable too, age. The researcher's interest lies in the change of CD4 while age changes. The ultimate aim of regression models is to make predictions about future cases/patients/ situations.

The choice of regression depends on the nature of the outcome variable, as per Figure 21.13; notice that the explanatory variables can be either numeric or categoric or a combination of both.

The simplest regression model is a linear model with one outcome and one predictor. It can be expressed as $Y = a + b \times X$ and graphically displayed as in Figure 21.14.

The constant or intercept ('a') is the value of Y when X is 0. Often, 'a' does not have a real-life interpretation because an X of 0 is not often meaningful. The regression coefficient ('b') of all models always represents the change in the outcome per unit change in the corresponding predictor, X. In other words, it is the slope of the line. For linear models, this is the change in the average outcome per unit change in X. If 'b' is negative, then Y decreases as X increases (negative slope).

Figure 21.13 The choice of regression

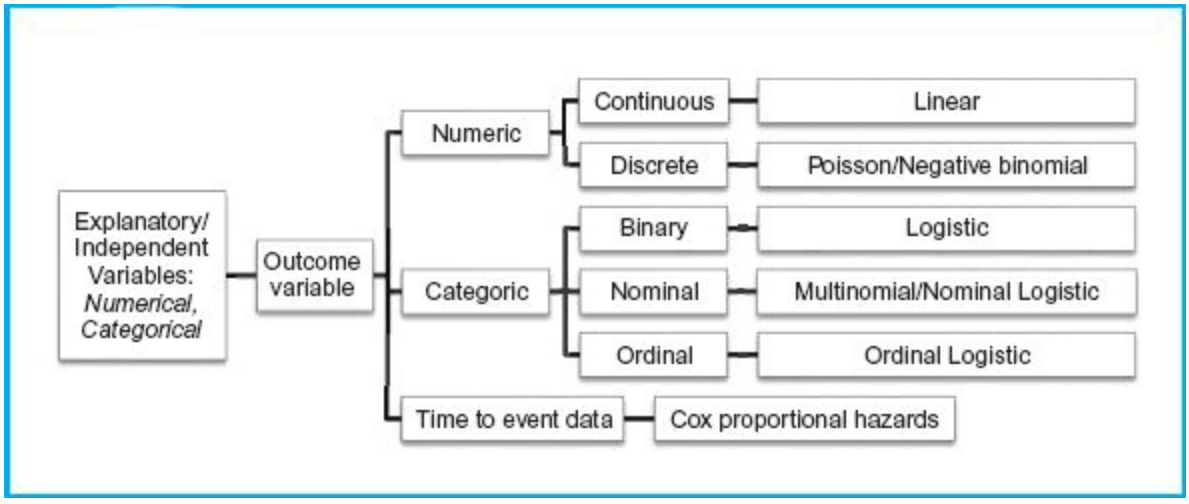
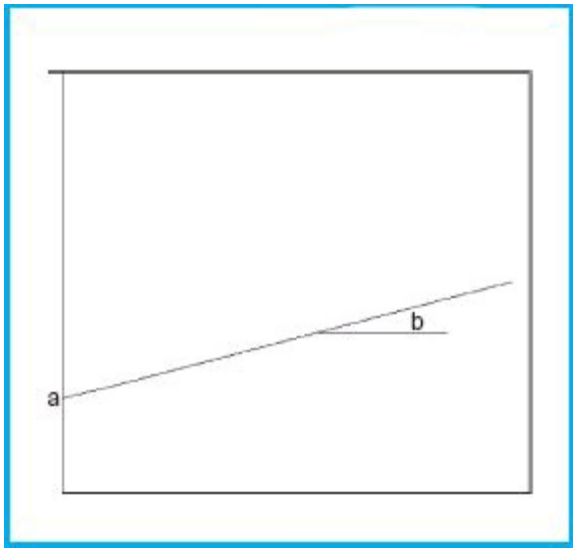


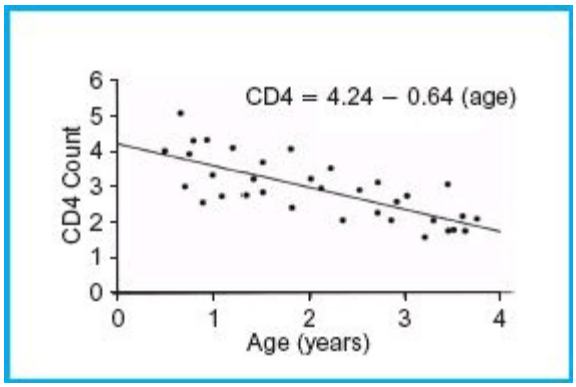
Figure 21.14 Linear regression: $Y = a + b \times X$



For example, for the age and CD4 question posed earlier, the data shown in Figure 21.15 lead to the displayed model. Hence, for every year increase in age, the average CD4 values drop by 0.64.

All regression coefficients should always be reported with confidence intervals (usually 95%), and their exact *p* value should also be presented. In addition, model diagnostics should be run to ensure that the model fits well. Model diagnostics involve checking the residuals of the model (distance between observed and fitted values, ie distance of each observed point/dot from its projection on the regression line), non-parametric measures of overall fit (eg deviance, AIC, BIC) and various influential measures that explore the effect of outliers in the model.

Figure 21.15 CD4 and age



21.6 SCREENING TESTS

Screening tests are often used to identify individuals at risk of disease. Individuals who are positive on screening may be investigated further to determine whether they actually have the disease.

- Some of those who screen positive will not have the disease
- Some of those who have the disease may be missed by the screening (ie test negative).

Table 21.5 shows an example of a contingency table containing data for a screening test.

- **Sensitivity** is the proportion of true positives correctly identified by the test: $a/(a + c)$
- **Specificity** is the proportion of true negatives correctly identified by the test: $d/(b + d)$

- **Positive predictive value** is the proportion of those who test positive who actually have the disease: $a/(a + b)$
- **Negative predictive value** is the proportion of those who test negative who do not have the disease: $d/(c + d)$.

Note that the positive and negative predictive values depend on the prevalence of the disease and may vary from population to population.

Likelihood ratios (LR) are an additional measure of great usefulness in the field of screening tests. They are a ratio of the probability of a positive (LR+) or negative (LR-) test result in subjects that have the disease to those that do not. In other words, LR+

Table 21.5 Contingency table for a screening test

Test result	Diseased	Disease-free
Positive (indicating disease)	a	b
Negative	c	d

summarises how many times more likely subjects with the disease are to have the particular test result than subjects without the disease. Unlike positive/ negative predictive values, which are prevalence dependent, likelihood ratios do not depend on the prevalence of disease in the sample.

- The likelihood ratio (LR) for a positive test result is:

  LR+ = sensitivity/(1 – specificity)

- The likelihood ratio for a negative test result is:

  LR– = (1 – sensitivity)/specificity

One of the uses of likelihood ratios is being multiplied by pretest odds of disease to give post-test odds of disease.

For example, a screening test is applied to patients with and without disease. Of 100 who have the disease, 60 test positive; of 200 without the disease, only 20 test positive (Table 21.6).

Table 21.6 Likelihood ratios

Test result	Diseased	Disease-free	Totals
Positive (indicating disease)	60	20	80
Negative	40	180	220
Totals	100	200	300

Therefore, the following are true:

- The pretest odds of having the disease are set (decided by the researcher) to 1.5 based on existing literature/other evidence/experience; meaning that an individual is 1.5 times more likely to have the disease than not to have it, in other words the probability of disease before testing is 0.6

  (odds = probability/(1 − probability) → probability = odds/(1 + odds))

- Prevalence of the disease **in this sample** is 100/(100 + 200) = 0.33 or 33%
- Sensitivity = 60/100 = 0.6 or 60% of true positives are identified by the test
- Specificity = 180/200 = 0.9 or 90% of true negatives are identified by the test
- Positive predictive value is 60/(60 + 20) = 0.75 or 75% of those who test positive actually have the disease **in this sample**
- Negative predictive value is 180/(180 + 40) = 0.82 or 82% of those who test negative actually do not have the disease **in this sample**
- LR+ = 0.6/(1 – 0.9) = 6, ie patients with the disease are 6 times as likely to test positive as patients without the disease
- LR– = (1 – 0.6)/0.9 = 0.44, ie patients with the disease are 0.44 times as likely to test negative as patients without the disease
- If the test is positive then the post-test odds of having the disease will be determined by the result of the screening test and will be 1.5 . 6 = 9, ie the patient is nine times more likely to have the disease than not, which equates to a probability of 9/10 or 0.9 (as opposed to 0.6 before testing)
- If the test is negative, the post-test odds of disease will be 1.5 . 0.44 = 0.66, ie posterior odds of 0.66 equates to a probability of 0.66/1.66 or 0.4 (as opposed to 0.6 before testing).

Note that, as expected, the odds of having the disease rise if the test is positive and fall if the test is negative.

Index

Where more than one page number appears against a heading, page numbers in bold indicate the main treatment of a subject.