Color Atlas and Text of

Clinical Medicine

2nd edition

Charles D Forbes  DSc MD FRCP FRSE
Professor of Medicine
Ninewells Hospital and Medical School
Dundee
Scotland

William F Jackson  MA MB BChir MRCP
Medical Writer
Formerly Honorary Consultant
Department of Medicine
Guy’s Hospital
London
England

Mosby-Wolfe

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## INTRODUCTION

Infections are the largest cause of morbidity and mortality worldwide. The most common infections are the diarrhoeal diseases, respiratory infection, malaria, measles, hepatitis, schistosomiasis, whooping cough and neonatal tetanus. The course and severity of infection depends on a variety of factors, including the virulence of the strain of infecting organism, the resistance of the population or individual, which may be reduced by famine or intercurrent disease (1.1), social factors such as lack of sanitation, poor housing and a contaminated water supply, and the availability of medical facilities providing vaccination or diagnosis and treatment. Ultimately it is always the interaction between the patient (host) and the pathogen that determines the outcome of any infection.

Over the past 30 years the availability and cheapness of air travel has allowed ‘new’ diseases to appear rapidly and unexpectedly in new places. A recent example of this ‘jet age’ transmission is HIV infection, which rapidly crossed international boundaries both by population movement (homosexual and heterosexual carriers) and in blood products, notably the factor VIII used in the treatment of haemophilia.

### FACTORS THAT MAY AFFECT THE COURSE OF INFECTIONS

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Infections acquired in hospital (nosocomial infections) have become increasingly important in the developed world. Many nosocomial infections affect patients who are immunocompromised as a result of another disease or its treatment. Such infections may involve otherwise non-pathogenic organisms or may produce symptoms and signs that differ from those seen in non-immunocompromised patients. Important clinical problems in these patients include infections associated with intravenous lines, fungaemias, multiple-drug-resistant Gram-negative bacteraemia and other difficult-to-treat infections.

Many (but not all) of the infections considered in this chapter produce fever in the host, and the investigation of a patient with unexplained fever is a medical challenge that requires careful history taking, a meticulous examination and appropriate planned investigations. To take an effective history it is important to be aware of the reservoirs of infection and potential routes of transmission.

Reservoirs act as a source of infection within which the infective agent may often divide and multiply and from which the agent may be disseminated. Animal reservoirs are particularly important, as it is often impossible to eliminate them; public health measures aim to prevent spread to the human population. Examples of animal reservoirs include:

- **viral** – rabies virus in infected domestic and wild animals
- **bacterial** – *Salmonella* species in contaminated eggs and poultry
- **fungal** – *Histoplasma capsulatum* in infected bird and bat droppings
- **protozoal** – *Leishmania* species in infected rodents
- **helminthic** – toxocariasis in dogs and cats.

Human reservoirs are important, especially in viral infections. Examples include the following:

- **viral** – upper respiratory tract virus infections (1.2) and HIV

1.1 Factors that may affect the course of infections.
INFECTIONS

• **bacterial** – acute streptococcal pharyngitis (1.3) and sexually transmitted diseases such as gonorrhoea and syphilis
• **fungal** – candidiasis and dermatophyte infections (1.4)
• **protozoal** – *Trichomonas vaginalis* (transmitted sexually)
• **helminthic** – *Enterobius vermicularis* (threadworms).

Natural reservoirs include soil, water and vegetation. Many infecting organisms are found in nature, and some infect humans via intermediate hosts. Examples include
• **viral** – hepatitis A in faecally contaminated water (1.5)
• **bacterial** – cholera in faecally contaminated water (1.5)
• **fungal** – *Aspergillus* spores are ubiquitous in soil and vegetation and are often released when old buildings are demolished
• **protozoal** – amoebae may live for weeks or months in the encysted form
• **helminthic** – schistosomes spend part of their life cycle in an intermediate host (water snail).

The transmission of infection can take many forms, and understanding these is the key to designing public health measures effective in preventing the spread of diseases. Important routes of transmission include
• **contact**, as with sexually transmitted diseases, herpes simplex (1.6), chickenpox, impetigo; via fomites (books, crockery, towels, etc.), as with many bacteria, especially tuberculosis, and yaws; and from animal reservoirs (1.7)

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1.3 Acute streptococcal pharyngitis. There is pus in the tonsillar crypts, and some palatal petechiae are also seen. The patient acts as a reservoir of *Streptococcus pyogenes*: the organisms multiply in the pharynx and may be disseminated to others by coughing, sneezing or direct contact with oral secretions. A similar appearance may be seen in patients with infectious mononucleosis. Treatment with a penicillin is indicated for streptococcal pharyngitis, but ampicillin and related drugs may cause a drug rash if the true diagnosis is infectious mononucleosis.

1.4 Tinea (ringworm). Patients with dermatophyte infections act as reservoirs of infection, and ringworm may also sometimes be ‘caught’ through contact with infected animals. This florid case resulted from infection with *Microsporum canis*.

1.5 The river Ganges – an ancient epicentre of cholera. Mass bathing leads to a constant risk of faecal-oral transmission of hepatitis, cholera and other infections. Patients with mild and asymptomatic infections are very important in the epidemiology of cholera.

1.6 Primary herpes simplex in and around the mouth. The infection is usually acquired from siblings or parents, and is readily transmitted to other contacts. The infection commonly persists in a dormant phase, but the 'secondary' lesions that occur on reactivation (see p. 27) are also a common source of infection.
### Zoonoses

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<td><em>Microsporum</em> sp.* Trichophyton* sp. Epidermophyton* sp.</td>
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<td><em>Salmonella</em> sp.</td>
<td>All poultry, pigs, cattle, sheep; human carriers</td>
<td>Poorly prepared, inadequately frozen or cooked meat, milk, cream, cheese; faecal-oral from food handlers</td>
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<td><em>Escherichia coli</em> type 0157 (verotoxin-producing)</td>
<td>Cattle; human carriers</td>
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<td>Milk, meat (usually undercooked), contaminated drinking water, food handlers</td>
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<td>Leptospirosis</td>
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<td><em>Coxiella burnetii</em></td>
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INFECTIONS

- **parent-to-child transmission** as for rubella (1.8), syphilis, toxoplasmosis, hepatitis B, HIV infection
- **aerosols** — from human reservoirs, as with the common cold, influenza, streptococci and meningococci and tubercle bacilli; from the environment, as for *Legionella* and *Aspergillus*; and from animals or their excreta, histoplasmosis and psittacosis for example
- **faecal-oral**, e.g. infective diarrhoeas, hepatitis A, typhoid, amoebiasis, giardiasis
- **via a vector** — malaria (1.9), leishmaniasis, plague, viral encephalitis, Lyme disease, trypanosomiasis
- **direct entry** — through intact skin, as with leptospirosis and schistosomiasis; by bites, as for rabies; by transfusion (1.10), e.g. hepatitis B, hepatitis C, cytomegalovirus, HIV, malaria, leishmaniasis, syphilis; by ingestion, e.g. *Salmonella*, *Listeria*, hydatid disease, tapeworms; and through trauma or surgery, a variety of infections mainly bacterial.

HISTORY

A careful history can often localize the site of a possible infection and may suggest its nature. Viral infections are the most common worldwide. They occur in epidemics, often initially in school-age children, and are passed on to adults. Upper respiratory and diarrhoeal illnesses account for the largest number of cases. Points to be elicited in an assessment of history include

- recent contact with infected persons
- previous exposure to infections
- vaccination status
- occupation, social pursuits and hobbies
- contact with animals (wild or domestic)
- recent foreign travel, including types of endemic and epidemic diseases and the kind of travel (urban, rural, 'backpacking', etc.)
- immigrants should be asked for details of their country and place of origin
- recent dietary history, especially the type/source of food and water
- insect bites
- previous surgery, accidents and the presence of prosthetic devices (1.11)
- history of intravenous drug misuse (1.12)
- sexual activity and proclivity
- tattooing
- blood transfusion and injections
- recent drug history, especially documentation of native remedies and generic content of foreign or branded drugs.

1.9 Malaria is transmitted by female *Anopheles* mosquitoes. Insect vectors are also important in a number of other infections.

1.8 Mother-to-child transmission is important in a number of infections. This infant has congenital rubella, presenting as a small-for-dates baby with a purpuric rash caused by thrombocytopenia. Children born with congenital rubella are a potential source of infection to others, and it is important that appropriate steps are taken to protect other patients and staff.

1.10 Intravenous infusion is an important route of direct-entry infection, especially if blood or blood products are transfused. Bloodborne infections may be introduced in a medical setting or through illicit intravenous drug misuse. Local infection may also be introduced by any puncture of the skin unless a careful aseptic technique is used.
CLINICAL EXAMINATION

A careful and complete clinical examination often provides clues to the nature and site of infection. Special attention should be paid to the skin (for nodules, rashes, bites), eyes, lymph nodes (enlargement of which may be local or generalized), the liver and the spleen. With sexually transmitted disease in particular, it is important to examine the genitalia, the perineum, the anus and the mouth. A thorough examination should include taking the patient’s temperature and plotting any fever (1.13), a general examination for signs of jaundice, dehydration, weight loss, nutritional status, anaemia and oedema and examination of

- the mouth, pharynx and throat for ulcers or membranes
- the conjunctiva and retina for petechiae, inflammation and choroidal deposits (1.14)

1.11 Prosthetic surgical devices are associated with an increased risk of systemic or local infection. This patient has undergone triple valve replacement with Starr-Edwards’ valves, and – like all those who have had heart valve surgery – is at increased risk of contracting infective endocarditis. Similarly, patients who have joint prostheses or other implants are at greater risk of systemic and local infection.

1.13 High swinging fever, plotted in a patient who presented with pyrexia. Blood culture revealed infection with Brucella abortus. The patient had recently returned from a holiday in the Greek islands.

1.14 Choroidal tubercles in acute miliary tuberculosis. This appearance is virtually diagnostic, so it is essential to examine the fundi of any patient in whom miliary tuberculosis is a possibility.
INFECTIONS

- the tympanic membrane for otitis media (1.15)
- the skin for rashes (1.16), nodules, ulcers or signs of scratching
- lymph nodes (1.17) and spleen (1.18), which may be tender to touch
- the liver for tender and non-tender local swellings and generalized enlargement
- the heart for evidence of endocarditis or cardiac failure
- the genitalia for ulcers or discharge of pus
- the lungs for the production of sputum and consolidation or cavitation
- the central nervous system for meningism, impairment of conscious level or focal neurological signs
- urine for evidence of infection or bleeding.

INVESTIGATIONS

A number of tests are often needed to give clues to the cause, site and extent of the disease. Many may also be of value in following the progress of the infection and the effects of therapy.

1.15 Severe acute otitis media, with bulging and hyperaemia of the tympanic membrane. The middle ear is filled with purulent fluid. Otitis media is usually symptomatic, but young children may be unable to communicate their earache, so examination with the auriscope is essential.

1.17 Enlarged lymph nodes in the posterior triangle on the neck. Lymphadenopathy is a feature of many infectious diseases, and aspiration biopsy of the enlarged nodes is sometimes helpful in diagnosis. This patient presented no other clinical clues to the diagnosis, but histology demonstrated the typical caseating granulomas of tuberculosis (see p. 43-46).

1.16 The face in measles. Rashes may take many forms and have many different distributions in infectious diseases. This miserable child has a characteristic appearance, with a fine, light red maculopapular rash on the skin. Unfortunately, not all rashes are so directly diagnostic.

1.18 Gross splenomegaly has been marked on the abdomen of this Filipino boy who has schistosomiasis.
Useful investigations include:
- a full blood count with a differential count — eosinophilia is an important finding in parasitic infections (1.19); lymphocytosis is usually found in viral infections
- erythrocyte sedimentation rate, plasma viscosity or C-reactive protein level (non-specific tests that may be of value in monitoring the course of diseases)
- examination of thick and thin blood films for parasites, especially malaria (1.194), trypanosomiasis (1.20) and filariasis (1.206)
- examination of smears using direct staining (1.21), dark-field illumination or fluorescent antibodies
- urinalysis for blood, bile, protein, pus cells and ova of schistosomiasis
- stool microscopy for amoebae, cysts (1.22), ova and parasites
- renal and liver function tests
- lumbar puncture for examination of cerebrospinal fluid (CSF) in suspected meningitis (1.23)
- cultures of blood, urine, stools, throat swab, CSF, pus and so on for viruses, bacteria and fungi
- immunoglobulin levels
- serological tests for specific infections
- rapid diagnostic tests, for example antigen detection and polymerase chain reaction (PCR)
- chest and abdominal X-rays
- stool electron microscopy for rotavirus.

1.19 Eosinophilia is a common and important finding in parasitic worm infections. Allergies and drug reactions may also cause eosinophilia but rarely to the same extreme degree as parasite infections, which should always be considered and often searched for when eosinophilia is found.

1.20 Blood smear showing Trypanosoma brucei, one of the causes of African trypanosomiasis. This finding is diagnostic.

1.21 Intracellular gonococci in a smear of urethral discharge. This appearance is strongly suggestive of gonorrhoea, but definitive diagnosis depends on culture and identification of the organism.

1.22 The mature cyst form of Entamoeba histolytica, on stool microscopy, showing the typical appearance with four nuclei. (Iodine, x 1800)

1.23 Purulent cerebrospinal fluid, allowing a provisional diagnosis of pyogenic meningitis. Culture is required for confirmation, although the combination of this finding with the sudden onset of meningitis in a young person or with a rash is strongly suggestive of bacterial meningitis caused by Neisseria meningitidis, Haemophilus influenzae or Salmonella pneumonias (see pp. 479 and 492).
Further specific investigations may be needed to localize the site of the infection, including tomography, ultrasound, isotope scanning (1.24), CT (1.25, 1.26) and MRI.

Biopsy may be required for a tissue diagnosis. Endoscopy is valuable in obtaining tissue from the lung and alimentary tract, and laparoscopy enables direct inspection and biopsy of the abdominal contents. Tissues that may provide a diagnosis include:

- bone marrow (direct cytology and culture)
- skin (fresh preparations and histology)
- liver (histology and aspiration of abscesses)
- lung – transbronchial biopsy (1.27) or aspiration of bronchial washings
- lymph node or spleen
- large and small intestine.

Failure to find the cause or type of infection is not uncommon, in which case a 'best guess' trial of appropriate chemotherapy is often used. Indeed, in the very sick patient treatment should be started immediately with supportive measures and 'blind' drug therapy, which should be continued until the results of investigations dictate a change.

It is important to remember that multiple infections may occur in the same patient. It is common for secondary bacterial infections to occur in patients with primary viral infections.

1.24 Isotope scanning, revealing a collection of pus in the left lower quadrant of the abdomen. Here the technique used involved labelling some of the patient's white cells with technetium hexamethylpropylamine oxime (Tc-HMPAO). This patient had developed a pelvic abscess as a complication of pelvic inflammatory disease (see p. 81).

1.25 A CT scan showing a large subphrenic abscess in a patient who developed a persistent fever in association with rather vague pain in his abdomen and shoulder. A large collection of fluid can be seen posteriorly (arrows). Other cuts showed this collection to be between the spleen and the diaphragm.

1.26 Percutaneous drainage under CT control yielded 1300 ml of pus, allowing immediate relief of symptoms and culture and sensitivity testing of the contents of the abscess. Part of the drainage catheter can be seen in this view at the same level as 1.25. The spleen (arrow) has moved up on drainage of the abscess, and the contrast-containing stomach is also seen.

1.27 Pneumocystis carinii, dark stained using the Grocott method, in a transbronchial biopsy of the lung. Diagnosis of infections from tissue biopsy is necessary when the organisms are difficult or impossible to culture, as is the case with a number of the secondary infections that occur in AIDS, and with protozoal and helminthic infections. Similar staining of sputum or centrifuged bronchioalveolar lavage fluid may also allow identification of organisms.
for example; and in patients with gross immunosuppression, such as those with AIDS, several infections often coexist.

**IMMUNIZATION**

Some infections that previously caused major morbidity and mortality can be prevented through appropriate immunization (vaccination). Indeed, vaccination against smallpox was used to eliminate this infection worldwide. Immunization in childhood and before international travel is now routine in developed countries. Precise immunization schedules vary from one country to another. The schedule currently recommended in the UK is shown in 1.28.

The rest of this chapter is subdivided according to the nature of the infecting organisms. Because some infections are strongly organ-specific, they are covered in other chapters. The tables that appear at the start of each section of this chapter allow rapid reference to the correct page while reminding the reader of the classification and inter-relationship of the causative organisms.

---

### ROUTINE IMMUNIZATION SCHEDULE IN THE UK

<table>
<thead>
<tr>
<th>Age given</th>
<th>Immunization</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>First year of life</td>
<td>Diphtheria/Tetanus/Pertussis (DTP)</td>
<td>First dose at 2 months followed by two further doses at monthly intervals</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em> b (Hib), Polio</td>
<td></td>
</tr>
<tr>
<td>Second year</td>
<td>Measles/Mumps/Rubella <em>Haemophilus influenzae</em> b if not already given</td>
<td></td>
</tr>
<tr>
<td>Fifth year</td>
<td>Diptheria/Tetanus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Measles/Mumps/Rubella if not already given</td>
<td></td>
</tr>
<tr>
<td>Early teens</td>
<td>BCG</td>
<td>For tuberculin test negatives</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td>For all girls, regardless of past history, if the immune status is not known</td>
</tr>
<tr>
<td>First employment</td>
<td>Polio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetanus</td>
<td></td>
</tr>
<tr>
<td>Adulthood</td>
<td>Polio</td>
<td>For those never immunized; for travellers to high-risk areas; for health care workers</td>
</tr>
<tr>
<td></td>
<td>Rubella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tetanus</td>
<td>For all women of child-bearing age who are seronegative</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>If previously inoculated and at 10-yearly intervals</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A and B</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pneumococcus</em></td>
<td>For high-risk groups</td>
</tr>
<tr>
<td></td>
<td>Other specific immunization before international travel</td>
<td>For high-risk groups</td>
</tr>
</tbody>
</table>

1.28 Routine immunization against infection as recommended in the UK. Recommended schedules in other countries may differ in detail.
<table>
<thead>
<tr>
<th>Family</th>
<th>Important human viruses</th>
<th>Relevant human disease</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroviridae</td>
<td>Human immune deficiency virus (HIV 1 and 2)</td>
<td>Acquired immune deficiency syndrome (AIDS)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Human T-cell leukaemia virus I and II (HTLV I and II)</td>
<td>Lymphoma/leukaemia</td>
<td>456, 447</td>
</tr>
<tr>
<td>Picornaviridae</td>
<td>Rhinovirus</td>
<td>Common cold</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Enterovirus</td>
<td>Poliomyelitis</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Poliovirus</td>
<td>Herpangina, skin eruptions, pericarditis, hand-foot-mouth disease, myocarditis, pleurodynia, aseptic meningitis</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Echoviruses and coxsackieviruses</td>
<td>Hepatitis</td>
<td>404</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A</td>
<td>Colorado tick fever, etc.</td>
<td>385</td>
</tr>
<tr>
<td></td>
<td>Rotavirus</td>
<td>Gastroenteritis</td>
<td></td>
</tr>
<tr>
<td>Reoviridae</td>
<td>Orbivirus</td>
<td>Rubella</td>
<td>20</td>
</tr>
<tr>
<td>Togaviridae</td>
<td>Rubella virus</td>
<td>Encephalitis</td>
<td>22, 494</td>
</tr>
<tr>
<td></td>
<td>Enterovirus</td>
<td>Yellow fever</td>
<td>21</td>
</tr>
<tr>
<td>Flaviridae</td>
<td>Yellow fever virus</td>
<td>Dengue</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Echoviruses and coxsackieviruses</td>
<td>Encephalitis</td>
<td>22, 494</td>
</tr>
<tr>
<td></td>
<td>Hepatitis C</td>
<td>Hepatitis</td>
<td>404</td>
</tr>
<tr>
<td></td>
<td>Measles virus</td>
<td>Measles</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Mumps virus</td>
<td>Mumps</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Respiratory syncytial virus</td>
<td>Respiratory infections</td>
<td>186, 190</td>
</tr>
<tr>
<td></td>
<td>Parainfluenza viruses</td>
<td>Respiratory infections</td>
<td>186, 190</td>
</tr>
<tr>
<td>Orthomyxovirida</td>
<td>Influenza viruses A, B, C</td>
<td>Influenza</td>
<td>24</td>
</tr>
<tr>
<td>Rhabdoviridae</td>
<td>Rabies virus</td>
<td>Rabies</td>
<td>24</td>
</tr>
<tr>
<td>Arenaviridae</td>
<td>Lassa fever virus</td>
<td>Lassa fever</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic choriomeningitis virus</td>
<td>Meningitis</td>
<td>492</td>
</tr>
<tr>
<td>Filoviridae</td>
<td>Marburg virus</td>
<td>Haemorrhagic fever</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Ebola virus</td>
<td>Haemorrhagic fever</td>
<td>26</td>
</tr>
<tr>
<td>Coronaviridae</td>
<td>Coronavirus</td>
<td>Respiratory infections</td>
<td>190</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>Bunyavirus</td>
<td>Haemorrhagic fever</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Hantavirus</td>
<td>Haemorrhagic fever</td>
<td>26</td>
</tr>
<tr>
<td>Caliciviridae</td>
<td>Norwalk agent</td>
<td>Gastroenteritis (winter vomiting)</td>
<td>385</td>
</tr>
<tr>
<td></td>
<td>Hepatitis D, E</td>
<td>Hepatitis</td>
<td>404</td>
</tr>
<tr>
<td>Unclassified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroviridae</td>
<td>Parovirus (B19)</td>
<td>Erythema infectiosum</td>
<td>26</td>
</tr>
<tr>
<td>Papovaviridae</td>
<td>Papillomavirus</td>
<td>Warts</td>
<td>76, 96</td>
</tr>
<tr>
<td>Hepadnavirida</td>
<td>Hepatitis B virus</td>
<td>Hepatitis, hepatocellular carcinoma</td>
<td>404</td>
</tr>
<tr>
<td>Adenoviridae</td>
<td>Adenovirus</td>
<td>Respiratory infections, diarrhoea</td>
<td>190, 385</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>Herpes simplex virus</td>
<td>Cold sore, genital infection, cervical dysplasia, encephalitis</td>
<td>26, 494</td>
</tr>
<tr>
<td></td>
<td>Varicella zoster virus</td>
<td>Chickenpox, shingles</td>
<td>28, 29</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
<td>Generalized infection</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus</td>
<td>Infectious mononucleosis</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burkitt's lymphoma</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasopharyngeal carcinoma</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Roseola infantum</td>
<td></td>
</tr>
<tr>
<td>Poxviridae</td>
<td>Human herpesvirus 6</td>
<td>Smallpox (now eradicated)</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Smallpox virus</td>
<td>Milker's nodules, orf</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Cowpox and orf viruses</td>
<td>Skin papules</td>
<td>97</td>
</tr>
</tbody>
</table>

1.29 Viral infections.
Acquired immune deficiency syndrome (AIDS) was first reported as a clinical entity in 1981 and is clearly related to infection with HIV 1 and 2. Transmission of the virus from human to human may occur through homosexual or heterosexual intercourse, blood contamination of needles shared by intravenous drug users, contaminated blood or blood products, from mother to fetus or by organ transplantation.

HIV infection produces a decline in T-helper/inducer cell counts, and its clinical consequences are predictable. The key indicator disorders of the progression to AIDS include Pneumocystis carinii pneumonia, Kaposi’s sarcoma, diarrhoea lasting more than 1 month with 10% weight loss (often due to Cryptosporidium or Isospora), diffuse Herpes simplex or cytomegalovirus infection, reactivation of mycobacterial infections, non-Hodgkin’s lymphoma, encephalopathy and dementia.

The diagnosis of AIDS requires a positive HIV antibody test, a decline in T-helper/inducer cell counts, the loss of response to skin-test antigens and the presence of opportunistic infections or related tumours. The Centers for Disease Control (CDC) have produced a clinical classification for HIV infection and now suggest that AIDS can be diagnosed from the presence of HIV antibody positivity with a low CD4 lymphocyte count (< 200 cells/μl). The typical inexorable progression of HIV infection is shown in 1.30.

1.30 HIV infection is a 'state of risk' rather than a single continuous illness. The patient suffers episodes of severe infection, being well for much of the intervening time. For the first few years, most patients with HIV infection remain well. After this latent period, they may develop persistent generalized lymphadenopathy. Progression to advanced HIV infection is often heralded by the onset of shingles. This may be followed by other minor infections before the first life-threatening infection, which is often with Pneumocystis carinii pneumonia. If the patient survives this infection, other opportunistic infections may follow, leading ultimately to death from a wasting syndrome or progressive HIV encephalopathy. This figure shows typical examples of the stages at which different complications may develop, but this may vary widely. The timescale for full progression ranges from 1 to more than 15 years.
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EARLY-STAGE INFECTION

The earliest clinical presentation may be at the time of seroconversion, which is usually 2–4 months (median 2.1 months) after exposure but on occasion may occur significantly later. The symptoms are of a glandular fever or flu-like illness with a sore throat, malaise, fever, maculopapular rash (1.31), lymph node enlargement, diarrhoea, arthralgia and occasionally encephalopathy, neuropathy or meningitis. At this time serum samples should be taken for antibody measurement (with the prior informed consent of the patient). In addition, the presence of the p24 antigen can be demonstrated, and measurement of the CD4–CD8 ratio will confirm immunosuppression. This acute phase may be recognized in about 50% of patients. The phase — CDC Group I — is usually transient. Symptoms and signs usually resolve, and patients enter a prolonged phase in which they may remain asymptomatic but are potentially infectious (Group II).

There is an insidious and variable progression to Group III, in which lymph node enlargement may occur as a result of hypertrophy associated with B-lymphocyte production. By definition (Group III), these lymph nodes must be greater than 1 cm in diameter and be present in two or more extrameningeal sites, and the hypertrophy must persist for at least 3 months (1.32). No other condition that could be associated with lymphadenopathy should be present. Additional information may be obtained through lymph node biopsy, especially if symptoms are generalized or lymph node enlargement is rapid. Tonsillar enlargement (1.33), episodes of unexplained fever and eruption of existing skin conditions (1.34) may also occur. Vasculitic skin lesions may occasionally be seen. This stage results from the progressive depletion of the CD4 cell count and is associated with a decline in reactivity to common skin antigens such as Candida and tuberculin. At this stage, reactivation of latent infections is likely.

1.32 Painless lymph node enlargement in HIV infection may develop at the time of seroconversion but usually resolves. Progressive lymph node enlargement at a later stage, to a diameter of more than 1 cm at two or more extrameningeal sites, is characteristic of Group III disease.

1.31 HIV-related rash in a 22-year-old homosexual man. In addition to this rash, the patient presented with fever, sore throat and headache. HIV serology was negative at this time, but seroconversion was noted 5 weeks later.

1.33 Gross tonsillar enlargement in an HIV-infected patient (CDC Group III).

SKIN DISORDERS THAT MAY BE EXACERBATED IN CDC GROUP III HIV INFECTION

<table>
<thead>
<tr>
<th>Skin Disorder</th>
<th>Exacerbated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>Drug eruptions</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Acne vulgaris</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Xeroderma</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Severe psoriasis</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Granuloma annulare</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Yellow nail syndrome</td>
</tr>
</tbody>
</table>

1.34 Skin disorders that may be exacerbated in CDC Group III HIV infection. Note that most of these conditions are common and benign in the absence of HIV infection.
ADVANCED HIV DISEASES (GROUP IV)

Subgroup A. Major constitutional symptom complexes
These include malaise, fever, night sweats, arthralgia, diarrhoea and weight loss. The weight loss often exceeds 10% of original body mass (7.139) and the diarrhoea may persist for over 4 weeks.

Subgroup B. Neurological involvement
In this group, it is usual to find alone, or in combination, dementia (1.51), myelopathy and peripheral neuropathy, for which the only explanation is HIV infection.

Subgroup C. Opportunistic infections
These result from the deficiency in cell-mediated immunity associated with HIV infection.

Category C, includes patients with symptomatic or invasive disease due to one or more of the following 12 specified secondary infections as listed by the CDC:
- *Pneumocystis carinii* pneumonia (1.41)
- Chronic cryptosporidiosis
- Toxoplasmosis (1.42)
- Extra-intestinal strongyloidiasis
- Isosporiasis
- Candidiasis (oesophageal, bronchial, pulmonary) (1.43)
- Cryptococcosis
- Histoplasmosis
- *Mycobacterium avium intracellulare* or *M. kansasii*
- Cytomegalovirus (1.44)
- Herpes simplex (disseminated or mucocutaneous – 1.37)
- Progressive multifocal leucoencephalopathy.

Category C, includes those with symptomatic or invasive disease:
- Oral hairy leukoplakia (1.36)
- Herpes zoster (multidermatomal – 1.38)
- Recurrent *Salmonella* bacteraemia
- Nocardiasis
- Tuberculosis
- Oral candidiasis.

1.35 Extensive oral infection with *Candida albicans* in a patient with HIV infection. Note the gross changes in the tongue and the angular cheilitis.

1.36 Hairy leukoplakia in a patient with HIV infection (CDC Group IV C2). Note the appearance of a ribbed whiteness along the sides of the tongue. The term 'hairy' refers to the histopathological appearance, and the cause appears to be a proliferation of Epstein–Barr virus in the superficial layers of the squamous epithelium of the tongue.

1.37 Severe perianal herpes simplex is a common problem in homosexual patients with HIV infection. It may cause great discomfort, but often responds to oral acyclovir treatment.
Infections causing gastrointestinal symptoms (diarrhoea and/or vomiting) in HIV disease

**Table: Infections causing gastrointestinal symptoms**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Fungi</th>
<th>Viruses</th>
<th>Protozoa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>Candida</td>
<td>Cytomegalovirus</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Campylobacter</td>
<td></td>
<td>Herpes simplex</td>
<td>Microsporidia</td>
</tr>
<tr>
<td>Shigella</td>
<td></td>
<td>Adenoviruses</td>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Mycobacterium avium intracellulare</td>
<td></td>
<td></td>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Subgroup D. Secondary cancers**

These may include Kaposi's sarcoma (1.45–1.49), non-Hodgkin's lymphoma (1.50) and primary lymphoma of the brain.

**Subgroup E. Other conditions**

Other conditions include chronic lymphoid interstitial pneumonitis and thrombocytopenia.

1.38 Herpes zoster (shingles) is often the first manifestation of immunosuppression in patients with HIV disease. It can also occur in many other patients (see p. 29) but multidermatomal involvement is particularly common in CDC Group IV C2 infection. In this patient the C4 and C5 dermatomes are affected.

1.39 Opportunistic infections in HIV disease.

1.40 Infections causing gastrointestinal symptoms (diarrhoea or vomiting, or both) in HIV disease.

1.41 Pneumocystis pneumonia is the most common life-threatening opportunistic infection in patients with AIDS and in other immunocompromised patients. In this patient there is an area of consolidation in the left lower zone, but the changes may be more widespread. There is a significant mortality in AIDS patients in their first episode of Pneumocystis pneumonia, but the combination of intensive care and appropriate chemotherapy, together with steroids, may achieve complete resolution of the infection. Prophylactic chemotherapy with co-trimoxazole or nebulized pentamidine reduces the risk of this complication.
The timescale of progression is extremely variable and the clinical associations are protean. The following may be relevant as prognostic indicators in the progression of disease severity:

- Decline in absolute CD4 levels
- Presence of HIV p24 antigen
- Serum levels of B₂-microglobulin and neopterin
- Serum levels of IgA, and interleukin-2 receptor levels
- Presence of Candida albicans.

OPPORTUNISTIC INFECTIONS IN HIV-RELATED DISEASE (1.39)

Infections are still the single most common presentation of HIV infection and remain one of the most frequent causes of death despite the introduction of methods of prophylaxis.

As the CD4 count declines below a critical value of 300 cells/µl, there may be reactivation of long-dormant infections such as tuberculosis, syphilis or Pneumocystis carinii. As the...
INFECTIONS

count falls further, new infections with viruses, bacteria, fungi and protozoa occur. The most common infection is *Pneumocystis carinii* pneumonia (see 1.41 and p. 193) which appears as the CD4 count falls below 200 cells/μl. The onset of the disease is initially insidious but gathers rapid momentum as the alveoli become filled with inflammatory exudate full of cysts and trophozoites (1.27). Treatment with pentamidine or sulphonamides is usually effective when a diagnosis has been established by bronchial lavage or biopsy. Relapse is, however, extremely common despite prophylaxis, which should be given to all patients with CD4 cell counts below 200 cells/μl.

Activation of previous tuberculosis is now a well recognized complication and has produced a major public health problem (see p. 43), especially in sub-Saharan Africa. Mycobacterium avium complex (MAC) develops in HIV-infected patients as their CD4 counts fall below 100 cells/μl (see p. 47) as occurs in 30% of advanced cases. Treatment depends on the culture and sensitivity of the organism and may include isoniazid plus rifampicin, pyrazinamide and ethambutol.

Oral candidiasis (1.35) is often one of the first manifestations of HIV infection; oral or oesophageal candidiasis may be an early pointer towards the need for serological testing. Candidiasis tends to be resistant to therapy and likely to recur. In advanced disease, systemic antifungal treatment may be required (see p. 61-62).

1.45-1.49 Kaposi's sarcoma is a common complication in patients with AIDS, especially in those who contracted the disease by sexual transmission. In 1.45 note the generalized lesions, many of which show peripheral bruising. 1.46 shows the appearance of similar involvement in a black African patient. Kaposi's sarcoma may also affect mucous membranes, as seen in 1.47, where there are two obvious plaques of Kaposi's sarcoma on the palate. Similar lesions may be seen throughout the gut and the bronchial tree. The lesions are often aligned with skin creases, as shown on the neck of the patient in 1.48. Kaposi's sarcoma may occur anywhere on the surface of the body, including the penis and scrotum (1.49).
Cryptococcal infections are found in approximately 10% of individuals with HIV infection, and cryptococcal meningitis carries an extremely poor prognosis. Therapy consists of combinations of antifungal agents (see p. 60).

Toxoplasmosis is found in about 5% of HIV patients; they usually present with encephalitis (see p. 64) as the CD4 count falls below 100 cells/µl. The diagnosis is often made by contrast CT scanning of the brain, and the infection is the most common cause of ring-enhancing lesions in patients with HIV infection (1.42). There may also be evidence of concomitant cerebral oedema, which requires steroid therapy. Occasionally brain biopsy is required to provide a definitive diagnosis. Treatment involves the use of combinations of pyrimethamine, sulphonamides and clindamycin.

Herpes simplex infections of skin, mouth, oesophagus, perianal region (1.37) and genitalia are common as the CD4 falls below 400 cells/µl (see also p. 26 and p. 494). In HIV-infected patients these infections tend to be more severe and more extensive, with a prolonged course, and are likely to be associated with encephalitis. Treatment is with an antiviral drug such as acyclovir. Long-term prophylactic therapy is indicated. Resistant infections are well recognized and foscarnet or trifluorothymidine may be required for treatment. Herpes zoster is one of the most common manifestations of HIV disease and often involves multiple dermatomes (see p. 29).

Cytomegalovirus infection is frequently reactivated when CD4 cells are severely depleted (< 100 cells/µl) and presents with cytomegalovirus retinitis (1.44), pneumonia (1.89) gastroenteritis, colitis or disseminated disease with thrombocytopenia (p. 30). Encephalitis may occur or carries a poor prognosis. Treatment is with antiviral agents alone or in combination. There is no evidence that prophylaxis with antiviral agents is worthwhile.

HIV-RELATED MALIGNANCIES

Malignancies account for death in about 40% of HIV-infected patients and this number is increasing as deaths from infection are prevented and the life span of these patients increases. The commonest malignancies are Kaposi’s sarcoma, non-Hodgkin’s lymphoma, primary CNS lymphoma and anal carcinoma.

Kaposi’s sarcoma (1.45–1.49)

Aggressive Kaposi’s sarcoma is found in up to 25% of homosexual patients with AIDS and in 5% of other patients with AIDS, with the exception of the haemophilic AIDS group in whom Kaposi’s sarcoma is rare. This suggests that Kaposi’s sarcoma may result from an infective agent other than HIV. Kaposi’s sarcoma develops as multiple, small dusky purple-red or purple nodular, painless lesions of the skin or buccal mucosa, but may also be found anywhere in the gastrointestinal tract or bronchial mucosa. There is rapid spread by lymphatics and by blood. The diagnosis is made by histological examination of biopsies of the skin, lymph nodes or internal organs. Studies with cell markers suggest that the cell of origin may be vascular or lymphatic endothelium.

There is no standard treatment regimen. Advanced disease requires chemotherapy such as doxorubicin, bleomycin or vincristine, alone or in combination. Individual local lesions which produce symptoms respond to local radiotherapy.

Non-Hodgkin’s lymphoma (1.50)

Lymphoma is the presenting feature of AIDS in approximately 5% of patients and its incidence seems to be increasing as the better prophylaxis of infections leads to longer survival. These tumours range from high-grade B-cell lymphomas to low-grade B- and T-cell lymphomas. Extranodal sites are common and lymphoma is found in up to 90% of patients in the brain, liver, bone marrow and gastrointestinal tract. In these patients there is a high incidence of systemic symptoms (fever and weight loss – B-group lymphoma staging; see p. 454) at presentation. The development of non-Hodgkin’s lymphoma carries a poor prognosis. For diagnosis CT or MRI are valuable, but biopsy of the lesion may often be necessary (see also p. 456).

WASTING AND HIV-ASSOCIATED DIARRHOEA

Weight loss greater than 10% of previous weight and chronic diarrhoea lasting longer than 30 days is a common presentation of HIV infection and AIDS (7.139). This is seen in African patients (‘slim disease’) and also in Europe and the USA.
INFECTIONS

It is probable that there are at least two different mechanisms for the diarrhoea: infection by pathogenic bacteria, and direct HIV infection of the intestinal wall. In approximately one-half of the patients one or more other pathogens are identified. These include bacteria, fungi, viruses and protozoa (see 1.39). *Giardia lamblia* and *Entamoeba histolytica* are particularly likely to be found in homosexual men.

In many patients no pathogenic organisms may be found and it is presumed that malabsorption is due to direct effects of HIV on the intestinal wall, linked to suppression of mucosal cell immunity.

The possibility of tumours of the intestine causing diarrhoea should always be remembered, especially Kaposi’s sarcoma, non-Hodgkin’s lymphoma and colonic carcinoma. Colonoscopy should be performed routinely in those with persistent diarrhoea.

Management is orientated towards finding a treatable infection. If no infection is found, then supportive measures, including psychological counselling and stress management, are all that can be offered. This part of the spectrum of HIV disease usually runs a protracted course over years.

HIV AND THE CENTRAL NERVOUS SYSTEM

About 10% of patients with HIV present with clinical neurological features and 75% have CNS involvement at autopsy. The CNS may be directly involved by the virus, there may be opportunistic infections (see p. 15) or there may be tumours (see p. 17).

In children, HIV encephalopathy results in delayed development and behavioural changes. A range of neurological features may develop, including spastic diplegia, ataxia and pseudobulbar palsy.

In adults, the early features include personality changes with apathy, loss of memory and poor concentration. Such features may be compounded by severe depression as the diagnosis becomes clear, and by the physical consequences of other intercurrent illnesses such as infections and tumours. CT or MRI may show cortical atrophy (1.51). In addition to these central changes about 20% of advanced cases show evidence of peripheral neuropathy with both motor and sensory loss. Weakness may also be due to myopathy.

MANAGEMENT OF HIV INFECTION

Specific antiviral therapy alone or in combination may slow down HIV disease progression, especially if given at an early stage of the illness; but current therapies are associated with a large number of side effects which include general malaise, gastrointestinal upset, rashes, anaemia, muscle weakness and occasionally seizures. Opportunistic infections require additional specific therapy and prophylaxis. As with all serious illnesses, patients with AIDS require full medical, social and psychological support, and the support of family and friends is also important.

Prevention of the spread of HIV infection involves the screening of blood donors, advice on safer sexual practices, measures to curtail intravenous drug abuse and the provision of syringe and needle exchange centres. It is hoped that eventually a safe and effective vaccine will become available for prevention of the disease.

THE COMMON COLD

The common cold (acute coryza) is the most common disease caused by infection in the developed world, and the most frequent symptomatic manifestation of upper respiratory tract infection (URTII). These infections may be caused by a range of viruses, including rhinoviruses, respiratory syncytial virus, parainfluenza viruses, coronavirus and adenoviruses.

Uncomplicated acute coryza leads to nasal congestion (1.52), a watery nasal discharge (1.2) that may become purulent and often a sore throat. Most cases resolve spontaneously, but the common cold may be complicated by secondary bacterial infection, leading to sinusitis, otitis media and infection of the lower respiratory tract.
1.52 Acute rhinitis in the common cold. The nasal mucous membrane is oedematous, so the inferior turbinate abuts against the septum causing obstruction, as seen here in a view through a nasal speculum.

ENTEROVIRUS INFECTIONS

The enteroviruses can be subdivided into three main subgroups: polioviruses, coxsackieviruses and echoviruses (hepatitis A, p. 404, is also caused by an enterovirus). All infect man by the faecal–oral route. Initial viral replication takes place in the gut mucosa, with subsequent shedding of virus in the stools. If host immunity is poor, virus enters the blood stream and may be disseminated to target organs such as the meninges, nervous tissue, heart and skin.

Enteroviruses can be isolated from stool, pharyngeal secretions, CSF, pericardial fluid and, occasionally, from blood in severe neonatal infections. Rising antibody titres may be demonstrated to specific enteroviruses. Treatment of enterovirus infections is symptomatic.

Poliomyelitis

Poliomyelitis has an incubation period of up to 14 days and is characterized by an initial ‘flu-like’ illness followed, if host immunity is poor, by aseptic meningitis. The virus then enters nervous tissue, the main attack being on the anterior horn cells of the spinal cord, causing flaccid paralysis of limb muscles that tends to be asymmetrical and is usually permanent (1.53, 1.54). In severe cases, muscles of swallowing and respiration may be involved.

Management is symptomatic, but paralytic poliomyelitis requires skilled physiotherapy. Patients may also need long-term ventilation and, later, the provision of mechanical aids or corrective surgery, or both.

An injectable killed virus vaccine (Salk vaccine) and a live attenuated oral vaccine (Sabin vaccine) are available for prevention of poliomyelitis. This disease is now very rare in the Western world, but still occurs in developing countries where indigenous children and nonimmunized expatriates of all ages are vulnerable.

1.55 Echovirus type 19 infection causing a maculopapular rash. Rashes of this kind may be very difficult to distinguish from rubella (see p. 20), and antibody studies may be required for a firm diagnosis.
Coxsackieviruses (groups A&B) and echoviruses
Coxsackieviruses and echoviruses produce a wide variety of clinical syndromes after a short but variable incubation period, including nonspecific febrile illness, rashes (1.55), myocarditis, pericarditis, meningitis, meningo-encephalitis and, rarely, paralytic disease. Herpangina (ulcerative lesions on the palate and fauces) and hand—foot—mouth disease (1.56, 1.57) are caused by Group A coxsackieviruses. Epidemic myalgia (Bornholm disease) is a common presentation of infection with Group B coxsackieviruses. Both echoviruses and coxsackieviruses can cause severe generalized infection in neonates. The postviral fatigue syndrome may follow coxsackievirus infection.

RUBELLA
The causal agent of rubella is a togavirus that causes a mild illness and is spread by droplets from the respiratory tract. The incubation period is 18–19 days. A pink maculopapular rash appears on the second day of illness (1.58, 1.59). On the trunk, the rash becomes confluent and may resemble the rash of scarlet fever. There is usually mild inflammation of the throat and palate, and the posterior cervical lymph nodes become enlarged and tender. The rash fades in about 48 hours and recovery, especially in children, is rapid. Complications include arthralgia (more common in adults), thrombocytopenia and very rarely encephalitis.
VIRAL INFECTIONS

The diagnosis is confirmed by the detection of rising titre of IgM antibody in the serum. Treatment is not usually necessary but arthralgia requires relief of pain with analgesics.

Rubella in either childhood or adult life is usually a trivial, self-limiting illness, but the virus can cause serious damage to the developing fetus. Fetal infection can occur at any stage of pregnancy, but the damage tends to be most marked in the first trimester. The sequelae may include signs of infection at birth (1.8), microcephaly, deafness, blindness (1.60) and congenital cardiac malformations (see p. 242).

Suspected rubella in early pregnancy should be confirmed serologically; appropriate advice on risk to the fetus and availability of abortion should be given to the parents, if the disease is confirmed. If there is contact with rubella in early pregnancy, it is important to establish the diagnosis in the index case and to check the antibody status of the pregnant contact as soon as possible. A nonimmune contact in early pregnancy should be given the option of abortion if rubella develops. If abortion is not performed, hyperimmune globulin can be given and is protective in about 40% of patients.

Prevention may be accomplished by live attenuated vaccine, used on its own or combined with measles and mumps vaccine (MMR). Rubella vaccine should not be given during pregnancy.

YELLOW FEVER

This is an acute mosquito-borne infection caused by a flavivirus which results in a pyrexial illness, with liver and renal involvement and disseminated intravascular coagulation (DIC—see p. 464). It is found in both Africa and Central and Southern America in a narrow band about the equator, but not in Asia. There are two important cycles of transmission: in the urban type the yellow fever virus is transmitted from an infected person to a nonimmune recipient by mosquitoes (Aedes spp.); in the sylvan (or jungle) type there is a monkey reservoir and the vector is the Aedes spp. in Africa or Haemagogus spp. in America.

The spectrum of clinical illness varies from a very mild, transient, pyrexial illness to a rapid, progressively fatal form. The incubation period is short (4–6 days). The appearance of jaundice (not usually severe), proteinuria and haemorrhage give clues to the diagnosis. Haemorrhage is often apparent initially in the skin but haematemeses may occur and is a poor prognostic sign (1.61). In fulminant cases there is progression of liver and renal failure to coma and death. The mortality rate is about 40% in these severe cases.

There is no specific antiviral therapy, and general supportive measures are required for severely ill patients. Yellow fever vaccine gives protection for up to 10 years.
DENGUE HAEMORRHAGIC FEVER

Dengue haemorrhagic fever is one of the haemorrhagic fevers found in Africa, South-East Asia and India. It is transmitted by the mosquito *Aedes aegypti*, which is itself infected by the dengue virus (or one of six subtypes). The incubation is short (1–2 days), and the clinical presentation is abrupt with extreme nausea, vomiting and fever. Purpura appears on the second or third day and disseminated intravascular coagulation (DIC, p. 464) with bleeding from a variety of sites dominates the clinical picture (1.62, p. 464). Viraemia and blood loss produce a profound state of shock.

There is no specific treatment, but symptomatic treatment with oxygen and blood volume expanders is often essential. Despite this, there is a mortality rate of up to 50% in severe cases. Public health measures for mosquito control are important. The severe nature of this disease results from sequential infection with two subtypes of virus.

Classic dengue fever is not so severe in presentation and has a lower mortality.

EPIDEMIC ENCEPHALITIS

Several flaviviruses and togaviruses cause mosquito-transmitted encephalitis in various parts of the world. These include several forms of equine encephalitis in the American continent, Japanese encephalitis (1.63) and St Louis encephalitis. Russian spring–summer encephalitis and powassan are similar diseases transmitted by ticks. Encephalitis results rapidly, and the patients present with fever and rigors. There is often rapid deterioration of mental status (see p. 494). Mortality is high (up to 40%) and there is a high morbidity in the survivors (up to 30%), with residual neurological deficits. There is no specific treatment. Vaccination against Japanese B encephalitis is now available for those travelling to endemic areas.

MEASLES

The causal agent for measles is a paramyxovirus, and the disease is highly infectious. It is spread by droplets from the respiratory tract and preschool children are particularly at risk.

After an incubation of 10–11 days, the illness starts with fever and coryzal symptoms. Small white spots (Koplik's spots) appear on the buccal mucosa (1.64) on the second day. A red, blotchy, maculopapular rash starts on the neck, usually on the fourth day of illness. Thereafter, the rash spreads to the face (1.16), trunk and finally to the limbs (1.65). As the rash fades, there may be temporary purplish haemorrhagic staining of the skin.

Complications of measles include pneumonia, croup, otitis media, gastroenteritis and, rarely, encephalitis. In the Third World, these complications lead to a high morbidity and mortality, especially in undernourished children (1.66, 1.67). In the developed world, atypical measles may be seen in patients who received early, unsuccessful vaccines.

The diagnosis is usually made on clinical grounds, but if necessary can be confirmed by viral isolation or by serology. Treatment is symptomatic in uncomplicated cases. Appropriate
antibiotic therapy is required for bacterial complications such as pneumonia and otitis media. Pneumonia may be rapidly fatal in undernourished children with measles and in immunocompromised patients.

Active immunization is available; combined with mumps and rubella vaccine (MMR), it should be offered to all children aged between 1 and 2 years. Passive immunization with normal human immunoglobulin can prevent the disease if given early in the incubation period, but immunity is short-lasting.

MUMPS

The causal organism of mumps is a paramyxovirus which spreads by droplets and saliva. The incubation period is 18–21 days. Most patients with mumps present with swelling of the salivary glands (1.68), but other glands may be involved, including the pancreas, the gonads (adults only) and the thyroid gland. The virus may also attack the meninges or the brain, causing aseptic meningitis or encephalitis. Transient deafness can occur during the course of mumps, but permanent nerve deafness is a rare complication.

Salivary gland swelling usually subsides within 2 weeks. About 10–15% of postpubertal males will develop orchitis (1.69) which may be unilateral or bilateral. Breasts and ovaries are occasionally involved in females.

The diagnosis can be confirmed if necessary by viral isolation and serology. This is important in patients who present without salivary gland involvement.

No specific therapy is available. If there is salivary gland involvement, attention must be paid to oral hygiene and fluid intake. Diet should be bland. The pain and swelling of orchitis usually responds to a short course of steroid therapy. Antiemetics and intravenous fluids may be required for pancreatitis. Mumps meningitis is a benign illness and needs only bed rest and symptomatic treatment.

Active immunization is available (alone or combined in MMR) and it should be offered to children and adults without a history of the disease.
INFLUENZA

Influenza is an acute viral infection which is spread by droplets from person to person. It is caused by three groups of related myxoviruses which produce fever, prostration, myalgia, headache and anorexia. The viruses undergo frequent antigenic changes, do not produce cross-immunity to each other and give rise to epidemics and pandemics. Five pandemics have occurred in the twentieth century with massive mortality. For example, up to 20 million people died in 1918, with millions more having continued morbidity from respiratory and neurological sequelae (postencephalitic parkinsonism, see p. 503).

Acute infection may present with a spectrum of symptoms ranging from a very mild pyrexia which is rapidly self-limiting to an overwhelming infection with severe myalgia, headache, fever, sore throat, acute tracheitis and even pleurisy. In addition, encephalitis, myositis and myocarditis may supervene, especially in the elderly. Secondary bacterial infection, often with Staphylococcus aureus, Haemophilus influenzae and Streptococcus pneumoniae, is a common complication in the debilitated elderly patient (1.70, see p.192). Treatment is usually symptomatic, but antiviral drugs such as amantadine may be of value in ameliorating symptoms more rapidly if given early in the course of the disease.

Vaccination may give partial immunity, and should be offered to high-risk groups, such as the elderly, patients with pre-existing respiratory disease, those who are immunocompromised and those receiving oral steroid therapy.

The influenza viruses A and B constantly alter their antigenic structure, especially the haemagglutinins and neuraminidases on the surface coat. To be effective in a current epidemic the vaccine must contain these antigens. As the vaccine is prepared in chick embryos its use is contraindicated in patients hypersensitive to eggs. Its use is mainly for people at risk, including the elderly, especially in residential care, asthmatics and those with COPD, the immunocompromised, diabetics and patients with chronic renal disease.

RABIES

Rabies is caused by an RNA virus of the Rhabdoviridae family. Man is infected through bites from a rabid animal usually a dog (1.71), or cat, but occasionally a vampire bat, fox, squirrel or rodent. Rarely, the virus may gain entry through a cut, abrasion or area of eczema. The incubation period may be as short as 2 weeks, but in some cases may be as long as 1 year. The virus, once in the body, spreads via peripheral nerves to the CNS causing encephalomyelitis which is almost uniformly fatal. The time from bite to first symptom ranges from about 35 days for bites on the face to 52 days for bites on the limbs.

1.70 Secondary bacterial chest infection is the most frequent serious consequence of influenza. In this elderly patient, there is a left mid-zone cavitating pneumonia (note the fluid level in the cavity) and an accompanying left pleural effusion. The causative organism was Staphylococcus aureus.

1.71 A dog bite is the usual route through which rabies virus gains access to the nervous system. Even in a country free from rabies such as the UK, the possibility of an illegally imported rabid animal should be considered.
Initial symptoms include pain and tingling at the inoculation site, extreme restlessness, ('furious rabies'), followed by severe spasms of the larynx and pharynx which are brought on by attempts to swallow water, giving rise to the term hydrophobia (1.72). Eventually flaccid paralysis develops (1.73) and the patient lapses into coma. Some patients, especially those bitten by vampire bats, present initially with flaccid paralysis which often begins in the bitten limb, but which rapidly becomes generalized (dumb rabies). Death results from respiratory paralysis.

If possible, the diagnosis should be confirmed in the animal by histopathological examination of the brain. In humans the virus can be identified by immunofluorescence on skin or corneal impression smears or by brain biopsy. Serological tests may also be diagnostic, but may be difficult to interpret if vaccination has been given since exposure to the virus.

Management of bitten people includes thorough cleaning of the bite, passive immunization with human rabies immunoglobulin and an immediate course of human diploid cell rabies vaccine. The outlook is poor if treatment is started after the onset of symptoms.

Patients must be nursed in an intensive care unit. Heavy sedation and positive pressure ventilation are required. The disease is usually fatal but there have been several documented cases of recovery.

Prevention includes regular immunization of domestic animals in endemic areas and pre-exposure immunization of people at risk.

**LASSA FEVER**

Lassa fever is caused by infection with an arenavirus (Lassa fever virus) and is found predominantly in West Africa. Infection with similar viruses causes Argentine and Bolivian haemorrhagic fevers in South America. The vector is the rodent, *Mastomys natalensis*.

Onset of the clinical disease is gradual, with fever, headache and myalgia that particularly affects the legs. In addition there may be conjunctivitis, aphthous ulceration of the mouth, a fine generalized petechial rash and facial oedema (1.74). As the platelet count falls, haemorrhage may occur from a variety of sites. A combination of viraemia and haemorrhage produces shock and this may be associated with evidence of viral myocarditis. Encephalitis and permanent cranial nerve impairment may also occur. In severe cases a mortality of up to 20% has been found.

There is no specific treatment for the disease, but specific antiviral agents are promising. Symptomatic control of haemorrhage and shock are important. Prevention of spread of the disease depends on public health measures to control contact with rodents and with virus-laden rodent excreta. Hospital outbreaks involve careful handling of all blood and excreta of patients.
AFRICAN HAEMORRHAGIC FEVER

African haemorrhagic fever is an acute onset fever, characterized by papular rash (1.75), proteinuria, pancreatitis, hepatitis and haemorrhage. It is caused by infection with either Marburg or Ebola viruses. Marburg disease was originally found in people in contact with green monkeys (Cercopithecus aethiops) which were obtained from Uganda. Subsequently there was evidence of transmission by needles and directly from person to person. Both viruses cause acute disseminated intravascular coagulation (DIC, see p. 464), and profound haemorrhage is the usual cause of death. There is no specific treatment, but the patients require intensive circulatory support and control of the DIC with heparin; they may benefit from plasma containing virus-specific antibodies. Extensive precautions are needed to prevent the spread of infection.

Haemorrhagic fever occurs widely throughout the world. Other causes include dengue (see p. 22), yellow fever (see p. 21), bunyavirus and hantavirus infections. All are potentially fatal conditions.

ERYTHEMA INFECTIOSUM

This acute self-limiting disease, also known as fifth disease or slapped cheek disease, is caused by human parvovirus B19. It occurs in outbreaks, most often in spring and summer. Any age may be affected but it is most common in children, in whom the usual presentation is a mild febrile illness followed by marked erythema of the cheeks and the appearance of a pink maculopapular rash (1.76). The rash may become confluent and is most marked on the limbs; as it fades, it takes on a lace-like appearance. The rash may come and go over about 2-3 weeks. Adenopathy, arthralgia and arthritis are common especially in adults infected with the virus. Joints most involved are wrists and knees. The arthritis may, if prolonged, be mistaken for other forms of rheumatism. Transient marrow depression may occur during the course of the illness. In patients with congenital haemolytic anaemia, an aplastic crisis may be induced (see p. 434).

The diagnosis can be confirmed by finding a specific IgM antibody in the serum.

As the disease is self-limiting, children require no therapy. Analgesics and anti-inflammatory drugs may be needed for relief of joint pain in adults. If there is an aplastic crisis, blood transfusion is indicated. No vaccine is available for this disease.

HERPES SIMPLEX

The causal agents of herpes simplex are herpes simplex virus types I and II. Type II is associated with sexually transmitted genital infection, whereas most other infections are caused by type I. Following the primary infection, the virus remains latent in the tissues and may re-emerge at a later stage to produce local lesions.

Primary infection with type I virus usually occurs in childhood and takes the form of acute gingivostomatitis with multiple painful, shallow ulcers on the tongue, buccal mucosa and lips (1.6, 1.77). In genital herpes, ulcers are on the vulva, vagina, cervix or penis (1.78). In both instances, the primary lesions are self-limiting and clear in about 10 days. The local eruption may be accompanied by fever and malaise and, in the case of children, refusal to eat or drink. Other sites of primary infection are the fingers (herpetic whitlow) and the cornea (dendritic ulcer, 1.79). Herpes simplex encephalitis is a rare but very serious presentation (see p. 494). In the neonate, disseminated herpes simplex is a life-threatening illness. Patients with eczema may present with widespread lesions on the eczematous areas (eczema herpeticum, 2.26).

Reactivation of latent herpes simplex usually occurs in sites related to the primary infection (1.80). In the immunocompromised patient, reactivation of virus may cause very severe local lesions (1.37), with generalized viraemia and encephalitis.

Genital herpes has reached epidemic proportions and differs from other sexually transmitted diseases because of the likelihood of spontaneous recurrence. It is extremely conta-
VIRAL INFECTIONS

There is a causal relationship between genital herpes, cervical cell metaplasia and cervical carcinoma. Herpes simplex virus II is the most common infecting agent in young women. The primary lesions appear within a day or so of exposure and are thin-walled vesicles which are painful. In women there is usually a vaginal discharge followed by tender lymphadenopathy with generalized fever. In men the lesions are found on the glans, foreskin and penile shaft (1.78). In addition, lesions may be found in the perineum and perianal regions of homosexual men (1.37).

Recurrence of genital herpes is common and may be precipitated by local trauma, menstruation, pregnancy, stress, depression, intercurrent illness or immunosuppression. The recurrence tends to be more localized and not as severe as the first attack. Patients often recognize the prodrome of recurrence with local itching and tingling.

The virus can be cultured from vesicle fluid or from swabs from genital or mouth ulcers. Viral particles can also be identified under the electron microscope. Rising antibody titres may be found in primary herpes simplex.

Most primary lesions are self-limiting and specific therapy is not usually required. If applied very early, acyclovir cream may abort the development of ‘cold sores’. Acyclovir is the treatment of choice for primary genital herpes and for recurrence (patients can start treatment at the first prodromal sign of recurrence). Intravenous acyclovir should be used to treat herpes encephalitis and severe infections in the immunocompromised host and in the neonate. An ophthalmological opinion should be sought when there is involvement of the eye.

1.77 Severe herpetic gingivostomatitis. This young child was acutely ill with a high fever and had multiple vesicular lesions on the tongue, lips and buccal mucosa. In adult patients, a more common manifestation of herpetic stomatitis is the cold sore; this is usually a reactivation of latent infection.

1.78 Primary genital herpes. Note the numerous lesions on the penis and the associated tissue reaction.

1.79 A primary herpetic dendritic ulcer, stained with fluorescein. Herpes simplex virus proliferates in the epithelial layer of the cornea. Urgent treatment with antiviral drops or ointment is indicated.

1.80 Recurrent herpes simplex on the cervix. The ulcers have recurred in a common primary site for genital infection. Other common sites include the external genitalia and the lips.
VARICELLA ZOSTER

Varicella zoster causes two distinct diseases – chickenpox (varicella) and shingles (herpes zoster).

Chickenpox
Chickenpox is a highly infectious disease caused by the Varicella zoster virus. It is usually mild in children but can be severe in adults and in immunocompromised patients. The incubation period is usually 14–15 days. In adults especially, there may be a short prodromal illness with fever, malaise, headache and occasionally a transient erythematous rash. The true rash is vesicular with a central distribution in the body (1.81). The spots are elliptical and come out in crops over a few days (1.82). Mucous membranes may also be affected (1.83). Scabs form rapidly and most have separated in 10–14 days. The most common complication, especially in children, is skin sepsis, usually due to superinfection with Staphylococcus aureus or Streptococcus pyogenes. Varicella pneumonia, which can be life-threatening, occurs mainly in adults who smoke and in the immunocompromised (1.84, 10.73, 10.100). Other rare complications include encephalitis, cerebral ataxia and haemorrhagic chickenpox.

The diagnosis is usually made on clinical grounds but electron microscopy, viral culture and serology may be required in difficult cases.

No specific therapy is usually required. Children should be prevented, if possible, from scratching the spots. If the disease is severe, especially in the immunocompromised patient, the antiviral drug acyclovir may be used either parenterally or orally. There is no active vaccine against Varicella zoster, though a live vaccine is in the late stages of development. Varicella zoster immune globulin may modify or prevent the disease if given within 1 week of contact. Acyclovir may also be given prophylactically to immunocompromised patients who have been exposed to the disease.
Shingles
Shingles is caused by reactivation of latent varicella virus in sensory root ganglia in patients previously infected with chickenpox. Reactivation is common in the elderly and in immunocompromised patients (1.38). The skin eruption, which is always unilateral, appears along the line of one or two dermatomes (1.85). The lesions are vesicular on an erythematous base. In ophthalmic herpes (1.86), especially if the nasociliary branch of the nerve is affected, there may be corneal ulceration (as in herpes simplex, 1.79) and iridocyclitis. Ophthalmic herpes zoster is a medical emergency: corneal scarring (1.87) and other serious complications may occur. Dissemination of virus in the bloodstream may result in the appearance of scattered chickenpox lesions elsewhere on the body. Viraemia may be overwhelming in immunocompromised patients. Pain may precede the skin rash, and postherpetic neuralgia can be prolonged and severe, especially in the elderly.

The most common complications are bacterial superinfection of the skin lesions and postherpetic neuralgia. Occasionally there may be motor nerve involvement, as in the Ramsay Hunt syndrome when seventh nerve paresis occurs (1.88). Meningoencephalitis is a more serious but rarer complication.

Acyclovir given orally within 72 hours, or in severe cases intravenously, along with local applications of acyclovir skin cream may hasten healing and reduce viral shedding, but there is little evidence that acyclovir prevents or reduces postherpetic neuralgia. Analgesics are almost always required for pain control. If there is involvement of the eye, acyclovir should be given and an ophthalmological opinion should be sought.

1.85 Herpes zoster affecting the L2 dermatome. The rash shows the characteristic 'band' distribution, starting from the midline, where some vesicles can be seen.

1.86 Ophthalmic herpes. The vesicular skin eruptions are in the distribution of the ophthalmic division of the fifth cranial nerve. Serious ophthalmic complications are a real threat, especially when the tip of the nose is affected (this indicates involvement of the nasociliary nerve, which also supplies the cornea).

1.87 Corneal scarring is a late complication of ophthalmic herpes, resulting from corneal anaesthesia. In this patient a protective lateral tarsorrhaphy has been carried out.

1.88 Ramsay Hunt syndrome (geniculate zoster). The patient has a right seventh nerve paresis. Full recovery occurs in about 50% of cases.
INFECTIONS

CYTOMEGALOVIRUS

Like other herpesviruses, cytomegalovirus remains latent in the body after primary infection and may only reactivate if the patient is stressed or becomes immunocompromised. The virus may be transmitted by respiratory secretions, sexually, by blood transfusion or by organ transplantation. Maternal infection spreads transplacentally or perinatally to the fetus.

Most cytomegalovirus infections in the immunocompetent are subclinical, but there may be a glandular fever-like syndrome with fever, generalized lymphadenopathy, abnormal liver function tests and atypical mononuclear cells in the blood. Primary infection or reactivation of latent infection in the immunocompromised patient may cause serious illness with pneumonia (1.89), chorioretinitis (1.44), gastroenteritis, involvement of the CNS, haemolytic anaemia and thrombocytopenia. Intrauterine infection may cause fetal death. Severe neonatal cytomegalovirus infection causes jaundice, hepatosplenomegaly (1.90), purpura, neurological damage and chorioretinitis. The infected infant may, however, appear normal at birth, and develop symptoms later.

The finding of specific IgM in serum is diagnostic of acute infection. Isolation of virus from urine or sputum may simply indicate prolonged excretion after past infection.

Cytomegalovirus inclusion bodies in biopsy specimens from the lung or gastrointestinal tract are diagnostic, so biopsy provides definitive diagnosis in the immunocompromised patient.

Most acquired infections are self-limiting but severe disease, especially in the immunocompromised, should be treated with intravenous ganciclovir or phosphonoformate. Treatment may have to be prolonged; relapses are common unless maintenance therapy is continued on a long-term basis.

1.89 Cytomegalovirus (CMV) pneumonia is often known as CMV pneumonitis, as the infection is generalized, and consolidation may not be seen on X-ray. CMV is second only to Pneumocystis as a cause of pulmonary disease in patients with HIV infection, and it is also seen in other immunocompromised patients, including those on anticancer therapy, systemic steroids, and drugs such as azathioprine and cyclophosphamide used to prevent organ transplant rejection. CMV pneumonia cannot be diagnosed on clinical grounds or X-ray appearances alone.

1.90 Congenital cytomegalovirus infection. This infant has massive splenomegaly, hepatomegaly and a purpuric rash. A similar picture may be caused by a number of prenatal virus infections.

1.91 Infectious mononucleosis. Numerous petechial haemorrhages are seen in the hard palate. In many patients there is also a tonsillitis, indistinguishable from that seen in acute streptococcal pharyngitis (1.3).
EPSTEIN–BARR VIRUS INFECTIONS

Infectious mononucleosis

The Epstein–Barr virus (EBV) is the causal agent of infectious mononucleosis. Primary infection with EBV is often subclinical, especially in young children. Older children and young adults usually present with symptoms of glandular fever.

In the most common form of the disease, there is enlargement of glands both in the anterior and posterior triangles of the neck, and usually in the axillae and groins. The fauces and palate become inflamed and oedematous. There may be palatal haemorrhages and a whitish or yellow pseudomembrane appears on the tonsils (1.91). There is usually marked nasopharyngitis and often puffiness of the face.

In the more generalized form of the disease, throat involvement is less marked. Presenting features are fever, generalized adenitis, splenomegaly and occasionally jaundice. There may also be a pink, maculopapular rash on the trunk and limbs (1.92). A rash is more often seen in patients who have been given ampicillin or related drugs (1.93).

Complications of infectious mononucleosis include myocarditis, autoimmune haemolytic anaemia, thrombocytopenia and meningo-encephalitis. Splenic rupture is a rare complication which is usually associated with trauma. Postviral fatigue syndrome may follow EBV infection.

The diagnosis is aided by the identification of atypical mononuclear cells in peripheral blood (1.94). The Paul–Bunnell test for heterophil antibodies usually becomes positive in the second or third week of the illness. In children under about 7 years, the Paul–Bunnell test is rarely positive, and diagnosis should be confirmed by EBV serology.

Treatment is symptomatic. Antibiotics are not indicated and ampicillin and related drugs should not be prescribed because of the high incidence of allergic reactions. Steroid therapy may be indicated if there is respiratory obstruction or autoimmune manifestations.

1.92 Rash in infectious mononucleosis may be the result of the infection itself, as here. The maculopapular rash usually emerges during the second week of illness, and it is often indistinguishable from that of rubella (1.59).

1.93 Rashes in infectious mononucleosis are most commonly caused by the administration of ampicillin or related penicillin compounds (these are often administered early in the disease on the presumption that the patient has bacterial pharyngitis). Ampicillin rashes occur more commonly in patients with infectious mononucleosis than in other patients, so the appearance of this kind of rash in a patient with typical symptoms points strongly to the diagnosis of infectious mononucleosis.

1.94 Blood film in infectious mononucleosis showing two atypical mononuclear cells. There is a wide variation in cell size and shape and mitotic activity is greatly enhanced, but the cellular structure is not fundamentally deranged.
INFECTIONS

Burkitt’s lymphoma and nasopharyngeal carcinoma
EBV has been implicated in the aetiology of Burkitt’s lymphoma, a transmissible neoplastic tumour particularly involving the head and neck (1.95) that is found in tropical Africa. The disease has a similar range of distribution to malaria, and it is thought that the virus may be transmitted via mosquitoes. EBV has also been implicated in some nasopharyngeal carcinomas, and it may play a role in the genesis of hairy leukoplakia (1.36) and in other premalignant and malignant disease.

ROSEOLA (SIXTH DISEASE)
Roseola infantum is a common, benign exanthematous disease of young children. After a rapid onset high fever, which lasts for a few days and then resolves, a generalized rubelliform rash appears (1.96). There may be cervical node enlargement and febrile convulsions may complicate the acute stage. The rash fades after 24–48 hours, and the patient usually makes a complete and uncomplicated recovery.

The disease is caused by herpes 6 virus (and the disease is also known as sixth disease).

ORF
Orf (contagious pustular dermatitis) is a paravaccinia virus infection of sheep and goats, which causes an eruption on the animals’ lips. It is sometimes contracted by those who work with these animals, and in humans it usually causes a single papule on the skin of the hand, which develops from a flat vesicle to a haemorrhagic bulla. Occasionally, more than one papule may occur (1.97). The lesions are usually self-limiting, but may ulcerate and may act as a trigger for the onset of erythema multiforme (see p. 94). Regional lymph node enlargement is common. Milker’s nodules are similar lesions, caused by cowpox virus and seen in farm workers dealing with cattle. Other differential diagnoses include anthrax, vaccinial infection and infection with Erysipelothrix rhusiopathiae.

1.95 Burkitt’s lymphoma, apparently originating in the maxilla and causing gross facial swelling in an African child.

1.96 Roseola infantum. An erythematous macular or rubelliform rash appears. It is often particularly prominent on the buttocks and fades within 2 days. If the child has been treated with an antibiotic for the fever, the rash may be mistaken for drug sensitivity.

1.97 Orf. 3–7 days after inoculation from an infected sheep or goat, one or more firm, painless, dark papules may appear on the finger or hand. These develop into pustules, but the condition is self-limiting, usually clearing within 4–8 weeks.
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<td>S. epidermidis</td>
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<td>Streptococcus: S. pyogenes S. pneumoniae S. viridans Enterococcus: E. faecalis</td>
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## INFECTIONS

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<td><em>B. vincentii</em></td>
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<td><em>B. burgdorferi</em></td>
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1.98 Bacterial infections
BACTERIAL INFECTIONS

STAPHYLOCOCCAL INFECTIONS

Staphylococcus aureus, a Gram-positive coccus, causes a wide variety of community-acquired and nosocomial infections. S. aureus is found in the nose in 15% of adults in the community and is also commonly carried on the skin. Carriage rates are higher in hospital personnel. Organisms are transmitted by direct contact, by fomites and by aerosol (sneezing). They survive for long periods on dry surfaces but are easily killed by disinfectants and antiseptic solutions. In hospitals, patients with a higher risk of carriage include those taking steroids, those with diabetes mellitus, intravenous drug misusers and those on haemodialysis. The emergence of strains of the organism with multiple resistance to antibiotics is causing major problems of management and infection control.

Certain areas of the body, especially the nasal mucosa and the skin of the axilla, groin and perineum, may become colonized by staphylococci; given favourable circumstances, the organisms may invade the skin and subcutaneous tissue. Tissue breakdown and abscess formation are characteristic of staphylococcal lesions (1.99). Staphylococci may also enter the blood with subsequent involvement of other organs such as bone (p. 159), joints, lungs (1.70, 1.100, 4.31, 4.32), heart valves (p. 247), brain or meninges.

In addition to causing local sepsis, S. aureus produces a number of toxins. Epidermolytic (exfoliative) toxin is responsible for the syndrome of toxic epidermal necrolysis (Lyell’s disease, scalded skin syndrome). In this, there is sudden onset of fever and marked generalized erythema of the skin, followed by loss of large areas of the superficial layers of the epidermis, which produces an appearance resembling severe scalding. This condition occurs mainly in children (1.101). Ritter’s disease is a neonatal form of the same condition.

Staphylococcal toxic shock syndrome is a relatively rare condition (about 40 cases in 58 million people in the UK per year). It is due to the production of an exotoxin by S. aureus. Sufferers present with an acute onset influenza-like illness with sudden high fever (> 39°C), vomiting, diarrhoea, muscle aches and a sunburn-like rash resembling that of scarlet fever (see 1.104). The patients often become rapidly disorientated. There is a

1.99 A massive staphylococcal carbuncle, in which the infection has caused tissue breakdown and multiple interconnected abscesses. Lesions of this kind are found most commonly in diabetic patients.

1.100 Staphylococcal pneumonia in a 20-year-old intravenous drug misuser. The organisms were introduced by a contaminated intravenous injection, but a similar picture may occur in debilitated or immunocompromised patients secondary to staphylococcal skin infection. Note the presence of a large cavity (septic infarct) in the right upper zone. The possibility of right-sided endocarditis should always be considered when this picture is seen in an injecting drug misuser.

1.101 Toxic epidermal necrolysis (scalded skin syndrome), in which the skin is extremely painful, and large patches of necrotic epidermis slide off the underlying layers at the slightest pressure, leaving extensive raw areas. The condition occurs mainly in children, but a similar syndrome may occur at any age as a consequence of drug hypersensitivity (2.149).
INFECTIONS

A mortality rate of about 5–10%. Many of the initial cases were in young women using superabsorbent tampons. This group now accounts for one-half of the cases; others include patients after surgery, and those with burns, boils and insect bites. Men, women and children may be affected. The diagnosis may be confirmed by culture of swabs from the lesion or from a tampon. Patients usually have a high white cell count, lowered platelets (from DIC), renal impairment and elevated creatine phosphokinase (CPK) from muscle injury.

Most \textit{S. aureus} organisms are resistant to penicillin and ampicillin, so the drugs of choice for most infections are penicillinase-resistant antibiotics. In patients with an allergy to the penicillins, and especially if the organisms have multiple resistance to antibiotics, choice of appropriate antibiotic therapy must depend on sensitivity testing; therefore, close cooperation with microbiologists is essential. Methicillin-resistant \textit{S. aureus} (MRSA) is resistant to methicillin, flucloxacillin and gentamicin. Epidemics of infections with MRSA have now occurred in many countries. These organisms, like other \textit{S. aureus}, are carried in the nose and skin, particularly of patients or staff with eczema. MRSA accounts for between 10 and 15% of nosocomial infections. Admission of such a patient to a ward requires rigorous measures to control infection, which may involve closing wards or hospitals. Staphylococcal abscesses should be drained (1.102, 1.103), and full supportive measures are required for all serious infections including toxic epidermal necrolysis and toxic shock syndrome.

\textit{S. epidermidis} and related coagulase-negative staphylococci are important causes of infection in patients with prosthetic devices (especially heart valves (1.11), joints, shunts and vascular grafts) and in patients undergoing chronic peritoneal dialysis. They are the most common cause of hospital-acquired bacteraemia, and are increasingly penicillin resistant. Specialist advice should be sought on treatment, which may need to be protracted. Infection can also occur on heart valves that have been damaged as a result of acute rheumatism or are congenitally abnormal (p. 247).

STREPTOCOCCAL INFECTIONS

\textit{Streptococcus pyogenes} is carried harmlessly by up to 15% of the population, but causes a wide variety of infections including tonsillitis, scarlet fever, skin lesions (impetigo, erysipelas and cellulitis), puerperal sepsis and septicaemia. The organisms are transmitted by direct contact, by droplets from the respiratory tract or indirectly through food, dust or fomites. Late complications of \textit{S. pyogenes} infections include acute rheumatic fever, post-streptococcal glomerulonephritis, Henoch–Schönlein purpura, toxic shock and erythema nodosum.

Streptococcal tonsillitis is an acute illness with fever, marked general malaise and pain on swallowing. There is inflammation and oedema of the palate and fauces with spotty exudate on the tonsils (1.3). The anterior cervical lymph nodes are

1.102, 1.103 Staphylococcal abscesses should be drained, as they are very unlikely to respond to antibiotic treatment alone. On the surface, this breast abscess did not appear large, but a large volume of pus was released when it was incised. After evacuation of the pus, the wound should be packed and left open.

1.104 Scarlet fever showing a typical erythematous rash on the trunk and a hint of the classic circumoral pallor, with some oedema of the face.
enlarged and tender. Local complications include otitis media, streptococcal rhinitis, sinusitis and peritonsillar abscess (quinsy). As with all streptococcal infections, late complications may appear about 10 days after the onset of the illness, especially in patients not treated with antibiotics. The diagnosis of streptococcal tonsillitis can be confirmed by culture of throat swabs. There is usually a marked polymorph leucocytosis in peripheral blood. The diagnosis may be confirmed in retrospect, by the finding of a raised anti-streptolysin O titre (ASOT).

Scarlet fever is a streptococcal infection characterized by the appearance of an erythematous rash (1.104). The disease is seen mainly in children, who are susceptible to streptococcal erythrogenic toxin. Scarlet fever is usually associated with streptococcal tonsillitis but it may also follow infection of wounds or burns (streptococcal toxic shock syndrome). The rash is a generalized punctate erythema which affects the trunk and limbs. As the rash fades, there may be desquamation of skin.

Other characteristics of the disease are circumoral pallor (1.104) and white strawberry tongue (1.105). Complications of scarlet fever are similar to those of streptococcal tonsillitis.

**Streptococcal infections of skin and tissues**

Erysipelas and cellulitis are skin and tissue infections with *S. pyogenes* which are usually found in middle aged and elderly patients. Sites most often involved are the face (1.106), legs, hands and arms (1.107). General symptoms include fever, malaise, rigors and sometimes delirium. The local lesion consists of an area of spreading erythema with a well demarcated edge. Regional lymph nodes become tender and enlarged. There is a tendency for erysipelas to recur in a previously affected area.

A similar clinical picture, erysipeloïd, may be produced by infection with *Erysipelothrix rhusiopathiae* (1.108), though systemic symptoms are rare. This is an occupationally acquired infection in farmers, meat and fish processors and veterinary surgeons.

1.106 Erysipelas of the face. During the acute stage, the eyelids may become so swollen that they cannot be opened. The entire face may become erythematous, and this appearance is accompanied by an unpleasant sensation of tightness and burning.

1.108 Erysipeloid (fish handler’s disease) produces a similar clinical picture to erysipelas, although the systemic reaction is usually relatively slight.

1.105 White strawberry tongue in scarlet fever. The oedematous red papillae protrude through a thick, white, furry membrane. This appearance is typical of the first 2 days, but later the white fur peels off, to leave a deep red strawberry tongue.

1.107 Cellulitis caused by streptococcal infection which entered through an apparently trivial knuckle injury. Other common sites of entry for the bacteria are areas of infected eczema and fungal infections of the toe-web with fissuring.
Necrotizing fasciitis is due to subcutaneous infection usually with beta-haemolytic streptococci but sometimes with *S. aureus* or other anaerobic organisms. Patients who have diabetes mellitus or are on steroids are more likely to be affected. The organisms may be introduced by penetrating trauma or after surgery (1.109). The patients are usually febrile and shocked with local tenderness, occasionally with crepitus over the affected area and with a dusky red-blue appearance of the skin. Gas may be found on X-ray (as in gas gangrene; 1.115). Treatment consists of urgent surgical intervention with débridement of the affected area. The organism may be identified by blood culture, culture of the affected tissue or Gram staining of the tissue.

Impetigo is most commonly seen in children and is a superficial infection of skin, usually caused by either *Streptococcus pyogenes* or *Staphylococcus aureus*. It may occur *de novo* or as a secondary infection in areas of eczema or in pediculosis of the scalp. The lesions, which are often on the face, start as thin-walled vesicles that rupture and form yellowish crusts (1.110). Infection is often spread by scratching.

Penicillin is the drug of choice for infections with *S. pyogenes*. Antibiotic therapy should be continued for 10 days in order to lessen the risk of rheumatic fever. In cases of allergy to penicillin, erythromycin is the second choice drug. Impetigo usually responds to topical antibiotic therapy.

**MENINGOCOCCAL INFECTION**

The causal agent of meningococcal infection is *Neisseria meningitidis*, a Gram-negative diplococcus with a number of serogroups. Infection results from inhalation of droplets. Meningococci colonize the pharynx, often giving rise to a carrier state (in 4–20% of the normal population); they may, however, spread from the pharynx to the blood and meninges. No age is exempt from meningococcal disease but young children and young adults are most at risk, especially those in a closed environment such as a school or camp. Transmission is by respiratory droplets.
The incubation period is usually less than 1 week. Infection produces a wide spectrum of illness from fulminating septicaemia, which can kill in a few hours, to a subacute illness with intermittent fever and a 'flea-bite' type rash. The most common presentation is meningitis (see p. 492) with or without septicaemia – the main features of which are high fever, severe headache, signs of acute meningeal irritation, often a purpuric rash and rapid deterioration of consciousness. Fulminating septicaemia (Waterhouse-Friderichsen syndrome) is a devastating illness with extensive skin haemorrhage (1.111, 1.112), disseminated intravascular coagulation (DIC – 10.126, 10.131) and circulatory failure due to adrenal haemorrhage. These patients usually do not live long enough to develop meningitis.

Meningococci can be cultured from blood, pharynx, skin lesions and CSF. If examined, the CSF is found to be purulent (1.23) with a marked polymorph leucocytosis. Lumbar puncture may, however, be hazardous because 'coning' of the brainstem may occur with disastrous consequences. If the clinical diagnosis is not in doubt, therapy can be started without CSF examination.

The clinical state and laboratory findings are a poor guide to prognosis, and meningococcal infection should always be treated urgently. Intravenous benzylpenicillin is still the drug of choice and should be given for 5–7 days. Intensive care nursing with full supportive therapy is required, especially for fulminating septicaemic cases.

Close contacts of the index case should receive prophylactic therapy – usually with rifampicin or ciprofloxacin. Vaccines may be used to contain epidemics. These include the group A + C bivalent vaccine and the A + C + Y + W-135 tetravalent vaccine. These produce immunity for 2–3 years in patients over the age of 2 years, but do not alter the rate of nasal carriage. Vaccines are not yet available against group B – the most common cause of meningococcaemia in the UK and some other countries.

ANTHRAX

The causal agent of anthrax is Bacillus anthracis, a spore-bearing organism. Most human infections result from contact with animals or animal products, such as hides, wool or bones, and therefore most cases occur in farmers, vets and abattoir workers. Anthrax has an unfortunate potential for use in germ warfare, and anthrax spores may persist in an infected environment for many years.

Cutaneous lesions are usually single and are most common on exposed sites, especially hands, arms, head or neck. The classic anthrax lesion is the malignant pustule (1.113). This starts as a red papular lesion that vesiculates and becomes necrotic in the central area and finally dries up to form a thick, blackish scab which may take several weeks to separate. There is usually marked erythema and oedema of the surrounding tissues. Fever, headache and malaise accompany most lesions. Anthrax septicaemia is much less frequent in humans than in animals. Pulmonary anthrax (inhalation of spores) and gastrointestinal anthrax (ingestion of spores) are rare forms of the disease and carry a high mortality.

Anthrax bacilli can be identified in stained smears from the lesion. Confirmation is by culture or animal inoculation. Benzylpenicillin is the treatment of choice. Erythromycin can be used if there is penicillin allergy. A killed vaccine is available for human use, but this is reserved for people in high-risk occupations. Other preventive measures include improvement of working practices, animal vaccination, proper disposal of animal carcasses and sterilization of animal products such as bone meal. A vaccine prepared from an alum precipitate of a B. anthracis antigen is available for human use.

1.112 Fulminating meningococcal septicaemia is characterized by extensive purpuric lesions, a high fever, shock and evidence of disseminated intravascular coagulation (DIC—see p. 463).

1.113 Anthrax. A single malignant pustule in a typical position on the neck. The patient was a porter who carried animal hides over his shoulders.
CLOSTRIDIAL TISSUE INFECTIONS

Deep, penetrating wounds are often contaminated by a range of *Clostridium* spp. (including *C. tetani*, *perfringens*, *septicum* and *novyi*). These organisms may produce two main syndromes:

- clostridial cellulitis
- clostridial myonecrosis with the release of gas into the tissues ('gas gangrene').

Clostridial cellulitis may be superficial and of relatively minor consequence, but it may lead to rapidly progressive tissue destruction. In anaerobic conditions, associated with large amounts of devitalized tissue, clostridia may produce extensive myonecrosis and release gas, which tracks along the tissue planes. Gas gangrene has also been recorded at the site of intramuscular injections.

The clinical features of myonecrosis occur within a few days of injury, especially in wounds with muscle damage, fractures, retained foreign bodies and impairment of the arterial supply.

Patients present with severe pain in the proximity of the wound, which rapidly becomes swollen with 'woody hard' oedema (1.114). A thin, watery, sweet-smelling discharge is often noted, and this becomes brown or frankly bloody later. Gas in the tissue planes may be apparent on X-ray before it can be felt (1.115). If a limb is involved, the part distal to the infection rapidly becomes cold, oedematous and pulseless before frank gangrene appears. The patient remains conscious during this time and has few other features, the clinical state being dominated by great pain at the site. There may be a slight fever. Progression of the condition leads to anorexia, profuse diarrhoea, circulatory collapse and renal and hepatic failure. There may be massive haemolysis.

Treatment consists of extensive early surgical debridement of the affected part under penicillin cover. The use of specific antitoxins and hyperbaric oxygen is controversial. Circulatory support is necessary to prevent renal failure. Death is inevitable if treatment is not available, and often occurs suddenly and unexpectedly during surgery.
**TETANUS**

_Clostridium tetani_ is a spore-bearing organism that produces a powerful exotoxin that acts on the CNS, preventing feedback inhibition of neural discharges. Spores are present in the soil, and humans may be infected by inoculation of spores, usually into a deep wound, but sometimes even through minor breaks in the skin. Agricultural workers, athletes, road traffic accident casualties and the elderly (with waning immunity) are particularly at risk. Neonates are also at risk (1.116), especially if the umbilicus is handled in an unclean manner (e.g. dung dressings which are used in parts of the developing world).

After an incubation period ranging from a few days to about 3 weeks, muscle rigidity develops. This is often first noted as jaw stiffness (trismus), but later becomes generalized, producing opisthotonos (1.117). Painful muscle spasms occur and these are often triggered by sensory stimuli such as loud noises (1.118). There may also be involvement of the autonomic nervous system. The severity of the disease is inversely proportional to the length of the incubation period.

The diagnosis is made on the history and clinical features of the disease. Patients with tetanus require intensive care nursing. Obvious wounds should be cleaned and debrided. Human tetanus immunoglobulin and penicillin should be administered as soon as possible. Moderate spasms can be controlled by diazepam, but severe tetanus may require full muscle relaxation and intermittent positive pressure ventilation.

Primary immunization should be achieved in early childhood with three doses of diphtheria, pertussis and tetanus (DPT) vaccine. Booster doses of tetanus toxoid are required every 10 years to maintain immunity, especially before pregnancy. After a penetrating injury an additional booster dose of toxoid should be given unless the previous booster dose was within 5 years. If the history of previous immunization is uncertain and if wounds are heavily contaminated, anti-tetanus human immunoglobulin should be given and a course of tetanus toxoid started.

**BOTULISM**

Botulism results from ingestion of the endotoxin of _Clostridium botulinum_ or, in some cases, from the release of endotoxin by surviving ingested organisms in the gut. This is usually caused by bacterial or spore contamination of improperly canned or preserved meat and meat products, which allows growth of the organism and toxin production. Rarely, wounds may be infected with _C. botulinum_. The toxin interferes with the release of acetylcholine at the neuromuscular junction and, as a result progressive descending muscle paralysis dominates the clinical picture with diplopia, laryngeal and pharyngeal palsy and generalized symmetrical paralysis of muscles, especially those of the cranial and respiratory systems. Loss of the pupillary reflex is an early sign.

The diagnosis is confirmed by finding toxin in the food, gastric contents or faeces. Airway support with assisted ventilation is the keystone of treatment. Antitoxin is of value and antibiotics may have a role if organisms survive in the gut. Mortality is about 50%. Public health measures are aimed at prevention during food preparation for preservation, especially when this is done at home. A trivalent antitoxin is available for prophylaxis after exposure and also for those presenting with early symptoms. It neutralizes the toxins of _C. botulinum_ types A, B and E. Contraindications to its use are a history of hay fever, asthma or other allergy.
INFECTIONS

DIPHTHERIA

Diphtheria is now rare in the developed world, as a result of effective immunization campaigns, but is still relatively common in some countries, including Russia and other countries in the CIS. It may be found in travellers returning from endemic areas. The causal agent is Corynebacterium diphtheriae. The most common type of diphtheria is faucial—pharyngeal in which the local lesion takes the form of a greyish-white translucent membrane, which may start on the tonsils (1.119), but which tends to spread to the palate, uvula and pharynx. Other sites of the local lesion include the anterior nares, larynx and skin. The organisms multiplying in the local lesion produce a powerful exotoxin which especially affects the heart and the CNS.

Toxic complications include cardiogenic shock (1.120), cardiac arrhythmias and sudden cardiac arrest. Nervous system damage is due to demyelination of motor nerves. This may lead to paralysis of extraocular muscles, palate and pharynx and more rarely to paralysis of limbs and respiratory muscles (1.121). Obstruction of the airway by a membrane is a life-threatening complication of laryngeal diphtheria, in which exhaustion due to respiratory muscular effort is rapidly followed by death (1.122).

The diagnosis is confirmed by culture of the organism from the local lesion. Diphtheria antitoxin should be given with penicillin or erythromycin, but antitoxin is prepared from horse serum and allergic reactions are common; it should only be given when the index of suspicion for diphtheria is high. Bed rest is important, especially in the presence of cardiac involvement. Laryngeal obstruction may require intubation or tracheotomy.

Infants should be immunized against the disease with combined diphtheria, pertussis and tetanus vaccine. The Schick test can determine immune status, but is now rarely used. Low-dose diphtheria vaccine should be given to adults whose immunity is uncertain if there is a chance of exposure (e.g. travellers to an endemic area or workers in infectious disease units).

1.120 Diphtheritic myocarditis led to cardiac failure and acute pulmonary oedema in this child (see also p. 244).

1.119 Diphtheria membrane in the pharynx. The membrane is usually white or greyish-yellow in colour, and the child may have relatively few symptoms at this stage.

1.121 Polyneuritis is a relatively rare complication of diphtheria. In this Sudanese child, it has led to a generalized flaccid paralysis.

1.122 Respiratory obstruction is a life-threatening complication of diphtheria, and the need for urgent tracheostomy was the reason that most doctors carried a small penknife before the advent of effective immunization. This child has a palatal palsy (hence the nasogastric tube), and a ‘bull neck’ (a characteristic appearance of cervical oedema).
ACTINOMYCOSIS

Infection with Actinomyces israelii, an anaerobic filamentous bacterium, is uncommon in the West. The organism can be found as a commensal in the mouth and intestine, and it may invade any part of the body when immunity is suppressed. Three sites are commonly involved:

• cervicofacial actinomycosis, in which the presentation is a reddish indurated subcutaneous mass in the anterior triangle of the neck or submandibular region; there may be slight tenderness with low-grade fever and general symptoms of malaise

• pulmonary actinomycosis usually involves previously damaged lungs, for example cavitation after pulmonary tuberculosis (see p. 194)

• abdominal actinomycosis usually involves the appendix and caecum and presents with lower abdominal pain, low-grade fever and a slow-growing abdominal mass; it may occasionally be seen in association with an intrauterine device.

In all these sites, the infection may ultimately discharge through the skin, forming sinuses (1.123). Classically, these sinuses discharge typical sulphur granules (1.124).

A prolonged course of high-dose penicillin is the treatment of choice.

NOCARDIASIS

Nocardiasis can be an acute, subacute or chronic infection by a family of Gram-positive filamentous 'higher' bacteria. These are usually inhaled, but occasionally may enter via penetrating wounds of the skin (usually the foot). The organisms have a worldwide distribution and are soil saprophytes. Most infections occur in people who have pre-existing immunosuppression resulting from cancer, cancer therapy, steroid therapy, alcoholism or HIV infection. Pulmonary nocardiasis appears similar to any other pneumonia, with fever, productive cough and progressive signs of lung consolidation. Despite antibiotics, the disease progresses to cavitation, and there may be direct spread to the pleural cavity with empyema formation. Bloodborne spread to the brain and other organs occurs. Surgical drainage of the abscesses is required, along with prolonged antimicrobial therapy.

TUBERCULOSIS

After a period of decline lasting for most of the twentieth century, the incidence of tuberculosis (TB) is now increasing again in the UK, USA and much of the rest of the developed world. TB has always been endemic in poorer countries, and the incidence there is also on the increase. The World Health Organization (WHO) estimates that one-third of the world's population is already infected with TB, and that a further 300 million people worldwide will become infected over the next decade.

The twentieth century reduction in the incidence of TB in the developed world was probably encouraged by improved social conditions, mass miniature radiography, good contact tracing, BCG (Bacillus Calmette-Guérin) vaccination of schoolchildren and the use of effective antituberculous therapy. Cases continued to occur in the elderly, the debilitated, alcoholics, diabetics, immunocompromised patients and recent
migrants from developing countries. Tuberculosis is a frequent (and treatable) complication of HIV infection, but patients with HIV account for only a minority of new cases in the UK and USA. The most potent risk factor for TB in the developed world seems to be socioeconomic deprivation.

In the developing world, socioeconomic deprivation is of great importance, as is interaction with HIV infection, especially in sub-Saharan Africa.

*Mycobacterium tuberculosis* is spread mainly by droplets, and relatively casual contact may be sufficient to ensure spread. The organisms gain entry to the body by inhalation, ingestion or occasionally by inoculation through the skin. Primary infection usually involves the lungs (1.125, 1.126), but parts of the gastrointestinal tract may also be affected, and there is usually lymph node involvement. The organisms provoke granuloma formation, often with caseation and cavitation.

Occasionally, primary infection may lead directly to more widespread disease — usually by haematogenous spread that may occur at any stage of the disease. More commonly, the primary focus of infection in the lung heals, but the healed granuloma continues to contain viable organisms. If host resistance is lowered in later life, TB may be reactivated, spreading locally and, via the blood stream, throughout the body and producing many possible manifestations. Major complications include

- miliary TB — diffuse haematogenous spread throughout the body, often visible as miliary mottling in the chest X-ray (1.127)
- pulmonary TB (see p. 194)
- gastrointestinal TB in the ileocaecal area (see p. 385)
- genitourinary TB affecting the kidneys and other parts of the genitourinary tract (see p. 302)
- tuberculous meningitis and space-occupying tuberculomas of the brain (1.128, see p. 492)
- tuberculous osteomyelitis (see p. 160)
- tuberculous arthritis (see p. 135)
- skin manifestations, including lupus vulgaris (2.51) and erythema nodosum (2.45)
- eye involvement (1.14)
- constrictive pericarditis (see p. 254)
- adrenal involvement leading to Addison's disease (see p. 316)
- lymph node enlargement (1.129–1.131).

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1.125, 1.126 Primary tuberculosis in the apical segment of the right lower lobe. The PA film shows the primary focus, and its position, just below the fissure, is confirmed by the lateral film. The PA film also shows slight hilar enlargement. In most cases, the primary focus heals with extensive calcification, but viable organisms remain within the healed focus. This patient was a 23-year-old Indian woman who had recently come to the UK, and the infection responded to combined antituberculous chemotherapy.
TB in people in or from the developing world is often extrapulmonary and investigation of any such patient with unexplained pyrexia should include chest X-ray, tuberculin skin test, culture for tuberculosis of sputum, urine and stool and, if indicated, gland or marrow biopsy. TB in the immunocompromised patient, including patients with HIV infection, may be a primary infection or a reactivation of a previously inactive infection. By the time of diagnosis, the disease may be widely disseminated and careful investigation and management is required.

Treatment of infection with typical *M. tuberculosis* requires combination drug therapy to prevent the emergence of resistant strains of the organism. Drugs available for use include isoniazid, rifampicin, ethambutol, pyrazinamide, thiacetazone and streptomycin. Conventional drug therapy, as used in the developed world, lasts for 6–9 months or more, depending upon the combination of drugs used. WHO's strategy for curing patients with TB is to use directly observed treatment (DOT), with a short-course regime lasting no more than 6 months. In DOT, patients are observed taking each dose of
treatment by a member of the medical team. Patients who have not attended for therapy can then be followed up, with the aim of controlling TB in the individual and the population.

The general level of mycobacterial resistance is low, and correctly treated TB is curable in at least 98% of cases. However, there has recently been much concern about the development of multidrug-resistant tuberculosis (MDRTB). Outbreaks of MDRTB have been reported in HIV care facilities and prisons in the USA, and elsewhere, including the UK, mainly in HIV-positive patients. Spread of MDRTB is best prevented by early diagnosis, culture and sensitivity testing of tubercle bacilli, careful monitoring of therapy and its effects and appropriate precautions against cross-infection.

Cell-mediated delayed hypersensitivity to TB can be demonstrated by the use of tuberculin tests, including the Mantoux, Heaf and tine skin tests (1.132). Patients who have latent TB infection usually react positively to these tests; however, their main value is in conjunction with vaccination programmes. Those found to be ‘tuberculin negative’ can be immunized. BCG is a live vaccine prepared from an attenuated strain of \( M. \text{bovis} \). This stimulates a hypersensitivity reaction to \( M. \text{tuberculosis} \). A papule or benign ulceration develops within a few weeks and this slowly heals; delayed healing, extensive ulceration (> 10 mm; 1.133), subcutaneous abscess formation or regional lymph node enlargement are recognized complications.

BCG vaccination offers a 70–80% degree of protection against TB infection and is recommended for the following groups if they are negative on tuberculin testing:

- contacts of patients with open TB
- health care workers who have direct patient contact (especially those working with immunocompromised patients)
- children aged between 10 and 14 years
- handlers of animal species liable to develop tuberculosis
- travellers to countries where TB is endemic.

**1.131 Hilar node enlargement** is a common finding in tuberculosis, usually in association with pulmonary involvement. The right hilar nodes are seen to be enlarged in this close-up view.

**1.133 A BCG ulcer, which appeared 8 weeks after BCG vaccination.** The administration of BCG is usually uncomplicated, but occasionally a severe reaction may occur, and an abscess or ulcer may be accompanied by regional lymph node enlargement.

**1.132 Mantoux test – positive reaction.** The test is carried out with purified old tuberculin, which is injected intradermally. In those who have had previous exposure to tubercle bacilli, a positive reaction appears within 48 hours. This consists of erythema and induration, and may be graded in intensity and size. The distance between the tips of the skin markers on each side is 1 cm.
OTHER MYCOBACTERIAL INFECTIONS

A number of mycobacteria may produce tuberculosis-like disease. *Mycobacterium bovis*, formerly a common cause of tuberculosis in the West, is now a rare cause of the disease in man, as a result of the careful control of the infection in cattle.

Patients with HIV infection and other immunosuppressed patients are susceptible not only to infection with *M. tuberculosis* but also to infection with other mycobacteria — often termed 'atypical mycobacteria'. *M. scrofulaceum* is particularly likely to produce lymph node infections (1.129, 1.130), whereas other organisms such as *M. avium-intracellulare* (MAI) and *M. kansasii* may produce almost any of the manifestations of typical tuberculosis. MAI is a particularly important cause of disseminated disease in patients with HIV infection (it may also occasionally produce a low-grade pneumonia in otherwise normal individuals). The organisms may be found on blood culture, acid-fast staining of stool smears, or culture or histology of bone marrow. Infections with these organisms are often very difficult to treat because of multiple drug resistance.

*M. marinum* and related mycobacteria may cause fish tank or swimming pool granulomas (1.134). *M. marinum* and *M. ulcerans* grow preferentially at cooler temperatures and usually affect the skin where they produce nodular lesions locally and along the line of draining lymphatics. The nodules slowly break down to produce ulcers. Antimicrobial drugs may be necessary.

LEPROSY

Leprosy, which is caused by *Mycobacterium leprae*, remains an important disease in tropical and subtropical countries. Infection is spread by droplets from infected nasal mucosa, but prolonged close contact is required. The incubation period is usually between 3 and 15 years. The spectrum of disease activity in leprosy depends upon the host's immune response to the infection.

Lepromatous leprosy develops when the response is poor. In this form, there are widespread lesions which contain enormous numbers of bacilli. There is involvement of nasal mucosa, skin (1.135, 1.136), testicular tissue and later of nerves. Marked

1.135 Lepromatous leprosy. There is infiltration and oedema of the cheek and thickening of the ear.

1.136 Lepromatous leprosy, showing the typical perforating ulcers resulting from neuropathy. On the lateral surface, the skin has ulcerated to expose the metatarsal head. There is associated local infection. There is also ulceration of the ball of the foot, and the big toe has been lost.
destructive lesions of the face and palate may result, and neurotrophic atrophy may lead to loss of the extremities (1.136–1.139).

In tuberculoid leprosy host immunity is good and bacilli are rarely seen in lesions. Patients present with erythematous or hypopigmented skin lesions (1.140) and with asymmetrical thickening of nerves (1.141).

The term ‘borderline leprosy’ is used when there are features of both lepromatous and tuberculoid disease. This may eventually evolve into one or other form of the disease.

The diagnosis is easily made when bacilli are demonstrated in smears from nasal mucosa or skin in lepromatous disease. Biopsy of skin or affected nerve is required for diagnosis of tuberculoid disease.

Multiple drug therapy with rifampicin, dapsone and clofazimine is now recommended. Good supportive measures, including surgical correction of deformities, are also important. No specific vaccine is available at present but the BCG vaccine may have a useful role in stimulating immunity.

LISTERIOSIS

The bacterium *Listeria monocytogenes* has a worldwide distribution and is found in nature in rotting vegetation, water and in 5% of human faeces. Despite this, human disease is uncommon, affecting principally pregnant women and patients who are immunocompromised. Transplacental transmission results in fetal infection that often overwhelms and kills the fetus, which is then aborted. Occasionally, the child is born with severe malformations. Infection acquired at term delivery usually presents with meningitis at 4–6 weeks, but these babies have disseminated disease with cardiorespiratory failure, diarrhoea and shock. The mortality in this condition is high, despite modern therapy. About one-half the infections occur in adults, especially in the presence of HIV infection, lymphoreticular neoplasia, treatment with steroids and cytotoxins, alcoholism, diabetes mellitus and tuberculosis. Infection presents acutely with fever, vomiting, diarrhoea and often signs of meningism. There may also be a purulent conjunctivitis that
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BACTERIAL INFECTIONS

can produce corneal ulceration and the regional lymph nodes may be involved. The mortality is high, despite the use of antibiotics. Broad-spectrum penicillins are the drugs of choice.

ESCHERICHIA COLI INFECTIONS

Escherichia coli serotypes are a common cause of infection in most organs of the body. In particular, E. coli is a common cause of urinary tract infection (p. 301), gastroenteritis (p. 385), pneumonia (p. 192), meningitis (p. 492) and septicemia.

Verocytotoxin-producing E. coli (VTEC) is an epidemic disease with a high incidence in summer and early autumn. The most common VTEC implicated in human infection is E. coli 0157, which produces a range of illnesses that include a mild self-limiting gastroenteritis and haemorrhagic colitis with severe fever, colic and bloody diarrhoea. The main reservoirs are cattle, and meat products such as beefburgers are often implicated, together with milk products, raw vegetables and drinking water. A small number of severe cases develop haemolytic uraemic syndrome (HUS). In HUS-induced renal failure there is a very significant morbidity with long-term renal impairment and a mortality of about 10%. The condition is more likely to occur in young children. In adults disseminated intravascular coagulation (DIC, see p. 464) may develop.

The diagnosis depends on culture of E. coli 0157 from faeces. DNA probes can detect verocytotoxin in faecal samples and serology can be used to detect a rising antibody titre and the 0157 antigen.

SALMONELLOSIS

Salmonella organisms cause a range of clinical syndromes:
• Enteric fever (typhoid or paratyphoid fever)
• Focal infections (e.g. osteomyelitis; see p. 159)
• Enterocolitis (food poisoning) (see p. 385)
• Asymptomatic carrier state.

Enteric fever

The causal organisms of enteric fever are S. typhi and S. paratyphi A, B and C. These organisms are species-specific to man, and transmission is by the faecal-oral route, either by direct contact or indirectly through contamination of water or food. Most cases diagnosed in Western countries are imported.

Enteric fever is primarily a septicaemic illness that starts after an incubation period of 7–14 days, with nonspecific flu-like symptoms that increase in severity during the first 2 weeks of the illness. The temperature rises in a step-like fashion (1.142), reaching its highest level in the second week, by which time there is marked toxæmia. There may be diarrhoea, but many patients remain constipated throughout the illness. Signs include furred tongue, rose spots on the trunk (1.143), abdominal distension and splenomegaly. During the third week, the temperature declines, but at this stage a number of potentially fatal complications may occur, including intestinal haemorrhage and perforation, pneumonia, cholecystitis, meningitis and osteomyelitis. Osteomyelitis is especially common in patients who have sickle-cell anaemia (3.155, 10.52). Death earlier in the illness is usually related to septicæmia and toxæmia. Paratyphoid is a similar but less severe illness than typhoid.

Diagnosis is by blood, stool and urine culture. The Widal test measures agglutinating antibody titres but may be difficult to interpret in immunized patients and, for this reason is now rarely used. Chloramphenicol has been widely used in treatment despite the associated (low) risk of aplastic anaemia, but drug resistance is now common and ciprofloxacin is the usual treatment of choice. Approximately 3% of patients will become long-term carriers, usually harbouring the organisms in the biliary tract.

Prophylaxis is by the use of one of two injectable vaccines, or by a live-attenuated oral vaccine, but the maximum efficacy of prophylaxis is probably about 70%.

1.142 The temperature chart in a patient with typhoid shows a step-wise increase to day 4 of admission. The high fever was accompanied by confusion and severe prostration. At this point, chloramphenicol treatment was started, and the temperature showed a rapid, if occasionally incomplete, response.

1.143 Rose spots in typhoid fever consist of pinkish macules or maculopapules, measuring 2–4 mm in diameter. The spots blanch on pressure.
INFECTIONS

PLAGUE

Focal epidemics of plague still occur in some countries (including the USA) despite public health measures. The organism responsible is Yersinia pestis which is retained in a reservoir of woodland rodents (sylvatic plague) and the domestic rat (murine plague). The vector from rat to man (and occasionally cats and dogs) is usually the rat flea, but cases of infection have been reported by direct transmission from an infected animal and by aerosol from infected patients.

The most common type is bubonic plague in which, after an incubation period of 2–4 days, the patient develops a fulminant illness with fever, headache and enlarged matted inguinal or axillary lymph nodes (buboes) (1.144) that may suppurate and discharge. DIC is common and results in bleeding from many sites, especially from the nose, and alimentary, respiratory and urinary tracts. The diagnosis can be made at this time by blood culture and by direct aspiration of the nodes. A fluorescent antibody test is also available.

When the organism is inhaled, there is rapid onset of an overwhelming pneumonia with severe toxaemia and rapid death (pneumonic plague). Treatment is required urgently with streptomycin, tetracycline or co-trimoxazole.

Public health measures to control the rat population in urban situations and the migration of rats are important, as there are no reasonable methods available to control the potential sylvan reservoir. Control of the flea population is possible with insecticides, but these are environmentally dangerous. Vaccination is possible in selected individuals at risk.

CHOLERA

Cholera is an acute diarrhoeal illness that results from colonization of the small intestine with the organism Vibrio cholerae, which produces a specific exotoxin that interferes with the sodium and water homeostasis of the lining cells of the intestine. The result is massive secretion of isotonic fluid into the gut and severe extracellular fluid loss with hypovolaemic shock, potassium depletion and acid–base disturbance.

The disease is usually transmitted by the faecal–oral route, often in contaminated water (1.5). The incubation period may vary from a few hours to a few days before the abrupt onset of profuse watery painless diarrhoea (rice water stools – 1.145). Muscle cramps may appear as the levels of electrolytes fall. Circulatory shock rapidly supervenes if treatment is not available. The patient has a typical appearance with extreme dehydration — sunken eyes (1.146), poor skin turgor, tachycardia, thready pulse and hypotension.

Acute tubular necrosis causes renal failure and this, together with severe hypovolaemic shock, is the common cause of death.

The diagnosis is made clinically and prompt replacement of water and electrolytes is the key to success. The widespread use of oral rehydration with a solution of water, sugar and salt can greatly increase survival rates in cholera epidemics. Hydration status can be monitored clinically (determination of eyeball pressure or skin turgor, or by assessment of jugular venous pressure). Biochemical control of acid–base balance and sodium and potassium levels is helpful if available. Administration of oral broad-spectrum antibiotics eradicates the infection rapidly. Public health measures to improve sanitation and provide a

1.144 Bubonic plague. One of the most characteristic clinical features is lymphadenopathy with suppuration, especially in the inguinal and axillary regions.

1.145 Rice-water stool in cholera. The large-volume watery stool is not blood-stained, because of the non-invasive nature of the infection, but flecks of mucus and shed gut mucosal cells cause turbidity.

1.146 Choleraic facies. Extreme dehydration has led to the typical appearance of deeply sunken cheeks and eyes. Despite the moribund appearance of the patient with cholera, rehydration can lead to complete recovery if started before the onset of renal failure.
source of fresh water are of paramount importance. Cholera vaccine provides little protection against acquiring the disease and does not alter its spread.

**HAEMOPHILUS INFLUENZAE INFECTIONS**

*Haemophilus influenzae*, a Gram-negative coccobacillus, may be a commensal in the upper respiratory tract. It may, however, also be involved in lower respiratory tract infections (p. 192) or meningitis, especially in children under the age of 2 years and, occasionally, the elderly. Meningitis is often caused by the type b strain. Vaccination is now available against type b (Hib) and is usually given at the same time as diphtheria, pertussis and tetanus (DPT) and polio vaccinations.

**LEGIONELLOSIS**

The Legionellaceae are aerobic Gram-negative bacilli which have been found worldwide and are associated with outbreaks of pneumonia and lesser pyrexial illnesses. An increased risk of Legionella infection is associated with old age, male sex, cigarette smokers, alcohol excess, chronic chest disease or immunosuppression. The airborne route of transmission has been proven in many outbreaks, usually by water aerosols from air-conditioning systems, humidifiers, shower heads and taps. Direct person-to-person transmission has not been shown, nor has infection from drinking contaminated water. The incubation period is 2–10 days.

Two distinct diseases may occur after infection with *L. pneumophila*: Pontiac fever and legionnaires’ disease.
- Pontiac fever, named after the city in which it was first described, is an acute pyrexial illness with fever, headache and myalgia. The disease is self-limiting over the course of 1 week
- Legionnaires’ disease has a spectrum of clinical severity. The features range from trivial to an acute-onset multisystem infection with pneumonia (1.147), encephalitis and liver and renal impairment. The dominant feature is the progressive nature of the pneumonia, which is associated with a 20% mortality (see p. 193). Diagnosis depends on sputum culture, detection of urinary antigen (the most rapid investigation) and serology. Treatment may require respiratory and renal support. Erythromycin with or without rifampicin, plus ciprofloxacin in severe cases, are the drugs of choice. Public health measures include the addition of biocides to the water used in air-conditioning cooling plants.

**BACTEROIDES INFECTION**

The most common and most important of the *Bacteroides* spp. is *B. fragilis*, an anaerobic Gram-negative bacillus that is a commensal of the human bowel. It may become pathogenic in the presence of tissue injury and anoxia. It is frequently found in pus from abdominal wounds, after pelvic surgery, in liver abscesses, in empyema after aspiration, and in brain abscesses. The pus is particularly foul smelling. *B. fragilis* infection is also found in spreading gangrene of skin and muscle, for example in Fournier's gangrene (1.148). Treatment is with metronidazole.

1.148 Fournier's gangrene of the penis and scrotum. The causative organism was *Bacteroides fragilis*. Good wound care and split skin grafting resulted in complete healing.

1.147 Chest X-ray in legionnaires' disease, showing extensive pneumonic shadowing in the right upper zone. The patient was severely ill, with a high fever and delirium.
INFECTIONS

BRUCELLOSIS

Brucellosis in humans is caused by infection with one of three species of *Brucella* organisms, depending on the animal source of infection: *B. mellitensis* (goats), *B. abortus* (cattle) or *B. suis* (pigs). The organism infects the genitourinary tracts of animals and may be ingested in milk and milk products or meat, or directly through cuts in the skin. The disease occurs frequently in workers in contact with animals, for example farmers, abattoir workers, veterinary surgeons and butchers. Epidemics may occur from the ingestion of unpasteurized milk and milk products.

The incubation period is usually up to 3 weeks, but the first symptoms may not appear for many months and are usually low-grade 'undulant' fever (1.13, 1.149), headache, myalgia, anorexia, pains in the joints and over the spine, orchitis and general debility. A more acute presentation may be high swinging fever, lymphadenopathy and tender hepatosplenomegaly. Almost every organ of the body may be involved in the acute process, which gradually subsides to be replaced by a chronic disease characterized by progressive asthenia, depression, loss of weight associated with intermittent fever, chronic bone and joint degeneration (1.150) and hepatosplenomegaly.

The diagnosis is made by blood culture during the acute phase or a rising titre of agglutinins. Specific immunoglobulin (IgM) tests are now available. Treatment is with tetracycline plus rifampicin for 6 weeks or co-trimoxazole in children. Public health measures include testing cattle with the brucellin skin test, certification of disease-free stock and pasteurization of milk.

PERTUSSIS

Pertussis (whooping cough) is a serious illness that mainly affects young children but is increasingly also seen in adults who were not immunized in childhood or whose immunity has lessened with age. The causal agent is *Bordetella pertussis*, and spread is by droplets from the respiratory tract.

Catarrhal symptoms and cough appear after an incubation period of 7–10 days. By about the tenth day of illness, the cough has usually become spasmodic and may be followed by a whoop. At the end of a spasm of coughing, mucus is expectorated and there is frequently vomiting. In severe cases there may be 20–30 spasms of coughing per day, and frequent vomiting may lead to weight loss and dehydration. The illness usu-

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1.149 Temperature chart in brucellosis, showing typical 'undulant' fever, which is remittent and variable in character.

1.150 Degenerative osteoarthritis in brucellosis, as shown by a technetium-99m MDP bone scan. The patient was a Bedouin shepherd, who had suffered from fever, painful joint swellings and backache for over a year. This is a common complication of chronic brucellosis.

1.151 Subconjunctival haemorrhage in pertussis occurs because the intrathoracic pressure rises sharply during violent paroxysms of coughing and leads to sudden surges in capillary pressure. In this child, the subconjunctival haemorrhage is accompanied by bleeding into the lower lid — a rarer complication. No permanent harm results, and these complications resolve rapidly.

1.152 A swollen, bitten tongue is a common complication of pertussis because of the paroxysms of coughing and choking. Ulcers of the frenum of the tongue may also occur.
BACTERIAL INFECTIONS

Pneumonia and otitis media may occur as a result of bacterial superinfection. There may be mechanical complications, such as subconjunctival haemorrhage (1.151), epistaxis, haemoptysis or ulcers of the tongue (1.152). Hernias may develop and there may be rectal prolapse. Atelectasis results from mucous plugging of bronchi or bronchioles. Convulsions, either anoxic or caused by encephalopathy, can be life-threatening.

The causal organism can be identified in pernasal swabs, by culture or by immunofluorescence. The white blood cell count is usually raised with marked lymphocytosis.

Physiotherapy during spasms aids mucus expectoration. Small, frequent meals and attention to fluid intake prevent weight loss and dehydration. Antibiotics are of little benefit in the established case. Erythromycin given very early in the disease may have some effect and it has a place in prophylaxis in child contacts. Cough suppressants are contraindicated and sedation should be reserved for patients with convulsions.

Prophylaxis is available with combined diphtheria, pertussis and tetanus (DPT) vaccine.

TULARAEMIA

Tularaemia is a zoonosis caused by the Gram-negative rod Francisella tularensis. It is acquired from an animal reservoir (usually a rodent) directly, by contaminated food or water, by inhalation, by handling an infected carcass or indirectly by ticks. Tularaemia may occur in most parts of the world. The clinical presentation is often with a febrile illness with a skin ulcer and enlargement of the regional lymph nodes (1.153).

There may be a secondary necrotizing pneumonia from the primary lesion, or inhalation of the organism may produce a primary pneumonia. Pericarditis and meningitis are rare but serious complications with a high mortality. The organisms are sensitive to streptomycin, gentamicin and tetracycline. A vaccine is available for those who are at high risk of exposure to the organism, for example laboratory workers, forest rangers and hunters.

NONVENEREAL TREPONEMATOSES

For venereally transmitted treponemal disease (syphilis) see p.78.

Yaws

Yaws is a chronic infection with Treponema pertenue that has a worldwide tropical distribution. Children are often infected through pre-existing skin lesions when in contact with a person with infectious yaws, but congenital infection does not occur. There is an incubation period of 4-6 weeks and the primary lesion is a papule that grows and discharges ('mother yaw'). There is usually inguinal lymphadenopathy. This primary lesion heals over a period of 4-8 months. A crop of secondary lesions occurs over a period of 6 months – these often involve the skin (1.154) and long bones. Longer-term infection results in multiple destructive lesions of bones (1.155),...
infections

joints and skin. Diagnosis is made by demonstration of the treponemes and by serology. Treatment of the early lesions is with penicillin. Public health measures include improvements in personal hygiene, dressing of open wounds and community prophylaxis with antibiotics.

Pinta

Pinta is a chronic skin infection with *T. carateum* found in South America, which causes a generalized multicoloured rash. The lesions start slate blue and become brown and eventually white, leaving the skin mottled and blotchy (1.156). There is no general hazard to health and the effects are cosmetic and psychological. Penicillin controls the progress of the disease.

Bejel

Bejel is a chronic inflammatory disease of skin and mucous membranes caused by a nonvenereal treponeme that eventually produces chronic granulomas of skin and bone. It occurs in childhood, and is found particularly in the dry regions of Africa, the Balkans and Australia. The secondary features include a maculopapular rash (1.157) with regional lymphadenopathy. Transmission is by direct person-to-person contact or by fomites. Widespread use of penicillin has led to a decline in incidence with eradication in some countries.

Cancrum oris

Cancrum oris is caused by infection with a mixed flora of anaerobic organisms, including *Borrelia vincentii*. The condition is seen in malnourished, deprived children who have become immunosuppressed or who are debilitated with another disease such as measles or acute leukaemia. The infection usually starts as gingivitis and rapidly spreads to involve the buccal mucosa, the cheek, the mandible and the maxilla (1.158). If the gangrenous areas heal, they leave major disfigurement. The mortality is very high despite antibiotic treatment.

Lyme disease

Lyme disease was originally diagnosed in the village of Old Lyme, Connecticut, USA and the infecting organism, *Borrelia burgdorferi*, identified and isolated. The organisms infect the skin, nervous system, heart and joints. Most cases in North America have rheumatological features but in Europe there is a preponderance of dermatological and neurological features. The organism is transmitted by the bite of infected ticks (*Ixodes ricinus* in Europe and *I. scapularis* in North America) which are to be found on sheep, deer and horses. Ticks are most active in summer and autumn, and this correlates with human activity in the wilds, which results in ticks attaching themselves to humans. The populations most likely to be affected are those working in forest areas, for example wood-cutters and shepherds, and those passing through, such as ramblers, climbers or hikers.

There are three clinical signs:

- The first stage is local skin infection spreading from the tick bite. This is erythema chronicum migrans – a chronic indurated rash with a characteristic red margin and central clearing (1.159, 5.88). This is associated with generalized fever and systemic upset. Multiple skin lesions may appear
BACTERIAL INFECTIONS

at different stages of development and there may be regional lymphadenopathy, myalgia and arthralgia. There may be early clinical evidence of involvement of the CNS.

• The second stage reflects early disseminated infection and is found some weeks to months later. There may be clear evidence of CNS involvement, with neuritis (the VIIth nerve is often affected), encephalitis, myelitis and cerebral vasculitis, and optic neuropathy. Carditis is often present with rhythm disturbances, transient atrioventricular block, pericarditis and heart failure. Arthralgia and myalgia represent early features of involvement of the musculoskeletal system. Frank arthritis and myositis is commonly seen in North American patients, whereas neurological involvement is more common in European patients.

• The third stage represents chronic organ involvement, months to years after the initial infection. In North America the joints are particularly targeted, especially the knee joints, and 10–20% of patients have chronic disease (1.160). Chronic infection of the brain may appear as spastic paresis with ataxia. Chronic polyneuropathy may be associated with acrodermatitis chronica atrophicans; this mainly affects the extensor surfaces of the extremities which become bluish-red. The skin may also become atrophic and wrinkly and fibrous nodules may appear adjacent to the joints.

The diagnosis is made on clinical grounds as culture of B. burgdorferi is difficult from body fluids. Serological tests are available but must be interpreted with care. The polymerase chain reaction is of potential value, but currently ELISA and Western blot assays are available.

A wide range of antibiotics have been used singly and in combination. Despite this, a significant number of patients have disease progression and may require a change of therapy. Therapy should be given in high dosage for a prolonged period. Of major importance is the prevention of tick bites by protective clothing and prompt removal of ticks. There is no evidence that prophylactic antibiotics are of any value.

LEPTOSPIROSIS

Humans acquire leptospirosis from direct or indirect contact with animals, especially cattle and rodents. The most common rodent carrier is the brown rat, Rattus norvegicus. Farm workers, vets, sewer workers and fish-farm workers are particularly at risk and account for 50% of reported cases, and other at-risk groups include people in contact with rat-infested water, for example canoeists, swimmers and wind surfers on inland waterways. The causal organisms are members of the species Leptospira interrogans of which there are 202 serovars. L. hardjo (cattle) and L. icterohaemorrhagiae (rats) are the serovars most often associated with human diseases.

Leptospires can penetrate the mucous membranes of the eyes and nasopharynx or may enter from skin cuts or abrasions; within 24 hours most tissues of the body are infected. The disease course is then biphasic.

In the first week of illness there are influenza-like symptoms, with fever, shivering, headache, myalgia and conjunctival suffusion (1.161).

1.159 Erythema chronicum migrans. This characteristic rash should raise a strong clinical suspicion of the diagnosis of Lyme disease. Unless this is noted, the diagnosis may often be missed. Note the chronic induration, with a characteristic red margin and central clearing. Sometimes (not in this patient) an eschar from the tick bite may be seen near the centre of the lesion.

1.160 Chronic arthritis in Lyme disease. These severe arthritic changes in the foot occurred in a patient who had first noted the characteristic skin rash more than 10 years earlier.

1.161 Leptospirosis causing conjunctival suffusion. This patient washed regularly in rat-infested water.
The second phase of the illness is characterized by multisystem involvement, by the disappearance of the organism from the blood and the appearance of antibodies. In classic Weil's disease (*icterohaemorrhagiae*) the patient becomes jaundiced and haemorrhages appear on skin and mucous membranes. There are signs of meningitis, renal failure, adult respiratory distress syndrome, uveitis and DIC.

Death may occur in the second or third week from cardiac or renal failure in 10-20% of patients.

There is usually a polymorph leucocytosis in leptospiral infection. Early in the illness, organisms can be identified in the blood, CSF and urine by culture or dark-ground microscopy. Diagnosis is confirmed by the finding of rising titres of specific IgM antibodies in paired sera.

In severe infection the patient usually requires intensive care facilities. Dialysis may be required for renal failure. Antibiotics are effective only if given very early in the illness. High-dose benzylpenicillin is the drug of choice, but tetracycline and erythromycin may also be used.

Prevention methods include rodent control in farms and industrial areas, avoidance of rat-infested waters and wearing protective clothes.

**TRACHOMA**

Trachoma is a type of chronic conjunctivitis caused by infection with *Chlamydia trachomatis*, which has a worldwide distribution. In endemic areas it is transmitted from eye to eye by hands or flies, and in nonendemic areas it may be transmitted from the genital tract to the eye, especially in the newborn. A patient with trachoma presents with the features of conjunctivitis; minute lymphoid follicles in the conjunctiva are typical of early infection (1.162). Chronic inflammation leads to scarring and formation of a pannus. Further scarring leads to distortion of the eyelid, with turning-in of the eyelashes (entropion), which abrades the cornea further (trichiasis). Destruction of the goblet cells leads to a 'dry eye', which in turn exacerbates the corneal injury and rapidly results in blindness (1.163). The diagnosis is made from the clinical picture and the therapeutic response to tetracycline. Public health measures are of paramount importance. Corneal grafting is of value in selected patients.

*C. trachomatis* is also a common cause of non-gonococcal urethritis and pelvic inflammatory disease (see p. 81); and a strain of *C. trachomatis* is the cause of lymphogranuloma venereum (see p. 80).

**PSITTACOSIS**

Psittacosis is an infection caused by *Chlamydia psittaci*, which infects parrots, parakeets, turkeys, pigeons, ducks, chickens and other birds. Infection is acquired by inhalation of dried infected bird faeces and more rarely by handling the feathers or the carcass, by a bird bite or by other close contact. The disease is found in people working with birds, such as pet shop employees, pigeon handlers and poultry workers. The incubation period is about 7–10 days followed by a mild influenza-like illness. More severe infections are associated with fever, malaise, anorexia, myalgia and headache. Chest features predominate with cough, mucoid sputum that may be blood-stained and, rarely, pleuritic pain from pneumonia. Splenomegaly in a patient with pneumonia is an important diagnostic sign. Spontaneous recovery usually occurs over several weeks, but neurological signs, liver or renal failure indicate a poor prognosis. The diagnosis of pneumonia is confirmed by a chest X-ray (see p. 192); there may be some elevation in white cell count and erythrocyte sedimentation rate (ESR); the diagnosis is made by isolation of the organism or, usually, by serology. Tetracyclines remain the drugs of choice.

**TWAR PNEUMONIA**

TWAR pneumonia is a rather common (20% of blood donors in the UK have the antibody), usually mild, variety of lower respiratory tract infection by *Chlamydia pneumoniae* (the term TWAR was from the identifying letters of the first two isolates). The route of transmission is from person to person by way of droplets of respiratory secretions. Hoarseness as a result of pharyngitis is the most common problem followed by a fever, cough and general malaise from a mild form of pneumonia. Chest X-ray may show changes, usually confined to a single lobe of the lung. Elderly patients may develop more severe pneumonia.

The diagnosis depends on the serological testing and finding of a rising antibody titre on serotype specific immunofluorescence.

The treatment of choice is tetracycline.
**MYCOPLASMA INFECTION**

Mycoplasmas are the smallest free-living organisms, and differ from other bacteria in that they lack a cell wall. The most important mycoplasmas infecting man are *Mycoplasma pneumoniae, M. hominis* and *Ureaplasma urealyticum. M. pneumoniae* is a frequent cause of respiratory infections in children and young adults, being spread by airborne droplets. The other mycoplasma organisms are associated with infections of the urogenital tract (see p. 81).

The spectrum of illness caused by *M. pneumoniae* ranges from mild upper respiratory infection to severe atypical pneumonia. There may also be involvement of other organs with acute myocarditis, pancreatitis, aseptic meningitis and encephalitis, ear infection (bullous) and skin involvement (erythema multiforme — see p. 94) and Stevens–Johnson syndrome (see p. 95). Patients with atypical pneumonia present with fever, lassitude, malaise and a nonproductive cough. Chest pain is not usually prominent. Physical signs on examination of the chest are often less impressive than the X-ray findings, which may be unilateral or bilateral (4.115). Segmental lobular consolidation is frequently seen, but there may be changes suggesting bronchopneumonia or simply a general haziness fanning out from the hilum.

Laboratory findings include a high ESR and relatively low white blood cell count. Cold agglutinins appear in the blood in about 50% of patients and, if present, may be associated with haemolytic anaemia. The diagnosis is confirmed by demonstration of a specific IgM antibody to *M. pneumoniae*. Mild infection usually resolves spontaneously. Moderate or severe infections should respond to a course of erythromycin or tetracycline.

**TYPHUS AND RELATED INFECTIONS**

A range of diseases caused by the family Rickettsiaceae are harboured in the intestines of a range of arthropods (lice, fleas, ticks). They infect animals and man, often in epidemic form. Such infections are found worldwide and all have similar clinical presentations as the rickettsia invades the endothelium of blood vessels to produce vasculitis and local thrombosis followed by tissue necrosis.

The most important disease historically is typhus, which is caused by infection with *Rickettsia prowazekii*, carried by the human louse. Epidemics of infection are usually associated with disasters such as war or earthquakes. After a short incubation period (up to 7 days) there is rapid onset of fever, headache, myalgia and prostration. A rash appears soon afterwards (1.164), which is petechial initially before becoming confluent. Gangrene of the feet and hands (1.165) may then appear with areas of skin necrosis, renal failure and coma. Diagnosis is serological because culture exposes laboratory personnel to an unnecessary hazard. Tetracycline is the drug of choice and vaccination is available. Public health measures to control lice are mandatory.

Related disorders include Rocky Mountain spotted fever, murine typhus, scrub typhus and trench fever all of which are caused by different rickettsiae carried by different vectors.
INFECTIONS

Q FEVER

Q fever is an acute pyrexial illness that is caused by infection by a rickettsial-like organism, *Coxiella burnetii*. Infection is usually acquired from an animal source by inhalation of dust, from infected milk, or by direct handling. The usual animal sources are cows, sheep and goats and the organism is spread by ticks. After exposure, the incubation period is about 2–3 weeks before the onset of fever, myalgia, petechial rash, headache followed by cough and pleuritic chest pain caused by pneumonia (1.166 and see p. 193). Most patients recover rapidly, but occasionally progression occurs with hepatitis (see p. 404), endocarditis (see p. 247), uveitis and orchitis. The diagnosis is dependent on serology and treatment is with tetracycline or rifampicin.

FUNGAL INFECTIONS

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**Fungal infections.** *Pneumocystis* has recently been reclassified as a fungus (it was previously classified as a protozoan).

HISTOPLASMOSIS

Histoplasmosis occurs in many areas of the world and is particularly common in parts of the American Midwest. It is caused by a fungus, *Histoplasma capsulatum*, which is found in the soil, and transmitted by inhalation of fungal spores. The incubation period is usually 5–20 days.

In several respects, the clinical picture of histoplasmosis resembles that of tuberculosis:

- primary pulmonary histoplasmosis — which is often asymptomatic — is the first manifestation. It produces radiological features identical to those of the primary focus in tuberculosis (1.125, 1.126) and heals in a similar way. The radiological appearance may sometimes resemble miliary tuberculosis (1.168), and calcification may eventually occur (1.169). Complications at this stage may include pneumonia, pleural effusions, erythema nodosum (2.45) or erythema multiforme (2.47, 2.48).
- chronic pulmonary histoplasmosis is usually clinically indistinguishable from pulmonary tuberculosis, producing a similar range of complications (see p. 194).
- disseminated histoplasmosis may occur at any stage of the disease, leading to complications that include chronic pericarditis, granulomatous hepatitis, chronic meningitis and destructive lesions of skin and bone.

Definitive diagnosis is made by culture or histology, and serology and histoplasmin skin testing are also useful. In endemic areas, over 90% of the population have serological evidence of previous infection.

Only severe histoplasmosis requires treatment with antifungal therapy (amphotericin B).
African histoplasmosis is caused by *H. duboisii*. It does not cause pulmonary lesions, but skin lesions (1.170), lymph node involvement and lytic bone lesions are common.

**ASPERGILLOSIS**

Inhalation of the spores of the ubiquitous fungus, *Aspergillus fumigatus* (occasionally *A. flavus* and *A. niger*) may produce three forms of disease in the lung.

- In normal people, inhalation of spores may give rise to an acute pneumonia, which is usually self-limiting over several weeks. In patients who are immunosuppressed, bloodborne dissemination may take place to orbit, brain and skin.
- In patients with pre-existing lung disease, especially in those with bronchiectasis or cavities, *Aspergillus* can form large colonies. Balls of hyphae may reach several inches in diameter (aspergilloma) (1.171, 4.44, 4.45). These are usually found on routine X-ray, but may occur with haemoptysis.
- In allergic bronchopulmonary aspergillosis (ABPA), which

**1.168 Primary pulmonary histoplasmosis** may be asymptomatic, or it may result in a transient symptomatic respiratory infection. In this patient, the appearance of miliary mottling could represent miliary tuberculosis, pneumoconiosis or pulmonary metastases, and other tests are necessary to confirm the diagnosis.

**1.170 African histoplasmosis** producing a large destructive skin lesion. Similar appearances may occur in disseminated infection with *Histoplasma capsulatum*, especially in immunosuppressed patients.

**1.169 Healed pulmonary histoplasmosis.** Again, the residual fibrosis and calcification are reminiscent of TB, or of healed chickenpox pneumonia.

**1.171 Bilateral aspergillomas**, occurring in upper lobe cavities caused by old tuberculosis. If left untreated, the balls of fungus might ultimately grow to fill the cavities completely.
usually occurs in previously asthmatic patients, infection is followed by intermittent episodes of asthma and pneumonia, with eosinophilia and bronchial plugging with mucus. Repeated episodes of pneumonia may produce progressive pulmonary fibrosis or bronchiectasis, or both (1.172, see p. 190).

Systemic aspergillosis is an important form of nosocomial infection that occurs mainly in patients with neutropenia or immune deficiency (most commonly in those with acute leukaemia, or after renal or cardiac transplantation). It is commonly fatal unless diagnosed early and treated aggressively. It may present as pneumonia.

The diagnosis of aspergillosis depends on the demonstration of hyphae in the sputum, positive serology, positive skin prick test (in ABPA; see p. 167) or typical radiological appearances. Corticosteroids are of value in treating allergic pneumonitis. Amphotericin B and itroconazole are used in invasive disease. Surgery may be required to remove the cavity that contains an aspergiloma.

**CRYPTOCOCCOSIS**

*Cryptococcus neoformans* is a fungus with a worldwide distribution and is thought to be spread in bird droppings. Inhalation of the spores of this and related fungi gives rise to a low-grade granulomatous pneumonia. This may heal spontaneously, but it is occasionally complicated by cavitation, bilateral hilar lymphadenopathy and pulmonary fibrosis.

The most serious complication is meningo-encephalitis (1.173), a particularly common problem in patients with AIDS who have opportunistic cryptococcal infection. In addition, chronic infection of skin, bone, liver, heart and kidney may occur.

Cryptococcal infection cannot be diagnosed on clinical grounds. The detection of cryptococcal antigen in the CSF by polymerase chain reaction is the 'gold standard' for the diagnosis of cryptococcal meningitis. In other sites, biopsy is usually necessary.

CNS infection is still potentially fatal, but treatment with amphotericin B, fluconazole or flucytosine has reduced the mortality rate.

**COCCIDIOIDOMYCOSIS**

Coccidioidomycosis is a common disease in South America and the southern USA that results from the inhalation of the fungal spores of *Coccidioides immitis*, which are widely disseminated in soil. Most infections are asymptomatic and the presence of the organism is detected by skin testing. In a small number of patients there is an acute pneumonia, often associated with arthralgia and erythema nodosum (2.45) or erythema multiforme (2.47, 2.48). The disease may be severe in pregnancy and in patients who are immunosuppressed. Chronic lung infection may follow (1.174) and there may be evidence of general dissemination to bones, joints, brain and skin. Diagnosis depends on the identification of mycelia and on serology. Treatment is with amphotericin B or ketoconazole. Surgery may be indicated for chronic pulmonary or bone lesions.

Paracoccidioidomycosis and blastomycosis are broadly similar diseases that are caused by inhalation of the fungi *Paracoccidioides brasiliensis* and *Blastomyces dermatitidis*, respectively. They are found mainly in the American continent. The diseases tend to be milder than coccidioidomycosis, but skin lesions are prominent in blastomycosis and occasional dissemination of both conditions has been reported.
CANDIDIASIS

Candidiasis results from infection by Candida albicans, a budding yeast-like organism that can infect the skin and the mucosa of the mouth, intestine and genital tract. Young infants, pregnant women, diabetics, people with prosthetic heart valves, patients on broad-spectrum antibiotics and people immunocompromised by drugs or disease are especially susceptible to Candida infections. Candida is an important and common cause of nosocomial infections. In immunocompromised patients, dissemination of infection via the bloodstream may be life-threatening. Oral or genital candidiasis is often the first opportunistic infection to appear in HIV infection; if mucocutaneous candidiasis occurs in an adult patient who is neither diabetic nor taking an oral contraceptive preparation HIV infection is a likely underlying cause.

On mucous membranes, candidiasis appears as curd-like spots or plaques ('thrush') on a red base (1.35, 1.175, 1.176, 10.74). Vaginal (1.177) or penile candidiasis is usually accompanied by irritation and itching of the region. Oesophageal candidiasis

1.174 Chronic coccidioidomycosis. The nature of the coin lesion (arrow) seen in the right lower zone (a coccidioidoma) was confirmed by aspiration needle biopsy.

1.175 Oral thrush showing the characteristic curdy white patches of acute candida infection. In all but newborn babies this infection implies underlying disease or debility, and further investigation of the patient may be necessary. It is important not to confuse thrush with other causes of white oral mucosal lesions (e.g. lichen planus, 2.70).

1.176 Chronic candidiasis of the mouth. The deep fissuring of the tongue is the end result of long-term candida infection (compare this appearance with the acutely infected tongue seen in 1.35).

1.177 Vaginal thrush is a common problem in adult women during or after antibiotic treatment, in pregnancy and during oral contraceptive use. The curdy white discharge is characteristic.
(1.43, 8.35) causes retrosternal pain and dysphagia. Moist areas of skin are susceptible to infection (2.61) and the nails may be infected (2.62). Infants with oral candidiasis often have involvement of the skin of the groin and perineum (1.178). Almost any organ of the body may be involved in systemic candidiasis.

*Candida* organisms can easily be identified in smears made from skin or mucosal lesions and stained with methylene blue. Confirmation of infection is by culture from the local lesions or from the blood in systemic candidiasis.

Mucocutaneous candidiasis usually responds to local therapy with antifungal agents in preparations suitable for the site of infection. Oral fluconazole may be required for severe gastrointestinal or genital candidiasis. Systemic candidiasis requires intravenous therapy with fluconazole or amphotericin B alone, or combined with flucytosine. Predisposing factors such as diabetes and HIV infection should be sought and treated.

### PROTOZOAL INFECTIONS

![1.178 Vulvovaginitis in a baby, caused by *Candida albicans.* Infection at this age is not unusual, but in older children and adults it may suggest an underlying disorder such as diabetes.](image)

**TABLE 1.179**

<table>
<thead>
<tr>
<th>Genus</th>
<th>Important human protozoa</th>
<th>Relevant human disease</th>
<th>Page reference</th>
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</thead>
<tbody>
<tr>
<td><strong>Amoeba</strong></td>
<td><em>Entamoeba histolytica,</em> <em>E. polecki</em></td>
<td>Dysentery, liver abscess, skin infection</td>
<td>62, 386, 412</td>
</tr>
<tr>
<td><strong>Giardia</strong></td>
<td><em>G. lamblia</em></td>
<td><em>Diarrhoea, malabsorption</em></td>
<td>385</td>
</tr>
<tr>
<td><strong>Balantidium</strong></td>
<td><em>B. coli</em></td>
<td><em>Diarrhoea</em></td>
<td>385</td>
</tr>
<tr>
<td><strong>Isospora</strong></td>
<td><em>I. belli</em></td>
<td><em>Diarrhoea</em></td>
<td>385</td>
</tr>
<tr>
<td><strong>Cryptosporidium</strong></td>
<td><em>Cryptosporidium</em></td>
<td><em>Diarrhoea, acute fluid loss</em></td>
<td>385</td>
</tr>
<tr>
<td><strong>Trichomonas</strong></td>
<td><em>Trichomonas vaginalis</em></td>
<td><em>Vaginitis, balanitis</em></td>
<td>81</td>
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<tr>
<td><strong>Toxoplasma</strong></td>
<td><em>T. gondii</em></td>
<td><em>Generalized toxoplasma infection,</em></td>
<td>64</td>
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<tr>
<td><strong>Plasmodium</strong></td>
<td><em>P. vivax, P. ovale,</em> <em>P. malariae, P. falciparum</em></td>
<td><em>Congenital infection</em></td>
<td>64</td>
</tr>
<tr>
<td><strong>Leishmania</strong></td>
<td><em>L. donovani,</em> <em>L. tropica,</em> <em>L. braziliensis</em></td>
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<tr>
<td><strong>Trypanosoma</strong></td>
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<td><em>Visceral and cutaneous leishmaniasis,</em></td>
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<td></td>
<td><em>T. cruzi</em></td>
<td><em>African sleeping sickness</em></td>
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<td></td>
<td></td>
<td><em>American trypanosomiasis,</em> <em>Chagas' disease</em></td>
<td>67</td>
</tr>
</tbody>
</table>

**1.179 Protozoal infection.**

**AMOEBIASIS**

Amoebiasis is endemic in many tropical areas where sanitation is poor. Spread of infection is by the faecal–oral route, usually through ingestion of amoebic cysts in contaminated water or food. The causal agent is *Entamoeba histolytica* and the time from ingestion of cysts to the appearance of symptoms may be up to 1 year.

Patients infected with *E. histolytica* may present in several ways:
- With acute dysenteric symptoms: malaise, fever, abdominal pain and the passage of frequent loose stools containing blood and mucus (amoebic colitis, see p. 386)
- With less severe relapsing diarrhoea over a period of weeks or months
- With symptoms mimicking those of an intestinal tumour
caused by granulomatous masses (amoebomata) in the bowel wall (8.124, see also p. 386)

- Carrier states exist without obvious clinical illness
- Liver abscess may occur without evidence of concurrent or previous bowel infection (see p. 412)
- Pleura, lung and pericardium may be involved in spread from the liver.
- Skin may be involved by abscess formation (1.180) or directly as a result of sexual contact (1.181).

Vegetative forms of amoebae should be sought in fresh (hot) stools or in scrapings from bowel ulcers seen at sigmoidoscopy.

Suspected liver abscess is diagnosed by ultrasound, isotope scanning, CT scanning (1.182) or by diagnostic aspiration (1.183, 1.184). Antibody levels to amoebae are raised in most cases of liver abscess, but are of less value in dysenteric illness.

Both amoebic dysentery and amoebic liver abscesses respond to metronidazole. Chloroquine may be used as additional therapy in liver abscess. Therapeutic aspiration of the abscess is now rarely required but progress towards healing should be monitored by ultrasound scanning. Diloxanide furoate is effective in clearing amoebic cysts from the gut in the carrier state.
TOXOPLASMOSIS

The causal organism of toxoplasmosis is *Toxoplasma gondii*, a protozoan parasite. The organism has many vertebrate hosts but the sexual cycle occurs only in cats, which pass the infective oocysts in their faeces. Man is infected by eating meat containing tissue cysts or by the ingestion of oocytes from cat faeces.

Women infected during pregnancy may transmit the organism transplacentally to the fetus. Abortion is likely if the fetus is infected in early pregnancy. Congenital toxoplasmosis may be a severe life-threatening illness with fever, hepatosplenomegaly, rash, hydrocephalus, brain damage (1.185, 1.186) and choroidoretinitis (1.187). Infants may, however, appear normal at birth or may have only minor clinical abnormalities.

Toxoplasmosis acquired in childhood or adult life is often subclinical and can usually be diagnosed only by serology. There may, however, be a glandular fever-like syndrome with fever, malaise and swelling of one or more glands. Occasionally the disease is more widespread with involvement of liver, spleen, heart, meninges, brain and eyes (1.187). Primary infection or reactivation of latent infection in immunocompromised patients, including those with HIV infection, is likely to cause particularly severe illness, including cerebral abscesses (1.42). *Toxoplasma* is the most common cause of CNS infection in patients with AIDS.

The diagnosis is confirmed by serology. In cerebral toxoplasmosis skull X-ray and CT or MRI scanning may aid diagnosis and histology of a lymph node biopsy may also be helpful.

Acquired toxoplasmosis in immunocompetent patients usually requires no treatment. Congenital toxoplasmosis and severe illness, especially in immunocompromised people, should be treated with pyrimethamine plus sulphonamide or pyrimethamine plus clindamycin. Therapy may have to be prolonged and in the immunocompromised patient maintenance therapy may be required for life. Spiramycin is advised for use in pregnancy.

Prevention includes thorough cooking of meat and meat products and the avoidance of areas, such as children's sand pits, likely to be contaminated with cat faeces.

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**MALARIA**

Malaria is the major cause of morbidity and mortality in many tropical and subtropical countries. The number of cases imported into nonendemic countries grows each year as a result of ever-increasing world travel.

Four species of the genus *Plasmodium* cause human malaria:

- *P. falciparum* - malignant tertian
- *P. vivax* - benign tertian
- *P. ovale* - ovale tertian
- *P. malariae* - quartan.
The insect vector is the female *Anopheles* mosquito. Infection with *P. falciparum* causes the most severe illness. Increasing geographic spread of resistance of this organism to chloroquine and other antimalarial drugs is causing major problems in the management and control of the disease.

Presenting features of an acute malarial attack are protean and may include fever (1.188), rigors, sweating, headache, myalgia, gastrointestinal upset and respiratory symptoms. The initial presentation may be with mild influenza-like symptoms, for example, so it is essential to consider the possibility of malaria in any patient in or returning from an endemic area, and even in those who live near or work in international airports. In severe falciparum malaria there may be collapse, convulsions and coma (cerebral malaria, 1.189). The presence of retinal haemorrhage in the noncomatose patient heralds the rapid onset of cerebral symptoms (1.190). Splenomegaly and anaemia are usual in the acute attack. Acute haemolytic crises may be associated with haemoglobinuria (blackwater fever, 1.191).

Chronic infection may be associated with massive splenomegaly (tropical splenomegaly syndrome (TSS) – 1.192) or with the nephrotic syndrome (1.193).

The diagnosis is confirmed by examination of thick and thin blood films and the identification of parasites in red cells (1.194).

1.188 The temperature chart in malaria reflects the typical tertian and quartan fever patterns. The asexual blood stages of *P. falciparum*, *P. vivax* and *P. ovale* require 48 hours to complete their schizogony. Fever is produced when the schizonts mature, that is, at 48-hour intervals. This gives the classic tertian periodicity of *P. vivax* and *P. ovale* infection, which is, however, uncommon in a primary attack of *P. falciparum* malaria. *P. malariae* requires 72 hours and is associated with quartan fever, that is, 72 hours between paroxysms.

1.191 'Blackwater' (B) compared with normal urine (A). Acute haemolytic crises resulting in haemoglobinuria occur in severe attacks of falciparum malaria (blackwater fever).

1.192 Tropical splenomegaly syndrome (TSS) is associated with chronic malaria infection and is thought to result from an abnormal immunological response. Note the outline of the massive spleen. The scars result from the local application of traditional healing techniques.

1.193 Nephrotic syndrome in a child with *P. malariae* infection. Note the gross facial and neck oedema and ascites.

1.194 Blood film in *P. malariae* infection showing ring form trophozoites in red cells. All blood stages in the life cycle of the parasite may be seen in films taken at different times, and blood film examination remains the cornerstone of diagnosis.
Chloroquine is the treatment of choice for benign tertian or quartan malaria. Chloroquine resistance is spreading and up-to-date advice is required before falciparum malaria is treated. Quinine is now used to treat falciparum malaria from most regions because of the worry of potential resistance to chloroquine. A course of primaquine should also be given to patients with benign tertian or quartan malaria to prevent recurrence.

Preventive measures include mosquito control, personal measures to avoid mosquito bites and, often, prophylactic therapy for people entering or living in a malarious area. Advice given to travellers should take account of the relative risk of acquiring infection, the degree of resistance of parasites in the area and the potential side effects of drugs used in prophylaxis. Global control of malaria may be achieved if a reliable vaccine becomes available.

**LEISHMANIASIS**

Leishmaniasis is a common tropical disorder caused by infection with protozoa of the genus *Leishmania*, which is transmitted between people or from animals by the bite of the infected female sandfly. The protozoa may cause either visceral or cutaneous infection. WHO estimates that at least 12 million people are infected worldwide, and that 350 million are at risk of infection.

In the visceral form, the organism (*L. donovani*) multiplies in macrophages. After an incubation period of 2–6 months there is extensive reticulo-endothelial proliferation (kala-azar, literally ‘black sickness’, so called because deepening pigmentation of the skin is commonly seen). Clinically these patients present with recurrent fever, lymphadenopathy, firm nontender massive splenomegaly (1.195) and bone marrow suppression. Leucopenia with a relative lymphocytosis is often present. In light-skinned patients there may be hyperpigmentation of the skin, especially on the hands, feet and abdomen. The death rate in untreated patients is high from intercurrent infections, marrow suppression or bleeding. Antimony salts are still the treatment of choice. After successful treatment of visceral leishmaniasis, dermal lesions may reappear (post kala-azar dermal leishmaniasis, PKDL, 1.196).

The various cutaneous forms of leishmaniasis present with single or multiple chronic but localized skin ulcers (1.197), and, with some species, chronic mucocutaneous lesions. They are subdivided into ‘Old World’ and ‘New World’ cutaneous leishmaniasis and are known by a wide range of local names in different countries. Transmission occurs via sandflies or directly by contact with open lesions. The diagnosis is made by finding parasites in smears of skin adjacent to the sores or by a positive leishmanin skin test. Specific antibody tests and DNA probes are now also available. Treatment of these local lesions is often unsatisfactory, but they may respond to direct heating to 40°C, to antimony salts or to levamisole.

**TRYPANOSOMIASIS**

There are two major types of trypanosome infection, African trypanosomiasis, including sleeping sickness, and American Chagas’ disease.

African trypanosomiasis is caused by subspecies of *Trypanosoma brucei* and the natural vector is the tsetse fly. About 8–12 days after a bite by an infected tsetse fly, a trypanosomal chancre may develop at the site (1.198). After a
period that may vary from months to years, a systemic reaction occurs, associated with fever and lymphadenopathy (1.199). After an indeterminate time, the infection involves the CNS starting with mild behavioural changes and rapidly progressing to coma and death (1.200).

American trypanosomiasis (Chagas' disease) is a result of infection by *T. cruzi* and is found in Central and South America. The disease is transmitted by the faeces of bloodsucking triatomid bugs. In the acute infection, there may be a mild pyrexia and skin rash with patients occasionally developing myocarditis. The initial local skin lesion is the chagoma which is painful and swollen (1.201). Most patients present with chronic disease many years after the infection. The common presentations are chronic cardiomypathy (1.202), and dilatation of the oesophagus (see p. 365) or colon. The disease may be diagnosed on blood or lymph node films, by animal culture or by serology.

1.198 African trypanosomiasis – the trypanosomal 'chancre'. The lesion marks the site at which the tsetse fly inoculated the patient with the trypanosome. Chancres are rare in indigenous patients, but common in visitors.

1.199 Puncture of an enlarged supraclavicular lymph node and examination of the aspirate is a valuable aid to diagnosis in African trypanosomiasis, especially in the Gambian form of the disease.

1.200 Sleeping sickness. In the Gambian form of the disease, the patient becomes more wasted and comatose, finally showing the classic picture of sleeping sickness as the CNS becomes involved. In the 'Rhodesian' form of the disease, the CNS features are usually less marked and the disease more acute.

1.201 'Chagoma' in American trypanosomiasis. In this case, the inoculation occurred within the conjunctival sac, and the chagoma has caused marked local oedema with lid swelling and chemosis. This is a common site of inoculation, and this unilateral appearance is termed Romana's sign.

1.202 ECG in Chagas' disease, showing complete heart block (grade 3). There is no discernible relationship between P waves and QRS complexes, and the atria and ventricles are beating independently of each other. Dysrhythmias of various types and degrees are common in Chagas' disease, and death may result from Stokes–Adams attacks.
**WORM INFECTIONS**

<table>
<thead>
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<th>Important human pathogen</th>
<th>Human disease</th>
<th>Page reference</th>
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<td><em>Brugia malayi,</em></td>
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<td></td>
<td><em>Brugia timori</em></td>
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<td></td>
<td><em>Loa loa</em></td>
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<tr>
<td></td>
<td><em>Onchocerca volvulus</em></td>
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<td></td>
<td><em>Dracunculus medinensis</em></td>
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<td></td>
<td><em>Toxocara canis, T. cati</em></td>
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<td></td>
<td><em>Trichinella spiralis</em></td>
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<td><em>Enterobius vermicularis</em></td>
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<td><em>Acaris lumbricoides</em></td>
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<td><em>Trichuris trichuria</em></td>
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<td></td>
<td><em>Ancylostoma duodenale,</em></td>
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<td><em>Necator americanus</em></td>
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<td><em>Strongyloides stercoralis</em></td>
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<td><em>Schistosoma mansoni</em></td>
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<td>Lung cysts, haemoptysis, cerebral involvement</td>
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<td></td>
<td><em>Paragonimus westermani</em></td>
<td>Abdominal pain and diarrhoea, allergy</td>
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<td></td>
<td><em>Fasciolopsis buski</em></td>
<td>Hepatitis, obstructive jaundice</td>
<td>387</td>
</tr>
<tr>
<td></td>
<td><em>Fasciola hepatica</em></td>
<td>Hepatitis, obstructive jaundice</td>
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<td><em>Opisthorchis sinensis</em></td>
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<td></td>
<td><em>Echinococcus granulosus</em></td>
<td>Liver cysts</td>
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<tr>
<td></td>
<td><em>E. multilocularis</em></td>
<td>Usually asymptomatic. Diarrhoea occasionally.</td>
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<tr>
<td></td>
<td><em>Taenia solium, T. saginata</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Diphyllobothrium latum</em></td>
<td>Usually asymptomatic. Vitamin B12 deficiency anaemia (rare)</td>
<td>387</td>
</tr>
<tr>
<td>Cestodes</td>
<td><em>Echinococcus granulosus</em></td>
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<td><em>E. multilocularis</em></td>
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<tr>
<td></td>
<td><em>Diphyllobothrium latum</em></td>
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</table>

**LYMPHATIC FILARIAIS**

The infecting nematodes, *Wuchereria bancrofti, Brugia malayi* and *B. timori*, are found in the tropics worldwide and produce disease in man by lymphatic obstruction. Mosquitoes of the species *Culex, Anopheles* and *Aedes* transmit the larvae of *W. bancrofti*, and *Mansonia* and *Anopheles* mosquitoes transmit *B. malayi* and *B. timori*. The larvae enter the regional lymphatics and mature. They may live in this situation for many years.

Within 3 months of infection there is intermittent fever and sweats, with photophobia, myalgia and lymphangitis in most areas of the body. Localized areas of swelling follow, for example leg oedema (1.204), ascites, hydrocele, pleural effusion. Local abscess formation and chronic sinuses may form. Massive chronic oedema of the legs produces elephantiasis (1.205). The diagnosis is made by demonstration of the parasite in blood films (1.206). Treatment is with diethylcarbamazine.

**LOIASIS**

Loiasis is filarial infection with *Loa loa* and is found in western Central Africa. The disease is transmitted by the bite of tabanid flies of the genus *Chrysops*, which live in tropical rain forests (*C. dimidiata* and *C. silacea*). Larvae enter the human skin, where they mature. The adult females migrate continuously throughout the subcutaneous tissues and may pass in front of the eyes, under the conjunctiva, where they produce severe discomfort (1.207). The intense subcutaneous inflammatory reaction involved in the passage of the adult worms produces skin nodules (Calabar swellings, 1.208). In the heart, the microfilariae may cause endomyocardial fibrosis. The diagnosis may be confirmed by finding sheathed microfilariae in biopsy samples of the swellings. The migrating worms may be removed under local anaesthesia (1.209). Treatment is with diethylcarbamazine.
ONCHOCECIASIS

Onchocerciasis is a variety of cutaneous filariasis caused by infection by the tissue-dwelling *Onchocerca volvulus*. It is found predominantly in Africa (where it is known as 'river blindness'), Yemen and South America. Larvae enter the skin via the bite of the blackfly vector of the genus *Simulium* and then migrate to the subcutaneous tissues where they mature into adults. The adult worms may live for 10–15 years. Larvae develop from the female worms to form unshed microfilariae which migrate in the subcutaneous tissues and the eye. The major symptoms result from a hypersensitivity reaction to dead microfilariae. In the skin, this produces nodules which, if very large, may give an appearance called 'hanging groins' (1.210).

1.207 Adult *Loa loa* in the eye. The movement of the adult worm under the conjunctiva causes congestion and considerable irritation.

1.208 Calabar swelling in the right hand and arm caused by loiasis. Recurrent large swellings lasting about 3 days are characteristic and are most frequently seen in the hand, wrist and forearm. They indicate the tracks of the migrating adults in the connective tissue. A marked eosinophilia (60–90%) accompanies this phase of the infection.

1.209 Extraction of *Loa loa* worm from the eye. The adult worm can be extracted with fine forceps after anaesthetizing the conjunctiva.

1.210 'Hanging groins' in onchocerciasis are caused by the involvement of the inguinal lymph nodes in a hypersensitivity reaction to dead microfilarian worms.

1.204 Chronic lymphatic oedema in the right leg as a result of long-standing lymphatic filariasis. The patient was a seaman who had been working in the Far East coastal trade for 15 years.

1.205 Gross elephantiasis of the leg, scrotum and hand caused by *W. bancrofti* in a patient in Tahiti. Elephantiasis on this scale may cause incapacitating deformity and radical surgery may be required to remove surplus tissue.

1.206 Lymphatic filariasis can be diagnosed by demonstrating the parasite (in this case *W. bancrofti*) in a blood film.

1.203 Lymphatic filariasis in the right hand caused by *W. bancrofti*. The patient was a seaman who had been working in the Far East coastal trade for 15 years.

1.202 Onchocerciasis is a variety of cutaneous filariasis caused by infection by the tissue-dwelling Onchocerca volvulus. It is found predominantly in Africa (where it is known as 'river blindness'), Yemen and South America. Larvae enter the skin via the bite of the blackfly vector of the genus Simulium and then migrate to the subcutaneous tissues where they mature into adults. The adult worms may live for 10–15 years. Larvae develop from the female worms to form unshed microfilariae which migrate in the subcutaneous tissues and the eye. The major symptoms result from a hypersensitivity reaction to dead microfilariae. In the skin, this produces nodules which, if very large, may give an appearance called 'hanging groins' (1.210).

1.201 Calabar swelling in the right hand and arm caused by loiasis. Recurrent large swellings lasting about 3 days are characteristic and are most frequently seen in the hand, wrist and forearm. They indicate the tracks of the migrating adults in the connective tissue. A marked eosinophilia (60–90%) accompanies this phase of the infection.

1.200 Adult Loa loa in the eye. The movement of the adult worm under the conjunctiva causes congestion and considerable irritation.

1.204 Chronic lymphatic oedema in the right leg as a result of long-standing lymphatic filariasis. The patient was a seaman who had been working in the Far East coastal trade for 15 years.

1.205 Gross elephantiasis of the leg, scrotum and hand caused by *W. bancrofti* in a patient in Tahiti. Elephantiasis on this scale may cause incapacitating deformity and radical surgery may be required to remove surplus tissue.

1.206 Lymphatic filariasis can be diagnosed by demonstrating the parasite (in this case *W. bancrofti*) in a blood film.

1.207 Adult *Loa loa* in the eye. The movement of the adult worm under the conjunctiva causes congestion and considerable irritation.

1.208 Calabar swelling in the right hand and arm caused by loiasis. Recurrent large swellings lasting about 3 days are characteristic and are most frequently seen in the hand, wrist and forearm. They indicate the tracks of the migrating adults in the connective tissue. A marked eosinophilia (60–90%) accompanies this phase of the infection.

1.209 Extraction of *Loa loa* worm from the eye. The adult worm can be extracted with fine forceps after anaesthetizing the conjunctiva.

1.210 'Hanging groins' in onchocerciasis are caused by the involvement of the inguinal lymph nodes in a hypersensitivity reaction to dead microfilarian worms.
The eye lesions can be catastrophic for affected individuals and populations. They include keratitis (1.211) and choroiditis with eventual optic atrophy and blindness (1.212). The diagnosis is made by demonstrating motile microfilariae in a skin biopsy preparation (skin snip). Removal of the adult worms in the nodules by nodulectomy prevents the continued production of microfilariae.

Therapy is with diethylcarbamazine and suramin (which may cause severe reactions as the microfilariae are killed), or with ivermectin, which has fewer adverse effects. A current WHO campaign aims to eliminate onchocerciasis from the world.

**DRACUNCULOSIS**

Dracunculus medinensis (Guinea worm) is a nematode that migrates within the body tissues. It is widely distributed in Africa and Asia. Humans are infected by drinking water containing the microcrustacean Cyclops, which is infected with the larval form of D. medinensis. The larvae are liberated in the human stomach and migrate through the connective tissue planes of the body, a process that can take up to 1 year. Once fertilized, the female migrates to a limb where she produces a vesicle which ulcerates. This allows the female worm to protrude a loop of her uterus through the ulcerated skin. On contact with water, larvae are released and in fresh water wells the cycle continues. Patients usually present at the painful stage of vesiculation when the worms can be removed mechanically (1.213). If the worms die, they may be found in calcified subcutaneous nodules (1.214). Public health measures and education of the population are necessary for prevention. Surgery is possible for local lesions and a range of anthelmintics is available.

**TOXOCARIASIS (VISCERAL LARVA MIGRANS)**

The eggs of the ascarid worms, Toxocara canis and T. cati, are to be found in soil contaminated by dog and cat faeces. Infection occurs when they are accidentally ingested, usually by young children. The eggs hatch in the intestine and migrate...
in the bloodstream to the liver and lungs but do not develop beyond the larval form. Migration of the larval worm (visceral larva migrans) may produce haemorrhage and granuloma formation. Eosinophilia is a common finding and there may also be intermittent fever, cough, asthmatic attacks, dermatitis, occasionally hepatosplenomegaly and retinitis (1.215). Usually, the acute attack remains undiagnosed and the healed lesions may be found coincidentally in the eye where they must be differentiated from neoplasms. The diagnosis can be confirmed serologically. Prevention is possible if pet owners worm their animals regularly and stop the fouling of children's play areas. Occasionally, treatment is necessary and the drug of choice is diethylcarbamazine.

**CUTANEOUS LARVA MIGRANS**

Cutaneous larva migrans, also known as 'ground itch' or 'creeping eruption', is the result of intact skin penetration by the larvae of a range of hookworms whose normal host is non-human, for example *Ancylostoma braziliense*, *A. caninum*, *A. duodenale*, *Necator americanus* and *Strongyloides stercoralis* (see also p.387). The larvae cannot develop further in humans, but migrate in the subcutaneous tissues where they provoke a severe erythematous and vesicular reaction, with pruritus at the point of entry (1.216). These lesions are often complicated by a secondary bacterial infection. The feet and lower limbs are often involved and the condition is most common in children. The diagnosis is confirmed by finding larvae in biopsy material.

**TRICHINOSIS**

Trichinosis is a worldwide disease that results from the ingestion of pig, bear or wolf meat containing the encysted larvae of *Trichinella spiralis*. The larvae develop into adults in the small intestine and penetrate the wall to enter the bloodstream where they move to all body tissues, especially muscle and brain. Migrating larvae are associated with eosinophilia, fever, diarrhoea, myalgia and periorbital oedema (1.217). In severe infection, there may be evidence of meningo-encephalitis, psychiatric syndromes, myocarditis and pneumonia. The disease may be
INFECTIONS

suspected on clinical grounds, as it may occur as a localized outbreak, and the larvae can be found in muscle biopsies. Serology is also valuable. Thiabendazole is of value in the intestinal phase and systemic steroids may be required in severe encephalitis or myocarditis. Education in the need for thorough cooking of meat products is important in prevention and the deep freezing of pork has significantly reduced transmission.

SCHISTOSOMIASIS (BILHARZIA)

Schistosomiasis is an infection with a worldwide distribution caused by three types of blood flukes of the genus *Schistosoma*—*S. mansoni*, *S. haematobium* and *S. japonicum*. Humans are infected by the cercarial stage of the parasites released from freshwater snails in ponds, canals, lake edges and streams. Penetration of intact skin occurs rapidly and the schistosomes migrate into the portal system to mate and then to a part of the venous system to lay eggs. *S. haematobium* is found in the bladder and pelvic organs, whereas the others are usually found in the rectal venous plexus. Eggs laid in these venous plexuses are shed into the bladder or rectum and returned to the local water supply to complete the cycle through the snail population. Cercarial penetration of the skin may produce an itchy papular eruption (1.218) and this may be followed by myalgia, headache and abdominal pain.

In *S. mansoni* and *S. japonicum* infection, the late manifestations of the disease include abdominal pain, diarrhoea, malabsorption and, occasionally, intestinal obstruction and rectal prolapse. Cirrhosis of the liver is also frequently found with associated portal hypertension, splenomegaly (1.219) and oesophageal varices (1.220). In *S. haematobium* infection the major signs are in the urinary tract, with recurrent haematuria (1.221) and eventually bladder calcification, obstructive uropathy (1.222) and renal failure. Migration of eggs to the lungs may cause massive chronic fibrosis.

1.220 Oesophageal varices are a common accompaniment of portal hypertension (see p. 402). Massive varices, like those outlined on this barium swallow, occur commonly in advanced schistosomiasis caused by *S. mansoni* and *S. japonicum*; they may lead to death from haematemesis.

1.222 Intravenous urogram (IVU) in advanced *S. haematobium* infection, showing a severely contracted and irregular bladder, associated with severe constriction of the lower end of both ureters, and gross dilatation and tortuosity of the rest of the ureters with bilateral hydronephrosis.
WORM INFECTIONS

Diagnosis is by detection of the characteristic ova in the stools, urine or rectal biopsy (1.223) or with an ELISA test. Public health measures may inhibit the cycle of the parasite. Treatment of patients is with praziquantel given as a once-daily dose, depending on the patient’s weight.

PARAGONIMIASIS

Infection in humans occurs from eating uncooked freshwater crabs and crayfish, which harbour the metacercarial form of Paragonimus westermani (lung fluke). The disease is found worldwide, but especially in South East Asia. The larval worm hatches in the human stomach and migrates through the gastric wall into the peritoneal cavity, and through the diaphragm into the pleural cavity and lung. The mature adult worms produce local necrosis in the lungs (1.224) and the patient presents with haemoptysis, cough and fever. Cavitation with massive haemoptysis, pneumonia, pleurisy and empyema are also found. Healing takes place, with eventual pulmonary fibrosis. The liver and brain may also be infected. The diagnosis can be made from sputum and faecal examination. Eosinophilia is common and should trigger a search for ova. Radiography of the chest may show infiltration, cyst formation, effusion and empyema. Public health measures include proper sanitation, and education about adequate cooking of shellfish. Drug treatment is with praziquantel or bithionol.

HYDATID DISEASE

Human infection with Echinococcus granulosus is found worldwide, especially in countries with a large sheep industry. Accidental ingestion of the eggs results from contamination of food with canine faeces (usually dog). Hatching of the eggs in the intestine produces a six-hooked oncosphere which migrates through the intestinal wall and is carried to all body tissues by the circulation, especially to the liver and lungs, and more rarely to the CNS and bone, where cyst formation occurs. In humans that is the end of the cycle, but if the eggs were ingested by a herbivore (sheep, cattle, pig, deer) which was subsequently eaten by a member of the Canidae, the cysts would form adult tapeworms in the canine intestine and new egg production would be initiated.

In humans, the cysts may grow to a large size and produce daughter cysts and pressure on surrounding tissues. The clinical presentation depends on the organ(s) most affected.

Cysts are contained by a definite membrane; the fluid within, if liberated into the body cavities, may produce anaaphylactic shock and death, and it will lead to dissemination of tapeworm heads (protoscolices) that then form further cysts. Over the course of time, cysts may become calcified.

Cysts are demonstrated by conventional X-rays (1.225), ultrasound and CT scanning (1.226). Serological diagnosis (ELISA test) is also helpful and may be used as a screening test. Surgery may be required to remove cysts that are causing pressure symptoms. The fluid must be aspirated and the cyst cavity filled with formalin to kill the potentially infective protoscolices and to detoxify the residual fluid. The cyst lining should then be marsupialized. Public health measures involve public education in endemic areas about transmission, personal hygiene and the prevention of feeding offal to dogs.

A more serious disease is caused by E. multilocularis which is found in foxes, wolves, farm dogs and cats. Humans are infected in a similar fashion and the oncospheres migrate to
lung, liver and brain. The developing cyst is not covered by a membrane and tends to grow progressively in size. It may be mistaken for a cancer and may embolize to other tissues. It has an untreated mortality rate of about 80%.

Control of the disease requires at least a 10-year cycle of eradication in sheepdogs, in which the dogs are wormed every 6 weeks using praziquantel.

**SPARGANOSIS**

Sparganosis is mainly seen in the Far East. Infection in humans is acquired by drinking water or eating raw frog or snake contaminated by copepods (crustacea) that carry a larval tapeworm (*Diphyllobothrium mansoni*). Migration of the larvae to the skin, eyes and other tissues produces an acute inflammatory reaction; for example in the eye, severe periorbital oedema may be found. The adult worm may be removed from its subcutaneous or conjunctival site (1.227). Education and public health measures are important.

**OTHER INFECTIONS**

A number of other disorders are believed to be of infective origin, though the nature of the infecting organism is currently unknown. The association between *Helicobacter pylori* infection and peptic ulceration became clear only relatively recently (p. 367), and many believe that underlying, yet-to-be-identified infections may account for granulomatous conditions such as sarcoidosis, Crohn’s disease and temporal arteritis. Much research has focused on the possible role of infectious agents in rheumatoid arthritis and the connective tissue disorders, and underlying infective agents may even prove to play a role in coronary heart disease and other thrombotic disorders.

**KAWASAKI DISEASE (MUCOCUTANEOUS LYMPH NODE SYNDROME)**

The cause of Kawasaki disease remains unknown but is presumed to be an infection because of the occurrence of epidemics, clusters and seasonal peaks. The presentation is an acute onset febrile illness with conjunctivitis (1.228) that most commonly affects children under 5 years; in the UK there is an incidence of about 4 per 100,000 children in this age-group. There are major differences in countries round the world, for example in Japan it is at least 10 times more common than in the UK.

The most common site of disease is the coronary arteries, in which microaneurysms develop in about one-third of patients. The result may be death from myocardial infarction, arrhythmias and ruptured aneurysms. Most children recover, but they are at long-term risk of morbidity from accelerated atherosclerosis.

In addition to the dominant cardiac features, there may be arthritis, pneumonitis, hepatitis, splenomegaly, gastroenteritis, aseptic meningitis and nephritis.

As there is no recognized diagnostic test, the syndrome is diagnosed according to American Heart Association diagnostic guidelines, which require the presence of fever of 5 or more days duration and four of the following five symptoms: bilateral conjunctivitis; inflammation of mucous membranes of the upper respiratory tract; rash; cervical lymphadenopathy; and peripheral oedema, erythema or desquamation.

Treatment consists of the use of aspirin and intravenous gammaglobulin, which are believed to reduce the risk of coronary artery damage.

**PRION DISEASES**

A number of chronic progressive fatal neurological disorders of man and animals have now been shown to result from the transmission of a modified cell membrane protein called prion protein (PrP). The three most important in man are Creutzfeldt–Jakob disease (CJD), kuru and Gerstmann–Sträussler–Schniker syndrome (GSS).
Creutzfeldt–Jakob disease

CJD is a rare but rapidly progressing dementing illness that is invariably fatal. About one in 10 cases are familial. Most cases are sporadic and are found worldwide with an annual incidence of about 1 case per 1 million of the population. Case-to-case transmission by inoculation has been well documented and recently highlighted in people who have had organ transplants and processed pituitary extracts of growth hormone. Although there is no firm evidence, it is now considered possible that bovine spongiform encephalopathy (BSE), a prion-induced disease of cattle, may be transmissible to man by the ingestion of prion-containing bovine nervous or lymphatic tissue, and that such transmission may lead to a dementing illness similar to CJD.

The clinical presentations of CJD include focal neurological signs, dementia, myoclonus, akinetic mutism and cortical blindness. Death usually occurs within one year of onset.

The diagnosis is made on clinical grounds. The EEG may show pseudoperiodic triphasic waves (11.24) but these ‘classic’ features may only occur late in the disease. MRI and CT scans may be normal or show a degree of cerebral atrophy (11.41). Single photon emission tomography may show cerebral and cerebellar impairment of uptake of the tracer, hexamethylpropylenamine labelled with $^{99m}$Tc.

There is no specific treatment and management is directed at patient and family support.

Kuru

Kuru is localized to one tribe who live in the Papua New Guinea highlands and is related to cannibalism of dead relatives, especially from the brains and viscera. Women and children are most susceptible: they prepare the bodies for eating and the prion may enter via skin cuts and abrasions, via the conjunctiva or by ingestion. Affected individuals develop progressive cerebellar ataxia, dysarthria, dystonia and myoclonus (‘kuru’ means shivering or trembling). Dementia occurs late in the disease. There are no specific changes on EEG or CT scan. Since the apparent cessation of cannibalism the disease is rare.

Gerstmann–Sträussler–Schenker syndrome

GSS an extremely rare disease that may occur sporadically but is mainly transmitted as an autosomal dominant. It often presents in the early twenties and thirties with progressive cerebellar ataxia and loss of short-term memory. Dementia and bradykinesia are late features. Progression is much slower than CJD or kuru and life expectancy can be up to 10 years.

### SEXUALLY TRANSMITTED DISEASES

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1.229 Sexually transmitted diseases.
INFECTIONS

The WHO estimate that at least 333 million new cases of curable sexually transmitted disease (STD) occur annually worldwide. These new cases comprise *Trichomonas* (170 million), *Chlamydia* (89 million), gonorrhoea (62 million) and syphilis (12 million). These diseases are all preventable and curable, but they currently represent a major cause of morbidity in the developing and developed world (though the incidence of syphilis and gonorrhoea in the developed world has declined in recent years).

HIV infection (p. 11) is a major cause of incurable STD, and a number of other infectious diseases can be sexually transmitted (1.229). There is now good evidence that the presence of genital ulceration or inflammation resulting from curable STDs may greatly increase the risk of transmission of HIV infection.

Some STDs can also be transmitted by other routes. For example, HIV infection and hepatitis B and C can be transmitted by needle-sharing among drug misusers and in therapeutic blood products. Syphilis can be transmitted by unscreened blood transfusion; it is closely related to nonsexually transmitted endemic treponemal diseases (bejel, yaws and pinta – see p. 53–54).

In this section we cover most of those diseases that are predominantly or exclusively sexually transmitted (the STDs). HIV infection is covered on p. 11, genital herpes infection on page 26–27 and hepatitis B and C on p. 404.

The presentation, progression and treatment of all other STDs may be significantly altered in the presence of HIV infection.

GENITAL WARTS

Genital warts are sexually transmitted and are caused by DNA viruses, the human papillomaviruses (see also p. 96). They affect the genitalia and the perianal region and are found most commonly in men on the corona and frenum of the penis (1.230), and in women on the labial folds of the vulva (1.231), the lower third of the vagina and on the cervix. The time from sexual contact to the appearance of the lesion is about 2–3 months. The warts are usually multiple and they often grow together and spread to involve the whole perineum and anal region (condylomata acuminata – 8.10). The rate of spread is increased in patients who are immunocompromised.

Infection with human papillomavirus is probably a causative factor in cervical neoplasia. It is strongly associated with premalignant changes in the cervical epithelium, which may progress to invasive carcinoma of the cervix. Similar epithelial changes may occur on the penis, vulva and anus, though their significance is less clear.

Spontaneous healing of warts may take place and this can sometimes be accelerated with topical applications.

GONORRHoeA

Gonorrhea is caused by *Neisseria gonorrhoeae* (the 'gonococcus') and the disease is transmitted by sexual contact. Neonatal infection may also occur during passage of the infant through the birth canal.

The incubation period is less than 1 week. In men there is purulent urethral discharge (1.232) and dysuria, sometimes
with associated epididymitis and inflammation of regional lymph nodes. Proctitis occurs in homosexual men (1.233). Many women are asymptomatic, but there may be dysuria and vaginal discharge if there is cervicitis (1.234). Infection may spread to Bartholin’s glands, the uterus, the fallopian tubes and the pelvic peritoneum, where it is one cause of chronic pelvic inflammatory disease. Blood spread may occur causing fever, skin rash and painful arthritis (3.8). Lesions may be seen in the mouth and pharynx after oral sex. Infants infected during birth usually develop ophthalmia neonatorum (1.235).

The diagnosis is by microscopy (1.21) and culture of pus from the urethra, cervix, rectum, mouth or, in the case of neonates, the conjunctivae. Alternatively, nucleic acid probe, ELISA and polymerase chain reaction may be used.

Single-dose therapy with procaine penicillin or amoxycillin, each given with probenecid, is often effective, but penicillin-resistant strains are now common in some parts of the world (e.g. South-East Asia and Africa). Longer treatment may be required if there is spread of infection. If the organisms are resistant to penicillin, alternative drugs include spectinomycin, the cephalosporins and ciprofloxacin. Concomitant infection with Chlamydia trachomatis (p. 80-81) is common and may require additional treatment. Tracing and treatment of contacts is important to prevent spread of infection.

**CHANCROID**

Chancreoid is characterized by painful genital ulceration followed by tender inguinal lymphadenopathy. The organism responsible is Haemophilus ducreyi, a Gram-negative bacterium with a worldwide distribution (though infection in developed countries is now rare). It is most common in men, but this suggests significant underdiagnosis in women. The incubation period is usually 2-5 days. The first lesion is a tender, painful macule which becomes pustular and, on bursting, forms a painful ulcer which has a necrotic grey membrane. Lesions are usually found on the glans or shaft of the penis (1.236) or around the anus. In women, they may appear on the cervix, vagina, vulva or perianal region. They may also be found occasionally on other skin surfaces and in the mouth. Regional lymphadenopathy (buboes) is invariable and may occasionally suppurate and leave chronic fistulae.

The diagnosis can be made in most cases by culture of exudate or pus, or by polymerase chain reaction. Treatment is with co-trimoxazole or tetracycline. Sexual partners should be identified and screened if possible.
Granuloma inguinale is an infectious disease resulting from *Calymmatobacterium granulomatis*, a Gram-negative bacterium. It is usually transmitted sexually and is found predominantly in Africa, Papua New Guinea, India and the Caribbean but some cases have been reported in homosexual men in the USA and Europe. The clinical signs develop 1–10 weeks after exposure. An indurated papule usually forms on the penis, labia or anal margin but extragenital lesions are common on the face, lips and neck. These primary lesions may be tender and produce a foul-smelling discharge. Regional lymphadenopathy is usual (1.237) and suppuration and secondary infection are common. Extensive scarring may be found in the healing phase (1.238). Diagnosis is by finding the typical 'Donovan' bodies in Gram-stained exudate. Exclusion of the other venereal infections is essential.

**SYPHILIS**

Syphilis is an STD characterized by an initial illness followed by a long latent period before late manifestations of the disease appear. The causative organism is the spirochaete, *Treponema pallidum*. Congenital syphilis results from transplacental infection of the fetus.

Syphilis is still a common disease (12 million new cases per year), mainly in the developing world where many patients have advanced disease before they come to medical attention. This makes transmission to sexual partners and children more likely.

In the developed world, syphilis is relatively rare, but it is now seen more frequently in patients with HIV infection, in whom the disease progresses more rapidly.

Three stages of the disease are recognized.

- The primary stage occurs after an incubation period of about 3 weeks; a painless ulcerated lesion (chancre) develops at the site of inoculation. In men, the lesion is usually on the penis (1.239) or anus (in homosexuals). In women the lesion may be on the vulva (1.240), but if it is in the vagina or on the cervix it may be missed. Chancre are highly infective, but are self-limiting and heal in about 4–6 weeks.
- The secondary stage represents systemic spread of infection and follows about 2 months after the primary lesion. Features of this stage include fever, widespread macular rash (1.241), wart-like lesions (condylomata lata) in the genital area (1.242), snail-track ulcers on the buccal mucosa (1.243), generalized lymphadenopathy and occasionally aseptic meningitis. This stage is also self-limiting and is followed by a latent period of 2–20 years, before symptoms of the tertiary stage appear.
- Features of the tertiary stage include the development of chronic granulomatous lesions (gummata) in skin (1.244), mucosa and bone, vascular lesions (aortic aneurysm – 1.245) and lesions of the CNS (meningovascular syphilis (11.8), general paralysis of the insane, tabes dorsalis) which may also lead to destructive joint disease (1.246, 1.247). Neurosyphilis progresses rapidly and aggressively in patients who also have HIV infection. Adequate therapy in the early stages of syphilis should prevent the tertiary stage developing.

1.241 Secondary syphilis. This patient has a very typical papulo-squamous rash (syphilide). Note the facial lesions, the colour and the symmetrical distribution of the rash.

1.242 Secondary syphilis. Gross condylomata lata of the vulva and anus. Note the resemblance to warts (condylomata acuminata).

1.243 Secondary syphilis – classic ‘snail-track’ ulcer of the buccal mucosa. Other mucosal lesions at this stage may be round or oval in shape.

1.244 Tertiary syphilis – gummata of the skin. The lesions start as subcutaneous masses, which increase in size before breaking down to form typical gummatous ulcers. The ulcers are painless, and have sharply defined ‘punched out’ edges and an indurated base that is occupied at this stage by a slough of necrotic tissue. In contrast to the ulcerating lesions in primary and secondary syphilis, Treponema pallidum organisms cannot be found.

1.245 Tertiary syphilis – a large aortic aneurysm on chest X-ray. The aneurysm results from vasculitis affecting the vasa vasorum of the aorta.

1.246, 1.247 Tertiary syphilis – Charcot joints. In tabes dorsalis, impaired pain and position sensation, combined with muscular hypotonia, often lead to the destruction of joints and inappropriate new bone formation, as seen in these clinical and radiological examples. Charcot joints may also occur in patients with diabetes, leprosy and syringomyelia.
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- Congenital syphilis may result in abortion or stillbirth. Infants may be severely affected at birth or may appear normal and develop manifestations of disease in later childhood (1.248, 1.249).

  The diagnosis is confirmed by finding spirochaetes in the primary lesion or in exudates during the secondary stage. Serological tests include nonspecific antigen tests (e.g. VDRL) or specific antitreponemal tests (TPI, TPHA, FTA). CSF examination should be carried out if neurosyphilis is suspected.

  Parenteral penicillin is the drug of choice. Steroid cover should be used in the first few days of therapy to prevent a Jarisch–Herxheimer reaction (caused by toxins released by the dying spirochaetes). Alternative drugs for patients with penicillin allergy include erythromycin and tetracycline.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum is an STD caused by a strain of Chlamydia trachomatis (serovar L) that is found in many tropical countries. The primary lesion appears, within a few days of sexual contact, on the genitalia, in the anus or in the mouth as a small indurated papule, and heals rapidly without leaving a scar. Lymph node enlargement develops in 2–8 weeks and the nodes undergo suppuration and may discharge though the skin (1.250).

  There may be systemic upset with fever, arthralgia, splenomegaly, generalized lymphadenopathy and meningism. Healing may be associated with extensive scarring and local oedema resulting from lymphatic obstruction; strictures of the vagina, urethra or rectum may form.

  The diagnosis is made by finding the organism in the local lesions or by serology. Treatment is with tetracycline, and suppurating lymph nodes should be aspirated via normal skin to prevent fistulae forming.

OTHER CHLAMYDIA TRACHOMATIS INFECTIONS

Eight serovars of C. trachomatis (D–K) are spread by sexual contact and cause genital infections (serovars A–C cause trachoma – p. 56; serovar L causes lymphogranuloma venereum – see above).

  Infection with this organism in men accounts for about one-half the cases of non-gonococcal urethritis and about one-third of cases of acute epididymitis. In women, it accounts for about 60% of cases of pelvic inflammatory disease and 50% of cases of cervicitis.

  The usual symptoms in men are dysuria, urethral discharge and epididymitis (painful swollen scrotum). In women pelvic infection is accompanied by lower abdominal pain, fever and tenderness of the uterus on vaginal examination. About 30% of babies born to mothers with C. trachomatis in the vagina develop conjunctivitis and 20% develop chlamydial pneumonia. In addition, they may develop a reactive arthritis.

  The diagnosis is made by enzyme immunoassay of infected urethral, cervical samples or of ‘first-catch’ urine samples, or alternatively using nucleic acid probes or polymerase chain reaction techniques. Contact tracing is important.
NON-GONOCOCCAL URETHRITIS

*Chlamydia trachomatis* is one of the most common causes of sexually transmitted non-gonococcal urethritis. The incubation period is short (5–10 days) and is usually followed by a urethral (1.251) or vaginal discharge and severe dysuria. A variety of complications may occur including cervicitis, salpingitis and urethral strictures.

*Mycoplasma hominis, M. genitalium* and *Ureaplasma urealyticum* are other recognized causes of non-gonococcal urethritis.

Diagnosis is usually made by the finding of a leucocytic urethral exudate and excluding gonorrhoea, but *C. trachomatis* may be identified by other techniques (see above).

Treatment is with tetracycline for the patient and sexual partners.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is a general term for a range of infections of the female organs of reproduction. It is most commonly found in sexually active women in the 15–25 years age-group. The socioeconomic factors that predispose to pelvic inflammatory disease are early age of onset of sexual activity, multiple sexual partners, recent change of partner, previous STD, use of an IUCD, recent gynaecological procedure or recent pregnancy, and failure to use a condom. The results of long-term infection include recurrent pelvic pain, vaginal discharge, dysuria, infertility due to fibrosis, a high incidence of ectopic pregnancies and the risk of pelvic abscess (1.24).

Pelvic inflammatory disease is usually caused by ascending infection with the patients own vaginal organisms or with sexually transmitted organisms. *Chlamydia trachomatis* is the most common infection in the Western world, followed by *Neisseria gonorrhoea*, but *Bacteroides* sp., *Mycoplasma hominis* and *M. genitalium* may all cause pelvic inflammatory disease.

The diagnosis may require laparoscopy with direct viewing of the anatomical changes, followed by bacterial cultures and serology. Ultrasound is of value in excluding ectopic pregnancy or other major contributing pathology, such as fibroids of the uterus or ovarian cysts.

Treatment, for example with tetracycline and metronidazole, should be aimed at the likely infecting organisms.

Counselling and treatment should be offered to all partners. In addition, the possibility of concurrent HIV infection should always be remembered.

TRICHOMONIASIS

Trichomoniasis is an STD caused by the protozoan *Trichomonas vaginalis*. In women, it presents as an acute or recurring vaginitis characterized by an extremely irritant, foul-smelling vaginal discharge that is often frothy and yellow (1.252). The symptoms may subside, but the patient continues to carry the trichomonads and is infectious to her sexual partners. In men, the organism may cause recurrent urethritis and prostatitis. The diagnosis is made by the finding of numerous motile organisms in a wet mount of vaginal, prostatic or urethral secretions or a spun sample of urine, or by culture.

Treatment of all sexual partners with metronidazole is important.

ANAEROBIC BACTERIAL VAGINOSIS

Anaerobic bacterial vaginosis is accompanied by a profuse fishy-smelling vaginal discharge that is associated with vulvar itch and dysuria. There is usually a profuse white vaginal discharge and vulval or vaginal erythema, oedema or fissuring. The pH of the vaginal fluid is usually > 5. The ‘amine’ test can be performed on a drop of vaginal secretion on a slide by adding a drop of potassium hydroxide. If the test is positive there is a transient ammonia-like odour (positive sniff test). It is important to exclude the possibility of *Candida* infection (see p. 61).

Gram staining of the vaginal fluid shows epithelial cells, the surface of which is studded with bacteria (so-called ‘clue’ cells).

Culture usually grows anaerobes* Gardnerella vaginalis* and *Mycoplasma hominis*. Treatment involves local or systemic metronidazole or other antimicrobial agents, or both. The role of sexual transmission and whether there is a need to treat sexual partners is still unclear.
HISTORY AND EXAMINATION

A careful history and full examination of the dermatological patient is essential. First, establish the duration and evolution of a rash as this will provide the basis for further questions and investigations. For example, a lesion may have been present from birth, or have developed in the past few days or weeks. Rashes may precede or coincide with other events such as intercurrent illnesses, a course of drugs, contact with animals, chemicals or plants or perhaps travel abroad. There may have been a previous episode of a similar rash or someone else in the family may recently have had a similar problem.

The appearance and distribution of a rash are also commonly characteristic in many conditions. Often a rash will start with a typical lesion and then spread in a particular pattern, as for example the herald patch of pityriasis rosea. Lesions may be confined to one body site, such as the face in acne rosacea, or to light-exposed sites or to a group of sites such as scalp, eyelid and eyelashes, face and chest in seborrhoeic dermatitis. Psoriasis characteristically affects the extensor surfaces of limbs, whereas atopic dermatitis affects the flexor surfaces. Some rashes, such as erythema multiforme, tend to have peripheral lesions first, affecting hands and feet before moving centrally. Rashes may be symmetrical, more suggestive of an endogenous cause, or asymmetrical, when exogenous factors may be relevant. If a rash settles during a vacation, only to recur on return to work, a factor at the work site may be important.

An accurate description of the skin lesion is essential. The morphology of a lesion should be defined carefully as macular, papular, pustular or nodular. The presence of scale or crust, the colour of both recent and fading lesions, the presence of background sun damage in the form of wrinkles and skin thinning, abnormal pigmentation, changes in colour and distribution of hair all combine to make a characteristic picture that can often provide more information than subsequent investigations.

Finally the rash may be symptomatic: pain or pruritus are the most common symptoms. Painful lesions suggest active inflammation or infection; pruritus is very common and subjective, but can be useful in making a diagnosis. For example, the sudden onset of an itchy rash, worse at night, in a person with no previous skin problems is highly suggestive of scabies – but look for the characteristic lesions before making a diagnosis. Itch can be distressing, causing embarrassment and loss of sleep, and should be acknowledged sympathetically. Pain can precede the development of either herpes simplex or zoster lesions.

General health is also important. Many skin conditions are a reflection of underlying systemic conditions, so attention to a history of other illnesses, a brief systemic inquiry and recognition of other factors, such as arthritis, anaemia, weight gain or loss, thyroid enlargement, lymphadenopathy, all form part of the examination of the skin.

INVESTIGATIONS

SKIN BIOPSY

Skin biopsy is a useful and common investigation, as the histology of a lesion will establish, confirm or refute the clinical diagnosis in most cases. The biopsy should be well planned; early lesions are more informative as secondary infection or excoriation in mature lesions may mask underlying changes. A representative lesion should be selected, with attention to local anatomy, healing and potential scar formation. Although a punch biopsy is adequate for some conditions, an ellipse of skin, including normal and abnormal skin, is usually preferable (2.1).
The size and depth of biopsy depend on the nature of the lesion and the investigations required, but most biopsies should include dermis down to subcutaneous fat. Tissue should be sent for bacterial or viral culture, for routine histology (2.2) or for immunofluorescence staining (2.3, 2.75, 2.79, 3.11). Special stains, for example for fungal elements, should also be requested.

**SAMPLES FOR MICROBIOLOGICAL INVESTIGATIONS**

Swabs can be taken from lesions with exudate or pus; blister fluid can be aspirated for culture or microscopy for bacterial or viral infection. Interpreting results requires some knowledge of commensal organisms and potential pathogens (2.4).

Blood samples may be needed for culture, ASO titres, fluorescent treponema antibody-absorption (FTA-ABS) tests, paired samples for viral titres or serology for other infections such as viral hepatitis or HIV infection.

Fungal elements are found in keratin from nail clippings, hairs and skin scrapings. Examination under Wood’s lamp is occasionally helpful in identifying fungal infections (*Microsporon* species fluoresce blue-green, *Erythrasma* pink; 2.5, 2.6). The affected skin should be scraped firmly, using a scalpel blade held at 45 degrees to the skin surface. Scrapings are collected in a fold of black paper or on microscope slides; adequate quantities are required for both microscopy and culture. Direct microscopy of skin scrapings treated with potassium hydroxide may reveal fungal hyphae and spores (2.7), and culture allows identification of the dermatophyte species. Scabies infestation may be confirmed by looking for adult *Acaris* in skin scrapings (2.8).

**SKIN COMMENSALS AND COMMON PATHOGENS**

<table>
<thead>
<tr>
<th>COMMENSALS</th>
<th>PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corynebacterium</td>
<td><em>C. minutissimum</em> (erythrasma)</td>
</tr>
<tr>
<td><em>Diphtheroids</em></td>
<td><em>C. acnes</em> (acne vulgaris)</td>
</tr>
<tr>
<td>Micrococcae</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>e.g. <em>Proteus</em> 5–15%</td>
</tr>
<tr>
<td><em>Pityrosporum ovale</em></td>
<td>Yeast in sebaceous glands or scalp</td>
</tr>
<tr>
<td><em>Candida</em></td>
<td>Varying species, including <em>C. albicans</em></td>
</tr>
<tr>
<td><em>Demodex folliculorum</em></td>
<td>A mite on face or scalp</td>
</tr>
<tr>
<td><em>Corynebacterium</em></td>
<td></td>
</tr>
<tr>
<td><em>Micrococcae</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococci</em></td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td><em>Pseudomonas, Klebsiella, Escherichia coli</em></td>
</tr>
<tr>
<td><em>Yeasts</em></td>
<td><em>Candida albicans</em> (opportunist)</td>
</tr>
<tr>
<td><em>Fungi</em></td>
<td><em>Dermatophytes: Trichophyton, Epidermophyton and Microsporum</em></td>
</tr>
</tbody>
</table>
PATCH TESTING

Patch testing is designed to detect delayed hypersensitivity, or cell-mediated immune reactions, which may be the basis of an inflammatory rash. A careful history is very important for this investigation to be worthwhile. The patient may need to supply materials from suspect cosmetics, footwear or industrial processes. A visit to the work site of patients with suspected industrial dermatitis can be helpful. For this test, the suspect allergens are applied to the skin surface, using defined concentrations mixed in a paraffin ointment, under a special chamber (2.9, 2.10). After 72 hours a positive test shows erythema and...

2.5 & 2.6 Wood's light is a long-wave ultraviolet light (UVA), which is useful in evaluating a range of skin conditions. In this patient, a superficial fungal infection of the scalp fluoresces blue-green (2.5). The appearance of the scalp of the same patient in normal light is shown in 2.6. The patient has ringworm (see p. 100).

2.7 Fungal hyphae in skin scrapings can be clearly seen microscopically after treatment of the scrapings with KOH.

2.8 Scabies mite. The discovery of even a single mite or egg seen microscopically in skin scrapings confirms the diagnosis.

2.9 Preparation for patch testing. Common sensitizers are dissolved in water or soft paraffin ointment and applied in sequence to special aluminium chambers (Finn chambers).

2.10 Patch testing. The aluminium chambers are mounted on hypoallergenic tape and applied to the back.
SKIN

blistering at the contact site (2.11, 2.12). A vast range of potential allergens exists; choosing the correct ‘battery’ of test substances depends on the history, nature of the rash and knowledge of potential sensitizers (2.13). A standard battery of common sensitizers is available, together with extra lists, for example for patients with leg ulcers or chronic otitis externa, or for hairdressers; a range of common facial sensitizers, plant allergens or medicaments and bases of common topical therapies may be indicated. In recent years, contact dermatitis to topical steroids has been increasing and should be considered in patients who have used a wide range of preparations, usually over many months. Immediate contact patch tests for allergens suspected of causing urticarial reactions are occasionally helpful. The suspect allergen is applied directly to the skin and left on, unoccluded, for 30 minutes. An urticarial weal developing at the site of the allergen indicates a positive reaction. Photopatch testing involves the application of a suspected topical allergen together with ultraviolet irradiation. A range of wavelengths of ultraviolet may be used and non-irradiated control tests are included.

IgE AND RADIOALLERGOSORBENT TESTS

IgE is often but not always raised in atopic dermatitis, but does not reflect severity of rash or response to treatment. More often a raised level is due to associated asthma. Radioallergosorbent tests (RASTs) record levels of specific IgE, indicating potential sensitizers such as animal dander, house-dust mites and a range of other potential inhaled or ingested sensitizers.

OTHER DIAGNOSTIC SKIN TESTS

Skin-prick tests with allergen extracts result in immediate (type I) skin reactions; in atopic dermatitis frequent false positives occur and the test is more useful for hayfever or asthma sufferers (see p. 167).

Mantoux (p. 46) and Kveim (p. 198) tests require intradermal antigen injection, with tests read (and biopsied) at appropriate intervals.

OTHER INVESTIGATIONS

Haematological and biochemical tests are frequently used in primary skin disorders and the dermatological manifestations of systemic disease, and to monitor drug therapy with, for example, methotrexate, retinoids, dapsone or cyclosporin. Immunological investigations, including antinuclear antibody, immune complexes, complement levels and autoantibodies, may be required. Underlying medical or surgical problems should be investigated appropriately.

<table>
<thead>
<tr>
<th>COMMON CAUSES OF CONTACT DERMATITIS</th>
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</thead>
<tbody>
<tr>
<td><strong>Allergen</strong></td>
</tr>
<tr>
<td>Nickel</td>
</tr>
<tr>
<td>Formaldehyde</td>
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<tr>
<td>Ethylene diamine</td>
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<tr>
<td>Parabens</td>
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<tr>
<td>Wool alcohols</td>
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<tr>
<td>Chlorocresol</td>
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<tr>
<td>Chinofom</td>
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<tr>
<td>Neomycin</td>
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<tr>
<td>Paraphenylenediamine (PPD)</td>
</tr>
<tr>
<td>Thieram mix</td>
</tr>
<tr>
<td>Mercaptomix</td>
</tr>
<tr>
<td>Carba-mix</td>
</tr>
<tr>
<td>PPD-mix</td>
</tr>
</tbody>
</table>

2.13 Common causes of contact dermatitis.
Psoriasis is a common disorder affecting around 2% of the population. The onset may be at any age, with peaks around 20 and 60 years. Men and women are affected equally. A positive family history is found in 30% of patients; in those developing the disease at an earlier age there is an increased association with HLA CW6. The disease is characterized histologically by abnormal keratinocyte differentiation and hyperproliferation with inflammation, involving both lymphocytes and polymorphonuclear leucocytes and an associated vasodilatation of superficial dermal vessels. Investigations into the inherited basis of this disorder are complicated by genetic heterogeneity and to date no gene has been characterized. Environmental factors such as infection are also important.

Clinically, psoriasis is characterized by variability and unpredictability. The rash may be intermittent, undergo spontaneous remission or be lifelong. In general a chronic condition, it may flare acutely and, rarely, be life-threatening. Patients generally feel well but they can experience considerable emotional distress and social isolation. There is an association between the severity of psoriasis and alcohol intake.

The most common presentation is chronic plaque psoriasis, generally affecting extensor surfaces in a symmetrical pattern (2.14, 2.15, 3.54). Lesions are clearly demarcated erythematous plaques covered with coarse scales that may be removed by gentle scraping (2.16). Involvement of flexures, especially inframammary or groin areas (2.17), is also common. In these sites the rash is not usually scaly and is often confused with fungal or yeast infections. The scalp may be involved alone or with other lesions; psoriasis in the scalp may be both ‘felt’ and seen. The hairline (2.18) and behind the ears are common sites. A resistant plaque in the sacral area is also very common. Involvement of nails may be as coarse ‘pitting’ as on a thimble.
Guttate psoriasis is an abrupt onset of psoriasis with droplet-shaped erythematous scaly lesions scattered widely over trunk and limbs with no predilection for extensor surfaces (2.20). It may be triggered by a preceding streptococcal throat infection, and is more common in children and young adults. It usually clears completely but classic psoriasis may appear in later life.

Erythrodermic psoriasis (2.21) can be a life-threatening condition. The rash starts as common psoriasis but spreads to become confluent and often indistinguishable from other forms of erythroderma.

Arthropathy occurs in 10–15% of psoriatic patients. Classically, distal interphalangeal joints (3.55) and large joints such as ankles and knees are involved and the rheumatoid factor is negative. Rarely, the arthritis can be severe, producing an ‘arthritis mutilans’ of the hands and feet with resultant severe disability (3.56, 3.57).

Localized chronic pustular psoriasis may occur without other evidence of psoriasis (2.22, 3.58). Generalized pustular psoriasis is a rare presentation that may be fatal. It may be precipitated by topical or systemic steroid use, drug reactions or infections. Crops of sterile pustules occur, with fever and systemic upset.

The treatment of psoriasis depends upon its location and severity but may involve topical emollients, dithranol, tar or steroids. Ultraviolet B radiation alone, and ultraviolet A radiation combined with an oral psoralens (PUVA) are often effective for widespread disease, but systemic treatment with retinoids, methotrexate, cyclosporin A or other drugs may be necessary for stubborn disease.
DERMATITIS

Dermatitis and eczema are synonymous; in practice, the term eczema is usually restricted to dermatitis seen in atopic individuals. Dermatitis means inflammation in the skin. It may be acute with weeping, crusting and vesicle formation, subacute, or chronic with dryness, scaling and fissuring and lichenification (especially in atopic individuals; 2.23). The rash is almost always itchy and secondary infection is common. Dermatitis may be exogenous (contact, irritant, infective or photodermatitis) or endogenous (e.g. atopic, seborrhoeic, discoid). Most often the diagnosis can be established by the distribution pattern and morphology of the rash together with a detailed history.

Atopic dermatitis begins in childhood, between 2 and 6 months of age, affecting around 2% of the population, although the incidence does appear to be increasing. A family history of atopy is present in 70% of cases. Hayfever and solidus or asthma may develop as the child gets older. Over 90% of children are clear by the age of 12 years, but predicting this for an individual child is difficult. Few patients with the classic features are seen beyond the age of 30 years. In infants the face, neck and trunk are involved (2.24), with sparing of the napkin area. Flexural involvement appears later, behind knees, elbows, wrists and ankles (2.25) and lichenification may result from repeated scratching (2.23, 2.91). Hand dermatitis is common in later years. Secondary infection is common (2.26). Itch can be severe and causes much distress to patients and families. Food allergy, especially to eggs, fish and dairy products, may be relevant in some patients, but few benefit from exclusion diets.

2.23 Lichenified eczema results from repeated scratching of lesions in eczematous patients.

2.24 Infantile eczema in a dark-skinned child, affecting the face, neck and trunk. In a light-skinned child, the lesions are pinkish rather than bluish in colour.

2.25 Flexural atopic dermatitis. This girl shows the typical childhood distribution. As the lesions are itchy, they are usually scratched repeatedly and become excoriated. In the long term, lichenification results (see 2.23). Even non-flexural skin is dry and may be itchy.

2.26 Secondary infection in eczema. Patients with atopic dermatitis have defective cell-mediated immunity, and are more susceptible to bacterial, viral and fungal infections. This man has a herpes simplex infection (eczema herpeticum), which has prevented him from shaving (see p. 26).
A number of abnormalities may be detected in the skin in atopic dermatitis, but the underlying mechanisms are still unclear. Immunological abnormalities include a tendency to increased IgE levels, a predisposition to anaphylactic reactions, increased skin reactivity to skin-prick tests and a reduction in local cell-mediated immunity; the latter leads to an increased tendency to viral infections such as molluscum contagiosum, viral warts and herpes simplex, and a reduced resistance to viral infections such as molluscum contagiosum, viral warts and herpes simplex, and a reduced resistance to irritant substances.

Neurodermatitis or lichen simplex is a localized chronic dermatitis, perpetuated by the itch–scratch cycle. Common sites are the nape of neck or lower leg (2.27). The pruritus is often disproportionate to the rash and lichenification is common. The initial cause of the rash is often not established and the condition can be difficult to treat. There may be clinical overlap between this condition and chronic nodular prurigo, which is characterized by multiple small irritable patches widely scattered over the body (2.28).

Discoid dermatitis is characterized by discrete circular oval patches of dermatitis in a symmetrical pattern often on extensor surfaces, almost always in adults. Exogenous causation should be excluded but often no cause is found (2.29).

Pompholyx is a variant of eczema in which recurrent vesicles or bullae affect the palms (2.30) and fingers, or soles, or both. It is characterized by remissions and relapses, which are sometimes provoked by heat, emotional stress, or an active fungal infection of the feet. There have been reports that the ingestion of small amounts of nickel in susceptible patients may trigger an attack.

Contact dermatitis is an allergy (type IV, delayed hypersensitivity) to a substance present on the skin surface. The relevant factor may be immediately obvious—for example, nickel, perfume, shoe rubber or plants (2.31–2.33). A wide range of potential allergens exists in domestic and industrial life; a careful history and relevant patch tests should establish the causative allergens.
the diagnosis. The rash can be chronic, patchy and some distance from the allergen, for example nail varnish allergy may present with dermatitis on the face or neck.

**Stasis dermatitis** is associated with venous insufficiency. It is often complicated by oedema, infection, ulceration and contact dermatitis to topical medicaments or bandages (2.34). A secondary, widespread symmetrical dermatitis may develop.

**Seborrhoeic dermatitis** occurs in infancy as cradle cap, with scattered erythematous patches on the head and neck and an associated napkin rash (2.35). In adults, scaling in the scalp,

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### 2.31 Contact dermatitis to poison ivy

is a common problem in North America. This 15-year-old boy presented with linear eczematous lesions on his ankle.

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### 2.32 Contact dermatitis to nickel

affects 10% of European women. Nickel is a common component of jewellery such as rings, necklaces and earrings. Nickel in earrings gave rise to earlobe eczema in this young woman.

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### 2.33 Contact blepharitis.

Characterized by redness and swelling of the eyelid margins, this can result from contact dermatitis caused by eye make-up, as in this 22-year-old woman.

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### 2.34 Stasis eczema

is commonly seen in elderly women, in association with venous insufficiency or frank ulceration. Often, as here, there is also marked pigmentation as a result of haemosiderin deposition.

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### 2.35 Seborrhoeic dermatitis in infancy.

Napkin rash is associated with scattered erythematous patches on the abdomen, trunk and head and neck, but the extremities are spared.
blepharitis, red scaly patches in nasolabial folds (2.36), around the ears and on the presternal area are characteristic; intertrigo may occur. It occurs in 3–5% of young adults; extensive seborrhoeic dermatitis may occur in early HIV infection. The yeast *Pityrosporum ovale* is increased in the scaly epidermis in this condition and is now implicated in its pathogenesis, although the mechanism is not entirely clear.

In irritant dermatitis the rash is caused by physical or chemical irritation and damage of the skin; allergy is not usually implicated. Soaps, detergents, foods and DIY materials can all produce this pattern. Hand dermatitis is the most common form (2.37). Asteatotic dermatitis is common in elderly and hospitalized patients.

The principles of management in dermatitis are similar, whether the diagnosis is atopic eczema or contact dermatitis (2.38). Allergen or irritant avoidance is particularly important in contact dermatitis and if there is hand involvement.

Most eczema responds best to topical corticosteroids, but it is important to avoid the local (2.39, 2.91) and systemic side effects associated with excessive steroid use. In general, topical steroids should be used intensively for short periods, and chronic use should be avoided whenever possible. Occlusive

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**THE MANAGEMENT OF ECZEMA/DERMATITIS**

| Patient education | Allergen or irritant avoidance  
Foods or house-dust mite in selected patients with atopic eczema  
Allergens, irritants or photosensitizers in contact dermatitis |
|---|---|
| Topical treatments | Wet dressings  
Emollients  
*Bat oils*  
Ointments  
Creams  
Urea-containing compounds  
Corticosteroids  
Ointments or creams  
Weak, moderate, potent or very potent  
Tar, ichthammol or zinc |
| Other treatment | Antimicrobials for secondary infection  
Topical antiseptic  
Topical antibiotic  
Systemic antibiotic  
PUVA (psoralens and ultraviolet A)  
Oral antihistamines |

**2.36 Florid seborrhoeic dermatitis** in close-up, showing typical red, scaly lesions. This patient was HIV positive (see p. 12); however although this is a common problem in HIV-infected patients, most patients with seborrhoeic dermatitis do not have HIV infection.

**2.37 Irritant dermatitis** on the hands of a 39-year-old man. It resulted from exposure to irritant chemicals at work.

**2.39 Topical steroid-induced striae** on the thigh of a patient with atopic eczema. These were caused by overuse of potent steroid therapy. It is essential to avoid the inappropriate and/or excessive use of steroids in such treatment for all dermatological conditions. Additional complications of excessive corticosteroid therapy include other skin changes as seen in Cushing’s syndrome (7.27–7.29), delayed healing of wounds, masking of fungal and bacterial infections, and exacerbation of pustular acne.

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2.38 The management of eczema/dermatitis. The principles of management are similar, whatever the cause.
dressings may help to achieve the maximum short-term benefit from topical corticosteroid use.

In the long term, patients with dermatitis of any cause should avoid soap and use lubricants liberally. Other therapy as outlined in 2.38 is indicated in selected patients.

**URTICARIA**

Urticaria is common and usually patients present with acute, transient but recurrent, pruritic, erythematous swellings, resulting from localized oedema within the skin. Each weal usually lasts a few minutes to hours and clears leaving no residual marks. The number of lesions varies from one or two to a widespread rash (2.40). Patients may exhibit dermographism (which also occurs in 10% of the normal population; 2.41). The itch of urticaria can be severe. Rarely, urticaria is associated with angioedema of the face or lips and in a more life-threatening pattern with swelling of the tongue and respiratory tract (2.42, 2.43). Similar reactions can occur in other organs including the gastrointestinal tract or joints. The aetiology of urticaria is either obvious – as when associated with specific foods, for example strawberries or sea food – or more commonly unknown. Both immunological and non-immunological factors may be involved. Most patients require treatment with antihistamines and the rash generally settles quickly. In some cases it can become chronic, recurring for many months or years. Food diaries can be kept and exclusion diets may help in some cases. Patients should be warned to avoid aspirin and foods containing high amounts of azo dyes such as tartrazine, which can potentiate the urticaria (see p. 389). Urticarial lesions that persist for some days and leave bruising marks in the skin are suggestive of underlying vasculitis and need to be investigated more thoroughly.

2.40 **Urticaria in close-up**, showing characteristic weals, surrounded by an erythematous flare.

2.41 **Dermographism is a skin reaction pattern** in which the patient responds to anything more than a very light touch with a weal and flare reaction. This can be simply tested with firm finger pressure, as shown in this patient from a well-known London teaching hospital.

2.42 & 2.43 **Severe angioedema in a 9-year-old boy after a bee sting.** The patient required immediate treatment with adrenalin to overcome a generalized anaphylactic response, and showed gross facial swelling. 2.43 shows the same patient without angioedema.
**REACTIVE ERYTHEMAS**

Reactive erythema without urticaria may occur in response to many known or unknown stimuli and may take a number of different forms.

**Erythema nodosum** is primarily an inflammation of the subcutaneous fat (panniculitis), with involvement of the adjacent vasculature. It is an immunological reaction provoked by various infections, drugs, and a variety of other causes (2.44).

The characteristic lesions are tender, red nodules occurring on the lower legs and sometimes the forearms (2.45). Some patients also have painful joints and fever. The lesions resolve in 6–8 weeks, often leaving a bruise-like appearance. Management depends on the identification and elimination of the underlying cause.

**Erythema multiforme** is also immunologically mediated. It usually follows an infection or drug therapy, but other factors have occasionally been implicated, and no cause is apparent in up to 50% of cases (2.46). The eruption typically takes the form of annular plaques over the palms, soles, limbs and sometimes over the trunk (2.47). Characteristic ‘target’ lesions made up of two concentric plaques may blister in the centre (2.48). When

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**SOME CAUSES OF ERYTHEMA NODOSUM**

**Infections**
- Bacterial (e.g. streptococcal, tuberculosis, brucellosis, leprosy)
- Mycoplasma
- Rickettsia
- Chlamydia
- Viral
- Fungal (e.g. coccidioidomycosis, histoplasmosis)

**Drugs**
- e.g. sulphonamides, contraceptive pill

**Systemic disease**
- e.g. sarcoidosis, inflammatory bowel disease, Behçet’s disease

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2.44 Some causes of erythema nodosum.

**SOME CAUSES OF ERYTHEMA MULTIFORME**

**Viral infection**
- e.g. herpes simplex, hepatitis, orf

**Mycoplasma infection**

**Bacterial infections**

**Fungal infections** e.g. coccidioidomycosis

**Parasitic infections**

**Drugs**

**Pregnancy**

**Malignancy and its treatment with radiotherapy**

**Idiopathic (50%)**

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2.46 Some causes of erythema multiforme.
combined with mucous membrane involvement, erythema multiforme is called the Stevens-Johnson syndrome (2.49). Lesions in the tracheobronchial tree in such patients may lead to asphyxia, and conjunctival and corneal involvement may result in blindness. Genital ulcers may cause urinary retention and phimosis or vaginal stricture after they have healed. Severe Stevens-Johnson syndrome may progress to become indistinguishable from toxic epidermal necrolysis, a condition that may also be provoked directly by staphylococcal infection or drug therapy (1.101, 2.149).

Erythema chronicum migrans is another form of reactive erythema, which may be associated with Lyme disease (1.159) or rheumatic fever (5.88).

**INFECTIONS AND INFESTATIONS**

**BACTERIAL INFECTIONS**

Surface commensals include diphtheroids and micrococi — mainly *Staphylococcus epidermidis*. A minority of people carry *Staphylococcus aureus* in nares, perineum or axillae (2.4). Damaged epidermis predisposes to secondary infection.

Staphylococcal infections include impetigo (1.110), which is highly contagious (impetigo can also be caused by *Streptococcus pyogenes*). Furuncles (2.50) are boils that may occur singly or in crops; multiple or large lesions suggest underlying diabetes mellitus (1.99). Staphylococci may cause toxic epidermal necrolysis in children (1.101).

Erysipelas (1.106) is a streptococcal infection usually associated with systemic upset. Recurrent attacks may occur, leading to chronic lymphoedema. Necrotizing fasciitis, a rapidly progressive often fatal condition, may also be due to a group A beta-haemolytic streptococcal infection.

Syphilis should be remembered as a cause of skin rashes (see p. 78). The primary chancre is typically a painless ulcer. Secondary syphilis (1.241) must be distinguished from pityriasis rosea, measles, drug eruptions, guttate psoriasis and lichen planus. Tertiary syphilis (1.244) resembles granulomatous conditions such as sarcoid.

**2.48 Erythema multiforme.** A close-up view of a typical lesion on the palm. The centre of the target is beginning to blister.

**2.49 Stevens–Johnson syndrome.** In its severe form, is a widespread erythema multiforme with oral, genital and conjunctival involvement, and widespread skin lesions, as on this patient’s face. This form of the disease is most common in patients with *Mycoplasma pneumoniae* infection.

**2.50 A boil (furuncle) is caused by a staphylococcal infection of a hair follicle with the accumulation of pus. This results in severe pain, and is usually followed by the spontaneous discharge of yellow pus. A boil in this location carries the risk of septicemia and cavernous sinus thrombosis (see p. 502).**
Patients with tuberculosis (see p. 43) may present with lupus vulgaris, a chronic nodular scarring rash (2.51). Warty tuberculosis or scrofuloderma occur less commonly. Erythema nodosum (2.45) or induratum may be associated with tuberculosis.

Skin lesions in leprosy reflect the patient’s immune response (see p. 47)

**VIRAL INFECTIONS**

Viral warts are caused by the human papilloma virus (more than 50 subtypes exist). Warts are common; their morphology varies with anatomical site and viral subtype. Spontaneous resolution occurs (30% in 6 months) but painful or multiple lesions may need treatment (2.52, 2.53, 8.10, see p. 76).

Herpes simplex types I and II cause primary (sometimes asymptomatic) and recurrent infections on extragenital and genital sites. Recurrent lesions are preceded by tingling or pain, usually appear in the same place and are triggered by various factors such as infection or sun exposure. Grouped vesicles on an erythematous base persist for a few days (see p. 26). Secondary bacterial infection may occur. Infection may complicate atopic dermatitis (Kaposi’s varicelliform eruption).

Herpes zoster (shingles) is caused by the varicella-zoster virus, reactivated in a sensory nerve root (where it persists after chickenpox). Pain in the affected dermatome precedes the rash of scattered blisters and erythema (see p. 29). Haemorrhagic lesions and scattered lesions elsewhere on the body suggest underlying neoplasia or immunosuppression. Corneal ulcers and scarring may follow involvement of the ophthalmic branch of the trigeminal nerve. Postherpetic pain is common (see also p. 29).
Molluscum contagiosum is caused by a pox virus. The umbilicated pearly lesions (2.54), often multiple, are more common in childhood and resolve spontaneously after becoming inflamed. Residual marks may persist for some months.

Pityriasis rosea occurs in children and young adults (a viral aetiology is suspected but unproven). A herald patch (2.55) precedes subsequent lesions, which tend to be distributed along the rib lines (2.56). The lesions are usually asymptomatic but may be itchy. They persist for 4–6 weeks.

**FUNGAL AND YEAST INFECTIONS**

Dermatophyte fungi (genera *Trichophyton*, *Microsporum* and *Epidermophyton*) live on keratin and evoke a variable amount of inflammation. Clinical lesions are termed tinea or ringworm. Presentation depends on body site, but it is usually as plaques of scaling erythema, with variable itch (1.4, 2.5, 2.6, 2.7, 2.57, 2.58). Nail involvement causes onycholysis and dystrophy (2.59) and scalp infection patchy hair loss (2.60).
Candida infections caused by Candida albicans yeast commonly occur in moist, flexural sites (2.61). Predisposing factors include diabetes mellitus, pregnancy, broad-spectrum antibiotics and obesity (see also p. 61). Chronic candida paronychia may be complicated by additional bacterial infection; wet work or poor circulation are predisposing factors. Chronic mucocutaneous candidiasis is associated with widespread candida infection of the skin, mucous membranes and nails (2.62).

Pityriasis versicolor is caused by yeasts (Pityrosporum orbiculare) producing widespread scaly lesions on the upper trunk and back (2.63), pale in dark skins and darker in fair skins. Recurrent attacks are common.

**INFESTATIONS**

Infestations result from invasion of the body by arthropods, including insects, mites and ticks. Only a few are discussed here.

Insect bites are reactions to injected antigens, causing weals, persisting papules and sometimes blisters (2.64). Lesions may occur in recurrent crops (papular urticaria), and are often secondarily infected.

Scabies is caused by the mite Sarcoptes scabei var. hominis (2.8). Transmission occurs through close body contact. The adult mite lays eggs in burrows in the skin (2.65). Sensitization...
to the mites results in a widespread secondary eczema (2.66) and severe pruritus, worse at night. Household contacts must be treated to prevent recurrences.

Lice infestations are caused by *Pediculus humanus* (var. *capitis* and *corporis*) and *Phthirus pubis*. The lice suck blood, causing pruritus, scratching and secondary infection. Their eggs, known as nits, are attached to hairs (or clothing with body lice, (2.67). Head lice occur irrespective of cleanliness, whereas body lice are found on the vagrant or unhygienic. Pubic lice are commonly sexually transmitted.

### Lichen planus

Lichen planus accounts for only 1–2% of new referrals to the dermatology clinic. It affects both sexes equally and usually occurs in those aged 30–60 years.

The classic presentation is easy to diagnose with 'purple, pruritic, polygonal papules'. These commonly occur on the wrists, low back, ankles (where they may be chronic and hypertrophic) and feet (2.68) but lesions may be widespread. If severe, lesions may blister. The Koebner phenomenon may be seen (2.69).
Mucosal lesions are common and may present before or without those on other affected sites. Mouth lesions are diagnostic, with lacy white striae on the buccal mucosa (2.70). Ulceration may occur. Genital lesions especially affect the vulva or the glans and shaft of the penis.

Hair loss may occur, sometimes with irreversible scarring alopecia (2.71). Nail changes include irregular coarse pits or linear streaks, or adhesions between the skin and the nail plate, causing pterygium formation.

The histology is characteristic and should confirm the diagnosis if required.

Most cases settle within 1–2 years, but the rash may recur or become chronic. Post-inflammatory hyperpigmentation may persist. Topical or systemic steroid treatment may be required in severe cases.

The aetiology is unknown. There are interesting similarities between lichen planus and the skin lesions of chronic graft-versus-host disease, which suggest an autoimmune aetiology. An association with primary biliary cirrhosis and other autoimmune diseases has also been reported.

Lichenoid reactions, mimicking lichen planus, may result from therapy with drugs such as gold, chloroquine, methyldopa and thiazide diuretics, or after contact with colour photograph developer.

Bullous Disorders

Blisters develop when fluid collects between layers of the epidermis, or between the epidermis and dermis, as a result of inflammation (external or internal) or shearing forces. They are a feature of many conditions, for example dermatitis (p. 89), herpes simplex (p. 26) and insect bites (p. 98). The bullous disorders are distinguished by characteristic immunofluorescent staining either within the epidermis or at the dermoepidermal junction, in conjunction with the appropriate clinical features.

Dermatitis herpetiformis is an uncommon disorder in which groups of intensely itchy blisters appear on elbows (2.72), shoulders, buttocks (2.73) and knees. There may be an associated gluten enteropathy (see p. 372). Skin biopsy characteristically shows subepidermal microabscesses or blisters (2.2) and immunofluorescence shows granular IgA deposits in dermal papillae (2.3). Patients with this disorder have a high association with HLA B8 (85–90%) and DRw3. Although the disease is well controlled with dapsone and a gluten-free diet, treatment may be long term as the condition persists for many years, and there is some evidence to suggest a risk of small bowel lymphoma, as in coeliac disease.

Bullous pemphigoid is a condition predominantly affecting elderly patients in which large tense itchy blisters appear on any
body site (2.74). The blisters may be preceded by pruritus alone or with an urticarial type rash. Skin biopsy shows subepidermal blisters and immunofluorescence shows linear IgG (occasionally IgA) and C3 at the dermoepidermal junction (2.75). The pemphigoid antigen is located within the hemidesmosomes but there is no evidence to date that the antibody is directly pathogenic; it may have a role in activating complement pathways that then cause local inflammation. Circulating anti-basement membrane antibodies are present in up to 75% of patients, but the titre does not reflect disease activity. Oral lesions are uncommon. The disease runs a chronic, often self-rermitting course over months to years. Treatment with prednisolone and azathioprine can be helpful.

Pemphigus gestationis (formerly known as herpes gestationis) is a rare dermatosis of pregnancy resembling pemphigoid clinically and histologically (2.76). It remits post partum, but tends to recur with subsequent pregnancies.

Pemphigus vulgaris is a severe, chronic disorder affecting middle-aged to elderly patients. Many patients present with oral lesions before developing the skin lesions, which are pre-

2.74 Pemphigoid. Some of the blisters have become haemorrhagic, as often occurs.

2.73 Dermatitis herpetiformis in the sacral and buttock areas. The vesicles have been ruptured by scratching, and are healing, leaving pigmented scars.

2.75 Direct immunofluorescence in pemphigoid reveals IgG deposition in the basement membrane (arrow) in perilesional skin biopsies. Granular deposition of C3 is often observed.

2.76 Pemphigus gestationis. This rare disorder presents with vesicles and bullae during pregnancy or the puerperium. It resembles bullous pemphigoid, but can sometimes be distinguished from it by immunofluorescence techniques. The condition tends to recur in subsequent pregnancies.
dominantly erosions as the blisters are flaccid and easily ruptured (2.77, 2.78). Lesions occur predominantly on the trunk, face or pressure points, but all body sites can be affected. Skin biopsy shows intraepidermal blisters and immunofluorescence shows diffuse staining between epidermal cells, with IgG and C3 (2.79). Circulating autoantibodies are generally present and the titre reflects disease activity. Evidence is accumulating that this antibody, directed towards one of the desmosomal proteins, desmoglein, is pathogenic in the condition. The course of this disease is prolonged, often with serious complications despite therapy. The condition can be caused by drugs, such as penicillamine, captopril and rifampicin.

Blisters are a common feature of porphyrias (see pp. 349). Inherited blistering diseases are an uncommon group of disorders occurring in infancy or childhood. Recent advances in molecular biological techniques have enabled the cause of many of these conditions to be determined. Epidermolysis bullosa simplex is a group of disorders characterized by splitting of the basal cells of the epidermis, above the dermoepidermal junction. Many of these disorders have been shown to be caused by point mutations in the cytoskeletal proteins, the keratins, in particular keratins K5 and K14, which provide resilience to the basal epidermal cells. This condition is inherited as an autosomal dominant disorder, although many cases are sporadic. In the more severe, and less common, inherited blistering diseases known as dystrophic epidermolysis bullosa, the blister forms at or below the dermoepidermal junction (2.80). These disorders are due to point mutations in either laminin V, a protein integral to the basement membrane, or collagen VII, which connects the basement membrane to the underlying dermal structures. These variants of epidermolysis bullosa may be either dominantly or recessively inherited.
Acne vulgaris is a very common chronic inflammatory disorder of the pilosebaceous unit. It occurs in adolescence, usually earlier in girls, and may persist for some years (infantile acne may also occur rarely). It results from a combination of factors: there is increased sebum production (this alone does not cause acne), together with infection and inflammation due to Propionibacterium acnes within the sebaceous glands, where breakdown of fatty acids triggers inflammation. Increased end-organ sensitivity within the sebaceous gland to normal levels of androgen hormones may account for hormonal influences; acne may be associated with hirsutes and obesity in the polycystic ovary syndrome (see p. 322). Duct abnormalities and obstruction at the epidermal opening of the pilosebaceous unit also have a role. The face (2.81), back (2.82) and chest are affected with a range of lesions from small papules and pustules to comedones and deeper, painful cysts, on a background of seborrhoea. Subsequent scars may be depressed (2.83) or hypertrophic, but adequate treatment should prevent scar formation.

Less commonly, drug-induced acne may follow treatment with corticosteroids, androgenic hormones, oral contraceptives, anticonvulsant drugs, bromides or iodides.

Acne rosacea occurs in an older age group than acne vulgaris and has a vascular component to it. Flushing, often precipitated by hot foods, warm environment or sunlight, occurs in association with small papules and pustules over the forehead,
cheeks and chin in a symmetrical pattern (2.84, 9.45). Seborrhoea is not necessarily present. Despite the obvious improvement with antibiotic therapy (topical or systemic) no infective cause has been demonstrated; skin microflora are often normal and an association with the mite *Demodex folliculorum* (a skin commensal) has not been substantiated. Rosacea lymphoedema may develop and become persistent and rhinophyma (2.85) may develop. Inflammatory ocular conditions, — most commonly conjunctivitis but also rosacea keratitis, a more serious complication — may occur in up to 50% of patients and may precede the skin manifestations. The rash is exacerbated by topical steroids and sometimes aggravated by sunlight. Rosacea must be distinguished from seborrhoeic dermatitis, perioral dermatitis and the facial rash of systemic lupus erythematosus.

### DISORDERS OF PIGMENTATION

Most disorders of pigmentation result from excess or insufficient melanin, the dominant pigment in the skin. Other pigments include haemosiderin, bilirubin and carotene.

**Congenital disorders of pigmentation** include freckles, simple lentigines and café-au-lait patches in neurofibromatosis (2.86). Less common conditions include oculocutaneous albinism (defective melanin production that affects hair, eyes and skin, sparing pigmented naevi, 2.87), incontinentia pigmenti (initial blisters leave whorled pigmentary lesions in adult life) and lentigines round the mouth in Peutz–Jeghers syndrome (2.88). Xeroderma pigmentosum patients show excessive freckling in light-exposed areas (see p. 117).

#### 2.84 Acne rosacea. This patient shows typical papules and pustules, superimposed on a generally erythematous facial skin. His eyes are normal, but keratitis may occur.

#### 2.85 Rhinophyma usually occurs as a long-term complication of acne rosacea. The nose is characteristically red and bulbous. The ‘strawberry’ appearance results from hyperplasia of the sebaceous glands and connective tissue. The follicle openings become prominent.

#### 2.86 Neurofibromatosis (von Recklinghausen’s disease, type I, see p. 514). Note the subcutaneous nodular tumours arising in the sheaths of peripheral nerves, the pigmented pedunculated tumours on the skin surface and the brown (café-au-lait) patches.

#### 2.87 Albinism. This child has typical white skin and hair. His eyes were also affected; he had pink irises and photophobia.
pigmentosa occurs in childhood as scattered brownish-pink macules that urticate on rubbing.

Vitiligo (2.89) develops in 1% of the population. The white patches show total loss of melanocytes. A personal or family history of other autoimmune disorders may be present.

Hyperpigmentation may be a sign of underlying endocrine disease, such as Addison's disease, acromegaly, Cushing's syndrome or hyperthyroidism. Patchy facial pigmentation (chloasma or melasma) is common in pregnancy or with oral contraceptives. Tumours may cause diffuse pigmentation through ectopic adrenocorticotrophic hormone (ACTH) production or localized pigment changes such as acanthosis nigricans (2.90).

Hyperpigmentation is seen in cirrhosis, renal failure, haemachromatosis (slate grey colour; 9.52) and porphyria (7.157).

Connective tissue disorders such as systemic lupus erythematosus, dermatomyositis or morphea may cause local or diffuse pigment changes.

Drugs causing pigmentation include antimalarials, phenothiazines, hydantoin, minocycline, busulphan, cyclophosphamide, bleomycin and arsenic. Psoralens, used for phototherapy, produce a deep tan.

Exogenous causes of pigmentation include carotene (carotenaemia) and compounds containing silver (argyria). Tattoos are a common form of exogenous pigmentation.

Post-inflammatory hypopigmentation or hyperpigmentation may result from inflammatory conditions such as lichen planus, dermatitis (2.91), or discoid lupus erythematosus, especially in darker-skinned subjects.
SKIN

DISORDERS OF KERATINIZATION

Keratinization disorders result from abnormalities of epidermal maturation, with scaling and thickening of the skin, with or without inflammation. Gene defects have now been identified in several of these conditions, and study of these disorders has helped to clarify the mechanisms of differentiation in the normal epidermis and in other disorders of keratinization.

Ichthyosis vulgaris is a common (1:300) autosomal dominant condition of scaly skin that appears in early childhood (2.92). The scales are small and spare the flexural areas, and the condition improves with age. There is an association with keratosis pilaris. X-linked ichthyosis occurs in early infancy, with larger, darker scales and flexural involvement and persists into adult life. The gene defect is located on the X chromosome and affected individuals have a defect in the enzyme steroid sulfatase. This and lamellar ichthyosis, a rare condition (in some families a gene defect in the enzyme transglutaminase has been identified), may present as a 'colloidion baby' at birth. Bullous ichthyosiform erythroderma and the milder variant ichthyosis bullosa of Siemens are two rare forms of ichthyosis that occur with blistering in early life. These conditions are now known to be due to mutations in the genes for keratins K1, K10, and K2e, proteins present in the upper layers of the epidermis.

Keratoderma of palms and soles may be inherited or acquired. Various patterns such as punctate, striate or diffuse thickening occur. Rarely, diffuse keratoderma (tylosis) has been associated with underlying neoplasia (2.93). Some form of keratoderma are due to mutations in keratin genes K6 and K16. Darier's disease (keratosis follicularis) is a rare autosomal dominant condition that appears in the mid-teens as small reddish-brown papules on chest, back, scalp or flexures (2.95). Histology is diagnostic. Nail abnormalities include linear streaks and notching, and punctate lesions may be seen on hands or feet. The gene defect has been located but the candidate protein has yet to be identified.
HAIR DISORDERS

HAIR LOSS (ALOPECIA)

Hair loss can be diffuse or focal and may not be associated with any underlying inflammation or scarring. Androgenic alopecia is common in men (in whom the incidence approaches 100% in Caucasians) but also occurs in women. The pattern of hair loss includes frontal recession and thinning over the vertex, with more diffuse loss commoner in women. The extent and rate of hair loss are related to undefined genetic and hormonal factors.

Alopecia areata is a common cause of focal hair loss, characterized by many short exclamation mark hairs at the edges of the lesion. The underlying pathogenesis is a chronic inflammatory process triggered by a variety of environmental factors (e.g. infection) and probably represents a type of organ-specific autoimmune disease. Regrowth usually occurs within weeks or months, but further episodes may occur. Alopecia totalis and loss of all body hair (alopecia universalis) can occur, and associated fine pitting of the nails may be seen. A family history of alopecia areata occurs in up to 20% of cases and a family or personal history of atopy or other autoimmune disorders may also be present.

Fungal infection of the scalp causes patchy hair loss. If significantly inflammed, the lesion is called a kerion. Regrowth is usually good but permanent scarring may result from extensive inflammation.

Traction alopecia results from repeated tension on the hairs, as in some Afro-Caribbean and Asian hair styles.

Trichotillomania is patchy hair loss due to rubbing or pulling, commonly in childhood; hairs are broken off close to the surface.

Scarring alopecia may result from inflammatory dermatoses, such as lichen planus, discoid lupus erythematosus or scleroderma, and from trauma, burns or irradiation.

Diffuse hair loss after pregnancy, severe febrile illnesses or operations is termed telogen effluvium (loss in telogen growth phase). Cytotoxic drugs such as cyclophosphamide cause anagen effluvium. Iron-deficiency anaemia, hypothyroidism or hyperthyroidism, systemic lupus erythematosus and drugs such as heparin, vitamin A derivatives (retinoids) and oral contraceptives may cause hair loss.
EXCESSIVE HAIR

Hirsutes is an excess of terminal hair growth in a male pattern distribution in women (2.99, 7.58, 7.59). Mild facial hirsutes is common, increasing after the menopause. In younger women, especially when associated with menstrual irregularity or with other signs of virilization, investigations to exclude conditions such as polycystic ovaries, ovarian tumours, virilizing adrenal tumours or Cushing’s syndrome and congenital adrenal hyperplasia (heterozygote form) should be considered.

Hypertrichosis, a localized or overall increase in hair, may be drug induced, as with minoxidil, corticosteroids, diazoxide (2.100) or phenytoin, or associated with gross malnutrition, anorexia nervosa or some variants of porphyria. Localized hypertrichosis occurs with some pigmented naevi and in the lumbo-sacral region in association with diastematomyelia (11.115).

NAIL DISORDERS

Inherited abnormalities of nails are present in some genodermatoses, such as nail—patella syndrome, pachyonychia congenita (caused by a mutation in keratin K6, K16 or K17 genes) and ectodermal dysplasias. In these conditions often all finger nails and toe nails are affected (20-nail dystrophy). Scarring of nails occurs in some forms of epidermolysis bullosa dystrophica (2.80). Subungual exostoses cause overlying nail dystrophy.

2.99 Hirsutism was the presenting symptom in this woman who was found to have an arrhenoblastoma.

2.100 Gross hypertrichosis in a 32-year-old woman who was being treated with minoxidil for severe renal hypertension. Topical minoxidil is now used as a treatment for baldness in some countries.

2.101 Yellow nail syndrome is a disorder in which there is progressive yellowing and thickening of the nails with absence of the lunula and a degree of onycholysis. There is often an association with chronic lung disease and peripheral lymphoedema.

2.102 Leuconychia (opaque white nails) are a marker of chronic liver disease and of other conditions in which the serum albumin is low, such as nephrotic syndrome. In this patient, marked ridging of the nails is also present.
Acute or chronic trauma may cause subungual splinter haemorrhages (3.33) or haematomas, gross thickening of the nail (onychogryphosis) or onycholysis of individual nails. Habitual nail dystrophy of thumb nails and bitten nails, with damaged cuticles are common.

Yellow nails (2.101) are seen with chronic lymphoedema and in some chronic lung diseases. Other colour changes include leuconychia in liver disease (2.102), half-and-half nails in renal disease, and changes with some drugs such as antimalarials or tetracyclines.

Koilonychia is seen in iron-deficiency anaemia (2.103, 10.6, 10.21). Clubbing of nails (2.59, 2.104, 2.105, 4.2, 4.101, 4.148, 5.5, 11.121) is associated with cyanotic heart disease, carcinoma of the bronchus, some chronic lung diseases and some chronic gastrointestinal diseases; alternatively it may be congenital.

Beau's lines are horizontal grooves that appear on all nails after severe illness. Splinter haemorrhages may be seen in vasculitis in association with connective tissue diseases (3.33) or in bacterial endocarditis. Onycholysis (2.19, 2.59, 2.62) may be drug induced, due to fungal infection, psoriasis or associated with hyperthyroidism. Median nail dystrophy occurs without skin changes and the cause is unknown. Peripheral vascular disease predisposes to chronic paronychia (2.59, 2.62).

Changes occur in dermatological conditions such as psoriasis (2.19), dermatitis, lichen planus, fungal (2.59) and yeast (2.62) infections and alopecia areata. Tumours may develop under or around the nail base, including malignant melanoma (2.106), glomus tumours and myxoid cysts.
SKIN TUMOURS

Skin tumours are common and may originate from the epidermis, melanocytes or any of the dermal components. Early detection of malignant tumours is vital.

COMMON BENIGN TUMOURS

Seborrhoeic keratoses or basal cell papillomas occur in the middle years, mainly on the trunk and face, with a roughened warty, greasy surface and a superficial, stuck-on appearance (2.107). Lesions may be multiple, sometimes heavily pigmented, and they can be traumatized. They are commonly misdiagnosed as malignant melamons. Skin tags are simple papillomas that occur round the neck and in body folds (2.108).

Milia are common on the face or at the site of healed blisters (2.109). They are superficial cysts of sweat ducts. Keratoacanthoma (2.110) is a rapidly growing ulcerating tumour, more common in middle-aged or elderly subjects. It should resolve spontaneously, within 9 months. Clinical distinction from a squamous cell carcinoma can be impossible. If the history is uncertain, biopsy is essential. Cavernous haemangioma (2.111) appear at or soon after birth. Single or multiple lesions, of varying size, occur at any site. Ulceration and trauma with haemorrhage can occur but lesions are best left to regress spontaneously unless causing obstruction to vision. Capillary haemangioma (port-wine stains) are present at birth and do not fade with age. Cosmetic camouflage or laser treatment may be needed. Unilateral facial haemangioma may be associated with cerebral haemangioma in the Sturge–Weber syndrome (11.129).
Pyogenic granulomas grow rapidly, tend to occur at sites of trauma, may be single or multiple and can recur.

Dermatofibromas (2.112) are more common in women, often pigmented, may be multiple and generally occur on limbs.

Keloïds are persisting areas of exuberant scar tissue. Certain body sites, individuals and races are predisposed to this reaction.

Neurofibromata may be solitary or multiple and associated with café-au-lait patches in type I neurofibromatosis (2.86 and see p.514). Adenoma sebaceum is associated with tuberous sclerosis (11.132).

MELANOCYTIC TUMOURS

Congenital melanocytic naevi (moles) appear during the first few years of life. Most people have 20–30; some have many more. The common mole should be uniformly pigmented, with a regular margin (2.113–2.115). A halo of pale skin around a mole may be seen in adolescence. Occasionally congenital moles are large (greater than 1 cm; 2.116), multiple or confluent (bathing trunk pattern). These lesions carry a risk of malignant transformation. Moles deeper in the dermis appear blue in colour (2.117). Moles tend to regress in old age.

If moles change in size, become irregular in shape or pigmentation, itch or bleed they should be regarded as unstable and potentially malignant. Sunburn can irritate and activate moles. During pregnancy, moles tend to increase in size and darken.

Malignant melanomas (2.106, 2.118, 2.119) arise de novo or from pre-existing moles. The incidence of this tumour is increasing, especially in fair-skinned people with high sun-exposure. The prognosis is much better if tumours are detected early. Melanoma may develop after some years in a lentigo
lesion (2.120). Amelanotic melanomas may be missed, especially in periungual sites. Malignant melanomas may occur in the eye (2.121).

**NONEPITHELIAL MALIGNANT TUMOURS**

Secondary tumour deposits may occur in the skin. Common tumours that metastasize to the skin include breast (in addition to Paget’s disease of the nipple), stomach, bronchus (2.122, 4.178) and kidney. Hodgkin’s disease and B-cell lymphomas may have skin lesions (10.92).

*Mycosis fungoides* is a cutaneous T-cell lymphoma. It commonly manifests itself as a patchy superficial dermatitis (2.123) that evolves slowly into plaques and tumours.

*Kaposi’s sarcoma* is another important skin tumour. Formerly rare outside Africa, it has now become a common complication of HIV infection, especially in homosexual men (see p. 16).

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2.120 **Malignant lentigo.** Lentigo is a flat, dark brown lesion on the cheek of an elderly person. It should be regarded as a melanoma-*in situ*, and may become frankly malignant, as here.

2.121 A large choroidal malignant melanoma, revealed by ophthalmoscopy. Malignant melanomas may also occur in the iris and conjunctiva. This tumour was treated by enucleation of the eye.

2.122 **Skin secondaries,** in this case in the scalp from a primary carcinoma of the bronchus. Such lesions are relatively uncommon.

2.123 **Mycosis fungoides.** The individual lesions grow slowly over a period of years. They are red, thickened plaques, often with fine scales, which are itchy and may later ulcerate.

2.124 **Solar keratoses**— small, firm and scaly plaques—are commonly found on the extensor aspects of the hands and other exposed areas of skin in elderly people.

2.125 **Solar keratosis.** These lesions occur after long exposure to sunlight and are potentially malignant, with a latent period of at least 10 years.
SKIN TUMOURS

PREMALIGNANT AND MALIGNANT
EPITHELIAL TUMOURS

Solar keratoses (2.124, 2.125) occur on sun-exposed sites as patches of erythema and scale that gradually thicken. The adjacent skin shows signs of sun damage with wrinkling and loss of elasticity. Common sites are the face, ears and backs of hands. Malignant change occurs in a minority of lesions. Keratoses on the ears must be distinguished from chondrodermatitis nodularis helicis chronic, which is characteristically painful on pressure and almost always unilateral.

Bowen’s disease (2.126) appears as persistent erythematous slightly scaly patches, which gradually enlarge. The surface is usually flattened and occasionally ulcerates. Patches may be multiple and occur anywhere on the body, especially on lower legs.

Leucoplakia (2.127) occurs as persistent white patches on mucous membranes, in the mouth or vulva, and may be an indication of underlying dysplasia.

Basal cell carcinomas are slow growing, locally invasive malignant tumours (2.128, 2.129). A pearly margin, telangiectatic vessels and central recurrent ulceration are typical, but variations such as multifocal, pigmented and morphoeic lesions may occur. Basal cell carcinomas are especially common on the head and neck, but can occur on anywhere on the body.

Squamous cell carcinomas tend to occur on sun-exposed sites (2.130), but also in areas of chronic scarring or inflammation. Metastases occur more frequently from lesions at mucous membrane junctions such as on the lip.

2.126 Bowen’s disease – a persistent brownish patch that slowly enlarges and may become malignant. A carcinoma may develop under the crust or as a nodule, as here.

2.127 Leucoplakia may take several forms, all involving white patches on mucous membranes. In speckled leucoplakia, white areas alternate with areas of atrophic red epithelium. The risk of malignant transformation is high.

2.128 Multiple basal cell carcinomas. The lesion on the bridge of the nose is typical of the common presentation as a slowly enlarging nodule. The other lesions demonstrate various stages of progression to ulcerated lesions (rodent ulcers).

2.129 Basal cell carcinoma ulcerates at a later stage, usually with a shallow ulcer, with a very narrow indurated edge and a smooth shallow base.

2.130 Squamous cell carcinoma begins as a small nodule, but slowly grows to produce the typical lesion seen here. The ulcer has thick edges and an irregular granular base; and it usually produces a serous discharge.
VASCULITIS AND CONNECTIVE TISSUE DISORDERS

Vasculitis implies the presence of inflammation within blood vessel walls, with resultant vessel damage, haemorrhage or infarction. The clinical expression of this process depends on the size of vessel involved, from capillaries to small muscular or larger arteries. Circulating factors may initiate the inflammation (immune complexes, cryoglobulins); the vessel damage ranges from endothelial cell swelling to fibrinoid necrosis of the vessel wall or a granulomatous response (as in Wegener’s granuloma). The inflammatory infiltrate may involve polymorphonuclear leucocytes or lymphocytes. Skin lesions of vasculitis tend to be purpuric and palpable, may ulcerate and are painful (2.131, 2.132).

Conditions in which vasculitis is the predominant feature include Henoch–Schönlein purpura (2.133; small vessel vasculitis, with purpura, arthritis and glomerulonephritis – see also pp. 290, 460) and polyarteritis nodosa (see pp. 144, 292). Vasculitis may be a feature of other connective tissue disorders, such as systemic lupus erythematosus, drug reactions, malignant disease or infections.

2.131 Leucocytoclastic vasculitis. This 57-year-old woman with rheumatoid arthritis developed widespread, painful, palpable purpura on both legs. Initially, the lesions were scattered and discrete, but in this picture some have coalesced and become necrotic in the centre. Leucocytoclastic vasculitis is also known as allergic or hypersensitivity vasculitis or anaphylactoid purpura and it has many possible causes. The lesions result from the deposition of immune complexes in the postcapillary venules.

2.132 Livedo vasculitis in a 23-year-old Asian woman with systemic lupus erythematosus. The characteristic livedo or reticular appearance reflects the occurrence of small vessel vasculitis at a deeper level of the skin than in leucocytoclastic vasculitis.

2.133 Henoch–Schönlein purpura, associated with swelling of the left knee and renal involvement in a child aged 4 years. The rash was also present on the back of the legs and the buttocks.

2.134 Discoid lupus erythematosus. Slowly enlarging recalcitrant pink scaly plaques are seen on the face, ears and scalp. The lesions are aggravated by sunlight, and they clear centrally with atrophy and scarring.

2.135 Pyoderma gangrenosum. This West Indian man developed a pustule over the lower leg that progressed to a tender, superficial necrotic ulcer. Note the typical purple undermined edge. The lesion persisted for months and partially responded to topical corticosteroids and minocycline. Eventually, it responded to systemic corticosteroids. Pyoderma gangrenosum is usually suggestive of underlying systemic disease, but none was found in this patient.
Discoid lupus erythematosus (DLE) manifests itself as chronic plaques, commonly on face, scalp or ears (2.134), with erythema, scaling and follicular plugging. Lesions persist, with scarring and depigmentation, but systemic features are absent.

Systemic lupus erythematosus (SLE) may present with an acute facial rash, of butterfly distribution (3.76, 3.77), often photoaggravated (3.78). Vasculitis may occur (2.132). Other features of systemic lupus erythematosus are described on p. 139.

Rheumatoid arthritis may be associated with vasculitis (2.131) and subcutaneous nodules. It may also be accompanied by pyoderma gangrenosum, a destructive, necrotic ulcerative process that may destroy large areas of skin (2.135). Pyoderma gangrenosum may also complicate other diseases, especially ulcerative colitis, Crohn's disease, myelofibrosis and multiple myeloma.

Systemic sclerosis has several skin manifestations (see p. 141). Morphoea is localized plaques of dermal sclerosis, often pigmented, that appear without other underlying disease. Scarring occurs in the skin (2.136) and may affect adjacent bone, but the condition usually clears spontaneously.

Dermatomyositis commonly occurs with skin features (3.89, 3.90), as may other connective tissue disorders, including relapsing polychondritis (3.95), Reiter's syndrome (3.58–3.60) and Behçet's syndrome (3.102–3.105).

**THE SKIN IN OTHER MULTISYSTEM DISORDERS**

A number of other multisystem disorders have cutaneous manifestations or complications. These can be important clues for establishing a diagnosis and should be sought carefully.

Many systemic infections have skin manifestations (see Chapter 1), and a broad range of skin complications has been noted in HIV infection and AIDS (1.34).

Diabetes may be associated with a number of skin conditions, including acanthosis nigricans (2.90), staphylococcal (1.99, 2.50) and candidal infection (2.61, 2.62), gangrene (7.104) and trophic changes, such as ulcers, especially in the skin of the legs.

Two specific, and probably related, conditions are seen in diabetics, though they may also occur in nondiabetic patients.

- **Granuloma annulare** occurs as groups of flesh-coloured papules in rings or crescents, most commonly on the extensor surfaces of the hands and fingers (2.137).
- **Necrobiosis lipoidica** occurs as erythematous plaques over the shins (2.138). These gradually develop a waxy appearance and brown pigmentation. Care is needed to prevent skin breakdown and ulceration.

**2.136 Morphoea 'en coup de sabre'** (resembling the scar from a sabre cut). This form of localized morphoea can involve subcutaneous tissues and even bone. It is a variant of linear morphoea and, if the scalp is involved, can be associated with scarring and subsequent hair loss. Despite the severe local involvement, systemic sclerosis is not seen in this condition.

**2.137 Granuloma annulare** on the finger. Note the ring of flesh-coloured papules. This condition may occur in otherwise healthy individuals or in patients with diabetes.

**2.138 Necrobiosis lipoidica** in a 50-year-old woman with diabetes. Note the surface scaling and scarring. Ulceration may occur in more advanced and extensive lesions. Necrobiosis lipoidica is usually a complication of diabetes.
Xanthomas may be the first indication of underlying hyperlipidaemia, either primary or secondary to underlying disorders such as diabetes or renal disease (see pp. 340).

Generalized pruritus is a common presentation to the dermatologist. There may be a dermatological explanation for the itch, such as scabies, but, more often, especially in the elderly, no abnormality is detected in the skin, except scratch marks. Pruritus may be the first presentation of a wide range of conditions, including drug reactions, liver disease such as primary biliary cirrhosis (9.49, 9.50), chronic renal failure, haematological conditions such as anaemia or polycythaemia, hyperthyroidism or hypothyroidism, diabetes or malignant disease such as Hodgkin's disease, and needs careful investigation.

Sarcoidosis has several skin manifestations, some of which, such as lupus pernio, are diagnostic of the condition (see pp. 197).

Cutaneous signs of many other conditions are illustrated throughout this book.

### PHOTODERMATOSES

Many skin conditions are affected by ultraviolet radiation, either positively, as when it is used as a therapeutic agent, or adversely as the cause or an exacerbating factor of a rash. Within the ultraviolet radiation spectrum, the ultraviolet A and ultraviolet B wavebands are the most significant, as ultraviolet C is mainly absorbed within the atmosphere. Although most ultraviolet radiation comes from the sun, the use of sunbeds as artificial sunlight has resulted in a rising incidence of ultraviolet-induced disorders.

The wide range of photodermatoses is summarized in 2.139. Idiopathic photodermatoses should be distinguished from other dermatoses aggravated by ultraviolet radiation or the reactions of normal skin to ultraviolet radiation damage (such as inflammation, tanning, thickening of the epidermis and suppression of local cell-mediated immunity).

#### CLASSIFICATION OF PHOTODERMATOSES

<table>
<thead>
<tr>
<th>Acute</th>
<th>Idiopathic</th>
<th>Photoaggravated dermatosis</th>
<th>Exogenous chemical</th>
<th>Degenerative or neoplastic</th>
<th>Genetic or metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunburn</td>
<td>Polymorphous light eruption</td>
<td>Lupus erythematosus</td>
<td>Phototoxic and photoallergic reactions (drugs, plants or chemicals)</td>
<td>Solar keratoses (squamous cell carcinoma)</td>
<td>Xeroderma pigmentosum</td>
</tr>
<tr>
<td></td>
<td>Actinic prurigo</td>
<td>Dermatomyositis</td>
<td></td>
<td>Basal cell carcinoma</td>
<td>Rothmund-Thomson syndrome</td>
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<tr>
<td></td>
<td>Chronic actinic dermatitis (actinic reticuloid)</td>
<td>Darier's disease</td>
<td></td>
<td>Melanoma</td>
<td>Cockayne's syndrome</td>
</tr>
<tr>
<td></td>
<td>Solar urticaria</td>
<td>Acne rosacea</td>
<td></td>
<td>Photoageing</td>
<td>Bloom's syndrome</td>
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<td></td>
<td></td>
<td>Herpes simplex</td>
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<td></td>
<td>Porphyras</td>
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<td></td>
<td></td>
<td>Vitiligo</td>
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<td>Hartnup disease</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Albinism</td>
</tr>
</tbody>
</table>

2.139 Classification of photodermatoses.

2.140 Polymorphic light eruption. This female patient has typical itchy erythematous papules over the forearms and hands. The mechanism of this reaction — the most common form of 'sun allergy' — is not known, but it is provoked by ultraviolet B light in the sunburn range. The reaction commonly occurs on the face and arms, but may also appear in other sun-exposed areas. It may develop at any time from 2 hours to 5 days after sun exposure — most commonly it appears within 24 hours.

2.141 Chronic actinic dermatitis (photodermatitis) is a severe eczematous reaction which is limited to light-exposed areas. Note the typical distribution of a photodermatoses, with sparing behind the ears, under the chin and below the collar line. In this case, the cause was unknown and prevention of exposure to light was the major preventive measure. In many cases, however, a similar reaction may result from photosensitizing drug therapy.
Polymorphic light eruption is a common disorder affecting 10–20% of the population, predominantly females. It is generally worse in spring and early summer. The rash develops within a few hours of sun exposure as itchy erythematous papules, plaques or vesicles on exposed sites (2.140).

Chronic actinic dermatitis (also known as photodermatitis or actinic reticuloid) is a rare disorder that usually presents in older men, as a severe chronic dermatitis of exposed sites (2.141), often in association with multiple contact allergies. Other rare photodermatoses include solar urticaria, in which urticarial weals appear within minutes of sun exposure and resolve within 1–2 hours, hydroa vacciniforme, a painful vesicular rash on the face, and actinic prurigo, a persistent itchy papular or nodular eruption on exposed sites; the latter two are more common in children.

Many dermatoses can be photodermatitis. Chronic actinic dermatitis includes acne rosacea, systemic lupus erythematosus (3.78), lichen planus, and psoriasis and atopic dermatitis in some patients.

Photosensitive drug eruptions may be induced by ultraviolet radiation exposure with, for example, phenothiazines, thiazide diuretics, sulphonamides, or tetracyclines. These reactions may present as either an acute phototoxic reaction (2.142) or as a more chronic photodermatitis (2.141). Several plant families also contain substances that may induce photosensitivity (phytophotodermatitis) in the skin, including cow parsley, hogweed, rue, and bergamot. The sensitivity results from contact with psoralen compounds within the plants (2.143). Bergapten (the active ingredient in oil of bergamot) and other furocoumarins are also found in some perfumes.

Photosensitivity is a common problem in patients with several variants of porphyria (see p. 349), whereas patients with vitiligo and albinism lack the melanin protection in the skin and are liable to both acute and chronic ultraviolet radiation damage.

Patients with the rare inherited disorder xeroderma pigmentosum, who have inherited defects in DNA repair after ultraviolet exposure, are abnormally sensitive to the tumorigenic effects of ultraviolet B.

**DRUG REACTIONS IN THE SKIN**

Skin rashes are the most common sign of adverse reactions to drug therapy, although any organ system can be involved. Many drug reactions are not truly allergic in their nature and it is important to distinguish between the characteristics of non-allergic and allergic reactions (2.144). Drugs that have been frequently implicated in allergic reactions are listed in 2.145.

### Differences Between Non-Allergic and Allergic Drug Reactions

<table>
<thead>
<tr>
<th>Difference</th>
<th>Non-allergic</th>
<th>Allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantities required to provoke reaction</td>
<td>Large</td>
<td>Minute</td>
</tr>
<tr>
<td>Cumulative effect</td>
<td>Often necessary</td>
<td>Usually none</td>
</tr>
<tr>
<td>Relationship between allergic effect and pharmacological action</td>
<td>Often present</td>
<td>No connection</td>
</tr>
<tr>
<td>Same effect reproduced by pharmacologically different chemicals</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Clinical picture</td>
<td>Uniform</td>
<td>Varied</td>
</tr>
</tbody>
</table>

### Drugs Frequently Implicated in Allergic Drug Reactions

- Aspirin
- NSAIDs
- Penicillins
- Sulphonamides
- Antituberculous drugs
- Nitrofurans
- Antimalarials
- Griseofulvin
- Hypnotics
- Anticonvulsants
- Anaesthetic agents
- Muscle relaxants
- Tranquillisers
- Antihypertensives
- Antiarrhythmics
- Iodinated contrast media
- Antiserum and vaccines
- Organ extracts, e.g. insulin, ACTH
- Heavy metals
- Allopurinol
- Penicillamine
- Antithyroid drugs

2.142 A phototoxic drug eruption, occurring in exposed skin not covered by footwear. This woman had been treated with doxycycline.

2.144 Differences between non-allergic and allergic drug reactions.

2.143 Phytophotodermatitis most commonly presents as irregular streaks of erythema and hyperpigmentation occurring on the light-exposed parts of the body. On careful questioning, the patient usually gives a history of prior contact with a sensitizing plant. This gardener's skin had been exposed to giant hogweed.

2.145 Drugs frequently implicated in allergic drug reactions.
Drug therapy may lead to a wide range of skin pathologies, but some features are especially suggestive of drug eruptions. The rash is usually widespread and symmetrical. Typically, it develops within 10–14 days of the start of therapy, but it may develop sooner if there has been previous exposure to the same or a similar drug. Reactions may develop rapidly, within minutes, if a type I hypersensitivity reaction of anaphylaxis, angioedema or urticaria is present. Alternatively, drug eruptions can develop when a patient has been on treatment for some time, perhaps triggered by some additional, intercurrent factor. When a patient is on multiple drug therapy, drugs commonly associated with rashes should be identified, together with those that have been introduced recently, and withdrawal or substitution of alternative therapy carefully planned. It is important to recognize that an allergic reaction may not be caused by the active drug itself; it may be due to a preservative, colouring agent or bulking agent in the tablet or syrup. Factors such as infection may modify the development of a drug reaction, as with the ampicillin rash seen in patients with infectious mononucleosis (1.93).

Morbilliform and maculopapular eruptions are common (2.146, 2.147) and may develop into severe erythroderma (exfoliative dermatitis), clinically indistinguishable from that found in other conditions such as psoriasis (2.21).

True immediate-type hypersensitivity to penicillin and many other drugs may lead to urticaria (2.40), angioedema (2.42) and life-threatening anaphylaxis. Similar reactions may develop as a result of idiosyncratic direct release of inflammatory mediators such as histamine by nonallergic mechanisms, as in aspirin-sensitive individuals.

Fixed drug eruptions are rashes or solitary skin lesions that recur at the same site each time the causative drug is taken (2.148). Sulphonamides, barbiturates and the laxative phenolphthalein are common causes.

Erythema multiforme may be evoked by drug therapy (see p. 94). It is a component of, and may develop into, the life-threatening Stevens-Johnson syndrome (see p. 95).

Erythema nodosum (2.45) may be provoked by drug therapy; so too may vasculitic and purpuric reactions. Another major drug reaction is toxic epidermal necrolysis, the ‘scalded skin syndrome’ (2.149). Drug allergy is the most common cause of this syndrome in adults.

Some drugs are used despite a known high frequency of rashes. Gold therapy may be used for its powerful effect in severe rheumatoid arthritis, for example, but it often provokes a psoriasiform eruption, which may persist despite withdrawal of the drug (2.150).

A number of drugs may produce phototoxic or photoallergic reactions, in which the rash appears on light-exposed areas (2.141, 2.142). These patients must be distinguished from those with underlying photosensitivity caused by conditions such as systemic lupus erythematosus or porphyria.
2.148 Fixed drug eruption, so-called because the lesion recurs at the same site after each administration of the causative drug. A common cause, as here, is phenolphthalein, found in various proprietary laxative preparations. The lesion is intensely itchy.

2.149 Toxic epidermal necrolysis, the 'scalded skin syndrome' in an adult. The most common cause is drug allergy, but in children it is more commonly the result of infection (see 1.101).

2.150 Gold sensitivity is most commonly manifest as a psoriasisform eruption. Gold rashes are not uncommon in rheumatoid patients, and they may persist despite withdrawal of gold therapy.
HISTORY

In a patient with joint disease, a detailed clinical history and examination is essential to determine the severity of the disease and the nature and extent of subsequent investigations.

The most common symptoms are pain and stiffness. In inflammatory arthritis, these are worse in the morning and are relieved by movement of the joint or joints; there is redness, swelling and an increase in skin temperature over the joint. These features are uncommon in mechanical joint diseases and pain is worse on use of the joint and towards the end of the day. It is relieved by rest.

Information regarding the number and the distribution of joints affected is important. For example

- Gouty and septic arthritis tend to present with acute onset monoarthritis (one joint) (3.1, 3.2)

The peripheral joint involvement in ankylosing spondylitis and enteropathic arthritis is oligoarticular (four or fewer joints)
- Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are polyarticular (five or more joints) (3.3)
- A proximal and symmetrical distribution is suggestive of RA
- An asymmetrical presentation favours seronegative arthritis
- In seronegative arthritis, there may also be axial joint involvement with spinal and lower back pain.

The variation of the symptomatology over time also provides useful diagnostic information. For example

- RA tends to be relapsing and remitting
- Osteoarthritis (OA) is usually persistent and may be insidiously progressive
- Gouty arthritis is usually episodic.

Although most forms of arthritis are spontaneous in their onset, in some patients specific factors of aetiological importance can be identified. For example, trauma may precipitate an attack of gout and aggravate OA, and infection may cause non-specific polyarthralgia (e.g. parvovirus), Reiter’s syndrome (genital or intestinal infection) or a septic arthritis (gonorrhoea).

Extra-articular features are also important.

- Skin psoriasis suggests psoriatic arthritis
- Nodules occur in RA and tophi in gouty arthritis
- Ocular symptoms may occur in most forms of arthritis, but their manifestations are different, for example RA patients may complain of dryness of the eyes, and seronegative spondylarthritids patients may have a history of transient conjunctivitis or iritis, or both
- The seronegative arthropathies are also often complicated by mucocutaneous lesions.

Joint function can be assessed by asking patients simple questions about difficulty in dressing and washing unaided, working in the kitchen, climbing up and down stairs, getting in and out of a car, etc.

3.1 Monoarthritis. The acute onset of a hot, red, very tender metacarpophalangeal joint of the big toe is a classic presentation of gout (see p.138). In this patient, acute gout was complicated by secondary infection; but even in the absence of infection acute arthritis may produce such intense inflammation that it is confused with cellulitis (see 3.71, 3.72).

3.2 Monoarthritis of the knee. Here the surrounding skin is much less severely inflamed than in 3.1, and the major manifestations of acute arthritis are pain, especially on movement, and effusion into the joint space. The knee is swollen, tender to touch, warm on palpation and is held in flexion. A patellar tap can be demonstrated, and the effusion can be confirmed by aspiration.

3.3 Polyarthritis in chronic rheumatoid arthritis. The finger joints are not acutely inflamed, but there is major residual deformity of the hand. End-stage arthritis of this severity should now be rare when arthritis is well managed.
EXAMINATION

Simple general observation will provide much information. The patient may have difficulty sitting on, or rising from, a chair, have an abnormal gait and show reluctance to shake hands in fear of pain. Distribution of joint involvement should be noted. On inspection of the individual joints look for erythema, swelling, deformity and muscular atrophy resulting from disuse (3.4).

- Deformities are classified as either fixed or reducible, and in accordance with their deviation from the normal anatomical position (valgus, varus, ulnar, radial, flexion, etc.).
- The range of active movement should be assessed, so that limitation of joint movement is noted before palpation.
- On palpation, joint tenderness should be noted; an increase in skin temperature indicates active inflammation; the type of swelling may be appreciated (thickened synovium has a boggy feeling; osteophytes or tophi feel hard and irregular).
- Joint effusion may be demonstrated (3.2) and crepitation can be felt (fine crepitation caused by bone and cartilage irregularities).
- Grip strength can be assessed by asking the patient to squeeze the examiner's second and third fingers.

A comprehensive and systematic examination should also be carried out to reveal extra-articular features such as episcleritis, nodules (3.30) and vasculitis in RA; skin psoriasis and nail lesions in psoriatic arthropathy (2.19, 3.5); iritis (3.50), mucocutaneous lesions and cardiac complications in ankylosing spondylitis; conjunctivitis (3.6) and urethritis in Reiter's syndrome; tophus deposition in gouty arthritis (3.7); and septic vesicular lesions in gonococcal arthritis (3.8).

3.4 Rheumatoid arthritis.
There is swelling of the metacarpophalangeal and the proximal interphalangeal joints, subluxation with ulnar deformity, and a fixed flexion deformity in the first metacarpophalangeal joint. Note also the disuse atrophy of the intrinsic muscles of the hands.

3.5 Pitting of the nails may be a clue to the diagnosis of psoriatic arthropathy. This patient also has a small psoriatic plaque on the finger. More severe nail changes may occur (see 2.16).

3.6 Conjunctivitis is a frequent extra-articular feature in many rheumatic disorders.

3.7 Tophaceous deposits in the ear and elsewhere may occur in chronic gout. They may discharge a thick toothpaste-like material, which can be shown on polarized light microscopy to be urate crystals (see 3.13).

3.8 Gonococcal arthritis of the knee. The association of extra-articular skin lesions, such as the vesicular lesion seen here on the volar surface of the wrist (arrowed), with the arthritis points to a systemic infection.
INVESTIGATIONS

An investigative programme for the rheumatological patient may include haematology, immunopathology, blood biochemistry, joint fluid analysis and radiography.

HAEMATOLOGY

Full blood count
- Leucocytosis and thrombocytosis suggest an inflammatory process
- Thrombocytopenia may occur in SLE
- A normochromic, normocytic anaemia may indicate a chronic disease such as RA

A microcytic anaemia (3.9) may indicate chronic gastrointestinal blood loss caused by the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Erythrocyte sedimentation rate (ESR)
- A raised ESR or plasma viscosity suggests an inflammatory condition.

C-reactive protein (CRP)
- CRP is a more sensitive indicator of inflammatory activity than ESR or plasma viscosity, but the result is not available for at least 24 hours as it is measured by radioimmunodiffusion.

IMMUNOPATHOLOGY

Rheumatoid factor
- Positive in 80% of patients with RA; high titres indicate aggressive disease
- May also be found in other connective tissue disorders such as Sjögren's syndrome, SLE and systemic sclerosis
- May also be found in infectious disease, B-cell lymphoproliferative disorders and in healthy elderly people.

Antinuclear antibody (ANA)
- ANA (3.10, 3.11) is common in connective tissue disorders, but relatively nonspecific and may be found in normal individuals.

Other subclasses of ANA
- for example anti-DNA antibodies in SLE, anti-nRNP in mixed connective tissue disorder.

3.9 Microcytic anaemia in a patient with chronic rheumatoid arthritis. Most red cells have a central pallor (hypochromia) and a small diameter (microcytosis). The anaemia resulted from long-term gastrointestinal blood loss as a side effect of nonsteroidal anti-inflammatory drug use.

3.10 Antinuclear antibody as revealed by indirect immunofluorescence. The test serum came from a patient with systemic lupus erythematosus (see p. 139).

3.11 The lupus band test demonstrates the deposition of complement C3b and immunoglobulin in the skin at the dermo-epidermal junction, shown here as a continuous band of IgM (arrow) by direct immunofluorescence (the background fluorescence in the dermis is not significant). Non-lesional skin that has not been exposed to the sun should be used for this test. A positive result is strongly suggestive of a diagnosis of systemic lupus erythematosus.
BLOOD BIOCHEMISTRY

Renal and liver function
- Abnormal function may indicate extra-articular complications and provide guidance to treatment.

Uric acid level
- High level may suggest gouty arthritis.

Calcium level
- Hypercalcaemia in sarcoidosis (uncommon) and in some cases of chondrocalcinosis.

JOINT FLUID ANALYSIS

Naked eye appearance on aspiration (3.12)
- Colour, viscosity and turbidity; active synovial inflammation gives a thin turbid appearance.

Microscopy
- White cell count with differential count: polymorphonuclear cells predominant in RA, gouty arthritis and septic arthritis; mononuclear cells predominant in OA
- Under polarized light urate crystals are negatively birefringent (3.13); calcium pyrophosphate dihydrate crystals are weakly positively birefringent (3.14).

3.12 Joint aspiration may yield valuable information and may relieve symptoms. In this case, over 40 ml effusion was aspirated from the knee. The effusion was not purulent, and the presence of large numbers of mononuclear cells on microscopy was consistent with the diagnosis of OA.

3.13 Polarized light microscopy reveals strongly negative birefringence in the needle-shaped urate crystals found in a joint aspirate from a patient with acute gout.

3.14 Polarized light microscopy reveals weakly positive birefringence in the rhomboidal crystals of calcium pyrophosphate dihydrate ingested by leucocytes, which are found in joint aspirates from patients with pseudogout.

3.15, 3.16 Radiographs showing progressive changes of rheumatoid arthritis over a 5-year period from near normal (3.15) to severe erosion (3.16). In 3.16 note the multiple erosions of the metacarpals, the loss of joint space, the soft-tissue enlargement, the synovial thickening (in the left middle finger), the presence of bone cysts and the subluxation of the metacarpophalangeal joint of the thumb.
RADIOPHraphy

Plain radiographs
- Useful in assessing soft-tissue swelling, joint space loss, erosions, sclerosis, calcification, etc. (3.15, 3.16).

OTHER INVESTIGATIONS

These are less often requested and include
- Ultrasound (3.28)
- CT scanning
- MRI scanning (3.17)
- Arthrography (3.29)
- Arthroscopy and synovial tissue biopsy (3.18)
- Scintigraphy (3.19)
- Thermography
- HLA tissue typing.

THE ARTHROPATHIES

RHEUMATOID ARTHRITIS

RA is a common condition with a worldwide distribution, more prevalent in temperate climates. In Western communities the prevalence is approximately 3%, with women more commonly affected than men (3:1), and the peak age of onset is 30–50 years.

The aetiology is unknown, but is most probably multifactorial. The high risk conferred by HLA-D4 and common family history suggest a genetic component. Environmental factors such as viral infections have been suggested. The initial pathology is synovitis with oedema, vascular dilatation and polymorphonuclear cell infiltrate. This is followed by lymphocyte and plasma cell infiltration and proliferation of the synovial lining cells. As the disease progresses, the synovial tissue becomes fibrosed and granulation tissue (pannus) develops and erodes the cartilage (3.20).

3.17 MRI scanning has an evolving role in the imaging of bones and joints. The patient has synovial chondromatosis, a condition in which multiple cartilaginous bodies are present in the synovium. These were not visible on plain X-ray but are clearly seen on the scan (arrow). The gap between the two synovial layers reflects the presence of an effusion in the joint.

3.19 Acute monoarthritis of the right hip revealed by technetium bone scanning. The increased count over the right hip is a reflection of the increased blood flow to the joint associated with acute arthritis.

3.20 A diagramatic cross-section of a normal synovial joint (left) and a joint affected by rheumatoid arthritis (right).

3.18 Arthroscopy can be performed in many joints. The procedure sometimes allows a visual diagnosis, permits confirmatory biopsy and may also allow corrective surgery. Arthroscopy of the knee in this patient with rheumatoid arthritis revealed multiple synovial villi.
• In the knees, swelling may result from synovial hypertrophy (3.18) and effusion; varus and fixed flexion deformities of the knees are common and popliteal (Baker's) cysts are sometimes felt; rupture of these cysts causes sudden calf pain with swelling that can mimic deep vein thrombosis (3.27, 3.28, 3.29)
• The disease also commonly affects the elbows and in more advanced cases the hips and neck. Patients may present with extra-articular features, most of which are associated with vasculitis. These patients tend to have a poorer prognosis.
• Skin manifestations include
  - rheumatoid nodules (3.30)
  - skin rashes, often purpuric
  - ulceration (3.31)
  - nail-fold and finger-pulp infarcts (3.32, 3.33)
  - pyoderma gangrenosum (2.135)

3.26 Rheumatoid arthritis of the feet. Gross destructive changes with multiple subluxations cause painful deformity that severely limits mobility.

3.27 Advanced rheumatoid arthritis has resulted in a valgus deformity of the right knee and swelling of the left calf caused by the rupture of a Baker's cyst.

3.28 Baker's cyst of the knee, demonstrated by ultrasound, the usual diagnostic method. This cyst has not ruptured.

3.29 Arthrogram showing a ruptured Baker's cyst. Contrast has leaked from the Baker's cyst producing the clinical picture shown in 3.27.

3.30 Rheumatoid nodules. The upper forearm and elbow are the most common sites for skin nodules in rheumatoid arthritis. These nodules result from vasculitis, and they may ulcerate or become necrotic, as has occurred at the elbow in this patient. Such nodules are often painless and cause no symptoms, but surgery is occasionally indicated for cosmetic reasons.

3.31 Deep arterial ulceration of the legs in rheumatoid arthritis. Such ulcers result from vasculitis and are often very difficult to treat. They may respond to a combination of aggressive therapy for rheumatoid arthritis and meticulous local care, but amputation is sometimes necessary when such ulceration is severe and progressive.
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3.37 Pleural effusion is a common complication of rheumatoid arthritis, and it may precede joint symptoms. In this patient it occurred later in the disease, and was accompanied by some reticular nodular shadowing, representing early fibrosing alveolitis, in both lower zones.

- Raynaud's phenomenon may occur; it is characterized by finger blanching (vasospasm) and usually precipitated by cold or emotion (3.34, see p. 260)
- Keratoconjunctivitis sicca (dry eyes, either alone or as part of Sjögren's syndrome (see p. 143) and episcleritis are common ocular manifestations (3.35); scleritis and scleromalacia are rare but serious, as they can lead to eyeball perforation (3.36); steroid-induced cataracts and chloroquine-induced retinopathy may occur when these agents are used in treatment
- Cardiac and pulmonary complications are usually limited to pericardial and pleural involvement (3.37); rare cardiac complications may include constrictive pericarditis, myocarditis and endo-

3.32 Nail-fold infarction caused by vasculitis may occur in rheumatoid arthritis and some connective tissue diseases, but a very similar appearance may result from nail trauma in normal individuals.

3.33 Splinter haemorrhages may be another result of vasculitis in rheumatoid arthritis, but they are a rather nonspecific sign; they may be caused simply by trauma and have little value in diagnosis.

3.34 Raynaud's phenomenon, in which there is uncomfortable blanching of the fingers as a result of vasospasm, may occur in patients with rheumatoid arthritis and other connective tissue diseases (see p. 260).

3.35 Rheumatoid episcleritis may present acutely as a localized area of inflammation. It is a common ocular complication of rheumatoid arthritis but does not carry the same poor prognosis as scleritis.

3.36 Scleromalacia perforans in rheumatoid arthritis. Long-standing inflammation of the sclera (scleritis) has resulted in thinning, which exposes the underlying choroid to secondary infection and the risk of eyeball perforation.

3.37 Pleural effusion is a common complication of rheumatoid arthritis, and it may precede joint symptoms. In this patient it occurred later in the disease, and was accompanied by some reticular nodular shadowing, representing early fibrosing alveolitis, in both lower zones.
carditis; rheumatoid nodules may occur in the lung (3.38, 4.141); diffuse fibrosing alveolitis (3.37, 3.38, 4.140), Caplan's syndrome (4.158) and obliterative bronchiolitis are uncommon pulmonary complications.

- Neurological manifestations include mononeuritis, which is a true extra-articular complication, and carpal tunnel syndrome and cervical myelopathy, which are compression neuropathies secondary to the arthritis process; involvement of the cervical spine can result in cord transection and sudden death if the neck is manipulated inadvertently, for example under an anaesthetic.
- In the kidneys there may be amyloid deposition, but clinical manifestations are usually limited to mild proteinuria with only very few patients developing nephrotic syndrome or renal failure.

Immunological investigations show a positive rheumatoid factor (a circulating immunoglobulin of the IgM type) in about 80% of patients. The most common haematological manifestation is a normochromic, normocytic anaemia (see p. 431), but hypochromic anaemia may occur, especially if NSAID therapy has caused gastrointestinal blood loss (3.9, 8.53, see p. 429). The platelet and white cell count may be high and the ESR may be raised. Some patients may develop Felty's syndrome which is an association of splenomegaly and neutropenia with RA.

There may not be any radiological changes in the early stages (3.15), but later there is soft-tissue swelling and periarticular osteoporosis followed by joint-space narrowing and periarticular erosions (3.16). In long-standing cases subluxation, secondary OA and bony ankylosis are seen (3.39).

The principles in the management of all forms of arthritis are similar. The main object is to reduce pain and enable the patient to maintain as near normal a life as possible. Physiotherapists can recommend appropriate exercises to maintain full joint movement and strengthen weak muscles. Wax baths, ice packs, ultrasound and weak electrical current stimulation (interferential therapy) may also alleviate some of the joint symptoms. Aspiration of effusions, for example from the knees (3.12), followed by intra-articular steroid injection (3.40) may be of short-term value. Occupational therapists can advise on joint protection and can provide splints and other aids and appliances which allow sufferers to be independent.

The two main types of drug treatment used in RA are the NSAIDs and the so-called 'slow-acting anti-rheumatic drugs' (SAARDs).

- NSAIDs are the mainstay of treatment but may produce upper gastrointestinal side effects.
- SAARDs include gold in oral and injectable forms, penicillamine, sulphasalazine and hydroxychloroquine. They induce remission of the arthritis, but gold and penicillamine are particularly associated with high side-effect profiles such as bone marrow suppression, nephrotoxicity and hepatotoxicity. SAARDs should therefore be used only when first-line treatment fails or when patients develop extra-articular complications.

In advanced cases, immunosuppressive drugs such as low-dose methotrexate and azathioprine may be used. Corticosteroids have potent anti-inflammatory effects and may be useful in the treatment of an acute flare, although long-term...
use should be actively discouraged. Intra-articular injections of steroids are also useful in these cases (3.40), as is bed rest.

Surgery may have an important role, especially in the more advanced stages of RA. Useful operations range from the removal of local areas of diseased synovial tissue (3.41), to the removal of subluxed metatarsal heads, and the total replacement of hip, knee, shoulder and elbow joints or the small joints of the hands (3.42).

**Felty’s Syndrome**

Felty’s syndrome is a complication of long standing, seropositive, nodular deforming RA (3.25) in which splenomegaly of various degrees develops and is accompanied by severe leucopenia and a normochromic normocytic anaemia. In addition there may be weight loss, ulceration in the lower limbs (3.31) lymphadenopathy, hyperpigmentation, high titres of IgM rheumatoid factor and antinuclear antibodies.

As a consequence of severe leucopenia, infection is a common presenting feature, and is invariably seen when the polymorph count 1 x 10/litre. It is a common cause of death, especially in those who have skin ulcers, are on steroids, or have low levels of complement factors and high levels of immune complexes.

There is often suppression of all marrow elements (3.43) with diminished red and white cell and platelet production. The ESR and CRP are both elevated and there are low levels of components of the complement system. The level of rheumatoid factor, cryoglobulins and circulating immune complexes is high.

A low serum albumin is a reflection of chronic disease.

Management of Felty’s syndrome requires optimal management of rheumatoid disease with SAARDS. Steroids are contraindicated in the presence of neutropenia or overt infection. Splenectomy may be of value, especially in those with recurrent infection and perhaps also in those with leg ulceration.
JUVENILE CHRONIC ARTHRITIS
(JCA OR STILL’S DISEASE)

Arthritis is uncommon before the age of 16 years (incidence 0.7–1 per 1000) although arthralgia is a common problem. The essential criterion for JCA is persistent synovitis in one or more joints for at least 3 months.

There are five main types of JCA.

- Systemic Still’s disease has an equal sex incidence and is most common in 2–3-year-olds; it is characterized mainly by systemic features, including a high spiking fever, morbilliform rash, lymphadenopathy, hepatosplenomegaly and pleuropericarditis; arthritis is usually a minor feature
- Polyarticular Still’s disease, which is seronegative for rheumatoid factor (3.44); the features include micrognathia (secondary to temporomandibular joint involvement with abnormal mandibular growth) (3.45), loss of neck extension (cervical spine involvement, 3.46), unequal limb lengths (premature closure or overgrowth of the epiphyses) and fixed flexion deformities of the lower limbs
- Pauciarticular (four or fewer joints) Still’s disease, which usually affects the large joints of 2–5-year-old girls; anti-nuclear antibodies are usually positive and chronic iritis (3.47) may lead to blindness; regular slit-lamp examination is necessary, because iritis in Still’s disease may be asymptomatic
- Seropositive polyarthritis which resembles adult RA
- Juvenile ankylosing spondylitis, which is more common in HLA-B27-positive boys of 10–15 years of age; the clinical features resemble those of the adult form, although back pain is not prominent.

Treatment is with NSAIDs. SAARDs may be effective in the polyarticular type JCA but are associated with a high incidence of side effects. Corticosteroids should be avoided because of their retarding effect on growth. Physiotherapy and joint protection are important. Long periods of rest may sometimes be necessary.

SERONEGATIVE SPONDARTHROPATHIES

Seronegative spondarthritides describes a group of conditions with a number of common characteristics. These include the absence of rheumatoid factor and other autoantibodies in the blood, involvement of the spine, a peripheral inflammatory arthritis, similar extra-articular features (predominantly mucocutaneous) and a high incidence of the tissue antigen HLA-B27.

3.45 Micrognathia in a young adult who had juvenile chronic arthritis. The condition was associated with polyarticular Still’s disease and with cervical spine involvement (3.46).

3.46 Cervical spine involvement in Still’s disease. Ankylosis of the upper cervical spine is shown on this radiograph.

3.47 Iridocyclitis in pauciarticular Still’s disease. Distortion of the pupil is caused by adhesion of the iris to the lens (posterior synechiae).
Ankylosing spondylitis

Ankylosing (fusion) spondylitis (spinal vertebral joint inflammation) presents primarily in young men (9 males: 1 female), but is becoming more common in women, who tend to have milder disease. The aetiology is unknown but there appears to be a strong genetic component. A family history is common and over 90% of patients possess the HLA-B27 tissue antigen. However, 7% of the population are HLA-B27-positive and the prevalence of ankylosing spondylitis is 1%. Thus environmental factor(s) are also likely to be important.

Low back pain with morning stiffness occurs as a result of sacroiliac joint involvement. The pain is worse at rest and is often felt in the buttocks, especially when seated. It may radiate to the back of the thighs mimicking sciatica, although the latter is usually unilateral and relieved by rest. As the disease progresses upwards, pain is experienced at higher spinal levels. Patients with thoracic spine involvement may present with pleuritic chest pain but, unlike true pleurisy, it is usually bilateral. On examination, there is loss of lumbar lordosis and a fixed kyphosis usually compensated for by extension of the cervical
spine, eventually producing the stooped 'question mark' posture (3.48). The sacroiliac joints are tender on percussion and springing of the pelvis. Movements of the spine at various levels are restricted (3.49) and so is chest expansion. Changes in the peripheral joints, usually the larger ones, are similar to those seen in RA and show signs of inflammation. Extra-articular manifestations include iritis (30%) which may sometimes precede spinal involvement (3.50). About 4% of patients develop aortitis with signs of a collapsing pulse and the early diastolic murmur of aortic incompetence. Cardiac conduction defects occur in 10% of patients. Pulmonary restriction resulting from chest wall involvement and lung fibrosis (3.51) may also occur.

Blood tests are often not very helpful. ESR may be raised but rheumatoid factor is not present in the blood. HLA-B27 tissue typing is not of diagnostic value and may be useful only in the difficult case. Radiological changes of sacroiliitis include widening of joint space and juxtarticular erosion and sclerosis (3.52). In the spine there is squaring of the vertebrae caused by erosion of their corners. Syndesmophytes (bony deposition) form at the margins of the vertebrae. These may join together and produce the classic appearance of a 'bamboo spine' (3.53). There may also be radiological evidence of enthesopathy (calcification and new bone formation in the soft tissues) with erosions, sclerosis and soft-tissue calcification around the ischial tuberosities, iliac crests, greater trochanters, patellae and calcanea.

Physiotherapy is most important, and appropriate back exercises should be done daily in order to avoid spinal deformities. Hydrotherapy is also valuable. Pain control can usually be achieved by NSAIDs. Other drugs, including sulphasalazine and methotrexate, may sometimes be used in advanced cases, although their role is not fully confirmed. Iritis may be recurrent, leading to severe ocular damage, and should be treated vigorously with topical steroids. Spinal irradiation, which was popular in the 1950s, is not used now because of risks of the later development of malignancy.

Psoriatic arthropathy

Psoriatic arthropathy occurs in 7-8% of patients with psoriasis. There is a strong genetic influence and a family history is common. Skin psoriasis usually precedes the onset of the arthritis, but the reverse may happen occasionally. Skin lesions may be found on the scalp, behind the ears, in the umbilicus and the natal cleft, as well as in the common places such as the extensor aspect of the elbows and knees and the trunk (3.54 and see p. 87).

There are five forms of psoriatic arthropathy:

- The distal phalangeal type (3.55) is more common in men and is usually accompanied by nail lesions such as pitting (3.5), ridging, onycholysis (lifting of the nail, 2.19) and hyperkeratosis.
- The polyarthritic form may be indistinguishable from RA but it is persistently seronegative.
- Oligoarthritis usually affects the knees or the other large joints with an asymmetrical distribution.
- A spondylitic form resembles ankylosing spondylitis and 60-70% of these patients are HLA-B27-positive.
- Arthritis mutilans (5%) is rare but severe (3.56) and is usually associated with extensive skin psoriasis.

The pathology is similar to RA but there is more fibrosis of the joint tissues resulting in ankylosis, and bony changes with periosteal inflammation produce the classic sausage-shaped digits (dactylitis) (3.55). Extra-articular features are rare. Features in the blood are similar to those seen in ankylosing spondylitis. There are no specific radiological features, but the distribution of the arthritis can provide an important guide to the diagnosis. Periosteal new bone formation reflects periostitis. The 'pencil-in-cup' appearance of the hand radiograph is caused by periarticular bone dissolution with cupping of the proximal ends of the phalanges and whittling of the distal bone ends (3.57).

Most patients have mild arthritis and respond to standard NSAID treatment. In more advanced cases, corticosteroids and immunosuppressive agents such as methotrexate or azathioprine may be required. Unlike RA, patients do not respond to penicillamine.
3.56 Severe psoriatic arthritis (arthritis mutilans). There is a gross destructive arthropathy, involving all joints of the hands and wrists. The phalanges have ‘telescoped’ (see 3.57), resulting in shortening of the fingers and gross impairment of function.

3.57 Pencil-in-cup deformity of the distal phalanx in psoriatic arthropathy. There is loss of the head and splaying of the base of the distal phalanx.

3.58 Keratoderma blenorrhagicum is a hyperkeratotic skin condition found in Reiter’s syndrome. The lesions start as brown raised hyperkeratotic patches which grow and coalesce into raised yellow-brown patches. These are typically found on the soles of the feet but may be found in all skin areas, including the scalp. Pustular psoriasis may produce the same clinical and histological features (see p. 92).

Reiter’s syndrome
Reiter’s syndrome has a high male to female ratio (20:1) and up to 90% of patients possess the HLA-B27 antigen. It is likely to be a generalized reaction to an infection, either urogenital or intestinal, and is sometimes called ‘reactive arthritis’. *Chlamydia trachomatis* has been shown to be the infective organism of the genital type, whereas the dysenteric form may follow infection with many bacteria, including *Shigella flexneri*, *S. dysenteriae*, *Yersinia enterocolitica* and occasionally *Salmonella* species.

The classic symptom triad comprises urethritis, conjunctivitis (3.6) and arthritis, although all three may not be evident. Conjunctivitis is bilateral and usually mild with few symptoms. There may be a purulent but sterile discharge. Uveitis may be found in up to 30% of long standing diseases. The arthritis usually affects the large joints in the lower limbs. The spine is also frequently involved, especially the sacroiliac joints (20-30% of patients). Such patients develop features that are similar to those of ankylosing spondylitis. Small joints in the hands and feet may also be involved as may be tendons (especially Achilles) and the plantar fascia. Extra-articular complications are common and involve the skin (keratoderma blenorrhagicum, 3.58), nails and mucocutaneous surface — mouth ulcers (3.59), circinate balanitis (3.60) and cervicitis.

The acute episode may take a month or longer to settle and patients often respond to conservative treatment such as NSAIDs. Iritis, if severe, should be treated with topical steroids. Later there may be exacerbations with remissions and up to 80% of patients may develop chronic joint disease, visual problems or urethral strictures. The urethritis can be treated by erythromycin or tetracycline, but neither alters the course of the arthritis.
3.60 Circinate balanitis in Reiter’s syndrome. Small, discrete, round or oval red macules or erosions often become confluent.

Other seronegative spondarthritides
Other seronegative spondarthritides include arthritides associated with inflammatory bowel disease (Crohn’s disease and ulcerative colitis) and Whipple’s disease, a rare malabsorption condition. Treatment of the bowel conditions often leads to remission of the arthropathy.

INFECTIVE ARTHRITIS

Infective arthritis may be caused by bacteria, viruses or fungi that are usually borne in the blood to the joint. Arthritis may occur in viral infections with parvovirus B19, hepatitis B and HIV, and transient arthralgia may occur in many other viral infections.

In bacterial arthritis, a primary focus may be identified elsewhere, for example a boil on the skin or otitis media. The common infecting bacteria are shown in 3.61. Arthritis may be acute or chronic. Acute septic arthritis often involves joints that have been previously damaged by RA or OA, or occurs in patients who are immunocompromised. The patient usually presents with fever and rigors; the affected joint is swollen, tender to touch and has an effusion (3.1, 3.8).

There may be other clinical clues, for example purpura (see p. 457) and the joint may be held protected in flexion. In patients with pre-existing joint disease, there is often difficulty in deciding whether the changes are caused by a flare-up of the basic disease or infection, in which case the diagnosis is made by joint aspiration of a purulent aspirate (3.12); there is usually systemic leucocytosis and blood culture may be positive. Acute arthritis may also be revealed by other techniques including radiography, CT and scintigraphy (3.19).

Establishing the diagnosis and initiating treatment is a matter of urgency. Treatment with appropriate antibiotics is mandatory to stop cartilage erosion and repeated aspiration of the effusion or surgical drainage of the joint may be required.

Chronic infectious arthritis may be caused by organisms such as *Mycobacterium tuberculosis*, *Borrelia burgdorferi* (see p.54) and a range of fungi. Tuberculous arthritis remains a problem in the elderly, alcoholics, diabetics and those who are immunocompromised. In developing countries, tuberculosis remains a major public health problem associated with poverty, overcrowding and malnutrition. In areas of the world where AIDS is epidemic there has been a dramatic rise in the incidence of symptomatic tuberculosis.

Tuberculous arthritis is usually caused by dissemination of the disease from lung or kidney. It usually involves a single joint – most commonly the hip, knee (3.62), sacroiliac joints or
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intervertebral joints of the spine (3.63). The onset is insidious with systemic upset, malaise, anorexia, weight loss and night sweats followed by discomfort and swelling of the affected joint. There may be features of tuberculosis elsewhere in the patient, especially in the lung and kidney.

Diagnosis may be made by joint aspiration or synovial biopsy. Radiology is unhelpful initially, showing only soft-tissue changes, but with time there is progressive cartilage and bone erosion. Treatment is to immobilize the joint in the acute phase and give the appropriate antibiotic.

OA, a common degenerative disease of the joints, affects approximately 10% of all adults (men and women) and the prevalence increases with age. The disease is characterized by focal areas of destruction of articular cartilage, sclerosis of the underlying bone and hypertrophy of soft tissues.

The aetiology is multifactorial, although a polygenic inheritance pattern is recognized in the generalized 'nodal' form that causes distal and proximal interphalangeal arthritis of the hands, particularly in women. Mechanical factors include previous limb trauma, abnormal joint congruity, joint hypermobility, congenital dislocation of the hip and certain occupations – 'wicket keeper's thumb', 'Zulu dancer's hip', etc. OA may also be secondary to metabolic disorders such as ochronosis, acromegaly and gout or to other inflammatory arthropathies, for example RA.

OA most commonly affects the weight-bearing joints, in particular the knees, hips and spine, and the interphalangeal joints of the hands (3.64). The wrists, shoulders and ankles are less often involved. Not all patients with joint symptoms have radiographic changes; and not all radiographic changes are associ-
ated with symptoms. Pain can be severe and incapacitating and is worse on use of the joint and at the end of the day. Morning stiffness is not common, though stiffness after prolonged inactivity may occur. Clinical signs in advanced cases include crepitus, limitation of movement and joint deformities. The function of the hands is often affected (3.65). Heberden's nodes are found at the distal interphalangeal joints (3.66) and Bouchard's nodes at the proximal interphalangeal joints (3.67) of the hands. There may be valgus (knock knees) and varus (bow knees) (3.68), deformities of the knees and fixed flexion of the hip.

Blood tests are usually unhelpful, but they may sometimes reveal underlying metabolic disorders. X-rays (3.69, 3.70) may show loss of joint space resulting from cartilage damage. Osteophytosis (formation of new bone), altered bone contour, subchondral sclerosis (increased bone density) and cystic formation result from bony remodelling. There may also be soft-tissue swelling and periarticular calcification (calcium phosphate crystal deposition).

Treatment primarily involves pain relief, initially with simple analgesics. NSAIDs may be added if these are required,

3.66 Herberden's nodes in osteoarthritis are bony protuberances from the base of the terminal phalanx. They are usually painless, but may occasionally ache.

3.67 Bouchard's nodes in osteoarthritis occur at the proximal interphalangeal joints.

3.69 Osteoarthritis of the hands. This radiograph shows an advanced case, with severe changes in the distal and proximal interphalangeal joints: loss of joint space, subchondral sclerosis, osteophytosis and subarticular cysts.

3.70 Osteoarthritis of the left hip. There is irregular narrowing of the joint space associated with thinning of the cartilage. There are osteophytes (projections of new bone) around the left femoral head and generalized thinning of the bone in the left femoral head with early bone cyst formation. By comparison, the right hip is essentially normal.
though the use of these drugs in the elderly population should be minimized. Intra-articular steroid injections are useful when there are signs of inflammation. Obese patients should lose weight. Appropriate exercises should be taught to strengthen the various muscle groups acting on the affected joint. Surgery may be considered when pain becomes intractable and severe limitation of mobility is present. Secondary causes should be sought and treated.

CRYSTAL ARTHROPATHY

Gout

Gout is most common in men and postmenopausal women, affecting up to 1 in 100 of the population. The classic history is of an abrupt onset of pain and swelling (usually at night) in the big toe with red, shiny skin overlying it (3.1, 3.71), but any joint or joints may be affected (3.72). The serum uric acid level is high and joint aspiration reveals needle-shaped crystals (monosodium urate monohydrate) which appear negatively birefringent under a polarized light microscope (3.13). The acute episode subsides with desquamation of skin.

Uric acid is the breakdown product of the purine residues of nucleic acid. Two-thirds of it is excreted via the kidney and the rest via the gut. Most patients have primary gout, but possible secondary causes include:

- Increased dietary intake of purines, for example sweetmeats, offal
- Overproduction, as in the myelo- and lymphoproliferative disorders, carcinomatosis and the rare specific enzyme defects in purine biosynthesis and degradation, for example Lesch–Nyhan syndrome, a condition characterized by mental retardation and self-mutilation
- Decreased renal excretion in renal failure and with inhibition of the renal tubular excretion pathway, for example the use of thiazide diuretics, lead poisoning and in conditions causing acidaemia (diabetic ketoacidosis, starvation and excessive alcohol ingestion).

Not all patients with hyperuricaemia have gout. However, the likelihood of crystal formation increases as the uric acid level
increases, more so at low temperatures, and this explains the peripheral distribution of gout. As well as the first metatarsophalangeal joint (70%), the small joints in the hands, wrists, ankles and knees are also often involved. During the acute phase, there may be a leucocytosis and the ESR is usually raised. Radiography of the joints shows soft-tissue swelling. In chronic cases, there are additional features such as joint-space narrowing, subarticular (compared with RA, which is periarticular) ‘punched-out’ cystic lesions and secondary osteoarthritic changes (3.73).

NSAIDs are useful during acute attacks. Intra-articular steroids are also useful. Colchicine is rarely used because of its side effects. Chronic tophaceous gout is characterized by the deposition of urate (chalky, toothpaste-like appearance) in the periarticular and subcutaneous tissues. The distribution of tophi is similar to that of rheumatoid nodules – the most common sites being the extensor surfaces of the elbow, the fingers (3.72, 3.74), the anterior aspect of the knee, the Achilles tendon and the ear (3.7). Such tophi are now becoming rare as a result of the widespread use of allopurinol. Allopurinol may aggravate gout during an acute attack.

**Pseudogout**

Pseudogout is characterized by the deposition of calcium pyrophosphate dihydrate crystals in the cartilage and synovium (3.75). There is no evidence of an underlying disease in most patients, but a metabolic disorder, for example hyperparathyroidism, hypothyroidism or haemochromatosis, may be found in some patients. Calcium pyrophosphate dihydrate crystals are rhomboid and weakly positively birefringent (3.14). The clinical features are similar to those seen in gout, although the onset is slower and the course milder. Conservative treatments such as NSAIDs and intra-articular steroid injections are usually effective.

**CONNECTIVE TISSUE DISEASES**

The term ‘connective tissue diseases’ is synonymous with ‘collagen vascular diseases’. Both describe a group of conditions characterized by the occurrence of vasculitis, multisystem involvement, arthritis or arthralgia and abnormal immunological features, for example autoantibodies and immune complex deposition.

**SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)**

SLE, an autoimmune disorder, is uncommon in Caucasians (prevalence 0.1%), although it is being diagnosed more often with the development of increasingly sensitive diagnostic tests. It is more common in other races, with a prevalence of up to 1 in 250 among black women (3.76). The peak age of onset is 20–40 years and women are more often affected than men.

The aetiology is unknown, but there is a slight increase in incidence in the families of patients with SLE and in individuals with the histocompatibility markers DR2 and DR3. The aetiologial role of environmental factors, such as exposure to sunlight and certain viral infections, is being investigated but is not yet clear. Some drugs may produce a lupus-like syndrome, including hydrallazine, procainamide, phenothiazines,isoniazid and oral contraceptives. Almost all patients possess an antibody against nuclear antigens (ANA; 3.10). This is, however, a nonspecific marker and may be found in other connective tissue disorders. The antibodies to double stranded DNA (anti-dsDNA) and Smith antigens (anti-Sm) are found less frequently (40–70%) but are very specific for SLE. The primary pathology is that of a multisystem inflammatory process, probably secondary to antigen–antibody reactions.

3.75 Chondrocalcinosis of the right knee. The radiograph shows calcification in both menisci.

3.76 Systemic lupus erythematosus is most common in black women of child-bearing age, such as this 33-year-old West Indian woman who presented with a rash over her cheeks.
Patients may present with constitutional symptoms, such as anorexia, tiredness, fever and weight loss, and many organ systems may be involved.

- Skin involvement is most common; rashes may be local or generalized; the classic 'butterfly rash' on the face may occur in isolation (3.76, 3.77), but a more generalized rash may also occur – usually in sun-exposed areas (3.78). The inflammatory process may manifest itself as a vasculitis, with periungual infarcts (3.32, 3.91), erythematous nodules, palpable purpura, livedo reticularis (3.97) and Raynaud's phenomenon (3.34) being common findings. Alopecia, localized or generalized, may occur (see p. 107).
- Lung involvement results in pleurisy and pulmonary infarcts.
- Cardiac involvement results in pericarditis, myocarditis and endocarditis.
- Nephritis is often associated with a poor prognosis; the most common histological lesion is a diffuse proliferative glomerulonephritis (see p. 290).
- Neurological complications include epilepsy, focal neurological signs such as hemiparesis, aseptic meningitis, cranial and peripheral neuropathies (3.79) and psychiatric disturbances (3.80).
- Blood involvement may give rise to leucopenia, thrombocytopenia, lymphadenopathy and a thrombotic tendency which is more marked in those patients with positive antiphospholipid antibodies.
- Joint involvement may resemble RA, but there is usually no evidence of erosive changes on radiographs.

Investigations may show a raised ESR, plasma viscosity or CRP in addition to the above. ANA is present in over 90% of patients. Anti-dsDNA may also be present, as may other subclasses of ANA such as the anti-Ro and anti-Sm antibodies. The immunoglobulin levels may also be increased. The lupus band test on a skin biopsy may be of value (3.11). Radiography is usually unhelpful. Advances in diagnostic techniques and monitoring systems have improved both the morbidity and mortality (there is now a 95% 5-year survival rate in SLE from diagnosis). Patients should be advised to avoid excessive sunlight.
exposure. Sun-blocking creams can be very useful. Mild disease usually requires only symptomatic drug treatment, for example chloroquine is useful when there are troublesome skin lesions and for suppressing moderate joint disease. When the condition becomes active, systemic steroids and immunosuppressive agents, for example azathioprine and cyclophosphamide, are the mainstay of treatment. Pregnancy is not contraindicated, but there is an increased rate of fetal loss and complications during pregnancy. SLE may flare during the postpartum period.

**SYSTEMIC SCLEROSIS (SSc)**

SSc is an uncommon idiopathic multisystem disease, also known as scleroderma, that predominantly affects the skin and blood vessels. There is a female preponderance (female:male = 3:1). Progressive fibrosis and atrophy are the main pathological features.

There are two types of SSc.

- **The diffuse type** is characterized by skin and vascular changes and visceral involvement is common. The skin is thickened and tight and this sometimes results in contractures (3.81). Telangiectasia are a common feature (3.82), and Raynaud's phenomenon occurs in over 95% of patients (3.83, see p. 260). It is only occasionally accompanied by calcinosis. Involvement of the locomotor system may manifest itself as myositis and polyarthritis. Involvement of the gastrointestinal tract may appear as dysphagia (3.88), bowel distension, diarrhoea and weight loss resulting from malabsorption. Basal pulmonary fibrosis (see p. 199) develops in 45% of patients. Cardiac involvement may result in a restrictive cardiomyopathy or conduction defects. Renal involvement is associated with a high mortality, and patients usually present with proteinuria and hypertension, which may be malignant (see p. 298).

- **The limited type**, which has a better prognosis, is also known as the CRST or CREST syndrome and is characterized by calcinosis, which may lead to ulceration (3.83, 3.84, 3.85) and autoamputation of the digits (3.86), and may also be

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**3.81 Systemic sclerosis.** The skin around the mouth is tight, and the patient has opened her mouth as far as possible. Her skin is generally waxy and shiny.

**3.82 Systemic sclerosis.** Puckering of the perioral skin is seen; the skin is generally waxy and shiny, and multiple telangiectasia are visible on the face and neck.

**3.83, 3.84, 3.85 and 3.86 In the calcinosis of systemic sclerosis the calcium deposits are characteristically seen in the fingers.** The size of these hard, nontender nodules varies from a few millimetres to several centimetres. If very small they may not be visible under the skin (but can be palpated) or they may ulcerate through the skin (3.83). X-ray examination may show extensive calcinosis even in the absence of marked ulceration (3.84). In more advanced disease, extensive calcinosis, sclerodactyly and hand deformity are obvious (3.85), chalk-like material is discharged through the ulcerated skin, and progressive autoamputation of the fingertips may occur (3.86).
found elsewhere (3.87), Raynaud’s phenomenon (3.34), oesophageal involvement (3.88), sclerodactyly and telangiectasia (3.82). All of the visceral manifestations of diffuse scleroderma may also occur in the ‘limited’ disease, with the exception of renal disease, which is very rare.

There are no specific diagnostic tests. The ESR may be slightly raised and the full blood count may show an anaemia of chronic disorder. Both RA latex and ANA may be positive. The anti-scl 70 and anti-centromere antibodies are more specific autoantibodies and have been shown to be present in some but not all patients with the diffuse and limited types of SSc, respectively.

Treatment is symptomatic. Raynaud’s phenomenon may be controlled by simple measures such as stopping smoking and using warm gloves. In more severe cases, vasodilator drugs such as nifedipine can be used. Antacids or H2-antagonists, or both, are useful for patients with dyspeptic symptoms. Oesophageal dilatation may be useful in patients who have developed a stricture. Hypertension should be treated aggressively, usually with angiotensin-converting enzyme inhibitors. Specific treatment for SSc has been disappointing. Penicillamine has been tried, but it probably has only a limited use in patients with rapid skin progression.

POLYMYOSITIS AND DERMATOMYOSITIS

Polymyositis and dermatomyositis are closely related to each other and are uncommon. The incidence is not known, but is probably similar to that of SSc. There are five types.

- Primary dermatomyositis
- Primary polymyositis
- Secondary dermatomyositis or polymyositis (90% of cases have an underlying malignant condition)
- Childhood dermatomyositis or polymyositis
- Dermatomyositis or polymyositis associated with a collagen vascular disease.

The cause is unclear, but a viral aetiology has been suggested, such as rubella, influenza and Coxsackie infections.

The proximal (shoulder and pelvic girdle) muscle groups are commonly affected and patients may have difficulty lifting their arms and getting up and down stairs. Involvement of the skin gives rise to a heliotrope rash on the eyelids with periorbital oedema (3.89, 3.90). This rash may spread to the shoulders, chest, arms and hands. In the hands, Goddron’s patches may be found: these are scaly, erythematous lesions on the dorsum of the hands, knuckles and extensor surfaces of the other small joints. Nail-fold infarcts are common (3.91). Other features include dysphagia, arthralgia, calcification of the subcutaneous tissues and muscles (3.87), Raynaud’s phenomenon (3.34), and myocarditis. Pulmonary involvement, in the form of fibrosing alveolitis or aspiration pneumonia, is accompanied by a high mortality.

Laboratory investigations reveal raised muscle enzyme levels, abnormalities in the electromyograph and inflammatory cell infiltration in muscle biopsy. Treatment is with high-dose steroids, or immunosuppressive drugs such as azathioprine, cyclophosphamide and methotrexate, or both. Bed rest is imperative in the acute phases. A search for an underlying malignancy is mandatory in all adult cases.
parotid glands may be enlarged. Any mucous membrane covered areas may also be affected, for example nose, throat, larynx, bronchi and vagina. Other features include pancreatitis, pleuritis, vasculitis, renal tubular acidosis and chronic interstitial nephritis. There is an increased incidence of malignant lymphomas.

Rheumatoid factor (70%) and other autoantibodies (anti-Ro and anti-La antibodies) may be present. Schirmer's tear test, a simple bedside test, can be performed to detect the diminished tear production (3.93). Slit-lamp examination of the eyes is essential, and staining with rose bengal solution may also be diagnostic, as the superficial ulcers take up the stain (3.94).

No specific treatment is available, but artificial tears can be used to lubricate the eyes with good effect though artificial saliva (hypromellose or polyvinyl alcohol) is less effective. Attention should be paid to oral hygiene.
RELAPSING POLYCHONDRIX

Relapsing polychondritis is a rare condition in which there is softening and collapse of cartilaginous structures. Patients often present with painful swollen ears (3.95) and the disease may also involve cartilage in the nose, respiratory tract and joints, and the fibrous tissue in the globe of the eye. Steroid therapy may control symptoms.

3.95 Relapsing polychondritis causing painful ears in a 58-year-old man.

OVERLAP SYNDROMES AND MIXED CONNECTIVE TISSUE DISEASE (MCTD)

Occasionally, patients may present with a constellation of clinical and laboratory abnormalities which fit into more than one disease profile. These patients are said to have an overlap syndrome and most common among these are disorders with features of RA combined with those of SLE, or of SSc associated with those of SLE and of polymyositis. In the latter group, antibodies to the n-ribose nucleoprotein (nRNP) may be found. These cases are often referred to as MCTD. This condition has a more favourable prognosis than that of SLE or SSc alone and often responds to small doses of prednisolone.

THE VASCULITIDES

The vasculitides comprise a mixed group of conditions characterized by inflammatory infiltration of the blood vessels. They may be localized or systemic and the pathology may range from simple inflammation to necrotizing arteritis or granuloma formation. Blood vessels of all sizes may be affected, so there is a wide spectrum of presentation. Most cases are idiopathic, but some complicate other conditions as in the case of rheumatoid vasculitis, SLE and dermatomyositis or polymyositis.

POLYARTERITIS NODOSA

Polyarteritis nodosa is a rare condition that primarily affects young men (age 20-50 years). Any small or medium-sized arteries may be affected. There is fibrinoid necrosis and polymorphonuclear-cell (in some cases eosinophil) infiltration with narrowing of the lumen and thrombosis. Local ischaemia and healing by fibrosis leads to the formation of small aneurysms (nodosa). The aetiology is unknown, but 20-40% of patients possess the hepatitis B antigen (see p. 405).

Clinical features include general malaise, weight loss and arthralgia. A purpuric vasculitic skin rash is common (3.96). Vasculitic digital infarcts are common (3.32, 3.33, 3.91). Patients may also present with livedo reticularis (3.97), and this may progress to severe ulceration of the limbs (3.98). Cardiac involvement may appear as pericarditis, myocardial infarction or a persistent tachycardia. Pulmonary infarction may occur (4.139). In the gastrointestinal tract there may be small bowel infarcts, haemorrhage and intussusception. Infarction of the gall bladder and pancreatitis may also occur. Neurological complications include mononeuritis multiplex, polyneuritis and occasionally subarachnoid haemorrhage. One-half of these patients are hypertensive; this may be related to renal involvement, which is associated with a poor prognosis (see p. 292).

Investigations reveal an elevated ESR and a high white cell count, anaemia, hyperimmunoglobulinaemia and sometimes hepatitis B antigen. Biopsy of muscle or kidney shows fibrinoid necrosis of the wall of medium-sized arteries and arterioles with cellular infiltrates. Visceral angiography may reveal characteristic aneurysms (6.72).

Treatment is with high-dose corticosteroids, usually in combination with an immunosuppressive agent, for example azathioprine. The prognosis is variable. Although spontaneous remission is possible, death usually occurs in months to years as a result of renal complications.
3.97 Livedo reticularis usually results from vasculitis at a deeper level in the dermis than that which leads to a purpuric rash (3.96). Here the typical 'reticular' appearance is complicated by two localized necrotic lesions on the calf.

3.98 Severe, necrotic ulceration of the legs in a patient with polyarteritis nodosa. Note the underlying marble-like pattern of livedo reticularis. Patients with skin involvement of this type rarely have severe systemic involvement and have a generally good prognosis when compared with those with a purpuric rash, which is more likely to be associated with renal involvement.

WEGENER’S GRANULOMATOSIS

Wegner’s granulomatosis is another uncommon condition of unknown aetiology. Small to medium arteries are affected and the pathology is that of necrotizing granuloma formation. Wegener’s granulomatosis consists of the clinical triad of upper respiratory tract granuloma, fleeting lung shadows and necrotizing glomerulonephritis. Initial presentation may be with rhinorrhoea and nasal mucosal ulceration followed by collapse of the nasal septum (3.99). There is later involvement of the lungs (see p. 198) and kidneys (see p. 293). Anti-neutrophil cytoplasmic antibodies (ANCA), though not specific, may be present. Corticosteroid therapy and cyclophosphamide may be of benefit but the prognosis is poor.

CHURG–STRAUSS SYNDROME

Churg–Strauss syndrome is like polyarteritis nodosa but less generalized. The small arteries and veins are predominantly involved and there may be extravascular granuloma formation. Patients present with asthma and hypereosinophilia, and chest radiographs show pneumonic-like shadows (see p.198). There may also be peripheral nerve involvement but renal complications are less common. The condition often responds well to steroids.
POLYMYALGIA RHEUMATICA (PMR) AND TEMPORAL ARTERITIS (TA)

PMR is a disorder that affects middle-aged or elderly patients. It is twice as common in women as in men. It is often of abrupt onset and presents with fever, malaise, weight loss and pain and stiffness in the proximal (shoulder—pelvic girdle) muscles. Patients have difficulty getting out of bed and walking up and down the stairs. Full blood count reveals a normochromic, normocytic anaemia and the ESR, plasma viscosity and CRP are almost always elevated. The course of treated PMR is usually limited to 1-2 years.

PMR and TA are described together because they often coexist. About one in six patients with PMR have TA, and one in four patients with TA have PMR. TA is a synonym for giant-cell arteritis, which affects mainly the large arteries, most frequently the temporal artery, with inflammatory cell infiltration and giant-cell formation in all layers of the vessels. Involvement of the ophthalmic artery in TA may lead to blindness and stroke is a much rarer complication. Additional symptoms that may be present include headache, which is usually unilateral and throbbing, visual disturbance, scalp tenderness and jaw claudication. The temporal artery may appear thickened, tender and nonpulsatile (3.100, 11.39). The ESR is characteristically over 100 mm in the first hour. Temporal artery biopsy may show giant-cell lesions (3.101), but these are patchy and a negative biopsy does not rule out the diagnosis.

If TA is suspected, treatment with high-dose corticosteroids (e.g. prednisolone 60 mg/day) should be started immediately, before any biopsy results are available, in order to prevent irre-versible blindness. The dose should be continued for several weeks before tapering down. Lower doses of steroid (e.g. prednisolone 10–15 mg/day) may be used with good response if there is polymyalgia without cranial symptoms. The steroid dose should be very slowly reduced over the course of 1–2 years, using ESR, plasma viscosity or CRP, and clinical symptoms as guides to disease activity. Steroid-induced osteoporosis is a significant risk, particularly as patients with PMR and TA are commonly relatively immobile, elderly and female. The risk may be reduced by the addition of calcium and vitamin D supplements, or possibly by the use of etidronate if long-term steroid therapy is required.

BEHÇET’S SYNDROME

Behçet’s syndrome is a rare syndrome of unknown aetiology in which small blood vessels, especially small venules, become acutely inflamed (vasculitis). This results in areas of recurrent ulceration in many organs of the body, especially in the mouth and genitalia, inflammation in the eyes, acute inflammatory joint disease and CNS and gastrointestinal involvement. The disease has a worldwide distribution with a high incidence in Japan and the Middle East and this is associated strongly with HLA-B51.

Men tend to be more severely affected than women but the distribution is equal. The usual age of onset is between 20 and 35 years of age.

The common clinical manifestations are painful oral aphthous ulcers (3.102) which are recurrent and often heal without
3.102 Behçet’s syndrome. Acute ulceration of the lip, accompanied by scarring from previous episodes.

3.103 Behçet’s syndrome. A typical penile ulcer, with an erythematous margin.

3.104 Behçet’s syndrome. Ulceration of the labium minus in the same patient as in 3.102.

3.105 Uveitis in Behçet’s syndrome is most common in patients who have HLA-B51. In this patient, there are severe changes with scleral haemorrhage.

Scarring. These are accompanied by genital ulceration (3.103, 3.104) and ocular symptoms caused by uveitis (3.105). Joint involvement is usually asymmetrical, acutely affecting the large joints of the lower limb, which are not permanently damaged.

Superficial thrombophlebitis may be present in 25% of cases and deep vein thrombosis in 5%, usually in the lower limbs. Large and small, arteries may also be acutely occluded (3–5%). The presence of uveitis and other CNS involvement carries a poor prognosis with a high incidence of blindness and death.

Otherwise, the natural history is one of fluctuating disease activity with general abatement of activity over many years. There is no specific therapy for the disease. Corticosteroids and azathioprine are of some value, especially in the management of acute uveitis.

**SOFT TISSUE DISORDERS**

Soft-tissue disorders are a major cause of morbidity in the general population. Most result from trauma or strain and fall outside the remit of this book, but some are covered briefly here.

**FIBROMYALGIA**

This is a vague syndrome of chronic musculoskeletal aches and pains in which there is no evidence of synovitis or myositis. Using clinical diagnostic criteria, it is now felt to be present in up to 10% of the population, and it therefore represents a very significant part of the medical workload. The usual clinical features are localized tenderness at specific places (tender points).

Common precipitating factors probably include

- Viral type illnesses
- Physical trauma
- Depression
- Steroid withdrawal
- Chronic fatigue syndrome
- Possibly Lyme disease (Lyme borreliosis) (see p. 54).

Rheumatologists have defined 18 sites (i.e. nine sites bilaterally) of which 11 should be tender for confirmation of the diagnosis. These are occipital, low cervical, trapezius, supraspinatus, second rib at costochondral junction, lateral epitrochlear, gluteal, greater trochanter and knee. There is a great range of declaration of pain intensity.

Fatigue associated with sleep disturbances is also commonly reported. Headache, migraine, irritable bowel syndrome, Raynaud’s phenomenon and depression are present in up to 50% of patients. Chronic fatigue syndrome coexists in 70% of cases.

Clinical examination is generally unhelpful except for the finding of ‘tender spots’. In addition, muscle spasm may sometimes be found with skin hypersensitivity and dermatographism. Laboratory tests should be aimed at excluding other relevant pathology. Treatment is aimed at physical, psychiatric and social support. Patient and family education on the lack of sinister significance of the symptoms may be helpful.
REPETITIVE STRAIN INJURY (RSI)

RSI is a poorly understood condition that can only be diagnosed clinically. Chronic pain develops during repetitive movements or as a result of the requirements of a job to hold a static posture. RSI is often associated with compensation claims against employers for working practice deficits leading to disability, but as yet there is no accepted definition and no relevant laboratory or imaging tests. There may be a psychological component to the disease, as very few self-employed workers complain of symptoms.

There is usually no history of direct muscle, bone or joint trauma, but ergonomic factors such as abnormal posture, heavy lifting or excessive continuous movements are implicated. Such people often have a history of a low pain threshold and abnormal stress responses. The dominant clinical presentation is with pains and aches, often in the shoulder girdle and upper limb. The pain is usually constant but may be exacerbated by weather, physical activity and stress. There may be local features in the limb such as 'pins and needles', heaviness and numbness. In addition there may be central features such as excess tiredness, altered sleep pattern and related behavioural problems.

Clinical examination may be unhelpful, but there may be skin tenderness, skin vasomotor disturbance (increased swelling, palmar erythema), some general joint tenderness, dermatographism and some localized increase in muscle tone, especially in the neck muscles.

Investigations should be directed at the exclusion of other better defined pathology. There are no diagnostic tests. Management is directed towards relief of symptoms, especially pain. If the symptoms involve the upper limb, a soft cervical collar worn during sleep may be helpful. General physical fitness and mobility should be encouraged. There is no evidence that anti-inflammatory drugs are of value.

BACK PAIN

Back pain is epidemic in most industrialized countries, especially where industrial compensation is available. It is estimated that up to 65% of the population will have back pain at some time and low back pain is the single commonest cause of time lost from work in many countries.

It is likely that the most common cause is mechanical, causing soft-tissue injury, facet joint damage or disc protrusion. Ageing is also relevant, as the various tissues become less elastic and less pliable with age. Most cases show little on initial investigation, especially in the young, and the majority (90%) resolve with adequate analgesia and rapid, progressive return to normal activity, which has now been shown to be better than bed rest, physiotherapy or exercise therapy. Some patients progress to overt clinical evidence of root compression, and this is usually associated with a herniated intervertebral disc.

HERNIATED INTERVERTEBRAL DISCS

Herniation of an intervertebral disc is common and its accurate diagnosis and treatment has financial and social, as well as medical, implications.

The material from the central portion of the disc (nucleus pulposus) may herniate through the annulus in two directions: lateral to the posterior longitudinal ligament, to compress the spinal roots; or posteriorly, to compress the cord or the cauda equina. The acute protrusion may follow trauma, abnormal movement or weight-bearing, but other factors such as degeneration of the disc, spondylosis or congenital abnormalities of the vertebrae may also be relevant. The common sites affected are the cervical and lumbar spine and the signs and symptoms depend on the site(s) and extent of the disc protrusion. If the protrusion is large, several adjacent nerve roots may be affected.

In the cervical spine, the most common sites are between C5/C6 and C6/C7. In the lumbar spine, the common sites are L4/L5 and L5/S1. Thoracic disc herniations are not common.

Local pain is common and may be exacerbated by movement, coughing or sneezing. There is usually associated local spasm and the patient resists all movements. Compression of the associated nerve results in pain referred along its distribution. Stretching of the nerve root exacerbates the pain and this forms the basis of the straight-leg raising test (3.106). Local pain may also be induced by pressing over the back. Sensory and motor symptoms and signs may identify the root involved.

Herniation of the disc into the cord may produce remarkably few local signs, and the patient may present with symptoms and signs of cord compression – muscle weakness, sensory loss and upper motor neuron signs.

Diagnosis is usually made on clinical examination and straight
X-ray of the spine. CT and MRI may help to identify more accurately the size and site of the herniation (3.107, 3.108) and these have replaced myelography as the investigations of choice.

Adequate analgesia and early mobilization are now seen as the most important forms of treatment. Local injection of steroids, manipulation and traction may all have a place. Surgery is indicated for intractable pain, or when the cord is involved, and consists of removal of the central portion of the disc. An alternative to surgery is the injection of proteolytic enzymes into the disc space.

**SPONDYLOSIS**

Spondylosis is the term applied to chronic degenerative changes that occur with ageing in the intervertebral discs and the associated changes in the adjacent ligaments and vertebral bodies, including the outgrowth of osteophytes. In most instances changes are found incidentally on a routine examination and do not produce symptoms. However, in the cervical and lumbar spine there may be sufficient new growth to cause pressure on nerves or on the cord itself. Symptoms and signs are usually slowly progressive, in contradistinction to those of a disc protrusion, which are acute. Radicular compression produces pain, which may be referred, and there may be associated muscle spasm. Lower motor neuron weakness and wasting may also occur in the same distribution. Spinal movement may be reduced and movement may exacerbate pain. The patient may be aware of ‘creaking’ or ‘clicking’ on movement. If the cord is involved, there may be myelopathy with progressive upper motor neuron weakness of the upper and lower limbs, with sensory signs, including loss of vibration sense and proprioception, and with sphincter disturbance.

Osteophytic outgrowth may also involve the vertebral canal, so that movements of the neck constrict the vertebral arteries and produce cerebellar ischaemia. These patients present with dizziness or drop attacks (‘vertebrobasilar syndrome’).

Straight X-ray of the cervical spine shows the typical degenerative changes with osteophyte formation (3.109, 3.110). Of greater importance is an assessment of the diameter of the spinal canal in cases in which myelopathy is present. This is best done by myelography or CT scan (3.111). In the cervical canal, a reduction to 10 mm is diagnostic of cord compression caused by spondylosis – a diameter greater than 15 mm suggests that spondylosis is not the cause of the myelopathic symptoms.

Spontaneous resolution of symptoms of radiculopathy and myelopathy occurs frequently in cervical spondylosis and treatment with a collar and analgesia is often helpful. Some patients benefit from bed rest with neck traction. Progression of the symptoms and signs of myelopathy requires urgent surgery for decompression.

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3.107 and 3.108 Prolapsed intervertebral disc. Axial and sagittal MRI scans show a large disc protrusion at the L5/S1 level, with resultant compression of the right S1 nerve root.

3.109, 3.110 Cervical spondylosis at the most common level (C5/C6) demonstrated by X-rays taken in full flexion and extension. Note the narrowing of the intervertebral spaces and the prominent osteophyte formation that leads to obvious abnormalities in the shape of the vertebral bodies. This appearance is very common in patients over the age of 50 years, and it is often asymptomatic.

3.111 Cervical spondylosis. A CT scan demonstrates that spur formation (arrow) is distorting the thecal sac; but, although the spinal cord is slightly displaced, it is not compressed.
HYPERMOBILITY SYNDROMES

Hypermobility syndromes are a range of inherited disorders in which there is musculoskeletal hypermobility as a result of ligamentous laxity, and in which there is no systemic rheumatological disease. Over the course of a lifetime a range of clinical features may become apparent, including

- Hyperextensible skin
- Joint hypermobility
- Increased incidence of synovitis
- Increased incidence of OA and stress fractures.

Hypermobility is a recognized part of the spectrum of features of the Marfan and Ehlers–Danlos syndromes. Clinically the features fall into articular and nonarticular groups. Articular features include joint instability, recurrent dislocation, subluxation, inflammatory synovitis, osteoarthritis, rotator cuff lesions and disc prolapse. Extra-articular features may include skin laxity, mitral valve prolapse, aortic root dilatation, muscle weakness — especially of the pelvic floor, with rectal and uterine prolapse — and fragile bones with stress fractures.

The diagnosis of hypermobility depends on the clinical picture, as hypermobility is not always associated with Ehlers–Danlos or Marfan syndromes, which can also be identified by genetic methods. Investigations in 'pure' hypermobility are usually negative except for X-rays, which may show the complications of joint damage.

There is no specific treatment but awareness of the disease and its implications is important. Mitral valve prolapse requires the use of prophylactic antibiotics to cover dental extraction and other procedures (see p. 247).

EHLERS–DANLOS SYNDROME

The Ehlers–Danlos syndrome is a group of rare inherited disorders of connective tissue in which patients have hyperextensible skin, hypermobile joints, fragile tissues and a bleeding diathesis associated with poor wound healing. There are many subtypes associated with a range of collagen defects; the common ones are transmitted as autosomal dominant traits. Type 1 has been widely described clinically and has the most severe manifestations. The extremely hyperextensible skin (3.112) and the hypermobile joints (3.113) were often features found in side shows (India-rubber man). With time, the skin becomes redundant and sags, particularly over joints. It is liable to bleed and wound healing is defective; this results in large pigmented scars especially over the knees and elbows. As all tissues are involved, a wide range of signs may be found, including retinal detachment, blue sclerae, dislocated lens, mitral valve prolapse, conduction defects, and aneurysm formation caused by defects in large arteries. No specific treatment is available to correct the defects, but advice should be given for skin and joint protection.

3.112 Ehlers–Danlos syndrome showing hyperelasticity of the skin.

3.113 Ehlers–Danlos syndrome showing extreme extensibility of the fingers.

MARFAN SYNDROME

Marfan syndrome is the most common inherited connective tissue disorder (1:10 000) and is due to a defect in the production of fibrillin, an extracellular matrix glycoprotein that is critical to the physical strength and elasticity of skin, ligaments, tendons, periosteum, aortic wall and ciliary body of the eye. The fibrillin genes have been identified on chromosomes 15 and 5. Transmission is by an autosomal dominant route with almost full penetrance (3.114).

3.114 Marfan syndrome. A typical family pedigree showing autosomal dominant inheritance.
The physical features of a typical patient with Marfan syndrome include
- **Skeletal**
  - Tall stature (3.115)
  - Scoliosis
  - Long arms
  - Arachnodactyly (3.116)
  - Chest wall deformity
  - Laxity of joints (especially knees)
  - High arched palate (3.117)
- **Cardiovascular**
  - Mitral valve prolapse
  - Aortic dissection (see p. 264)
  - Aortic valve incompetence
- **Ocular**
  - Subluxation of the lens (3.118)
  - Myopia.

A firm diagnosis should be made if there are features in three different systems, or a positive family history and features from two systems.

There is no specific treatment. One of the most common causes of death is aortic root dissection and annual ultrasound examinations are of value to measure the aortic diameter. β-blockers may be of value in preventing this complication by reducing blood pressure, and they should be started by the age of 8 years. Prophylactic aortic surgery is required if the root diameter reaches 6 cm. Mitral valve disease, most commonly mitral valve prolapse and mitral valve incompetence, is common. Antibiotic prophylaxis is indicated for dental procedures.

Pregnancy represents a particular hazard. Such patients should have regular routine ultrasound of the aortic root and delivery should be carefully supervised to ensure that blood pressure is not elevated during labour; caesarian section has been advocated.

Genetic counselling should be offered to all parents.

**3.115-3.118 Marfan syndrome** is an autosomal dominant condition, in which there is tall stature, and reduced upper segment to lower segment ratio (3.115), long fingers (3.116) and toes, and often a high arched palate (3.117). It is commonly associated with laxity of the joints, dislocation of the lens in the eye (3.118), dissecting aneurysm of the aorta, aortic regurgitation and a floppy mitral valve. The patient in 3.115 has undergone surgery for aortic dissection. The length of the fingers can be demonstrated by the ‘wrist sign’ (3.116), in which the patient can encircle his wrist with the opposite thumb and fifth finger. The ability to do this is strongly suggestive of Marfan syndrome.
DISEASES OF BONE

Bone is a collagen-based matrix with mineral laid upon it, and its strength depends on both components. The mineral phase is composed mainly of calcium, magnesium and phosphorus. Vitamin D, parathyroid hormone (PTH) and calcitonin are important factors in bone mineralization. New bone is deposited by osteoblasts and old bone resorbed by osteoclasts. Bone is a living and dynamic tissue, constantly remodelling itself throughout life.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (brittle bone disease) is a genetically determined disease in which an abnormal bone matrix and secondary osteoporosis are associated with the likelihood of recurrent bone fractures (3.119), small stature, joint laxity and discoloured, soft teeth. Blue sclerae are a reflection of the generalized collagen defect (3.120).

There is no specific treatment. Attention must be paid to the prevention of fracture by the use of safety appliances, while keeping the patient mobile. Fracture-associated deformities must also be prevented when possible.

Genetic advice is required, and patients and families should be seen in a specialized unit because of the range of possible genetic defects. Accuracy of diagnosis is of great importance to prevent the risk of either missing or falsely diagnosing non-accidental injury (child abuse), which is the other major cause of multiple fractures in infants and young children.

OSTEOPOROSIS

Osteoporosis is the most common metabolic bone disease. Its frequency increases with age, and women are more commonly affected than men. The weakened bone fractures easily and accounts for much morbidity and indirect mortality in the elderly. There is an absolute decrease in bone mass (mineral and nonmineral) resulting from an increased bone resorption rate (3.121, 3.122). The aetiology of most cases remains unclear, but the effects of ageing, failure of oestrogen secretion at the time of menopause and lack of physical activity are probably of particular importance. Known risk factors for osteoporosis are listed in 3.123, and diseases associated with osteoporosis are shown in 3.124.

RISK FACTORS FOR OSTEOPOROSIS

- Genetic
- Female sex
- Deficient diet
- Increased age
- Sedentary occupation
- Caucasian race
- Premature menopause
- Cigarette smoking
- Excess alcohol intake
- History of amenorrhoea
- Underweight
- Systemic corticosteroid use
- Long-term heparin therapy
- Pregnancy
- Lack of hormone replacement therapy
Asymptomatic osteoporosis is common. In patients who are symptomatic, backache is a frequent complaint. There may be episodes of severe pain caused by fractures of the weakened bones. Collapse of vertebrae may result in loss of height (3.125). The lumbar and thoracic vertebrae, the upper end of the humerus (3.126), the lower end of the radius and the neck of the femur are the most common sites of fracture (3.127).

The bone radiographs show loss of bone density, reduction in the number and size of trabeculae and thinning of the cortex. The lumbar and thoracic vertebral bodies become biconcave in shape, with anterior wedging caused by compression or collapse (3.128, 3.129). Blood levels of calcium, phosphate and alkaline phosphatase are normal.

### Diseases Associated with Osteoporosis

- Multiple myeloma
- Thyrotoxiosis
- Cushing's syndrome
- Osteogenesis imperfecta
- Chronic renal failure
- Hypogonadism
- Hypopituitarism
- Post gastrectomy

3.124 Diseases associated with osteoporosis.

3.125 Osteoporosis results in loss of height, and vertebral collapse is associated with chronic backache, bouts of severe back pain and kyphosis (dowager's hump). Creases often appear in the skin, and the ribs may rub on the iliac crest.

3.126 Osteoporosis has caused a loss of cortical thickness and an opening up of the trabecular pattern in this radiograph of the humerus.

3.127 Osteoporosis is the usual underlying disorder in fracture of the neck of the femur in the elderly. This patient has a subcapital fracture, which may lead to osteonecrosis of the femoral head.

3.128 Osteoporosis leads to vertebral collapse. This radiograph shows wedge-shaped flattening of the vertebral bodies in the midthoracic region.

3.129 Vertebral thinning and collapse in osteoporosis demonstrated by MRI. The wedging and collapse is similar to that seen in 3.128. The patient experienced repeated episodes of severe back pain, radiating anteriorly on occasions as a result of nerve root compression.
Reversal of osteoporosis is unlikely once the condition is established and prophylaxis is preferable. Bone density can now be measured and repeatedly monitored by DEXA scanning (3.130), and this technique has a role in screening and follow-up for osteoporosis. Any primary factor, such as endocrine disease or the use of long-term corticosteroids, should be corrected if possible. Hormone replacement therapy in the postmenopausal woman is helpful if started early. Other prophylactic measures include regular exercise and adequate intake of vitamin D and calcium.

**OSTEOMALACIA AND RICKETS**

Deficiency of vitamin D, causing osteomalacia in adults and rickets in children, is now fairly uncommon in the Western world although it may occur in Asian immigrants and the elderly, as a result of a combination of dietary insufficiency and lack of exposure to sunlight. Other causes of osteomalacia and rickets are summarized in 3.131.

The main function of vitamin D is to ensure an adequate concentration of calcium for the formation of calcium salts in
bone. Deficiency results in poor bone mineralization and a reduction in tensile strength.

Childhood rickets usually manifests itself as bony deformity or failure of adequate growth. Signs include bossing of the frontal and parietal skull bones (3.132), delayed closure of the anterior fontanelle, rickety rosary (enlargement of the epiphyses at the costochondral junctions of the ribs), pigeon deformity of the chest and bowing or other deformities of the legs (3.133).

In the adult, osteomalacia may produce skeletal pain and tenderness and spontaneous bony fractures. Muscle weakness is often present and there may be a marked proximal myopathy.

In both conditions, tetany may be manifest by carpopedal spasm and facial twitching. Investigations show low or low-normal plasma calcium, low serum phosphate and increased alkaline phosphatase. Radiographs show rarefaction of bone (defective mineralization) and translucent bands (pseudofractures, Looser’s zones), especially in the pelvis, ribs and long bones (3.134). In children, there may be additional changes in the epiphyseal zone which becomes broadened (3.135). Bone biopsy may sometimes be required for diagnosis in adult cases (3.136).

Prevention is better than cure. Education and living standards should be improved in the susceptible populations. Free access to and adequate dietary intake of vitamin D should be ensured. Supplements should be given to epileptic patients on long-term anticonvulsants. High replacement doses are required in patients with renal disease and those with vitamin D resistance.

**HYPERPARATHYROIDISM**

Parathormone (PTH), from the parathyroid glands, controls the concentration of calcium and inorganic phosphorus in the blood. It raises the plasma calcium by enhancing the removal of mineral from the skeleton, increasing absorption from the bowel and reducing tubular reabsorption in the kidneys. It also increases the synthesis of vitamin D and lowers the serum phosphate by enhancing its excretion. Under normal physiological conditions, parathyroid hormone levels rise as the plasma calcium falls. Abnormally raised PTH levels may result from a parathyroid adenoma (primary hyperparathyroidism) and conditions that cause a tendency to hypocalcaemia, for example chronic renal failure (secondary hyperparathyroidism). If secondary hyperparathyroidism becomes long-standing, the glands may become autonomous and continue to secrete excess PTH (tertiary hyperparathyroidism).
Patients with mild hyperparathyroidism may be asymptomatic. Clinical features in the more severe cases are related to hypercalcaemia and patients complain of malaise, anorexia, nausea and vomiting, drowsiness or confusion. Peptic ulceration and acute pancreatitis may be the presenting features. Kidney involvement may manifest itself as renal colic from stones, haematuria, polyuria or nocturia from tubular damage. Bone pain suggests involvement of the bones and backache is common. Pseudogout may occur (see p. 139).

The plasma calcium may be high and the phosphate level low. Alkaline phosphatase is raised, reflecting increased osteoblastic activity in response to bone resorption. Radiological changes in the early stages include demineralization or subperiosteal erosions in the phalanges (3.137). Cystic changes (3.138) are rare. A lateral skull radiograph may reveal a typical 'ground glass' appearance (3.139). Other radiological features include nephrocalcinosis (see p. 304) and soft-tissue calcification elsewhere. Calcification may sometimes be seen in the eye (3.140).
It is important to exclude other causes of hypercalcaemia such as malignancy (particularly multiple myeloma p. 466), sarcoid and drugs, including excess vitamin D. Detection of PTH by radioimmunoassay in the presence of hypercalcaemia is diagnostic of hyperparathyroidism and the second stage is the localization of the tumour or tumours. The best approach is surgical exploration of the neck, which in experienced hands has a 90% success rate in locating and removing the adenoma. Other methods involve CT scanning, radionuclide scanning (3.141) and selective venous sampling for PTH. Definitive treatment is surgical resection.

Hyperparathyroidism may sometimes be a component of the multiple endocrine neoplasia (MEN Type 1) syndrome, in which there are multiple tumours of the anterior pituitary, parathyroids, pancreatic islet cells, adrenal medulla and thyroid in association with peptic ulceration (see also p. 319). The fundamental defect in this syndrome is in the differentiation of neural crest tissue. The parathyroid glands are most commonly affected, followed by pancreatic islet cells and the anterior pituitary. All four parathyroid glands are abnormally hyperplastic or adenomatous. There are usually few clinical features at first. The patient may have had renal stones and developed renal failure as the first presentation, and hypercalcaemia may be found when calcium levels are measured.

RENAL OSTEODYSTROPHY

Patients with chronic renal failure may develop various forms of bone disease. These include osteomalacia, hyperparathyroidism (secondary and tertiary) and osteosclerosis. Osteomalacia is caused by failure of the damaged kidneys to produce the metabolically active 1,25-dihydroxycholecalciferol. Poor absorption of dietary calcium and retention of phosphate lowers the serum calcium. This leads to the development of secondary hyperparathyroidism and, if this becomes long-standing, tertiary hyperparathyroidism. Clinical features and radiological appearances are as those described in the previous related sections and there may be extensive ectopic calcification in soft tissues (3.142) and arterial walls. The cause of osteosclerosis, the third type of bone lesion, is less clearly understood, although it may be a direct result of excess parathyroid hormone. It produces the characteristic 'rugger-jersey spine', a radiographic appearance caused by the formation of alternate bands of sclerotic and porotic bone in the vertebrae (3.143).

Renal osteodystrophy can be partially prevented and treated. Aluminium hydroxide gel given by mouth binds phosphate and lowers its concentration, and vitamin D resistance can be overcome by giving the newer biologically active derivatives. Resection of the parathyroid glands is now rarely indicated.

3.141 A large parathyroid adenoma (arrowed), demonstrated by radionuclide scanning. This is a subtraction scan, obtained by subtracting a technetium scan, which shows the thyroid only, from a thallium scan, which shows both the thyroid and the parathyroids.

3.142 Extensive ectopic calcification around the soft tissues of the shoulder in a patient with chronic renal failure and renal osteodystrophy.

3.143 'Rugger-jersey spine' in secondary hyperparathyroidism caused by the demineralization of the vertebral bodies, with simultaneous new bone formation at the subchondral plates.
OSTEONECROSIS (AVASCULAR NECROSIS)

Osteonecrosis is the final common pathway of a series of physical and chemical disturbances that lead to the cell death of both bone and marrow. The femoral and humeral heads are the most common sites.

The disease progression is often slow in onset and insidious. Pain over the affected joint is often low grade and may be present for many weeks in which the standard X-ray appearances are normal. There is then limitation of joint movement with shortening of the limb as the bone structure collapses.

MRI scanning shows early changes before CT or radionuclide imaging, and ultimately changes are also visible on plain X-ray (3.144). Some aetiological factors are shown in 3.145.

Treatment involves preventing the affected joint from bearing weight and stopping its use, removing or treating any obvious causative factor and resting the part until healing takes place in 6–8 weeks. Occasionally surgery and bone grafting are necessary.

AETIOLOGICAL FACTORS IN OSTEONECROSIS

<table>
<thead>
<tr>
<th>Causative</th>
<th>Trauma – fracture or dislocation</th>
<th>Radiotherapy</th>
<th>Caisson disease</th>
<th>Sickle-cell disease</th>
<th>Gaucher's disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associations</td>
<td>Cushion's disease or high-dose steroid use</td>
<td>Oclusive arterial disease</td>
<td>Diabetes mellitus</td>
<td>Osteomalacia</td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

3.144 Osteonecrosis (avascular necrosis) of the head of the humerus in a patient who had been treated with long-term systemic steroid therapy for Takayasu's arteritis.

3.145 Aetiological factors in osteonecrosis.

PAGET'S DISEASE OF THE BONE

Paget's disease of the bone, also known as osteitis deformans, is common in the elderly (up to 10%). The aetiology is unknown, but there is a weak familial tendency. Geographical clustering of this condition emphasizes the importance of environmental factors. There is an increase in osteoclastic activity, compensated for by an increase in osteoblastic activity which results in disorganization of the normal bone architecture and an increase in bone vascularity. Any bone can be affected, including especially the pelvis, lumbar spine, femur, thoracic spine, skull and tibia.

Patients are often asymptomatic and Paget's disease of the bone is commonly an incidental finding. Those who are symptomatic complain of constant and localized bone pain, unrelieved by posture or rest. There may be bone deformities such as frontal bossing (3.146), distorted facial features and bowing of the tibia (3.147). The affected bone may feel warm on palpation and a bruit may be heard. Complications include

3.146 Paget's disease. Frontal bossing of the skull leads to a distorted facial appearance. This patient has gross changes and she presented with deafness secondary to ossicular involvement.

3.147 Paget's disease. Bone deformity has led to bowing of the legs and compression of the trunk, giving the appearance of relatively long arms.
blindness caused by nerve compression, deafness secondary to ossicular involvement or to nerve compression by the enlarging bone, secondary OA, and pathological fractures (3.148). High-output cardiac failure and osteosarcoma are rare but serious complications.

Investigations show raised alkaline phosphatase, reflecting the compensatory increase in osteoblastic activity, but normal calcium and phosphate levels. There is also an increase in urine excretion of hydroxyproline. Radiographs show lucency zones, caused by bone resorption and osteolysis, and areas of increased bone density (3.148, 3.149). Bone scans with 99m-technetium-labelled bisphosphonates are useful and may show the extent of disease more effectively than other techniques (3.150).

Drug treatment is indicated only when patients become symptomatic or develop complications. In such cases, calcitonin and bisphosphonates may be used. Conservative measures, such as the use of simple analgesics, physiotherapy and correction of inequality of leg length, are also required.

## OSTEOMYELITIS

Infection in bone may result from bloodborne or direct spread of a number of microorganisms (3.151) and various conditions predispose to bone infection (3.152). Direct spread of infection to the bones occurs most commonly in diabetics with neuropathic
foot ulcers (3.153, 3.154) and in patients with penetrating bed sores.

Acute osteomyelitis is usually caused by *Staphylococcus aureus*. Patients often present with fever, pain and tenderness over the affected bone, but the presentation may be more nonspecific, without initial localizing features. Blood culture or needle biopsy are usually required for definitive diagnosis, but treatment can sometimes be started on clinical grounds alone.

Chronic osteomyelitis results from undiagnosed or inadequately treated acute osteomyelitis. Within 2 weeks of onset of acute osteomyelitis, radiographic changes can often be seen, and these progress to include periosteal elevation, bone erosion, areas of sclerosis and areas of cystic degeneration (3.154). Avascular necrosis of the bone leads to the development of a bony sequestrum (3.155). Intermittent episodes of acute flare up of the disease may occur over many years, with fever, local pain and sinus formation.

Treatment of chronic osteomyelitis often involves a combination of surgery and antibiotic therapy. Patients with sickle cell disease should receive long-term penicillin prophylaxis to prevent *Salmonella* osteomyelitis (3.155).

Chronic tuberculous osteomyelitis results from blood or lymphatic spread. The long bones and vertebral bodies are most commonly involved. Tracking of pus produces a ‘cold’ abscess (3.63) and destruction and subsequent collapse of the vertebra leads to gross kyphosis (Pott’s disease of the spine, 3.156). Surgery and antituberculous therapy are commonly required.

3.153 A purulent discharging ulcer at the base of the big toe in a diabetic patient. The ulcer is associated with osteomyelitis of the first metatarsal head (see 3.154).

3.154 Osteomyelitis at the base of the ulcer seen in 3.153, associated with X-ray changes, including bone erosion and sequestrum formation.

3.155 *Salmonella* osteomyelitis is a common complication of sickle-cell disease. In this child, extensive unilateral osteomyelitis has caused long bone sequestrum formation and a ‘bone within a bone’ appearance.

3.156 Pott’s disease of the spine. Chronic tuberculous osteomyelitis of the lower thoracic vertebrae has caused a typical angular kyphosis.
TUMOURS OF BONE

Primary tumours of bone are rare and occur mainly in the young (3.157).

Secondary metastases in bone are common, especially from malignant tumours of the lung, breast, prostate, thyroid and kidney. Most metastases are osteolytic (3.158), but secondaries from carcinoma of the prostate are often sclerotic in character (3.159). Multiple metastases are common (3.160), and lytic bone lesions are also a feature of multiple myeloma (see p. 466).

Bone secondaries are often painful and may cause hypercalcaemia. Symptomatic treatment is usually necessary, and specific hormone treatment or chemotherapy may be helpful in some cases.

3.157 Osteosarcoma of the humerus in a 15-year-old boy. The radiograph shows lytic defects within the bone, periosteal new bone formation and a characteristic 'sunray' spiculation in the soft tissues.

3.158 An isolated lytic secondary in the femur. The deposit is the site of a pathological fracture, but has otherwise stimulated little bone reaction. The primary tumour was in the thyroid gland.

3.159 A sclerotic secondary deposit (arrowed) occupying the body of the third lumbar vertebra. The primary tumour is carcinoma of the prostate.

3.160 Multiple bone metastases are seen in this 99m Tc-MDP bone scintigram of a 46-year-old woman with lung cancer. A similar appearance may occur with other metastases, for example from tumours of the breast or kidney.
RESPIRATORY

HISTORY

A full medical history is important in any patient with respiratory symptoms or signs. Specific questions should always be asked about

- cough
- sputum — production, volume and colour
- breathlessness — onset, duration and positional variations
- wheezing
- fever
- chest pain
- nasal or upper respiratory tract symptoms
- weight loss
- smoking history
- occupation.

EXAMINATION

On general examination, there may be clues to the underlying disease:

- cachexia (4.1) may occur in malignant disease, and in severe chronic lung diseases, including fibrosis, infection and emphysema
- ‘nicotine’ stained fingers occur in heavy smokers (4.2), and typical pigmented scars may occur in coal miners (4.3); in association with finger clubbing (2.59, 2.104, 2.105, 4.2, 4.101, 4.148, 11.121) both signs have an ominous significance, suggesting underlying bronchial carcinoma, pulmonary fibrosis, bronchiectasis or chronic sepsis
- cyanosis — best seen in the lips (4.98), tongue (4.4) and fingers — indicates significant desaturation of circulating haemoglobin

4.1 Cachexia may occur in a number of severe disorders, including chronic lung diseases such as pulmonary fibrosis, tuberculosis and emphysema, malignant disease, including bronchial carcinoma, and systemic infection, especially with HIV ('slim disease'). Note the obvious signs of weight loss, with widespread muscle and soft-tissue wasting.

4.2 ‘Nicotine’ stained fingers — a misnomer, because it is the tar from cigarettes which causes the staining. This patient smoked 40 cigarettes per day, but staining is more dependent on the action of smoking cigarettes right to the stub than on the total number smoked. This patient also has acute, recent onset clubbing (note the reddening and swelling of the nailfolds). He had bronchial carcinoma.
• a plethoric appearance may result from polycythaemia (4.5)
  most commonly secondary to chronic hypoxia in lung disease. 
On examination of the chest
• distortion of the thoracic cage suggests chronic disease and may take many forms; look for
  – barrel-shaped chest in obstructive airways disease (4.6)
  – flattening of the chest wall overlying lung damage or collapse
  – kyphosis or kyphoscoliosis may be a primary abnormality (4.7), or secondary to other disease (3.48, 3.125, 4.41)
  – scars from previous thoracic surgery
• the respiratory rate and depth may be raised or lowered
  – is there hypoventilation or hyperventilation?

4.3 Impregnation with coal dust is commonly found in the hands of coal miners, and may give a clue to the presence of occupational lung disease (pneumoconiosis).

4.4 Central cyanosis is seen in the tongue, lips and earlobes. It is caused by the presence of high levels of deoxygenated haemoglobin. Here, the cyanotic patient's tongue (left) is compared with that of a normal individual (right). The blue appearance is characteristic, and may occur in severe respiratory or cardiovascular disease.

4.5 Secondary polycythaemia has developed in the patient on the right as a consequence of chronic hypoxic lung disease. Compare her appearance with that of the normal woman on the left.

4.6 Barrel-shaped chest in a patient with chronic asthma. The hyperinflation results from air-trapping associated with inflammatory changes, hypersecretion of viscid mucus and smooth muscle contraction in the small airways. Note the associated indrawing of the intercostal muscles. Similar changes are seen in patients with chronic bronchitis and emphysema.

4.7 Severe kyphoscoliosis of unknown aetiology. Flexion (kyphosis) and lateral deviation (scoliosis) of the spine have the combined effect of reducing chest volume (see 4.41). This compromises respiratory function, so that otherwise minor chest infections may precipitate respiratory failure.

4.8 Dyspnoea in a patient with severe asthma. Note the contraction of the accessory muscles of respiration.
Physiologic signs in respiratory disease

- are the accessory muscles of respiration in use (4.8)?
- is the patient fatigued?
- does the patient breathe out through pursed lips (4.9)?
- respiratory movements may be asymmetrical
- cervical lymph nodes may be visible (4.10) or palpable

**4.9 Pursed lip expiration** is a common manoeuvre adopted by patients with severe chronic obstructive pulmonary disease. The patient starts to breathe out against closed or nearly closed lips to keep the intrabronchial pressure high and prevent collapse of the bronchial wall and expiratory obstruction. Later in expiration the lips are blown forwards and open, often with a grunt ('fish-mouth breathing').

- look and palpate for a goitre
- feel in the suprasternal notch for tracheal deviation
- examine a sputum sample if possible
- key findings in the main groups of lung disease on palpation, percussion and auscultation are summarized in 4.11.

**4.10 Gross enlargement of supraclavicular and cervical lymph nodes.** This appearance may develop in tuberculosis and similar enlargement may occur with lymphomas, chronic lymphatic leukaemia and disseminated malignant disease. Biopsy is usually necessary for definitive diagnosis.

### PHYSICAL SIGNS IN RESPIRATORY DISEASE

<table>
<thead>
<tr>
<th>Lung pathology</th>
<th>Chest expansion</th>
<th>Mediastinal shift</th>
<th>Percussion note</th>
<th>Breath sounds</th>
<th>Voice sounds</th>
<th>Added sounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Reduced on both sides</td>
<td>Nil</td>
<td>Normal</td>
<td>Vesicular with prolonged expiration</td>
<td>Normal</td>
<td>Expiratory wheeze</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>Reduced on both sides</td>
<td>Nil</td>
<td>Normal</td>
<td>Vesicular with prolonged expiration</td>
<td>Normal</td>
<td>Expiratory wheeze and crackles</td>
</tr>
<tr>
<td>Consolidation (lobar pneumonia)</td>
<td>Reduced on affected side</td>
<td>Nil</td>
<td>Impaired</td>
<td>Bronchial</td>
<td>Increased</td>
<td>Crackles</td>
</tr>
<tr>
<td>Lung or lobar collapse</td>
<td>Reduced on affected side</td>
<td>Towards affected side</td>
<td>Impaired</td>
<td>Diminished vesicular</td>
<td>Reduced</td>
<td>Nil</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Normal or reduced on both sides</td>
<td>Nil</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Coarse mid-inspiratory crackles</td>
</tr>
<tr>
<td>Fibrosing alveolitis</td>
<td>Reduced on both sides</td>
<td>Nil</td>
<td>Normal</td>
<td>Diminished vesicular (especially at bases)</td>
<td>Normal</td>
<td>Late inspiratory crackles</td>
</tr>
<tr>
<td>Localised fibrosis</td>
<td>Reduced on affected side</td>
<td>Towards affected side</td>
<td>Impaired</td>
<td>Bronchial</td>
<td>Increased</td>
<td>Crackles</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Reduced on affected side</td>
<td>To opposite side</td>
<td>Hyper-resonant</td>
<td>Diminished vesicular</td>
<td>Reduced</td>
<td>Nil</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Reduced on affected side</td>
<td>To opposite side</td>
<td>Stony dull</td>
<td>Diminished vesicular, occasionally bronchial at air fluid margin</td>
<td>Reduced</td>
<td>Rarely a pleural rub</td>
</tr>
</tbody>
</table>

4.11 Physical signs in respiratory disease.
INVESTIGATIONS

SPUTUM

Naked-eye examination of the sputum can give vital clinical information.
- Consistently large volumes (at least 1/2 cup/day) suggest bronchiectasis.
- Rupture of an abscess, empyema or cyst into a bronchus may produce a sudden increase in volume.
- Infected sputum is usually yellow or green because of the large number of polymorphs it contains.

- Blood in the sputum produces a pink tinge in the typical frothy sputum of left ventricular failure, deep red flecks in bronchial carcinoma and pulmonary embolism, and a rusty colour in pneumococcal pneumonia (4.12).
- Black sputum may be found in workers in a dusty environment or after smoke inhalation.
- Thick viscid sputum, sometimes taking the form of bronchial casts, is often seen in asthma and in allergic bronchopulmonary aspergillosis (4.13).
- Rupture of a hepatic amoebic abscess into the lung gives an 'anchovy sauce' appearance to sputum.
- Rupture of a hepatic hydatid cyst into a right lower lobe bronchus produces bile-stained sputum.

4.12 Rusty-red sputum (left) compared with fresh haemoptysis (right) in two sputum samples. The rusty red sputum comes from a patient with pneumococcal pneumonia, whereas the haemoptysis occurred in a patient with small-cell lung cancer.

4.13 Typical sputum plug of allergic bronchopulmonary aspergillosis. These are usually brownish and firm or rubbery. On microscopy or culture they show Aspergillus. This plug was aspirated at fibreoptic bronchoscopy in a patient with segmental collapse on the chest radiograph. Similar plugs may be seen in patients with asthma but without aspergillosis.

4.14 Asbestos body in sputum. The typical drumstick appearance represents an asbestos fibre surrounded by a ferroprotein complex. It is indicative of asbestos exposure with associated increased risks of bronchial malignancy and (with blue asbestos) mesothelioma.

4.15 Ziehl-Nielsen staining of sputum showed many red-staining tubercle bacilli in this patient with pulmonary tuberculosis.
Microscopic examination of sputum may show asbestos fibres (4.14), Charcot–Leyden crystals derived from eosinophils, fungal spores or clumps of pathogenic bacteria (4.15).

Sputum culture is of value in identifying bacteria and fungi and in testing for drug sensitivity. Culture normally takes 24–48 hours for pyogenic bacteria (up to 8 weeks for mycobacteria). Therapy should often be started without waiting for the results of culture.

For sputum cytology, as much sputum as possible should be sent fresh to the laboratory. The results are excellent with central tumours (80–90% positive, 4.16), but much less successful with peripheral tumours.

**SKIN TESTS**

Skin-prick testing may be useful in establishing the patient's immediate (type I) sensitivity to common allergens, thus confirming the patient's atopic state, and providing useful information about the possible role of allergens in disease.

Skin-prick testing may be useful in urticaria, asthma, rhinitis, allergic conjunctivitis and other allergic conditions, though false positive results are common in atopic eczema.

In skin-prick testing, a tiny quantity of allergen is introduced into the superficial layers of the stratum corneum (4.17).

A true positive skin-prick test reaction (4.18, 4.19) indicates that specific IgE is fixed to mast cells in the skin and has led to

4.16 Adenocarcinoma cells in a sputum smear. The assessment of the appearances on sputum cytology is a very specialized field, and an expert opinion is essential for the definitive diagnosis of malignancy.

4.17 Skin-prick testing. The volar surface of the forearm is cleaned, prick sites are marked, and drops of allergen extract in appropriate concentration are placed on the skin. The test should always include a negative control of 0.5% phenol saline, the suspending solution for the allergens, and histamine 1% as a positive control. A lance or a standard needle is introduced through each drop at 45° to the skin surface to a depth of about 1 mm, the skin is lifted slightly, and the lance withdrawn. The procedure is painless, and the puncture sites should not bleed. The skin is blotted dry, and the resultant reaction is assessed at 15–20 minutes (see 4.18).

4.18 Reading the skin-prick test results. The maximum reaction is usually seen after 15–20 minutes. The saline control (N) should be negative (unless the patient has dermographism; 2.41). The histamine control (H) should be positive; recent antihistamine administration may cause a negative result, and this invalidates other negative reactions. The presence of a positive skin response indicates the presence of specific IgE antibody in the blood, and there is a reasonable correlation between the size of the weal and the significance of different inhaled allergens in a single patient. Positive results are best recorded by measuring the diameter of the weal in millimetres, using a transparent gauge or a ruler. Here the strongest reaction is to grass pollen (GP), and significant positive reactions are also seen to cat (C) and the house-dust mite *Dermatophagoides pteronyssinus* (Dpt). The interpretation of the response depends on the clinical history.
a vasoactive response caused by release of histamine. When the allergen concentration is high, or the patient’s sensitivity is extreme, a late skin reaction may also follow 4–6 hours (or even as late as 24–48 hours) after the test, with erythema, swelling and induration.

When performed in patients with asthma, with appropriate positive (histamine) and negative (diluent) controls, skin test results correlate well with the results of bronchial challenge testing (which is not performed routinely), and thus give useful information on the allergens involved; however, the results must always be correlated with clinical history. For inhaled allergens, up to 15% of positive results are false positives, but fewer than 5% of negative results are false negatives. However, skin testing is relatively unreliable for ingested allergens including food, partly because of the nature of the available allergen preparations and partly because reactions to ingested substances are not always mediated by IgE.

Only a small number of allergens are needed for routine skin-prick testing in patients with asthma or rhinitis. A typical skin test battery can include four antigens, together with positive and negative controls (4.20). Additional antigens can be added when there is a clear possibility of the involvement of other allergens. The role of some allergens cannot be successfully investigated by skin-prick testing, and occupational allergens are also usually better identified by other means.

Strongly positive tuberculin tests (1.132) are of value in diagnosing tuberculosis in individual patients, and tuberculin testing also has a role in screening contacts and in pre-BCG (Bacillus Calmette–Guerin) assessment.

### BLOOD TESTS

Venous blood samples taken for automated blood counts may provide major clues or confirmation of a suspected respiratory disease. A high haemoglobin concentration may be a reflection of polycythaemia, either primary or secondary (4.5) and a low haemoglobin may cause breathlessness. The total white cell count may be elevated in a range of acute bacterial infections and its subsequent fall is a reflection of successful therapy. Normal or low white cell counts are found in mycoplasma or viral infections. Eosinophilia (1.19) suggests an allergic component or parasitic infection.

A range of serological tests that depend on agglutination, precipitation and complement fixation provide evidence of the presence in the patient’s serum of specific antibodies against viral, bacterial, fungal, protozoal and helminth infections. Samples of blood should be tested on admission and repeated after 10–14 days to detect a rising titre.

Radioallergoabsorbent tests (RASTs) on venous blood are an alternative to skin-prick tests as a method of identifying specific IgE antibodies.

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**ALLERGEN EXTRACTS COMMONLY USED IN SKIN TESTING**

**Routine short screen for atopy:**

- Phenol saline (negative control)
- Histamine (positive control)
- House dust mite*
- Grass pollen**
- Aspergillus fumigatus
- Cat

**Additional allergens which may be used:**

- Tree/weed/other plant pollens
- Alternaria
- Cladosporium
- Dog
- Any other relevant animals
- Any relevant foods
- Any other relevant inhaled allergens

* Mixed ‘house dust’ extracts may be used in the routine screen; alternatively specific allergens from Dermatophagoides pteronyssinus and/or Dermatophagoides farinae may be used.

** In some regions it is appropriate to include an alternative pollen antigen in the routine screen (e.g. birch in Scandinavia, ragweed in North America). The mix of grass pollens used may also vary between regions.

---

4.19 Multiple positive skin test results. Many asthmatics have multiple positive skin test reactions to common allergens, showing the ease with which they make IgE antibodies to common allergens in the environment. This British patient had positive reactions to grass, plane and silver birch pollens, cats, dogs and Alternaria. All may contribute to his asthma, which is perennial with a tendency to seasonal exacerbations during the period from April to August. The other allergens gave negative results; the flare reactions should be regarded as nonspecific (a common reaction in patients with eczema), and there was no measurable weal.

4.20 Allergen extracts commonly used in skin testing.
BLOOD GASES

The presence of respiratory failure may be suspected by the signs of central cyanosis. It is important to define the type and extent of failure of oxygenation and this is best done by measurement of arterial blood gas tensions (\(PaO_2\) and \(PaCO_2\)), oxygen saturation (\(SaO_2\)) and pH (4.21). The response to drugs and the therapeutic response to oxygen can then be monitored easily. Haemoglobin saturation reflects oxygen carriage by the blood and thus the adequacy of tissue oxygenation (if perfusion is satisfactory) and the requirement for oxygen therapy. This can be measured noninvasively by pulse oximetry (4.22, 4.23). The arterial partial pressure of carbon dioxide (\(PaCO_2\)) is a good indication of ventilation, low values indicating hyper-ventilation and vice versa; it is often more important than the \(PaO_2\) in assessing the need for assisted ventilation.

PULMONARY FUNCTION TESTS

Simple pulmonary function tests may easily be done at home or at the bedside using a peak flow meter or gauge (4.24). This gives

4.21 Arterial blood sampling can be carried out from the femoral, brachial or radial arteries, but the most common site is the radial artery in the patient’s nondominant arm. Firm pressure should be applied after withdrawal of the needle to prevent local haematoma formation.

4.22 & 4.23 Pulse oximeter. The widespread introduction of pulse oximeters has been a great benefit in many areas of medicine, as oxygen saturation may be monitored noninvasively via a probe on a finger or earlobe. The estimation of oxygen saturation is not accurate at very low levels but, in the usual range for all but the most severe respiratory failure, oximeters are accurate if cardiac output and local circulation are adequate.

4.23

4.24 Mini peak flow meter in use. The patient takes in a deep breath, and then makes a maximal expiratory effort through the instrument. The procedure is repeated three times and the highest peak expiratory flow (PEF) is recorded. This can be compared with a nomogram that shows the patient’s sex, age and weight, and plotted on a chart to show the progress or response to treatment.
reasonably reliable and repeatable results and can be used to monitor therapy in asthma and chronic obstructive airways disease.

By use of a spirometer (4.25) and other equipment, a number of volume and flow rates can be estimated (4.26).
- The peak expiratory flow (PEF) is the fastest flow rate recorded during expiration.
- The forced expiratory volume in 1 second (FEV₁) is the volume of gas expired in the first second of expiration.
- The forced vital capacity (FVC) is the total volume of gas expired.
- Flow-volume loops are particularly helpful in the assessment of airway obstruction (4.27).

**4.25 A spirometer** provides a simple means of assessing air flow obstruction. The patient takes a maximal inspiration and then exhales as fast as possible for as long as possible. The volume expired against time is measured, and the forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) can be simply calculated from the graph produced (4.29).

- After a full expiration, some gas remains in the lung, the residual volume (RV); in order to measure this it is necessary to measure the volume of gas in the lungs at full inspiration (total lung capacity, TLC) and obtain the residual volume by subtracting the vital capacity; TLC is usually measured by helium dilution; a subject rebreathes a known volume and concentration of helium, which is diluted in the lung so that the TLC can be calculated by measuring how much the helium has been diluted.
- Airways resistance can be measured by body plethysmography (4.28).
- There are methodological difficulties in measuring oxygen transfer from lung to blood, so carbon monoxide transfer

<table>
<thead>
<tr>
<th>COMMON TESTS OF RESPIRATORY FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>Forced expiratory flow in one second</td>
</tr>
<tr>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>Relaxed vital capacity</td>
</tr>
<tr>
<td>Total lung capacity</td>
</tr>
<tr>
<td>Residual volume</td>
</tr>
<tr>
<td>Functional residual capacity</td>
</tr>
<tr>
<td>Maximum expiratory flow at lower lung volumes</td>
</tr>
<tr>
<td>Airways resistance</td>
</tr>
<tr>
<td>Specific conductance</td>
</tr>
<tr>
<td>Transfer factor</td>
</tr>
<tr>
<td>Transfer factor per unit lung volume (diffusion coefficient)</td>
</tr>
</tbody>
</table>

**4.26 Common tests of respiratory function.**

**4.28 Body plethysmography** allows the simultaneous measurement of thoracic gas volume, airways resistance and specific conductance. Such techniques may provide valuable additional information, especially in relation to the assessment of the effects of drug therapy.
factor (TL\textsubscript{CO}) is commonly measured; the transfer of carbon monoxide depends on how much haemoglobin can be 'seen' by the inspired gas; therefore transfer is low when the pulmonary capillary bed is damaged or obscured by inequalities of ventilation or perfusion; it is also low in anaemia and can be increased with polycythaemia or if haemorrhage into the lungs has occurred.

The results of simple spirometry provide much useful information (4.29) and even simple lung function tests are of great value in following the course of disease and response to treatment.

**4.29 Typical results of spirometry** in a normal patient (A), a patient with a restrictive defect (B) and a patient with an obstructive defect (C). In a restrictive defect (B), the FEV\textsubscript{1}/FVC ratio is preserved at the normal level, but both absolute values are reduced. In an obstructive defect (C), both absolute values are again reduced, but the FEV\textsubscript{1}/FVC ratio is considerably reduced, as the forced expiratory time required to reach the FVC is greatly prolonged.

Bronchial challenge testing with allergen extracts, histamine or methacholine is valuable in the assessment of airway hyper-responsiveness in asthma, but is not in routine clinical use in most centres (4.30).

**IMAGING**

A posteroanterior (PA) chest X-ray will often provide valuable diagnostic information about the nature and location of respiratory disease (4.31–4.39).

A lateral chest X-ray is helpful in identifying the position of abnormalities seen on the posteroanterior film (4.40–4.43) and may occasionally show significant abnormalities not seen on the standard film.

Tomography allows a radiograph of a specific slice of the chest; it is particularly useful for demonstrating lung cavities (4.44, 4.45), the lumen of the trachea and major bronchi, and the position and nature of abnormal shadows noted on the plain radiograph.

**4.30 Bronchial challenge test.** The Wright nebulizer contained a low concentration of a house-dust mite extract. The nose clip is worn to prevent a nasal reaction. Similar challenges can be carried out with histamine, methacholine, other pharmacological stimuli or other allergens. Bronchial hyperresponsiveness is thought to reflect the degree of underlying inflammatory changes in the airways of patients with asthma, and the technique is widely used in assessing the effects of asthma therapy in clinical trials.

4.31 An early peripheral bronchial carcinoma in the right mid-zone, found by chance on a chest X-ray. The hilum appears normal, and this was confirmed at tomography. This patient underwent a successful and probably curative lobectomy.

4.32 Cannonball metastases in both lung fields. Single or multiple round, discrete shadows resulting from secondary deposits occur with a number of tumours, including those of the kidney, ovary, breast, pancreas and testicle, and they are also seen in malignant melanoma.
4.33 **Left upper lobe opacity.** The patient presented with pain in the chest and haemoptysis (4.12), and the underlying diagnosis proved to be small-cell carcinoma of the bronchus. Much of the shadowing is the result of infection and collapse of the lung distal to the point at which the tumour causes bronchial obstruction. Note the extensive calcification in the right hilum and lower zone - the result of healed tuberculosis.

4.34 **Carcinoma of the bronchus involving the right hilum and mediastinum.** Bronchoscopy showed widening of the carina, which suggested lymph node involvement in the mediastinum and a friable, bleeding tumour in the right main bronchus. CT scan confirmed involvement of the great vessels. The tumour was thus inoperable.

4.35 **'Snowstorm' mottling in both lung fields.** In this case, the underlying diagnosis was testicular seminoma, with disseminated haematogenous metastases. Such an extreme picture is usually the result of malignant disease, but the chest X-ray may look similar in a number of infectious conditions, especially miliary tuberculosis (see 1.127), and in dust diseases.

4.36 **The chest X-ray is a poor guide to the severity of asthma.** Although this patient had acute severe asthma requiring urgent treatment, his chest X-ray showed nothing more than mild hyperinflation with horizontally aligned ribs.

4.37 **Left pleural effusion,** which developed during an influenza-like illness in a young woman, and was associated with fever and pleuritic pain.

4.38 **Left pneumothorax** developed in this former coalminer with known pneumoconiosis. Note the obvious lung edge in the left chest and the diffuse miliary mottling of pneumoconiosis in both lungs.
4.41 **Kyphosis** resulting from tuberculosis involving the thoracic vertebral bodies (T6–8). The significant reduction of lung volume is obvious (see 4.7).

4.42 An opacity in the posterior segment of the left lower lobe shows clearly in this left lateral film, but was barely visible on the standard posteroanterior film, as it was behind the heart shadow. The lesion proved to be a benign hamartoma, as was suggested by its ‘popcorn’ calcification (see 4.165).

4.43 **An inhaled foreign body** – a nail – impacted in the right lower lobe bronchus. This young patient presented with a persistent cough and wheeze, but did not realize that he had inhaled a nail. Foreign bodies should always be borne in mind as a differential diagnosis of wheezing, especially in children.

4.44 & 4.45 **Tuberculous cavities containing aspergillomas at the left apex.** This patient’s left apical shadowing was further investigated by tomography, which clearly demonstrates the round mycetomas or fungus balls (1) within the chronic tuberculous cavities.

4.39 & 4.40 **Staphylococcal lung abscess in the right lung of an intravenous drug misuser.** The abscess is in the lower zone on the posteroanterior film, and the lateral film shows that it is above the oblique fissure, that is in the middle lobe of the lung. Note that there is also extensive calcification of the left hilum, which results from healed tuberculosis.
Computerized axial tomography (CT) of the lung is most commonly used for the assessment of the extent of lung cancer (4.46, 4.47) but is being increasingly used in diffuse lung disease (4.96, 4.124, 4.160) and has replaced bronchography as the first-line investigation of suspected bronchiectasis (4.110).

MRI shows cardiovascular structures in the chest. Its role in pulmonary disease is still developing.

Pulmonary and aortic angiography may be used to define the anatomy of the arterial tree (5.204).

Radionuclide scans of lung (V/Q scan) are particularly useful in suspected pulmonary embolism (4.48, 4.49, 5.203). In this technique, xenon gas is inhaled and a gamma-camera image is produced of the alveolar distribution of the radioactivity (4.48). Then an intravenous injection of macroaggregates of human albumin (each 100 μ) labelled with $^{99m}$Tc is injected. These microspheres embolize harmlessly in the lung vessels and the distribution of the radioactivity is a reflection of the pulmonary blood supply (4.49).

4.48 & 4.49 Radionuclide ventilation (4.48) and perfusion (4.49) scans. 4.48 shows a normal distribution of xenon during ventilation, whereas 4.49 shows multiple perfusion defects in both lung fields when $^{99m}$Tc-albumin microspheres were injected. This 'unmatched' perfusion defect is typical of multiple pulmonary emboli.

4.50 A flexible fibreoptic bronchoscope and a rigid bronchoscope. In general, the flexible bronchoscope is simpler, quicker, safer and less traumatic to use than the rigid bronchoscope, but the rigid bronchoscope allows larger biopsy samples to be obtained. Videobronchoscopes are now replacing fibreoptic bronoscopes in many centres.
PLEURAL ASPIRATION AND BIOPSY

Aspiration of pleural fluid is of major value for both diagnostic and therapeutic reasons. Naked-eye inspection may suggest the presence of pus, the effusion may be blood stained (4.56) suggesting carcinoma or pulmonary embolism, or milky white (chylous) as a result of obstruction of the thoracic duct, usually by tumour (4.57).

- Pleural transudates are associated with generalized oedema and are pale in colour (4.58) with a specific gravity of less than 1015, total protein less than 2.5 g/100 ml.
- Pleural exudates represent inflammation and are usually darker in colour with a specific gravity above 1018 and a total protein greater than 3 g/100 ml.
- Total white cell count and cell type are of value; polymorphs indicate bacterial infection and lymphocytes suggest tuberculosis; culture of the fluid may show the organism responsible and cytology the diagnosis of tumour.

At the time of pleural aspiration, it is often convenient to carry out a pleural biopsy with a side-cutting needle (4.59, 4.61). This is 'blind', but relatively atraumatic. Pleuroscopy and mediastinoscopy can be used to provide direct vision for biopsy.
If the diagnosis is already made, then an opportunity to instil antibiotics, cytotoxics or sclerosants may be taken.

Pleural aspiration and biopsy are not always harmless procedures. They may result in damage to the lung or abdominal organs, pneumothorax or haemothorax. In the longer term, biopsy of a mesothelioma may result in spread of the tumour (4.62).

**LYMPH-NODE ASPIRATION AND BIOPSY**

Aspiration of a palpable node, usually in the neck, may provide a rapid cytological diagnosis, and biopsy of a node is a further possibility in suspected malignant disease. When no nodes are felt, removal of the scalene node may provide diagnostic information.

**UPPER RESPIRATORY TRACT DISORDERS**

The common cold is discussed on p. 18, and rhinitis, sinusitis, tonsillitis, pharyngitis and laryngitis may also occur as part of a number of the childhood exanthemata such as measles (p. 22), and in infectious mononucleosis (p. 31) and streptococcal infection (p. 36).

Other medical disorders of the upper airway include other forms of rhinitis (4.63). Allergic rhinitis (4.64) may be seasonal, most commonly caused by allergy to grass or other pollens (hay fever), or perennial, most commonly caused by allergy to the faeces of the house-dust mite. Skin-prick testing is often helpful in diagnosis (see p. 167).

Nonallergic or vasomotor rhinitis produces similar symptoms, but the cause is usually obscure.

Allergic rhinitis is often associated with other atopic disorders, including conjunctivitis, asthma, urticaria and eczema. It usually responds to topical corticosteroid or sodium cromoglycate therapy. Unlike asthma, however, most of the symptoms of allergic rhinitis often respond to oral antihistamines.

<table>
<thead>
<tr>
<th>SOME COMMON CAUSES OF RHINITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGIC</strong></td>
</tr>
<tr>
<td>Perennial</td>
</tr>
<tr>
<td>House dust mite</td>
</tr>
<tr>
<td>Pets</td>
</tr>
<tr>
<td>Occupational causes</td>
</tr>
<tr>
<td>Seasonal</td>
</tr>
<tr>
<td>Pollens</td>
</tr>
<tr>
<td>Moulds</td>
</tr>
<tr>
<td><strong>NON-ALLERGIC</strong></td>
</tr>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Acute</td>
</tr>
<tr>
<td>Chronic (consider immunodeficiency/mucociliary problems)</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>β-blockers</td>
</tr>
<tr>
<td>Irritant</td>
</tr>
<tr>
<td><strong>Mucosal atrophy</strong></td>
</tr>
<tr>
<td><strong>Systemic diseases</strong></td>
</tr>
<tr>
<td><strong>Unknown cause</strong></td>
</tr>
<tr>
<td><strong>Hormonal</strong></td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Irritant</td>
</tr>
</tbody>
</table>

4.63 Some common causes of rhinitis.
Nasal polyps are benign, oedematous, inflammatory swellings, which originate in the mucosa of the ethmoid sinuses or middle turbinates and protrude into the nasal cavity, causing obstructive symptoms. They are particularly common in a group of patients who also have asthma and are sensitive to aspirin and dietary salicylates, and are also associated with other respiratory tract disorders (4.65). They may be viewed via a nasal speculum or endoscopically (4.66), and their extent may be assessed by CT scan. Occasionally they may be large enough to distort the external appearance of the nose (4.67). They may respond to topical steroid therapy, but systemic steroids or surgical removal may sometimes be needed to control obstructive symptoms.

**THE PREVALENCE OF NASAL POLYPOSIS IN VARIOUS DISORDERS**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence of nasal polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin intolerance</td>
<td>36-72%</td>
</tr>
<tr>
<td>Asthma</td>
<td>7%</td>
</tr>
<tr>
<td>Non-atopic</td>
<td>13%</td>
</tr>
<tr>
<td>Atopic</td>
<td>7%</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>2%</td>
</tr>
<tr>
<td>Non-atopic</td>
<td>5%</td>
</tr>
<tr>
<td>Atopic</td>
<td>1.5%</td>
</tr>
<tr>
<td>Childhood asthma/rhinosinusitis</td>
<td>0.1%</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>10% (children) - 50% (adults)</td>
</tr>
<tr>
<td>Young's syndrome</td>
<td>5%</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>5%</td>
</tr>
</tbody>
</table>

4.64 Allergic rhinitis produces a greyish appearance in the nasal mucous membrane, especially when chronic.

4.65 The prevalence of nasal polyposis in various disorders.

4.67 Nasal polyps produced near-total nasal obstruction and anosmia in this patient who had chronic aspirin-sensitive asthma. This degree of nasal enlargement is unusual. Polyps may exist in an externally normal nose.

4.66 An endoscopic view of nasal polyposis. This is a relatively frequent accompaniment of asthma and is particularly common in adult asthmatics with sensitivity to aspirin. Polyps may be reduced in size by topical or oral steroid therapy.
INHALATION OF FOREIGN BODIES

Foreign bodies may be inhaled and lodge at any level in the respiratory system (e.g. 4.43). Large objects may cause potentially fatal obstruction at the level of the larynx. Such obstruction may often be dislodged by finger sweeps in the mouth, by sharp blows to the back or by use of abdominal thrust techniques (4.68, 4.69).

If these techniques fail, emergency cricothyrotomy using an intravenous cannula (4.70) or even a sharp knife and the empty shaft of a ball-point pen may re-establish an airway.

At lower levels in the respiratory tract, inhaled foreign bodies are not usually immediately life-threatening (4.43); but failure to diagnose and remove foreign bodies may lead to traumatic damage to the lungs or to the collapse of segments of the lung distal to the obstruction with subsequent lobar pneumonia.

Chest X-ray is diagnostic for radio-opaque objects and bronchoscopy often allows removal of the foreign body.

4.68 The Heimlich abdominal thrust manoeuvre can be used in an attempt to dislodge an inhaled foreign body in a conscious patient. One fist is clenched and positioned in the epigastrium and the other hand is placed on top. The patient is squeezed suddenly so that the fist moves backwards and upwards, causing a violent expulsion of air from the lungs.

4.69 Abdominal thrust in an unconscious patient should be performed with the patient lying flat on a hard surface. Kneel over the patient and thrust upwards with both hands from below the xiphisternum. The technique should result in a violent expulsion of air from the lungs and may be repeated. Any dislodged foreign body should be removed from the mouth or pharynx by a finger sweep.

4.70 Cricothyrotomy is indicated in obstructive asphyxia when endotracheal intubation is impossible because of a foreign body, oedema or the absence of equipment. The surface marking for insertion of the needle is the space between the thyroid and cricoid cartilages. The syringe is aspirated to ensure that the needle and cannula are in the tracheal lumen, and the syringe and needle are then withdrawn, leaving the cannula in place.
ASTHMA

DEFINITION AND EPIDEMIOLOGY

Asthma is most simply defined as a disorder characterized by narrowing of airways that is reversible with time, either spontaneously or as a result of treatment.

A more detailed definition is that proposed in the recent International Consensus Report: 'Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells and eosinophils. In susceptible individuals, this inflammation causes symptoms that are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment and causes an associated increase in airway responsiveness to a variety of stimuli.'

This more detailed definition is valuable in focusing on both the inflammatory nature and the potential reversibility of asthma, and thus in suggesting the most appropriate forms of therapy. At present, it is not possible to characterize asthma by biochemical or genetic features, but there is much continuing research in these fields.

Asthma is a common disorder. It has been estimated that its total prevalence is around 7.2% of the world population (about 100 million individuals), with a world population prevalence of about 6% in adults and 10% in children. At least 40,000 deaths per year worldwide can probably be attributed to asthma.

The estimated prevalence of asthma varies in different regions of the world, and in different parts of each country. In general, asthma is more common in urban than rural areas. In developing countries, asthma becomes more common in areas that adopt a 'developed' form of housing and lifestyle. The prevalence of asthma is increasing worldwide, but the reasons for this increase are unclear. Atmospheric pollution is probably not the major factor in the increased prevalence of asthma. Occupational asthma is a well recognized problem in those exposed to sensitizing substances in industry.

MECHANISMS

Many patients develop symptoms in response to allergens such as house-dust mites (4.71), domestic animals (4.72) or, less commonly, pollen grains; but often, especially in adult patients, there are no obvious underlying allergies. Many provoking factors are involved in the development of asthma symptoms, and these can be divided into two main groups: inducers and triggers.

• Inducers of asthma include genetic factors, allergies, infections and, probably, other factors related to occupational
background or environment; they act mainly by inducing airway inflammation, which leads to airway hyperresponsiveness (AHR) and asthma symptoms.

- Triggers of asthma are factors which cause airway smooth muscle contraction and asthma symptoms on a background of pre-existing airway inflammation and airway hyperresponsiveness; these include a wide range of stimuli such as exercise, cold air, irritants, smoke, pollutants, β-blocking drugs and stress and, in susceptible individuals, drugs such as aspirin and other nonsteroidal anti-inflammatory drugs, foods and other inhaled or ingested substances.

It is now clear that asthma is a complex inflammatory condition involving many inflammatory cells, which release a wide variety of mediators. These mediators act on cells of the airway leading to smooth muscle contraction, mucous hypersecretion, plasma leakage, oedema, activation of cholinergic reflexes and activation of sensory nerves, which can lead to amplification of the ongoing inflammatory response. Chronic inflammation also leads to structural changes, such as subepithelial fibrosis and smooth muscle hypertrophy and hyperplasia, which are less easy to reverse than the acute processes. Inadequately treated chronic asthma is thus associated with structural changes in the lungs.

### TYPES OF ASTHMA

<table>
<thead>
<tr>
<th>Type</th>
<th>Common features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood onset</td>
<td>Patient usually atopic, marked variability, obvious trigger factors</td>
</tr>
<tr>
<td>Adult onset</td>
<td>Demonstrable atopy uncommon, usually persistent, infection a common trigger, but other identifiable triggers uncommon</td>
</tr>
<tr>
<td>Occupational</td>
<td>Under-diagnosed, careful assessment needed</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>May occur with all other types of asthma, indicates poor overall control and increased airway hyperresponsiveness</td>
</tr>
<tr>
<td>Prominent cough</td>
<td>A common presentation in childhood, may precede significant airflow obstruction, responsive to anti-inflammatory treatment</td>
</tr>
<tr>
<td>Exercise-induced</td>
<td>A common precipitant of other types of asthma, especially in childhood. May be the main problem in childhood</td>
</tr>
</tbody>
</table>

4.73 Types of asthma. More than one of these patterns may coexist in the same patient.

### AGENTS PROVOKING OCCUPATIONAL ASTHMA THAT ARE OFFICIALLY RECOGNIZED FOR COMPENSATION IN THE UK

- Isocyanates
- Soldering flux (colophony)
- Stainless steel welding
- Platinum salts
- Epoxy resin hardening agents
- Azodicarbonamide (PVC, plastics)
- Glutaraldehyde
- Persulphate salts
- Reactive dyes
- Proteolytic enzymes
- Drug manufacture (antibiotics, cinetidine, ispaghula, ipecacuanha)
- Animals or insects used as laboratory animals
- Animals or insects, larval forms
- Crustaceans
- Flour or grain dusts
- Castor bean dust
- Wood dust
- Soya bean dust
- Tea dust
- Green coffee beans

4.74 Agents provoking occupational asthma that are officially recognized for compensation in the UK.
MANAGEMENT OF ASTHMA

The treatment of severe acute asthma usually requires hospital admission for oxygen therapy, nebulized bronchodilators and systemic steroids (4.83). Intermittent positive-pressure ventilation may be required in very severe cases (4.76). It is essential that the patient’s maintenance therapy is established, with evidence of adequate control, before the patient is discharged from hospital.

Currently available drug therapy for asthma is summarized in 4.84. The mainstay of treatment for chronic asthma is regular inhaled steroid therapy, supplemented by inhaled \( \beta_2 \) agonists for occasional symptomatic relief. Other drugs have a role in some patients. The long-term use of oral steroids should be avoided because of the risk of side effects.

Inhaled drugs may be administered via a confusing number of devices, which have differing performance characteristics (4.85). Nebulized therapy has a role in severe asthma (4.86), but the three main types of inhaler are the pressurized metered-dose inhaler (pMDI; 4.87), the pMDI with a spacer device (4.88) and dry powder inhalers (DPI; 4.89). Some advantages and disadvantages of these devices are summarized in 4.90.

Patient education in all aspects of asthma, including inhaler use, is of great importance in long-term care (4.91).

The aim of asthma management is to achieve good, long-term control of the disease and its manifestations. The features of good control of asthma are shown in 4.92.

---

**4.83** An acute asthmatic patient in hospital, receiving nebulized \( \beta_2 \) agonist (the nebulizer is driven by oxygen) and intravenous hydrocortisone. Careful monitoring of therapy is required.

**4.84** Drug therapy in asthma.

### Preventive therapy
- Inhaled steroids
- Inhaled cromones
- Oral steroids
- Oral methylxanthines

### Reliever therapy
- Inhaled \( \beta \)-agonists
- Oral (or injected) \( \beta \)-agonists
- Oral steroid-sparing agents
- Oral leukotriene antagonists
- Oral anticholinergics
- Oral (or injected) methylxanthines

* Methylxanthines are used principally as reliever therapy, but may also exert some preventive, anti-inflammatory effect.

**4.85** Inhaler devices in asthma. This picture includes just some of the many devices available, including various pressurized metered-dose inhalers, spacer devices, dry powder inhalers and nebulizer chambers. The drug delivery and clinical performance of these inhalers varies widely.

**4.86** Nebulized therapy may be helpful in severe asthma. High doses of bronchodilators may be delivered by this method in carefully defined circumstances. Nebulized steroid therapy may provide an alternative to oral steroid therapy, or an aid to oral dose reduction.
**MANAGEMENT OF ASTHMA**

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**Table: Drug Therapy in Asthma**

<table>
<thead>
<tr>
<th>Preventive therapy</th>
<th>Oral methylxanthines*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled steroids</td>
<td>Oral leukotriene antagonists</td>
</tr>
<tr>
<td>Inhaled cromones</td>
<td>Oral steroid-sparing agents</td>
</tr>
<tr>
<td>Oral steroids</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reliever therapy</th>
<th>Oral (or injected) $\beta$-agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled $\beta$-agonists</td>
<td>Oral (or injected) methylxanthines</td>
</tr>
<tr>
<td>Inhaled anticholinergics</td>
<td></td>
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</tbody>
</table>

* Methylxanthines are used principally as reliever therapy, but may also exert some preventive, anti-inflammatory effect.

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**Figure 4.83**: An acute asthmatic patient in hospital, receiving nebulized $\beta_2$ agonist (the nebulizer is driven by oxygen) and intravenous hydrocortisone. Careful monitoring of therapy is required.

**Figure 4.85**: Inhaler devices in asthma. This picture includes just some of the many devices available, including various pressurized metered-dose inhalers, spacer devices, dry powder inhalers and nebulizer chambers. The drug delivery and clinical performance of these inhalers varies widely.

**Figure 4.86**: Nebulized therapy may be helpful in severe asthma. High doses of bronchodilators may be delivered by this method in carefully defined circumstances. Nebulized steroid therapy may provide an alternative to oral steroid therapy, or an aid to oral dose reduction.
4.87 A pressurized metered-dose inhaler (pMDI). All commonly used inhaled therapy for asthma is available in this form. Although convenient and portable, the pMDI requires good coordination between actuation and inhalation by the patient. The formulation of pMDIs is changing as CFC gases are eliminated for environmental reasons.

4.88 Large volume ‘spacer’ or extension chamber added to a pressurized metered-dose inhaler. Large volume spacers allow the aerosol cloud to slow down, and overcome problems of patient coordination. They may increase lung deposition and reduce oral impaction, a potentially useful feature with high-dose inhaled steroid therapy. They may also be used in acute attacks of asthma to deliver repeat aerosol doses of bronchodilator every few minutes.

4.89 A dry-powder, multidose inhaler (Turbohaler or Turbuhaler). Dry-powder inhalers are inspiratory flow-actuated and driven, so they overcome the coordination problems of pMDIs. The performance of different dry-powder inhalers varies, but Turbohaler achieves a substantially higher lung deposition of drug than pMDI, and a single inhaler holds up to 200 doses of the drug.

4.90 Some advantages and disadvantages of the three forms of portable inhaler.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pMDI</strong></td>
<td>Difficult inhalation technique</td>
</tr>
<tr>
<td>Quick to use</td>
<td>Propellants required</td>
</tr>
<tr>
<td>Compact and portable</td>
<td>High oropharyngeal deposition</td>
</tr>
<tr>
<td>Multidose</td>
<td></td>
</tr>
<tr>
<td>Often inexpensive</td>
<td>More bulky than pMDI</td>
</tr>
<tr>
<td></td>
<td>Propellants required</td>
</tr>
<tr>
<td></td>
<td>Static charge on wall may affect delivered dose</td>
</tr>
<tr>
<td><strong>pMDI + spacer device</strong></td>
<td></td>
</tr>
<tr>
<td>Practical advantages as for pMDI</td>
<td></td>
</tr>
<tr>
<td>Easier to use effectively than pMDI</td>
<td></td>
</tr>
<tr>
<td>Reduced oropharyngeal deposition</td>
<td></td>
</tr>
<tr>
<td><strong>Dry-powder inhaler</strong></td>
<td></td>
</tr>
<tr>
<td>Practical advantages similar to pMDI</td>
<td></td>
</tr>
<tr>
<td>(if multidose or multiple single-dose)</td>
<td></td>
</tr>
<tr>
<td>No propellants needed</td>
<td>Sometimes more costly than pMDI</td>
</tr>
<tr>
<td>Inspiratory flow-actuated</td>
<td>Some may be moisture sensitive</td>
</tr>
<tr>
<td>Easier to use than pMDI</td>
<td>Inspiratory flow-driven (potential problem at low</td>
</tr>
<tr>
<td></td>
<td>inspiratory force)</td>
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</table>

SOME ADVANTAGES AND DISADVANTAGES OF THE THREE FORMS OF PORTABLE INHALER
RESPIRATORY

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD, a term that embraces both chronic bronchitis and emphysema) is the third most common cause of death in men over 65 years (60 per 100 000), and is more common in men (8%) than women (3%). As it ultimately develops in at least 80% of smokers, this prevalence will change as more women smoke.

Chronic bronchitis is a clinical syndrome in which there is excess mucus secretion by bronchial goblet cells. This stimulates the cough reflex so that sputum is produced daily for at least 3 months of the year. There are often episodes of superimposed viral or bacterial infection in which the sputum may be yellow or green and often contains a fleck of blood. Many patients also have an intermittent wheeze with objective evidence of airways obstruction on pulmonary function tests and some may have acute severe bronchoconstriction in response to respiratory infections or to irritants or allergens (asthmatic bronchitis).

FEATURES OF GOOD CONTROL IN ASTHMA

- Minimal (ideally no) chronic symptoms
- No nocturnal symptoms
- No acute exacerbations
- Minimal need for short-acting bronchodilators
- No limitation of activity, including exercise
- Circadian variability of peak flow <20%
- Peak flow >80% of predicted or best achievable
- Minimal (ideally no) adverse effects from treatment

4.92 Features of good control in asthma.

4.93 Emphysema. The hyperinflation of the chest and associated kyphosis are typical but not diagnostic. A similar appearance may be seen in any chronic respiratory disorder. Note the typical ‘pursed lip’ appearance (4.9).

4.94 Emphysema. The PA chest X-ray shows hyperinflation of both lung fields, producing depression of both diaphragms and a characteristic long, thin mediastinum. There are also calcified lesions and some scarring at both apices and both hila as a result of old, healed tuberculosis.

4.95 Emphysema. The right lateral chest X-ray shows hyperinflation of the chest with sparse lung markings. There is a marked increase in the posteroanterior diameter of the chest, and the diaphragmatic depression is again seen. In this patient the hilar calcification resulting from old, healed tuberculosis is also well seen in the lateral view.
Emphysema is a pathological or radiological rather than a clinical diagnosis and is commonly associated with chronic bronchitis. Destruction of the alveolar septae results in the formation of multiple bullae in the lungs, with hyperinflation of the chest (4.93, 4.94, 4.95, 4.96) and impaired respiratory function.

The common combination of chronic bronchitis and emphysema has also been termed chronic obstructive airways disease (COAD) or chronic obstructive pulmonary disease (COPD). Up to 20% of adult men worldwide have the disease, and this proportion is higher in heavily industrialized countries. Chronic bronchitis occurs in the majority of heavy smokers, but significant airways obstruction or emphysema, or both, occurs in only a minority.

The characteristic clinical features of chronic bronchitis and emphysema are cough, productive of thick yellow–green sputum, wheeze and progressive breathlessness. The symptoms are usually worse in winter and exacerbated by atmospheric pollution, dry air, intercurrent infections and industrial exposure to irritant gases or dusts.

Two common presentations occur, which represent opposite ends of the spectrum of COPD.

- the ‘pink puffer’ (4.97) usually has significant emphysema with a barrel-shaped chest, but is thin and maintains a normal \( \text{PaCO}_2 \) by increasing his or her respiratory rate
- the ‘blue bloater’ (4.98) tends to be fatter, polycythaemic, centrally cyanosed and to show signs of pulmonary hypertension (4.99, 4.100, 5.122, see p. 247). As the disease progresses, the \( \text{PaCO}_2 \) rises and leads to a compensated respiratory acidosis (4.101, 4.102).

The most important step in management is to persuade the patient to stop smoking, though this may be difficult.
Bronchodilators may achieve some reversal of airways obstruction, and corticosteroids have a role in some patients. Surgical removal of large bullae is occasionally helpful. Complications such as right heart failure and polycythaemia (4.5) may require treatment. Long-term oxygen therapy (LTOT) for more than 15 hours daily has been shown to improve mortality and morbidity in some severely affected patients. There are four main types of LTOT equipment.

- compressed oxygen cylinders
- liquid oxygen
- molecular-sieve oxygen concentrators
- membrane separator oxygen enrichers.

A typical oxygen concentrator is shown in 4.103.

Care must be taken to choose the most suitable device for the individual patient. Oxygen concentrators are electricity driven and can deliver oxygen at 93% plus a flow rate of 2-3 l/min.

Oxygen is usually given via nasal cannulae (4.104), which are more comfortable than wearing a face mask over many hours. Occasionally transtracheal oxygen therapy (TTOT) via a small polyethylene catheter introduced directly into the trachea via the second tracheal interspace is of value.

Infections are frequent, and it is important to educate patients in the early recognition of symptoms and signs, for example change of sputum colour and quality, fever or increasing wheeze. Many patients should be given a supply of antibiotics to keep at home for self-medication. There is little evidence that long-term antibiotic prophylaxis is of value, but influenza vaccination each winter may be worthwhile. Mortality is closely associated with a declining FEV1, with hypoxaemia and a low carbon monoxide transfer.

Chronic bronchitis and emphysema are very rare in non-smokers. Airways obstruction in a nonsmoker or light smoker is usually caused by asthma, rarer causes being emphysema in α-1-antitrypsin deficiency, obliterative bronchiolitis or industrial lung disease, for example byssinosis.
CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

In Macleod's syndrome, unilateral emphysema may develop in association with hypoplasia of one lung (4.105). This abnormality probably results from infective lung damage in childhood.

SLEEP APNOEA SYNDROME

With the aid of sleep laboratories, a variety of disturbances in sleep patterns have now been recorded. The most common is the sleep apnoea syndrome, which occurs as a result of intermittent pharyngeal obstruction during REM sleep. It is most common in grossly obese chronic bronchitics who have nasal obstruction and abuse alcohol or take hypnotics. The clinical presentation is often from the spouse who complains of explosive episodes of snoring or snorting; general poor sleep-quality and recurrent daytime tiredness are the patient's major complaints, but other symptoms may include nocturnal choking, morning headache, nocturia, reduced libido, depression and personality changes.

Most patients (80%) are male and many are obese (50%). However, the syndrome is now being recognized more frequently in thinner men of all ages. Suspicion of the syndrome should be followed by appropriate tests in a sleep laboratory (4.106). The simplest of these is oximetry, which may show alarming falls in oxygen saturation during apnoeic episodes. However, many patients require overnight admission with recording of EEG, respiratory and oxygenation patterns in specialized units.

Treatment consists of weight loss, avoidance of evening alcohol and withdrawal of any sedatives. The keystone of treatment is continuous positive airway pressure (CPAP) therapy administered by a tight-fitting nasal mask which blows the throat open so that recurrent arousals are abolished, as is the loud snoring. This often results in dramatic cessation of daytime symptoms and may also reduce morbidity and mortality.

4.103 An oxygen concentrator in use. These devices are driven by mains electricity and can deliver oxygen in concentrations of 93% or higher at a film rate of 2-3 litres/minute.

4.105 Macleod’s syndrome. The left lung is smaller in volume than the right and is emphysematous. Hypoplasia of the lung is associated with a small left pulmonary artery and decreased peripheral vasculature.

4.106 Sleep apnoea under investigation in a sleep laboratory. Note the presence of an ear oximeter, and ECG and EEG monitoring. The syndrome should always be considered in patients with chronic respiratory disease who complain of daytime somnolence, or whose partners complain about the patient’s snoring or apnoeic episodes at night. Alarming falls in arterial oxygen saturation may be found during sleep apnoea, and the syndrome is a cause of sudden death at night.
RESPIRATORY INFECTIONS

ACUTE BRONCHITIS

Viral infections of the upper respiratory tract often lead to secondary bacterial infection of the lower respiratory tract, especially in patients with pre-existing respiratory disorders. These infections may damage bronchial epithelium, leading to exacerbations of asthma or obstructive airways disease and to bronchitis and pneumonia, most commonly with *Streptococcus pneumoniae* or *Haemophilus influenzae*.

BRONCHIECTASIS

Damage to the elastic and muscle fibres in the bronchial wall may lead to bronchiectasis – the abnormal dilatation of a bronchus (or bronchi). The pathological process by which the damage is initiated is often not clear, but a number of conditions are associated with subsequent development. These include:

- impairment of mucociliary function as seen in primary ciliary dyskinesia (4.107) and cystic fibrosis (p. 191)
- impairment of immunity as in hypogammaglobulinaemia, which predisposes to recurrent infection
- acute supplicative or necrotizing pneumonia resulting from viral or bacterial infections, including tuberculosis
- persistent infection with *Aspergillus*, as in asthmatics
- bronchial obstruction by lymph nodes or by a foreign body
- inhalation of corrosive materials, for example gastric contents or industrial hydrocarbons
- in some races there may be a hereditary element to bronchiectasis.

The end result of all these processes is a vicious circle of events in which there is alteration of normal drainage and mucus production, recurrent bacterial superinfection and acceleration of the lung damage.

The onset is usually insidious and the symptoms and signs are progressive. The first features include a chronic cough productive of increasing volumes of sputum that is intermittently infected (yellow or green) and often tinged with blood. Basal bronchiectasis may be associated with sudden coughing up of large volumes of sputum on changing posture...

Episodes of superinfection may be associated with fever, signs of pneumonia, lung abscess, empyema and septicemia. Copious foul-smelling sputum may be produced and occasionally major haemoptysis may lead to exsanguination. In the quiescent phase residual signs often persist, especially showers of coarse crepitations associated with areas of bronchial breathing. Finger clubbing (2.104, 2.105) is usual and may be progressive.

The clinical course is often progressive, with gradual loss of respiratory function and cor pulmonale is found in the late stages of the disease. Chronic disease may rarely be associated with secondary amyloid, which is associated with peripheral oedema and proteinuria (see p. 294).

Diagnosis is made on history and examination, and the disease localized by plain X-ray (4.108), tomogram, bronchogram (4.109) or CT scanning (4.110). Monitoring of respiratory

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4.107 Primary ciliary dyskinesia, with situs inversus (Kartagener’s syndrome). This rare autosomal recessive condition is associated with male infertility and chronic infection of the upper and lower respiratory tract, leading to nasal polyposis (p. 178) and bronchiectasis. In this patient there are some bronchiectatic changes in the left middle lobe and the situs inversus is obvious.

4.108 Cystic fibrosis. Widespread bronchiectatic changes are present, with an area of consolidation at the right costophrenic angle representing acute infection. An indwelling intravenous catheter for antibiotic administration is present. In such patients the common colonizing organisms are *Staphylococcus aureus, Haemophilus influenzae* and *Pseudomonas aeruginosa*, and these may require intensive parenteral antibiotic therapy.

4.109 Bronchiectasis. This bronchogram shows diffuse bronchiectasis in the right lung, with dilatation of many of the proximal bronchi, and pooling of the contrast medium in the lower bronchi. Bronchography has been largely superseded by high-resolution CT scanning.
function tests, blood gases and renal function is important. The white cell count and erythrocyte sedimentation rate (ESR) are raised in acute exacerbations.

Treatment consists of intensive physiotherapy and postural drainage. Antibiotics may be given for acute exacerbations or for prolonged periods as prophylaxis. Bronchodilators are of value when indicated by pulmonary function tests, and surgery should be considered for localized disease if the rest of the lung tissue is reasonably normal. Vaccination against influenza is probably of value as many acute exacerbations are precipitated by virus infections.

CYSTIC FIBROSIS

Cystic fibrosis is the most common fatal inherited disease in European populations; with a carrier frequency of 1:20, it affects 1:2000 children. Recently, the abnormal gene was located on chromosome 7 and the structure of an abnormal protein has been identified. Prenatal diagnosis can now be made precisely and population screening for heterozygotes is theoretically possible.

The disease is characterized by production of mucus of high viscosity and a severe biochemical derangement of the sweat glands, which secrete an excess of sodium and chloride (3–5 times greater than normal). A major clinical feature of the disease is bronchiectasis (4.108 and see p. 190); and the majority of patients have pancreatic malabsorption (4.111). Other complications include meconium ileus presenting at birth (4.112), pneumothorax, haemoptysis, cor pulmonale and diabetes mellitus.

Investigations include X-ray of chest, lung function tests and a sweat test. Measurement of immunoreactive trypsin allows detection at birth, before sweating is established.

In the past, most patients died in childhood from severe respiratory involvement, but the life expectancy of patients has increased with early diagnosis and prophylactic treatment. This has highlighted additional problems such as stunting of normal growth (resulting from malabsorption), infertility (because of lack of ciliary movement in the vas deferens) enhanced formation of gall stones and eventually cirrhosis of the liver.

Treatment of bronchiectasis with physiotherapy and antibiotics (4.108), and attention to nutrition are the mainstays of therapy. Nutritional treatment involves a high calorie, high fat diet with enteric-coated pancreatic enzymes (pancreatin) plus a broad range of vitamins. Some patients receive a successful heart–lung transplant, but many still die early from respiratory failure, although current treatment allows some to survive well into adult life. In affected families, genetic counselling is important and prenatal diagnosis should be offered.
PNEUMONIA

Pneumonia is an inflammation of the lung, usually caused by bacteria, viruses or protozoa. If the infection is localized to one or two lobes of a lung it is referred to as 'lobar pneumonia' and if the infection is more generalized and involves primarily the bronchi it is known as 'bronchopneumonia'. A wide range of infecting organisms has been implicated (4.113). In up to 30% of patients no organism is identified, usually because of prior antibiotic administration. In many patients there is a preceding history of an upper respiratory virus infection. Most community-acquired pneumonia can be managed at home, and has a low mortality; studies of such patients admitted to hospital have shown a mortality of 6–24% depending on the population studied and the presence or absence of such risk factors as old age and underlying disease.

The usual clinical presentation in pneumonia caused by Streptococcus pneumoniae is acute, with the abrupt onset of malaise, fever, rigors, cough, pleuritic pain, tachycardia and tachypnoea, often accompanied by confusion, especially in the elderly. The signs include a high temperature, consolidation and pleural rubs, and herpetic lesions may appear on the lips. There may also be signs of pre-existing disease, especially chronic bronchitis and emphysema or heart failure in the elderly. The sputum becomes rust coloured over the following 24 hours (4.12). The diagnosis is made on clinical grounds and confirmed by chest X-ray (4.114–4.116, 4.168). The white cell count and ESR are usually elevated. Blood should be sent for culture before antibiotic therapy is given and a baseline blood sample taken for serology. Sputum should be sent for culture. Direct Gram-staining of a fresh sputum sample may show the organism. Pneumococcal antigen can be identified in sputum, urine or serum. Antibiotic therapy should not be delayed while awaiting sputum culture results.

The symptoms usually resolve rapidly over 7–10 days and the signs over a slightly longer period. Radiological resolution should be complete by 12 weeks. Persistence of changes in the X-ray after this, or recurrence of pneumonia, suggests some other pathological process and should trigger a search for underlying carcinoma. Careful examination should be made at presentation for clinical features of AIDS (see p. 11).

Mycoplasma pneumoniae (p. 57) is the most common cause of the 'atypical' pneumonias. Infection usually occurs in older children and young adults, who present with pharyngitis and bronchitis; pneumonia occurs in the minority and is rarely severe (4.115). Psittacosis (p. 56) is acquired from birds and

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### PNEUMONIA: INFECTING ORGANISMS IN APPROXIMATE DESCENDING ORDER OF FREQUENCY

<table>
<thead>
<tr>
<th>Community acquired</th>
<th>Hospital acquired</th>
<th>Immunocompromised patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Gram-negative bacilli</td>
<td>Pneumocystis carinii</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>Staphylococcus aureus</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Influenza virus A</td>
<td></td>
<td></td>
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<tr>
<td>Haemophilus influenzae</td>
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<tr>
<td>Legionella pneumophila</td>
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<tr>
<td>Staphylococcus aureus</td>
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<td></td>
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<tr>
<td>Haemophilus influenzae</td>
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<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
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<td></td>
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<tr>
<td>Pseudomonas spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coxialliserburnetii</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia psittaci</td>
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4.113 Pneumonia: infecting organisms in approximate descending order of frequency.

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4.114 Pneumonia in the right upper lobe caused by Streptococcus pneumoniae. The consolidation involves the whole of the right upper lobe, and a small amount of fluid is present in the horizontal fissure. There are also some areas of consolidation in the right and left lower zones, probably as the result of transbronchial spread of infection. This patient produced typical rusty-red sputum (4.12).

4.115 Pneumonia caused by Mycoplasma pneumoniae. This patient presented with fever and left lower posterior pleuritic chest pain. There is patchy consolidation in the upper part of the left lower lobe, as seen in this left lateral film.
Q-fever (p. 58) from animals, commonly farm livestock; they also cause 'atypical pneumonia', although the Q-fever organism, Coxiella burnetii, may also cause endocarditis. The diagnosis of the 'atypical' pneumonias is usually made by serology.

Staphylococcal pneumonia typically occurs as a complication of influenza, especially in the elderly and, although uncommon, is important because of the attendant high mortality. It is a destructive pneumonia, which frequently leads to the formation of cavities within the lung (1.70, 1.100, 4.39, 4.40). Such cavitating pneumonia was most frequently caused by tuberculosis in the past but now Staphylococci, Klebsiella and anaerobic organisms are the most common causes.

Legionnaires' disease is pneumonia caused by Legionella pneumophila (see p. 51 and 1.147). Infection is most common in debilitated or immunocompromised patients. Most cases are sporadic, but outbreaks occur from contaminated water droplet sources. Patients may present with a wide spectrum of additional symptoms, such as headache, cerebellar ataxia, renal failure or hepatic involvement. Special medium is necessary for the culture of the organism and the diagnosis is usually made by serology.

Aspiration pneumonia results from the aspiration of gastric contents into the lung and is associated with impaired consciousness (e.g. anaesthesia - 4.116, epilepsy, alcoholism) or dysphagia. Multiple organisms may be isolated.

Nosocomial pneumonia occurs when infection takes place in hospital; patients may be debilitated, immunocompromised or have just undergone a major operation. The causative organism(s) are often Gram-negative or the Gram-positive coccus, Staphylococcus aureus. The high mortality is usually related to the severity of the underlying disease. Lung abscess or empyema (a collection of pus within the thoracic cavity), or both, may be caused by specific organisms or may complicate any aspiration pneumonia. Septic pulmonary emboli can lead to multiple lung abscesses, pulmonary infarcts may become infected cavities and abscesses can develop distal to lesions obstructing a bronchus.

Treatment of all pneumonias should be started immediately and the antibiotic chosen should be the 'best guess' (decided on by the origin of the pneumonia and its clinical severity). If community-acquired, then a high-dose parenteral penicillin (or erythromycin) will usually be effective. If legionnaires' disease is suspected on epidemiological grounds, rifampicin should be given with erythromycin. If staphylococcal pneumonia is suspected, because of preceding influenza, flucloxacillin should be added to the regime. In hospital-acquired pneumonia, combination therapy is required to cover the range of possible pathogenic organisms (especially Gram-negative bacilli). Combinations such as gentamicin with piperacillin or a cephalosporin may be used. In aspiration pneumonia, in which anaerobes may be present, metronidazole should be added to these combinations. Supportive measures should include oxygen, intravenous fluids, inotropic agents when necessary, bronchial suction and assisted ventilation. Physiotherapy and bronchodilators are of value in pneumonia complicating chronic bronchitis and emphysema.

Infection in the immunocompromised host

There has been a steady increase in the number of patients whose immune system has been damaged by malignancy, organ failure, drugs or the HIV virus. In such immunocompromised patients, infections of the lung are common and may be caused by organisms that are not usually pathogenic in the normal host. Invasive fungal infections tend to occur in neutropenic patients, whereas T-cell defects often lead to infection with viruses, mycobacteria and protozoa such as Pneumocystis carinii. The tempo of infection in the immunocompromised patient can be extremely rapid; it is important to take steps to identify the pathogen and to start therapy as soon as possible.

Pneumocystis carinii

Pneumocystis carinii is the most important cause of fatal pneumonia in immunosuppressed patients. It is believed that the infection is acquired in early childhood, and that reactivation occurs when the immune system becomes damaged. The incubation period is approximately 1–2 months before the insidious appearance of a low-grade progressive pneumonia, which manifests itself as severe dyspnoea with, at first, only minimal chest signs and X-ray changes (4.117). The pneumonia progresses rapidly, and within a few days obvious pneumonic changes may be seen on the chest X-ray (1.41). Diagnosis depends on demonstrating the organism in sputum,
Bronchial lavage or lung tissue, which may require a lung biopsy (4.54). Treatment is with cotrimoxazole or pentamidine; both of these may be used in prophylaxis. Mortality remains high despite treatment.

**PULMONARY TUBERCULOSIS**

Tuberculosis may infect many parts of the body (see p. 43), but pulmonary infection is its most common manifestation.

Primary infection usually involves the lungs (1.125, 1.126). Within months, further pulmonary complications may occur, including lobar collapse, bronchiectasis, miliary tuberculosis (1.127) or the development of a pleural effusion (4.118).

More commonly, the 'primary complex' in the lung heals and calcifies. The patient remains well, often for many years or even for life. If host resistance is lowered later in life, by malignant disease or its treatment, by diabetes mellitus, by malnutrition or by HIV infection, however, or if reinfection with large numbers of organisms occurs, the patient may develop active adult pulmonary tuberculosis.

Pulmonary tuberculosis is characterized by fever, tiredness, malaise, anorexia and weight loss, associated with an increasingly productive cough. There may be few or no signs on examination, but X-ray changes are always present, and may include patchy or nodular pneumonic shadowing in the upper zones (4.119), cavitation (4.119–4.121), calcification (4.122), fibrosis (4.123) and lymph node enlargement (1.129–1.131, 4.10). Pleural effusion (4.118) and calcification may also be seen. CT scan may also show changes (4.124).

4.118 Tuberculous pleural effusion. This patient presented with a 6-month history of malaise and weight loss, but no symptoms directly referable to the chest. The large right pleural effusion is accompanied by fluid in the horizontal fissure. Aspiration and culture confirmed the diagnosis.

4.119 & 4.120 Active tuberculosis in a Greek immigrant to the UK (4.119), who presented with weight loss, low-grade fever and fresh haemoptysis. He gave a family history of tuberculosis. This film shows multiple areas of shadowing, especially in the upper lobes, and several lesions have started to cavitate. Despite the extensive nature of the disease, chemotherapy resulted in dramatic healing of the lesions as seen in a film taken 3 years later (4.120), which shows only minimal residual scarring at both apices.

4.121 Cavitating right apical tuberculosis revealed on tomography. This 'slice' shows three separate cavities, surrounded by dense inflammation and fibrosis, with pulling of the trachea to the right. The chest wall has been surgically collapsed (thoracoplasty). This obsolete technique was used before effective chemotherapy became available in an attempt to accelerate the healing of the cavities.

4.122 Bilateral apical fibrosis resulting from pulmonary tuberculosis. The hila are elevated, and streaky linear shadows extend from the hila to the apices. Scattered calcified upper zone nodules are also present bilaterally.
The diagnosis may be strongly suggested by the X-ray appearances. However, microbiological confirmation is necessary to exclude chronic necrotizing pulmonary aspergillosis, which produces a similar picture, histoplasmosis (p. 58) and coccidioidomycosis (p. 60) — especially in those living in or who have visited an endemic area for these diseases — and cryptococcosis in immunocompromised patients. Similar appearances may also occur with atypical mycobacterial infections in normal and immunocompromised patients (see p. 47).

Pulmonary tuberculosis requires treatment with antituberculous chemotherapy for a period of 6–9 months. Investigation and immunization of contacts is essential (see p. 46), and in many countries tuberculosis is a notifiable disease. Patients with signs of previous tuberculosis (as in 4.119, 4.125), who are about to undergo immunosuppressive drug treatment or manoeuvres such as haemodialysis for renal failure, should be given prophylactic antituberculous therapy.

Sarcoidosis, a multisystem disorder, has a prevalence of 15–20 per 100 000 people, with the highest prevalence between the ages of 25 and 35 years. It is most often found in the lung parenchyma and related lymph nodes, but it can involve the skin, eyes, peripheral lymph nodes, gut, liver, bone and CNS. The pathological process is a granulomatous reaction of the type seen with insoluble antigens, but as yet no single factor has been positively identified. It is not contagious, but there is a slightly increased incidence within families and in women. In the USA it is much more common in black patients.

The most common clinical presentation of sarcoidosis is respiratory. It is often found on chest X-rays in patients with nonspecific features such as tiredness, weight loss or recurrent fever. The characteristic lesions are

- bilateral hilar lymphadenopathy (4.126), usually asymptomatic, which will subside without treatment in about 80–90% of patients
- pulmonary infiltration with bilateral hilar lymphadenopathy (4.127, 4.128), which may cause symptoms such as dyspnoea, cough and fever, but which subsides in 40% of patients
- pulmonary fibrosis after diffuse infiltration, ultimately leading to bullae formation or fibrosis (4.129, 4.130), or both, associated with symptoms and a restrictive defect on respiratory function testing.

Evidence of the disease should be sought in the skin, eye and peripheral lymph nodes.

The most common skin lesion in sarcoidosis is erythema nodosum (2.45). However, this is a nonspecific sign, the most common cause of which is a reaction to sulphonamides. Sarcoid nodules may be found in the skin in about 5% of cases particularly on the face, especially the nose (lupus pernio) (4.131, 4.132), in scars and elsewhere (4.133).

4.127 Pulmonary infiltration with bilateral hilar lymphadenopathy in a patient with sarcoidosis. Note the nodular pattern in both lung fields with relative sparing of the apices in this patient. In this young man, the important differential diagnosis included secondary deposits, especially as a cystic testicular swelling was found; but in this case the diagnosis of sarcoidosis was confirmed by lung biopsy, and the swelling was a simple hydrocoele.

4.128 Bronchoscopic findings in a patient with infiltrative sarcoidosis. The lumen of the left main bronchus (indicated by tip of dotted line) is so narrowed that a fibreoptic bronchoscope can hardly pass through it. There are dilated mucosal vessels, and multiple sarcoid nodules in the mucosa.

4.129 Extensive chronic fibrotic sarcoidosis. This degree of fibrosis results in severe irreversible impairment of respiratory function.

4.130 Calcification is often seen in chronic sarcoidosis, as in the left hilar nodes in this patient.
Patients with eye involvement may present acutely with a painful eye and acute impairment of vision (4.134). More often there is progressive visual impairment from posterior uveitis (4.135). There may also be involvement of the lacrimal glands (producing dry eyes) and of both parotids (uveoparotid fever) producing a dry mouth. The seventh cranial nerve may be involved by this process and sarcoidosis may affect other parts of the CNS (11.34). Localized involvement of bones may give tender swellings (4.136) and X-rays may show localized bone cysts. Involvement of heart, gut and liver are rare.

Hypercalcaemia is often found in established disease as a result of additional α-hydroxylation occurring in the sarcoid lesions in the lung. This may result in metastatic calcification or stone formation in the urinary tract (see p. 304).

4.131 Skin infiltration has resulted in destructive lesions of the nose in this patient with sarcoidosis. Note the presence of a separate lesion on the upper lip.

4.133 Sarcoid lesions may occur in the skin at any site, and they may take nodular, papular or plaque forms. Biopsy is usually necessary for diagnosis.

4.135 Posterior uveitis is a relatively common complication in sarcoidosis, and may cause choroiditis, retinitis and even blindness. In this patient, a focal retinal periphlebitis alternates with stretches of unaffected vein.

4.134 Acute anterior uveitis occurs in up to 25% of patients with sarcoidosis. Note the fluid level of pus in the anterior chamber (hypopyon) and the distortion of the pupil caused by the development of posterior synechiae. A cataract may form if this eye involvement does not receive prompt treatment.

4.132 Lupus pernio is the term used to describe a dusky-purple infiltration of the skin of the nose in chronic sarcoidosis. It is important to distinguish this appearance from rhinophyma and acne rosacea.

4.136 Dactylitis in sarcoidosis. The left index finger shows obvious signs of inflammation and swelling, particularly of the proximal phalanx and interphalangeal joint, and the other digits are also involved.
The diagnosis is made by biopsy of lymph nodes, skin or lung. Lung function tests often show a restrictive defect and the Mantoux test is often negative. The Kveim test is now of largely historical interest; the theoretical possibility of HIV transmission limits its use.

Treatment of sarcoidosis depends on the extent of the disease and the tissues involved. Parenchymal lung disease, acute eye involvement and CNS or heart signs require a prolonged course of steroids. Minor skin or lymph node involvement can be watched over a period of months for spontaneous resolution. The level of angiotensin-converting enzyme is often raised and may be used to follow the course of disease activity, but this is not a specific diagnostic test.

**HISTIOCYTOSIS X**

Histiocytosis X is a disease of unknown aetiology, which is associated with the presence of granulomas that are rich in eosinophils. There are two forms found in young children (Letterer–Siwe and Hand–Schüller–Christian disease) and one in adults (eosinophilic granuloma). The granulomas may be found in bones and in the lung parenchyma where they produce progressive restrictive lung disease and may produce pneumothorax (4.137). Hypothalamic–pituitary axis involvement may lead to diabetes insipidus, panhypopituitarism or obesity.

**VASCULITIS**

The vasculitic diseases most commonly affecting the lung are Wegener's granulomatosis and allergic granulomatosis. Classic polyarteritis nodosa rarely affects the upper and lower respiratory tracts; renal involvement (see p. 292) is much more common.

**WEGENER’S GRANULOMATOSIS**

Classic Wegener’s granulomatosis consists of the clinical triad of upper respiratory tract granulomas (3.99), fleeting lung shadows and necrotizing glomerulonephritis (see p. 145), but solitary lung lesions may also occur without renal involvement.

Chest X-rays show nodular masses and pneumatic infiltrates (4.138). Cavitation may also occur. In the early stages, the chest X-ray changes are 'fleeting': lesions clear from one area as new lesions appear elsewhere. Immunosuppressive therapy may help to reverse the lung changes, but renal involvement usually requires complex therapy (see p. 293).

Midline granuloma (known also as lethal midline granuloma) is a variant of Wegener’s granulomatosis in which progressive nasal ulceration is associated with lung and renal involvement. It carries a poor prognosis.

**ALLERGIC GRANULOMATOSIS**

Allergic granulomatosis (Churg–Strauss syndrome) occurs on a background of asthma that has usually been difficult to control and present for a year or more. A high blood eosinophilia is found, and tissue eosinophilia, granulomata and vasculitis develop in various organs. The lungs, nervous system, skin and heart are often involved, whereas renal involvement is not usually significant (unlike other forms of vasculitis). Treatment is with systemic steroids, with the addition of azathioprine if necessary.

**POLYARTERITIS NODOSA**

Polyarteritis nodosa is a multisystem disorder characterized by widespread vasculitis (see p. 144). Pulmonary involvement may rarely occur, presenting with cough, haemoptysis, fever or asthmatic symptoms. Chest X-ray may show pneumatic infiltration (4.139) and biopsy of lung or other tissue may be required for definitive diagnosis.
4.139 Polyarteritis nodosa with pulmonary infiltration in both lower zones. The appearance is not diagnostic, and the diagnosis must be based on the clinical picture and confirmed by angiography or biopsy, or both.

4.140 Fibrosing alveolitis causing diffuse lower zone shadowing in a patient with rheumatoid arthritis. The appearance is indistinguishable from that seen in patients with cryptogenic fibrosing alveolitis, and similar appearances may occur in other connective tissue disorders including systemic sclerosis. The apparent mediastinal shift in this film results largely from rotation of the patient, whose arthritis prevented accurate positioning.

4.141 A single rheumatoid nodule in the right mid-zone in a 55-year-old man with rheumatoid arthritis. Rheumatoid nodules are more common in men than in women, and solitary nodules often require biopsy to exclude malignancy.

PULMONARY COMPLICATIONS OF THE CONNECTIVE TISSUE DISEASES

Fibrosing alveolitis, indistinguishable from the cryptogenic variety (4.140) (see p. 201), may occur in any collagen disease, but is most commonly seen in rheumatoid arthritis. There is an excess mortality from respiratory infection in rheumatoid arthritis. Other pulmonary complications also occur, including bronchitis, obliterative bronchiolitis and bronchiectasis, multiple (3.38) or single (4.141) pulmonary nodules, which may cavitate, and pleural effusions (3.37), which occur predominantly in men. In Caplan’s syndrome, pulmonary lesions occur in a patient with rheumatoid arthritis who has been exposed to dust as a coal miner or in an industrial setting; they may progress to massive pulmonary fibrosis (4.158). Complications seen in other connective tissue diseases include pleurisy, pleural effusions and lung atelectasis in systemic lupus erythematosus and pulmonary hypertension and basal fibrosis (4.140) in systemic sclerosis.

PULMONARY INFILTRATION WITH EOSINOPHILIA

The association of blood eosinophilia and pulmonary shadowing may occur in a number of situations, some of which are imperfectly characterized (4.142).

Simple pulmonary eosinophilia is a short-lived illness in which cough and a slight fever are associated with transient pneumonic shadowing (4.143, 4.144) and blood eosinophilia.

CAUSES OF PULMONARY EOSINOPHILIA.

- Allergic bronchopulmonary aspergillosis (ABPA)
- Worm infestation
- Drugs
- Eosinophilic myalgic syndrome
- Acute or chronic eosinophilic pneumonia
- Allergic granulomatosis

4.142 Causes of pulmonary eosinophilia.

4.143 & 4.144 Pulmonary infiltration with eosinophilia (also known as Löffler’s syndrome) (4.143). In this patient the infiltration was mainly in the left lung, and it persisted for 2–3 weeks. The patient had a mild fever and a cough, but no other symptoms. 4.144 shows the appearance of the chest 4 weeks after 4.143. Spontaneous clearing of the lung shadowing within 1 month is usual, and the condition produces few, if any, symptoms.
It appears to be an allergic response, and the provoking allergen may be the result of worm infestation or drug therapy, though often no allergen can be identified. The condition is usually self-limiting.

Allergic aspergillosis (see p. 59) occurs in asthmatics and may produce chronic symptoms with the risk of permanent lung damage (1.172), as may tropical pulmonary eosinophilia, which is probably usually caused by a reaction to Wuchereria bancrofti infection (see p. 68), and the 'hypereosinophilic' syndrome, in which the provoking cause is unknown.

GOODPASTURE'S SYNDROME

Goodpasture's syndrome is a disease of unknown aetiology that often occurs after an upper respiratory infection. The patient usually has small repeated haemoptyses with progressive dyspnoea and cough, followed by massive intrapulmonary bleeding, and may present acutely with dyspnoea and massive haemoptysis (4.145). These appearances may precede the development of acute glomerulonephritis, which often progresses to renal failure (see p. 291). The disease is mediated by anti-glomerular basement membrane antibodies. Treatment is generally unsatisfactory in the established case.

PULMONARY OEDEMA: CARDIOGENIC AND NONCARDIOGENIC

In patients with heart disease, a rise in the hydrostatic pressure within the pulmonary capillaries produces pulmonary oedema. This is most commonly seen acutely, after a myocardial infarction, pulmonary embolus, arrhythmia or hypertension, or may happen chronically in patients with valve disease or a rise in pulmonary or systemic pressure (5.15, 5.27).

Acute pulmonary oedema may also be the result of a range of noncardiac conditions, the end result of which is to increase the permeability of the pulmonary capillaries (4.146). Most of these patients are admitted with an acute medical or surgical condition that is later followed, in hours or days, by progressive hypoxia, and dyspnoea associated with scattered rhonchi and crepitations over the lung fields (the ‘adult respiratory distress syndrome’). X-rays show diffuse patchy ‘infiltrates’ (4.147). These findings often progress rapidly to cardiorespiratory failure and death, and assisted ventilation may be urgently required.

**CAUSES OF THE ADULT RESPIRATORY DISTRESS SYNDROME.**

- Inhaled smoke
- Overwhelming infections
- Aspiration of gastric contents
- Drowning
- Uraemia
- Pancreatitis
- Massive blood transfusion
- Disseminated intravascular coagulation (DIC)
- Poisoning with paraquat and other toxins/drugs
- Post-cardiopulmonary bypass
- Acute radiation pneumonia
- Trauma
- Other causes of shock

**4.146 Causes of the adult respiratory distress syndrome.**

**4.145 Goodpasture's syndrome.**

Massive intrapulmonary bleeding has led to opacities ('white-out') of both mid and lower zones on chest X-ray. The mortality rate is high as a result of pulmonary and renal involvement.

**4.147 Adult respiratory distress syndrome.**

The chest X-ray appearances in this portable anteroposterior (AP) film are similar to those seen in cardiogenic pulmonary oedema, but the condition results from an increase in pulmonary capillary permeability rather than from heart failure. This patient had inhaled smoke in a domestic fire.
PULMONARY FIBROSIS

Many different lung diseases may result in pulmonary fibrosis, which may be localized or generalized. For example:
- localized unilateral fibrosis may result from a destructive pneumonia
- localized bilateral fibrosis may occur in tuberculosis, histoplasmosis and other chronic infections
- generalized fibrosis may occur as the end-stage of a range of parenchymal lung disorders, including industrial lung diseases, connective tissue diseases, ankylosing spondylitis (3.50) and sarcoidosis; and in cryptogenic fibrosing alveolitis and extrinsic allergic alveolitis.

CRYPTOGENIC FIBROSING ALVEOLITIS

Cryptogenic fibrosing alveolitis (CFA, idiopathic pulmonary fibrosis) is the most common of the interstitial lung diseases, affecting between 5 and 10 per 100,000 people, men more often than women (2:1), and most commonly seen in those over 65 years of age. Alveolitis leads to the destruction of alveoli and the laying down of scar tissue (fibrosis), which further disrupts the function of the lung. There is wide variation in the tempo of the illness. Patients may die from respiratory failure within a few months of presentation, or the disease may be identified by chance on chest X-ray and show little progression over many years. Most commonly, the disease progresses to respiratory failure over a few years. The principal symptoms are dyspnea, cough, generally unproductive, and arthralgia. Gross clubbing of the fingers is common (4.148) and late inspiratory crackles are heard, particularly at the lung bases. Chest X-ray shows predominantly lower zone shadowing (4.149) and comparison of X-rays over time often shows a loss of lung volume (if taken correctly in full inspiration, the chest X-ray is an indicator of total lung capacity). Pulmonary function tests show a restrictive defect, often with a greater reduction in transfer factor than would be expected for the loss of lung volume. The ESR or plasma viscosity is usually moderately raised. Blood tests may show positive autoantibodies and there is an association with other autoimmune diseases. Lung biopsy may be necessary for diagnosis and shows characteristic changes (4.150). Systemic corticosteroids lead to improvement in 75% of patients and must be continued for many months. The alternative option is immunosuppression with cyclophosphamide and azathioprine. The response to treatment is better if inflam-

4.148 Gross clubbing of the fingers is common in cryptogenic fibrosing alveolitis (see also 2.103, 2.104). Note also the tar staining of the fingers in this patient who continued to smoke despite his precarious respiratory state.

4.149 Cryptogenic fibrosing alveolitis typically causes predominantly basal pulmonary shadowing. Note that the appearance is very similar to that found in rheumatoid fibrosis (4.140).

4.150 Lung biopsy in cryptogenic fibrosing alveolitis (H&E) showing diffuse infiltration of the alveolar walls with lymphocytes and plasma cells and the alveolar spaces filled with an inflammatory exudate of macrophages and lymphocytes. There is also extensive fibrosis of the alveolar walls. In earlier disease, electron microscopy may show collagen deposition in the basement membrane of the alveolar epithelium and pulmonary vessels, and in the alveolar wall interstitium.
EXTRINSIC ALLERGIC ALVEOLITIS

Extrinsic allergic alveolitis (EAA, allergic bronchioalveolitis, hypersensitivity pneumonitis) develops as a result of a hypersensitivity reaction in the lungs, provoked by a wide range of organic dusts. Many of these are encountered at work, and a large number of occupational lung diseases fall within this classification, whereas other causes relate to hobbies, especially the keeping of birds. Some common causes are listed in 4.151. Farmer's lung is the most common cause, accounting for 50% of cases of extrinsic allergic alveolitis. About 1 in 10 homes in the UK keep a bird and extrinsic allergic alveolitis is found in about 5% of bird owners and 20% of pigeon keepers.

Repeated exposure of a susceptible individual to the offending antigen leads to the production of circulating precipitating antibodies and immune complexes and ultimately to macrophage activation and epithelioid cell granuloma formation.

The factors that predispose to allergic alveolitis are poorly understood. There is some evidence of genetic susceptibility but no link with atopy, or with elevated IgE or eosinophil levels.

Symptoms may develop within 6 hours of heavy exposure to the antigen or may appear insidiously over years. The most common presentation is with breathlessness, dry cough and influenza-like symptoms (malaise, fever and muscle pain). Chest X-ray in the acute phase shows a fine nodular shadowing (4.152), but repeated exposure may lead to chronic respiratory impairment caused by pulmonary fibrosis (4.153), which radiologically tends to be more marked in the upper zones, as with sarcoidosis, than in the lower zones, as with cryptogenic fibrosing alveolitis. Lung function shows restrictive ventilation (reduced TLC and FVC), accompanied by reduced compliance and gas transfer.

In the acute stage the provoking factor must be identified and removed. This alone may result in rapid control of symptoms. In very severe cases, systemic corticosteroids may be required and may accelerate recovery.

### SOME CAUSES OF EXTRINSIC ALLERGIC ALVEOLITIS.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Provoking activity</th>
<th>Antigen</th>
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<tbody>
<tr>
<td>Microorganisms</td>
<td></td>
<td></td>
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<tr>
<td>Farmers lung</td>
<td>Forking mouldy vegetable matter, especially mouldy hay</td>
<td>Thermophilic actinomycetes (Faenia rectivirgula)</td>
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<tr>
<td>Malt workers lung</td>
<td>Turning germinating barley</td>
<td>Aspergillus clavatus</td>
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<tr>
<td>Humidifier fever (or sauna takers lung)</td>
<td>Use of airconditioners/humidifiers</td>
<td>Range of bacteria fungi and protozoa esp Naegleria gruberi</td>
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<tr>
<td>Maple bark strippers lung</td>
<td>Mouldy maple bark</td>
<td>Cryptostroma corticale</td>
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<tr>
<td>Animals</td>
<td></td>
<td></td>
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<tr>
<td>Bird fanciers lung (pigeon fanciers lung)</td>
<td>Handling pigeons/cleaning out lofts or budgerigar cages</td>
<td>Bloom from feathers or from excreta</td>
</tr>
<tr>
<td>Rodent (rat) handlers lung</td>
<td>Involvement with rodents (rats)</td>
<td>Urinary protein</td>
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<tr>
<td>Chemicals</td>
<td></td>
<td></td>
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<tr>
<td>Vineyard sprayers lung</td>
<td>Spraying vines</td>
<td>Bordeaux mixture (copper sulphate and calcium hydroxide)</td>
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<tr>
<td>Vegetable matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffee workers lung</td>
<td>Preparation and drying of coffee beans</td>
<td>Chemicals in dust</td>
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<tr>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iatrogenic alveolitis</td>
<td>A large number of drugs used in cancer therapy produce a similar picture</td>
<td>Drug molecules or metabolites</td>
</tr>
</tbody>
</table>

4.151 Some causes of extrinsic allergic alveolitis.
In the more chronic form removal of the stimulus is important but may not be practicable. In this situation, an alternative way of reducing exposure should be implemented, for example by better ventilation and extraction of air. Corticosteroids may reduce symptoms.

4.152 Acute extrinsic allergic alveolitis — in this case pigeon fancier’s lung. This man presented with acute symptoms after cleaning out his pigeon loft. The X-ray shows diffuse, hazy opacification in both lung fields, which partially obscures the normal vascular markings.

4.153 Chronic extrinsic allergic alveolitis — budgerigar fancier’s lung. Budgerigar fanciers may develop similar X-ray changes to pigeon fanciers (4.152) or to those with farmer’s lung. Because they often keep their birds indoors, their exposure to antigen is more constant and they usually present with insidious chronic lung disease. This X-ray shows diffuse fibrosis and some bullae towards the hilum. The changes led to a permanent severe ventilatory restrictive and diffusion defect.

IATROGENIC LUNG DISEASE

The most common iatrogenic lung lesion results from radiotherapy, usually given for diseases such as cancer of the breast, bronchus, thymus or lymph nodes. The determining factors in lung damage are total radiation dose, duration of time over which the dose is given and the number of treatments. Acute radiation pneumonitis occurs a few days to some weeks after exposure and presents with a cough, fever and progresssive dyspnoea. Corticosteroids may ameliorate these acute symptoms. Fibrosis may develop over many months (4.154) and there is evidence of a progressive restrictive defect in the pulmonary function tests with a decrease in transfer of carbon monoxide.

A large number of drugs, alone or in combination, may produce a range of respiratory problems that include:
- asthma (e.g. β-blockers)
- infiltration or fibrosis (e.g. bleomycin, methotrexate)
- eosinophilia (e.g. nitrofurantoin)
- systemic lupus erythematosus-like syndromes (e.g. hydralazine)
- respiratory depression (e.g. opiates, barbiturates)
- opportunistic infection (e.g. high dose steroids, immunosuppressives).

4.154 Radiation fibrosis. This patient had undergone a right mastectomy (note missing breast shadow) for breast cancer, followed by a course of radiotherapy. There are fibrotic changes in the lung, with upper lobe shrinkage, especially on the right, and the trachea is pulled to the right. She also had some ununited rib fractures on the right, resulting from secondary deposits.
**OCCUPATIONAL LUNG DISEASE**

Lung diseases associated with industrial exposure are a common problem. They can be avoided if appropriate occupational regulations are enforced, especially efficient ventilation and individual protection by ventilators or masks. A range of common disorders related to dust inhalation are listed in 4.155. Asthma (p. 180) and extrinsic allergic alveolitis (p. 202) are other common problems.

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**COAL WORKERS’ PNEUMOCONIOSIS**

Pneumoconiosis is lung disease resulting from exposure to dust. Coal workers’ pneumoconiosis (CWP) was commonplace until dust exposure was reduced. Initially, it was believed that the disease was caused by the inhalation of silica (silicosis), but it is now clear that the disease can be caused by silica-free coal dust, although the mineral make-up of the dust influences the incidence and progression. CWP and silicosis are defined radiologically as simple if there is fine micronodulation, usually in the upper lobes (4.38, 4.156), or as complicated if the nodules coalesce to masses greater than 1 cm in diameter causing lung damage and significant functional impairment (4.157). These

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Dust</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Coal workers’ pneumoconiosis</td>
<td>Coal</td>
<td>Simple/complicated</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Crystalline silica</td>
<td>Simple/complicated</td>
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<tr>
<td>Asbestosis</td>
<td>Serpentine (chrysolite), Amphibole</td>
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<tr>
<td></td>
<td>(crocidolite, amosite, anthophyllite)</td>
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<tr>
<td>Pneumoconiosis</td>
<td>Talc, slate, kaolin</td>
<td>Rarely produces nodular fibrosis and</td>
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<tr>
<td></td>
<td></td>
<td>pleural plaques</td>
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<tr>
<td>Stannosis</td>
<td>Tin oxide</td>
<td>Rare</td>
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<tr>
<td>Baritosis</td>
<td>Barium sulphate</td>
<td>Rare</td>
</tr>
<tr>
<td>Berylliosis</td>
<td>Beryllium</td>
<td>May produce acute bronchiolitis, pneumo-</td>
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<td></td>
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<td>nia and pulmonary oedema</td>
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</table>

4.155 Lung diseases caused by dust inhalation.
diseases attract industrial compensation in many countries, and a spectrum of functional and radiological lung changes is recognized for this purpose. Tests of lung function may show a reduction in lung volume, especially when nodules are present, with some obstruction and restrictive defects. Patients who are developing complicated CWP complain of progressive dyspnoea on exertion and eventually at rest. Cough with black sputum is a common feature (melanoptysis). No treatment prevents the progression of the disease. The picture is often confused by the effects of chronic cigarette smoking and in some cases by coincidental infection with tuberculosis. Many of these patients also have COPD.

Caplan’s syndrome is the association of rheumatoid arthritis (or rheumatoid factor) with CWP. The lung nodules may enlarge rapidly and may cavitate (4.158). These appearances are usually associated with the presence of subcutaneous nodules, active rheumatoid joint disease and high titres of rheumatoid factor.

There is no specific treatment, but prevention is possible by reducing exposure to dust and by the use of respirators. Complications such as infection and heart failure require treatment.

SILICOSIS

Silicosis is a disease of miners, tunnellers and stonemasons, which results from inhalation of crystalline silicon dioxide (quartz). The result is progressive pulmonary fibrosis that ranges in appearance from micronodular fibrosis to progressive massive fibrosis, as in coal workers’ pneumoconiosis. The time taken for development of the changes depends on the amount of inhaled silica. With simple silicosis there are usually no clinical features and the condition is diagnosed on routine X-ray. Complicated silicosis is associated with progressive fibrosis over many years, and presents clinically with dyspnoea, weight loss, cough and recurrent chest infections, especially tuberculosis and other mycobacterial infections. The X-ray appearance is of progressive fibrosis (4.157); there may be a pleural reaction and the hilar lymph nodes may be enlarged and calcified. Pulmonary function tests become abnormal as the disease progresses and the defects are a mixture of restriction and obstruction. The disease may be compounded by cigarette smoking and infection with tuberculosis, fungi or bacteria. There is no specific treatment for the fibrous reaction. Prevention of exposure to silica dust is the key to prevention, and masks and respirators may aid this process.

ASBESTOS-RELATED DISEASE

Asbestos exists in a variety of chemical forms which have been widely used for insulation in building, pipe-lagging and shipbuilding. Inhalation of the fibres by workers during construction and demolition is the most common cause of lung disease, but this is now well recognized in the public living close to factories producing asbestos products, in the partners of asbestos workers and in those living in houses insulated with asbestos.

The risks of disease are greatest with crocidolite (blue asbestos) and chrysotile (white asbestos). When inhaled, most fibres are cleared by microcirculatory action and some by macrophages. Fibres which remain in the lung become coated with ferroproteins and may be seen in sputum (4.14). Such fibres after a long latent period cause a range of effects, including pulmonary fibrosis (asbestosis), pleural effusion, and eventually calcified pleural plaques, mesothelioma and bronchial carcinoma.

The clinical features of asbestosis at presentation may include an irritant cough and progressive shortness of breath. Examination shows finger clubbing (in 50% of patients) and diffuse fine crepitations over both bases, which spread with time. A history of cigarette smoking is important, as tobacco smoke and asbestos exposure seem to have a synergistic action in promoting the subsequent onset of bronchial carcinoma.

Lung function tests reflect the diffuse fibrosis with evidence of restrictive lung disease and impairment of gas transfer. X-ray of the chest shows a spectrum of abnormalities in the early stages of asbestosis, which include irregular opacities in
the lower zones (4.159, 4.160) and later pleural thickening and calcification that is usually bilateral (4.161, 4.162). Later features include mesothelioma (4.163) and bronchial carcinoma (4.164).

Mesothelioma is a highly malignant tumour of the pleurae, which is diagnosed by pleural biopsy, a procedure that may occasionally lead to local spread of the tumour (4.62). Mesotheliomas may also develop in the peritoneum.

Treatment of asbestos-related disease is ineffective and this underlines the importance of preventing exposure. Compensation schemes for the effects of asbestos exposure exist in many countries. About 50% of the patients with asbestosis who also smoke die of bronchial carcinoma and 10% die of mesothelioma.

4.160 CT scan in asbestosis. There are widespread fibrotic changes in both lungs and some patchy pleural calcification is seen.

4.161 Extensive pleural and pericardial calcification after long-term industrial asbestos exposure.

4.162 Pleural calcification shown by CT scan. The pleural calcification is particularly obvious in this cut posteriorly on the right; and anteriorly, the calcification in the right diaphragmatic pleura is clearly seen.

4.163 Mesothelioma of the right pleura. The patient had a long history of asbestos exposure and has now developed a large pleural mass, which can be seen by soft-tissue shadowing to have extended through the chest wall (see 4.62).

4.164 Carcinoma of the bronchus in asbestosis. Reticulonodular shadowing is present throughout both lungs, especially basally. A mass is seen behind the heart in the left lower lobe. Percutaneous needle biopsy showed a squamous cell carcinoma. The patient was a retired shipbuilder.
TUMOURS OF THE LUNG

BENIGN TUMOURS

Benign tumours of the lung account for about 2% of all tumours of lung and present either as solitary nodules on the chest X-ray or, if endobronchial, with cough, haemoptysis or pneumonia. The most common type is a hamartoma, which is usually found as a solitary nodule in a young asymptomatic adult (4.42, 4.165). Other benign tumours are rarely seen. Endobronchial carcinoid tumours may give rise to atelectasis, recurrent infections and sometimes bronchiectasis. The carcinoid syndrome may occasionally be seen, and carcinoid tumours may ultimately metastasize.

The treatment of all these tumours is surgical removal whenever possible.

BRONCHIAL CARCINOMA

Bronchial carcinoma (lung cancer) is the most common type of malignant disease worldwide. It causes about 35,000 deaths annually in England and Wales, almost 80% of which are in men. In the last few years the steady rise in male mortality from bronchial carcinoma seems to have peaked and begun its decline, but female mortality continues to increase. The development of lung cancer has been associated with exposure to a number of substances, but the overriding aetiological agent is tobacco. Cigarette smoking is associated with about 85% of bronchial carcinoma, but as only a minority of smokers develop bronchial carcinoma other factors must be important. There is some evidence that genetic and dietary factors may play a role, and exposure to asbestos and possibly to other inhaled substances may have a synergistic effect with smoking.

Presentation

Intrathoracic manifestations

The clinical presentation of bronchial carcinoma can vary enormously.

- In about 5% of patients, a symptomless abnormality is found on a ‘routine’ chest X-ray (4.31) and confirmed by CT (4.46, 4.47), bronchoscopy (4.53, 4.166) or lung biopsy, whereas other patients present with extensive disease and die rapidly (4.167).
- Cough is the most common presenting symptom; because the majority of cases are in smokers, a change in the character of the cough is more important than the cough itself.
- Haemoptysis occurs as an initial symptom in up to 50% of patients, and in a smoker over the age of 40 years is an indication for bronchoscopy (4.52), even in the absence of a radiological abnormality.
• Dyspnoea occurs commonly and may be caused by large airway obstruction with tumour, the development of pneumonia or collapse distal to the tumour (4.46, 4.47, 4.167, 4.168), the development of a large pleural effusion or, more rarely, involvement of the lung lymphatics (lymphangitis carcinomatosa, 4.169) or pericardium.

• Chest discomfort is a common symptom; it is often of an ill defined aching nature, but may be localized to the chest wall if there is direct invasion of the chest wall, metastasis to ribs or pleurisy associated with infection.

• Pain in the shoulder, radiating down the upper inner arm, can be the first sign of a Pancoast tumour situated in the apex of the lung, causing symptoms by invasion of the ribs, vertebral sympathetic trunk, brachial plexus and artery (4.170–4.173).

**RESPIRATORY**

4.168 Bronchial carcinoma with right upper pneumonic consolidation. The consolidation follows obstruction of the right upper lobe bronchus.

4.169 Lymphangitis carcinomatosa. Micronodular shadows are seen throughout the lungs especially on the left, and there is a streaky appearance, which results from tumour infiltration of lymphatic vessels.

4.170 Right apical bronchial carcinoma (Pancoast tumour). In this location, the tumour may cause other symptoms (see 4.171–4.173).

4.171 Right apical bronchial carcinoma invading the hilum and lung substance revealed by CT scan. This cut is at T4 level, just below the carina.

4.172 Wasting of the small muscles of the left hand (most noticeably the first dorsal interosseus) as a consequence of a left apical tumour.

4.173 Horner’s syndrome resulting from a right Pancoast tumour. The patient had a right ptosis and a constricted right pupil, caused by tumour infiltration of the inferior cervical sympathetic ganglia.
• wheeze is described by 10% of patients, and is often stridor caused by the narrowing of a major airway
• a hoarse voice may be caused by paralysis of the left recurrent laryngeal nerve as it loops round the arch of the aorta; in contradistinction to the hoarse voice of chronic laryngitis associated with smoking, the patient with a paralysed vocal cord is unable to produce an explosive cough, producing instead a ‘bovine’ cough (4.174)
• superior vena caval obstruction is most commonly caused by small-cell carcinoma, and presents with swelling of the head and neck, engorgement of the neck veins without visible pulsation and the development of collateral venous circulation over the chest wall (4.175, 4.176)
• another feature of mediastinal glandular involvement is compression of the oesophagus causing dysphagia.

Extrathoracic manifestations
About one-third of patients present with symptoms resulting from metastases; 20% of patients have bone pain at presentation (see p. 166). The lung is the most common origin of cerebral metastases (4.177); liver (see p. 413), adrenal and para-aortic lymph node involvement is also common and skin secondaries may occur (4.178).

4.174 Left vocal cord paralysis during phonation in a patient with recurrent laryngeal nerve involvement by a bronchial carcinoma. This endoscopic view shows that during phonation the normal right vocal cord (1) adducts to the midline, whereas the left vocal cord (2) appears bowed and lies at a lower level than the right vocal cord. Adduction to the midline is partial, resulting in incomplete glottic closure, so the patient has a breathy voice and a bovine cough. The right aryepiglottic fold (3) is tense and appears in the normal position during phonation, whereas the left aryepiglottic fold (4) has lost its tone and cannot conform to the normal position.

4.175 Superior vena caval obstruction in bronchial carcinoma. Note the swelling of the head and neck, engorgement of the neck veins and the development of a collateral circulation in the veins of the chest wall.

4.176 Superior vena caval obstruction caused by bronchial carcinoma. The superior vena cava (3) is invaded and compressed by the tumour (6), which has also invaded and enlarged a pretracheal lymph node (4). The ascending aorta is marked 1 and the descending aorta is marked 2. The mediastinal involvement demonstrated by this CT scan shows that the tumour is inoperable.
A number of non-metastatic syndromes are associated with bronchial carcinoma. Inappropriate secretion of antidiuretic hormone (ADH) and ectopic adrenocorticotropic hormone (ACTH) secretion are seen with small-cell lung cancer (4.179), whereas hypercalcaemia and more rarely gynaecomastia (4.180) and hyperthyroidism are associated with squamous cell cancer. Neuromyopathies (11.121, 11.122), dermatomyositis, encephalopathy and myelopathy have all been associated with bronchial carcinoma. Finger clubbing (2.104, 2.105, 4.2, 4.148) is common, except in small-cell cancer, and may progress to hypertrophic pulmonary osteoarthropathy, in which there is pain in the wrists and ankles associated with periosteal new bone formation in the long bones (4.181, 4.182). Anaemia and weight loss are common accompaniments of bronchial carcinoma. Thrombophlebitis, venous thrombosis and skin lesions such as acanthosis nigricans occur much less commonly.

**Diagnosis and treatment**

Most tumours are visible on chest X-ray, and a firm diagnosis is made by microscopic examination of sputum (4.16) or specimens obtained at bronchoscopy, or by the biopsy of metastatic lesions. Occasionally, closed or open lung biopsy is required. Although there are many types of lung tumour, the most simple, clinically useful classification is to distinguish between small-cell lung cancer, non-small-cell lung cancer and benign tumours.

- Small-cell carcinoma (4.183) has almost always metastasized by the time of diagnosis, and it is rare for surgical resection to be performed if this diagnosis is known; the tumour is sensitive to chemotherapy and radiotherapy, both of which can lead to a significant prolongation of useful life but not a cure.

**4.177 Large secondary deposit in the frontal lobe of the brain demonstrated by an unenhanced CT scan.** The patient was a 45-year-old woman smoker, and the primary deposit was a small-cell carcinoma of the lung.

**4.178 Multiple secondary deposit in the skin in a patient with carcinoma of the bronchus.** Note the signs of weight loss and the subcutaneous nodule on the right.

**4.179 Cushing's syndrome resulting from ectopic adrenocorticotropic hormone (ACTH) secretion by a small-cell bronchial carcinoma.** The facial appearance is similar to that of Cushing's disease of other causes, but the disease often runs a very rapid course (see p. 313).

**4.180 Unilateral gynaecomastia** developed in this male patient with squamous cell carcinoma of the bronchus. Note the positioning line for radiotherapy. The patient shows signs of weight loss and possible early generalized hyperpigmentation.
In non-small-cell lung cancer (4.184), the patients with the best outcome are those who undergo a successful resection; two criteria must be satisfied before a patient undergoes surgery: firstly, they must be fit enough to survive the operation and have sufficiently good lung function to have good-quality survival after lung removal; secondly, the surgery must be likely to remove all of the tumour and therefore it is usual to perform scanning before operation to identify metastases; radiotherapy is valuable for the treatment of bronchial bleeding, superior vena caval obstruction, and painful bony metastases.

Many patients with cancer fear a painful death, but simple analgesics, morphine, radiotherapy and techniques such as transcutaneous nerve stimulation will control pain in almost all patients. The prognosis of bronchial carcinoma is poor. About 5% of patients will survive 5 years, and the majority of these are patients who undergo successful surgery.

SECONDARY TUMOURS

Metastases in the lung are common. They may occur as one or more discrete nodules (4.32), as a finer pattern of multiple metastases (4.35) or as lymphangitis carcinomatosa (4.169). The most common primary sites are the kidney, breast, prostate, gut, cervix and ovary. Discrete metastases are often asymptomatic, but their presence is generally a bad prognostic sign. Surgical removal of secondaries is only very rarely possible.

4.181 Hypertrophic pulmonary osteoarthropathy (HPOA) at the ankle in a patient with bronchial carcinoma. New bone formation is shown by the double margin seen at the medial border of the tibia (arrowed).

4.182 Hypertrophic pulmonary osteoarthropathy (HPOA) in bronchial carcinoma, demonstrated by radionuclide bone scan. Extensive cortical new bone formation is demonstrated by the 'tramline' appearance of both femurs.

4.183 Small cell anaplastic ('oat-cell') lung cancer (H&E) arises from the bronchial epithelium and differentiates into neuroendocrine cells containing neurosecretory granules. This type of tumour grows rapidly and metastasises rapidly to the regional lymph nodes and via the blood stream. The typical appearance shown here is of dark, tightly packed sheets of cells (like grains of oats). The nuclei contain nucleoli and the cytoplasm is scanty. The cells often form into rosettes. Chemotherapy and radiotherapy is the best treatment option.

4.184 Squamous carcinoma of lung (H&E) is a form of non-small cell lung cancer that develops following metaplasia of airway epithelium to a squamous type, a change which results from chronic irritation by cigarette smoke. In this picture there are many well differentiated foci (cell nests) of tumour cells producing keratin in layers. Such tumours develop centrally, close to the carina, are slow-growing and are often amenable to surgery.
DISEASES OF THE PLEURA

PLEURAL EFFUSIONS

Pleural effusions are a common clinical problem (4.37, 4.185) and can be classified as transudates and exudates (see p. 176).

- Transudation of fluid (4.58) occurs with increased capillary pressure and reduced plasma oncotic pressure, and therefore is most common in cardiac failure and hypoalbuminaemic states.
- An exudative pleural effusion is caused by an inflammatory process, such as carcinoma, pneumonia (4.37), tuberculosis (4.118), rheumatoid arthritis (3.37), asbestosis or pulmonary infarction; pleural fluid cytology, Gram stain, culture, glucose, amylase, lactate dehydrogenase (LDH), pH and pleural biopsy can all contribute to the identification of aetiology.
- A bloody effusion (4.56) is most commonly seen with tumour involvement of the pleura (4.163), but can also occur in pulmonary infarction, tuberculosis, trauma, coagulation disorders or ruptured aneurysm.
- Damage to the thoracic duct, usually by trauma or mediastinal malignancy leads to drainage of chyle into the pleural cavity, a chylothorax (4.57).

4.185 A large left-sided pleural effusion. The patient presented with breathlessness, and had previously undergone 'lumpectomy' for carcinoma of the left breast. On aspiration, the effusion was bloodstained (4.56).

CAUSES OF SPONTANEOUS PNEUMOTHORAX

<table>
<thead>
<tr>
<th>Primary</th>
<th>Due to apical subpleural blebs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary to</td>
<td>Asthma, COPD, Bacterial pneumonia or pleurisy, Lung abscess, Whooping cough, Malignancy, Marfan's syndrome</td>
</tr>
</tbody>
</table>

Large pleural effusions may require aspiration to improve the patient’s respiratory state (see p. 213–4), but in general, it is most important to treat the underlying condition.

PNEUMOTHORAX

In pneumothorax air leaks into the pleural cavity, usually from the lung but occasionally from penetration of the chest wall (during surgery, penetrative trauma, etc.). The most common medical problem is a 'spontaneous' pneumothorax. This results from rupture of a congenital 'bleb' in the lung, which is usually apical and may be multiple. These are relatively common in young, tall, thin, healthy athletic men and pneumothoraces may come on at rest or after some major respiratory effort. Spontaneous pneumothorax also occurs in other medical disorders (4.186).

Clinical presentation is usually dramatic, with the sudden onset of unilateral pain of a pleuritic type and sometimes progressive dyspnoea. It is probable that most small pneumothoraces remain undiagnosed and resolve rapidly. Larger ones can be readily diagnosed by clinical examination, and chest X-rays usually confirm the diagnosis (4.38, 4.187). Usually a pneumothorax occupying less than 20% of the hemithorax may safely be left to resolve in an otherwise healthy individual as the ruptured bleb seals itself. Rarely, rupture of a bleb may leave a valve-like abnormality on the pleural surface, so that air continues to fill the pleural space, which expands and pushes over the mediastinum (tension pneumothorax). Urgent decompression is necessary and this may be done with an intrapleural catheter attached to an underwater seal drain. After conservative treatment the recurrence rate can be as high as 30%. Such patients should have thoracoscopy, which may identify a bleb or blebs that can be dealt with by oversewing using a minimally invasive technique. If the lung is apparently normal then talc may be inserted (poudrage) to achieve adhesion of the parietal and visceral pleura (pleurodesis).

4.186 Causes of spontaneous pneumothorax.

4.187 Right-sided pneumothorax in an adult woman with asthma. The edge of the collapsed lung is not so obvious as in 4.38, and it is important to consider pneumothorax whenever examining the chest X-ray of a patient with an acute respiratory problem. The edge of the collapsed lung is marked with an arrow.
Intercostal drainage
In the presence of an enlarging pneumothorax, or one with which significant dyspnoea is present, a tube should be inserted into the pleural space. Similar drains may also be used for very large or persistent pleural effusions. If there is a haemothorax, early removal of blood prevents later fibrosis.

The optimum site for drain insertion is in the axilla in the so-called triangle of safety – the three sides of which are the anterior axillary line, the lateral margin of pectoralis major and a horizontal line at the nipple level (4.188).

Silastic catheters of reasonable size are optimal as they cause less tissue reaction and are readily inserted (4.188, 4.189, 4.190).

Possible complications of chest drain insertion include:
- haemorrhage from damaged intercostal vessels
- injury to abdominal and thoracic organs
- wrong placement – usually too low
- blockage of tube with fibrin, blood clot, or pus
- kinking or migration of tube
- subcutaneous (surgical) emphysema (4.191).

Insertion of an intercostal drain.
The chosen site in the 6th intercostal space (4.188) is injected with local anaesthetic, a small incision is made through the skin, and a suitable drainage tube introduced with the aid of a trochar. The tube is held in place with a suture (4.189). The drainage tube can be attached to a one-way valve or, as here, to an underwater seal drain. If a tension pneumothorax is present, or if a large air leak from the lung persists, suction may be applied to the underwater seal. In this patient, drainage was required for symptomatic relief of a large pleural effusion.

Severe subcutaneous (surgical) emphysema, which developed after the insertion of a chest drain for the treatment of pneumothorax in a patient with COPD. The condition resolved spontaneously after repositioning of the catheter. Though usually of minor clinical importance, subcutaneous emphysema may occasionally compress vital structures with life-threatening consequences.
HISTORY

Many patients with heart disease are symptom free until a relatively late stage in the illness when a catastrophic event may occur. This is particularly the case when the progression of atheroma is concerned. Early lesions may be present from the early teens, but patients usually present with myocardial infarction, stroke or peripheral arterial disease in middle or old age. Valve diseases, congenital lesions, hyperlipidaemia and hypertension may also be asymptomatic for many years.

Most of the symptoms of heart disease result from myocardial ischaemia, abnormalities of rhythm or impaired pumping action. Many patients have nonspecific symptoms such as tiredness, easy fatigability and anorexia, but the two main symptoms are chest pain and breathlessness.

There are two main causes of cardiac pain: myocardial ischaemia and pericarditis. Ischaemic pain is usually of sudden onset, located centrally and stabbing or constricting; it may radiate to the left arm, occasionally to the right, into the neck and to the back. It may be brought on by exercise, emotion, fright or sexual intercourse. Angina pectoris usually lasts less than 30 minutes and may be relieved by rest or administration of trinitrin. The pain of myocardial infarction usually lasts for more than 30 minutes, often as long as several hours.

Failure of the heart to pump efficiently may lead to the accumulation of blood in the lungs and dyspnoea (breathlessness). Heart failure should be defined in the four categories of the New York Heart Association (5.1). Orthopnoea is the feeling of being out of breath when lying flat, which improves on sitting up. Paroxysmal nocturnal dyspnoea occurs when the patient lies flat in bed at night; as a result of redistribution of oedema from the periphery to the lungs there is sudden dyspnoea which makes the patient sit up or lean out of the window to get 'fresh air'.

Palpitations are an awareness of the heart beating. They can be normal in excitement, anxiety or after exercise, and may be provoked by excessive intake of caffeine, nicotine or chocolate, by heavy meals and indigestion or by sympathomimetic or vasodilator drugs; however, they may also result from cardiac rhythm disturbances.

Syncope results from failure to maintain an adequate circulation to the brain. The attacks may come on suddenly without any warning and result in sudden collapse. Syncope may have a number of causes (5.2).

Always note any family history of congenital heart disease or other genetic disorders with cardiac implications. Premature death in near relatives from myocardial infarction or stroke, or hyperlipidaemia or hypertension in family members are important findings.

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### FUNCTIONAL GRADING OF HEART DISEASE (NEW YORK HEART ASSOCIATION)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>No limitation of activities, i.e. free of symptoms</td>
</tr>
<tr>
<td>Grade II</td>
<td>No limitation under resting conditions, but symptoms appear on severe activity</td>
</tr>
<tr>
<td>Grade III</td>
<td>Limitation of activities on mild exertion</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Limitation of activities at rest, restricting the person to bed or a chair</td>
</tr>
</tbody>
</table>

5.1 Functional grading of heart disease (New York Heart Association).

### CAUSES OF SYNCPE

- Vasodilatation – vasovagal attack, drugs, micturition syncope
- Cardiac causes – heart block, paroxysmal tachycardia
- Outflow obstruction – aortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM)
- Reduced ventricular filling – pulmonary embolism, atrial myxoma
- Reduced blood volume – bleeding

5.2 Causes of syncope.
EXAMINATION
The most acute presentation of heart disease is cardiac arrest. The patient collapses, respiration ceases and no pulse can be felt (5.3). Death results unless resuscitation is carried out successfully (see p. 232).

Examination should start with the general appearance. There may be obvious breathlessness, even at rest, as a result of heart failure; this may make the patient sit up in bed, propped up on pillows. The skin of the face may have the bluish discolouration of cyanosis. Severe central cyanosis, best seen in the tongue and lips, is often a feature of congenital heart disease (4.4). A facial flush may be present (5.4). Arcus cornealis in a young patient (6.44, 7.126), xanthelasmas (7.127) or skin and tendon xanthomata (7.128–7.131) point to hyperlipidaemia. Jaundice may reflect hepatic disturbance from heart failure.

Finger clubbing may be caused by infective endocarditis or, more commonly, cyanotic congenital heart disease (5.5). Infective endocarditis may cause splinter haemorrhages in the nails (3.33) and tender nodules in the tips of fingers and toes (5.126).

Distended internal and external jugular veins (5.6) and abnormalities of the jugular venous waveform occur in right heart failure (5.4 Malar flush). Redness of the cheeks used to be described as a specific sign of mitral stenosis, but a similar appearance can be seen in other cardiovascular disorders and normal people. It is important to distinguish malar flush from the butterfly rash of systemic lupus erythematosus (3.76, 3.77) and from acne rosacea (2.84).

5.3 Cardiac arrest. The diagnosis is established clinically by feeling for the carotid pulse. The head should be slightly extended if possible, and the neck should be palpated for evidence of a carotid pulse on one side of the thyroid cartilage for 10 seconds. An absent carotid pulse indicates probable cardiac arrest, but peripheral pulselessness or the absence of heart sounds are unreliable signs.

5.5 Severe finger clubbing in a patient with cyanotic congenital heart disease. The drumstick appearance of the fingertip is similar to that seen in clubbing from other causes (2.104, 2.105), but the nailbeds are obviously cyanotic.

5.6 Elevated external jugular venous pressure (JVP). The pressure in the internal and external jugular veins is elevated in right heart failure. Abnormalities in waveform may provide evidence of tricuspid valve disease or cardiac arrhythmia, although these abnormalities are more reliably noted in the internal than the external jugular vein, which may be affected by position.
heart failure, with abnormalities of the tricuspid valve, and in
arrhythmias in which the right atrium contracts against a closed
tricuspid valve.

Patients with the disproportionately long arms and fingers
of Marfan's syndrome (3.115-3.118), are susceptible to the
development of aortic aneurysm and aortic regurgitation.

The abdomen may be distended in chronic heart failure,
because of the presence of ascites, and there may be pitting
oedema of the legs (5.7, 5.8) and the skin over the sacrum.
Unilateral leg swelling is suggestive of deep venous thrombo-
sis (5.195). Arterial embolism into the legs causes gangrene,
which may also result from diffuse atherothrombotic arterial
disease.

Examination of the radial artery pulse gives information
about heart rate and rhythm, and the character of the pulse may
suggest abnormalities of the aortic valve or pericardium, or car-
diomyopathies.

The position of the apex beat can indicate cardiac enlarge-
ment, and auscultation of the heart allows the detection of
abnormal heart sounds and murmurs caused by valve disease
and congenital malformations (5.9).

Crepitations in the lung fields that persist after coughing
usually indicate cardiac failure. In hypertensive patients, the
fundi may show evidence of retinal arterial damage (see p. 255).

5.7 & 5.8 Pitting
oe oedema in a patient with
cardiac failure. A
depression ('pit') remains
in the oedema for some
minutes after firm
fingertip pressure is
applied.

5.9 Common systolic and
diastolic murmurs and their
radiation patterns. 1: First heart
sound; 2: second heart sound; A:
Aortic component; P: pulmonary
component; OS: opening snap.
INVESTIGATIONS

The main investigatory techniques in cardiovascular disorders are electrocardiography, chest radiography, echocardiography, colour-flow Doppler, nuclear cardiology, cardiac catheterization, angiography and MRI.

The heart generates electrical activity that can be recorded on an electrocardiogram (ECG or EKG).

- The resting ECG is useful in the diagnosis of myocardial infarction, cardiac hypertrophy or abnormalities in rhythm; characteristic ECG abnormalities usually develop soon after coronary artery occlusion occurs, and some abnormalities usually persist after the patient’s recovery (see p. 231); the resting ECG can also detect ventricular hypertrophy and abnormalities of conduction, such as bundle branch block
- The resting ECG is often normal in patients with angina pectoris, but a recording during exercise, on a bicycle or treadmill, usually reveals characteristic changes indicating myocardial ischaemia (5.10, 5.12).

5.10 The exercise treadmill test may reveal signs of ischaemia on the ECG when the resting trace is normal (5.12).

5.12 A positive exercise test as shown in lead II. The trace taken before exercise is normal, but the second trace, recorded 2 minutes after the end of exercise, shows ST segment depression with T-wave inversion. Analysis of the full trace may show further evidence of ischaemia (5.62).

5.13 Ambulatory electrocardiography (‘Holter monitoring’). The patient undertakes a range of normal activities over a 24-hour period while wearing this lightweight ECG monitoring equipment. He can mark symptomatic episodes on the recording tape by pressing a button on the recorder, and the entire 24-hour recording can then be analysed for ischaemia or arrhythmias in a computer.
function of the left ventricle during systole or diastole.

- The original technique, M-mode echocardiography, is one-dimensional, but it allows the assessment of intracardiac dimensions and the simultaneous monitoring and visualization of the ECG (5.16).
- Doppler flow studies can be combined with M-mode or two-dimensional echocardiography to provide further dynamic information (5.17) and to study the function of the left ventricle during diastole.
- Two-dimensional imaging produces clearer anatomical images (5.18), and allows simple diagnosis of a range of cardiac abnormalities, including valvular heart disease, congenital abnormalities, cardiac tumours and pericardial effusions.

5.14 Situs inversus revealed by chest X-ray. The apex of the heart lies in the right side of the thorax (dextrocardia). The left dome of the diaphragm is higher than the right, because the liver is on the left and the spleen and the stomach are on the right. Situs inversus is usually a harmless abnormality with a normal life-expectancy, but it may be associated with ciliary abnormalities in Kartagener's syndrome (4.107), a hereditary disorder in which the patient also has sinusitis, bronchiectasis and, if male, infertility resulting from immotile spermatozoa. Isolated dextrocardia is usually associated with other major congenital heart disease.

5.15 Heart failure in a patient with mitral stenosis. The left atrial appendage is enlarged (arrowed), the upper zone blood vessels are distended and there are linear densities in the periphery of the lower zones (interstitial or Kerley's B lines). The lung-field changes are typical of moderate pulmonary oedema.

5.16 M-mode echocardiogram in mitral stenosis. Ultrasound waves are transmitted into the body in a one-dimensional ('ice-pick') form. They are reflected back each time they reach an interface between tissues of different acoustic impedance. This allows an assessment of the relative movement of different parts of the heart. This tracing shows impaired movement of the mitral valve leaflets, which is revealed as flattening of the normal mitral valve trace (arrow). The orientation of the view across the mitral valve is shown in the small two-dimensional view above, and the structures are labelled in the M-mode view (RV = right ventricle; VS = ventricular septum; LV = left ventricle; MV = mitral valve; PW = posterior wall of left ventricle).

5.17 Doppler flow study in mitral stenosis. In Doppler studies, ultrasound is reflected back from the red cells in the blood. This allows further assessment of haemodynamics. In this patient (the same patient as in 5.16) the flow through the mitral valve is diminished, and when analysed against the cardiac cycle — the velocity of flow during early diastole relates to the degree of stenosis. In this patient the velocity (A) has been used to calculate the valve area, which is 0.75 cm$^2$, compared with a possible normal value of 3.5 cm$^2$. 
• Colour-flow Doppler echocardiography allows further evaluation of blood flow within the heart; it has particularly aided the diagnosis of valvular stenosis and incompetence (5.19).
• Transoesophageal echocardiography (TOE) utilizes an ultrasonic window to the heart that avoids the problems of chest wall, ribs and lung; it is of value for patients whose transthoracic echocardiograms are unsatisfactory and who have lesions of the left atrium (5.128), the ascending aorta, the aortic valve (especially vegetations), and in atrial and ventricular septal defects; it may also be used intraoperatively and in intensive care, especially in dissection of the root of the aorta (5.182).

Nuclear cardiology is a useful method of assessing the function of cardiac muscle. Technetium-99m may be bound to albumin or red cells from the patient’s blood and thallium-201 (which is handled like potassium by the body) or technetium-tetrofosmin, which behaves similarly, may be injected intravenously. Radioactivity can be assessed from within the cavities of the heart (technetium erythrocyte or albumin technique), permitting evaluation of cardiac function (5.20), or from the walls of the heart (thallium or tetrofosmin technique), allowing assessment of ischaemia and infarction (5.21).

5.18 Two-dimensional cardiac ultrasound
allows imaging that can be monitored in real time. This long axis view is from a patient with mitral valve prolapse. The posterior cusp of the mitral valve is seen to prolapse into the left atrium in this systolic frame (LV = left ventricle; LA = left atrium; RA = right atrium).

5.19 Colour-flow mapping results from the parallel processing of both two-dimensional and Doppler flow data, which are combined in real time to provide a dynamic image of anatomical, functional and haemodynamic status. This systolic apical four-chamber view shows both mitral and tricuspid regurgitation. The left ventricle is the blue area at the top of the image, and the regurgitant flow through the mitral valve is seen on the right. Tricuspid regurgitation is seen as a narrower band of flow on the left.

5.20 Technetium blood pool study in a patient with chest pain but normal ventricular function. Typical diastolic and systolic frames are shown top left and top right, and the contours of the left ventricle are displayed graphically at bottom right. The area of the blood pool at each of 16 frames of the cardiac cycle is plotted bottom left and allows the calculation of the left ventricular ejection fraction, which is normal at 61%.

5.21 Nuclear tomograms after the injection of Tc-tetrofosmin, demonstrating myocardial perfusion. During exercise (stress), the inferior wall of the left ventricle is poorly perfused, as shown in the ventricular long axis (top left) and short axis (top right) views (arrows). After rest, a greater though still abnormally low level of perfusion is seen.
Cardiac catheterization and angiography are invasive techniques (5.22). Catheters are advanced to the right and left heart under X-ray screening. Pressures are measured at the tips of the catheters, permitting evaluation of valvular stenosis (5.23), and oxygen saturations can be assessed to diagnose septal defects. During angiography, radio-opaque contrast medium is injected through the catheters into the heart or vessels. Left ventriculography outlines the inside of the left ventricle and assesses systolic function and mitral regurgitation. Many of these catheter techniques have been largely superseded by (noninvasive) echocardiography, but coronary angiography is still the only accurate method of assessing the severity and extent of coronary disease – an essential preliminary to coronary artery surgery. A catheter is inserted into the coronary artery ostia and the vessels are injected with radio-opaque contrast (5.24). Coronary angioplasty may be carried out in the same session (5.25). Digital subtraction angiography permits the use of smaller amounts of contrast medium, which can be given intravenously. This is useful in imaging peripheral arteries.

MRI is a further noninvasive tool that can be synchronized with the ECG to allow diastolic and systolic images to be produced (5.26).

5.22 The cardiac catheter laboratory. Catheters may be advanced to the left and right heart in aseptic conditions and under X-ray control. Angiography and an increasing number of interventional techniques, including ablation of abnormal conduction pathways, may be performed, in addition to pressure and oxygen saturation studies.

5.24 & 5.25 Coronary angiography and angioplasty. The coronary angiogram in left lateral projection shows complete occlusion of the left anterior descending coronary artery. Only a stump is seen (5.24, arrow). After coronary angioplasty (see p. 230), there is good perfusion of the left anterior descending artery, although a residual stenosis is seen (5.25). This can, if necessary, be dealt with electively at a later stage by further angioplasty, stenting or surgery.

5.23 Pressure gradient across the aortic valve in aortic stenosis, as measured at cardiac catheterization. Note the low aortic (Ao) pressure compared with the left ventricular pressure (LV) and the delayed peak in aortic pressure – both characteristic of severe aortic stenosis. Such pressure studies are less commonly performed than in the past, because echocardiography and Doppler flow studies can provide much of the relevant information noninvasively.

5.24 & 5.25 Coronary angiography and angioplasty. The coronary angiogram in left lateral projection shows complete occlusion of the left anterior descending coronary artery. Only a stump is seen (5.24, arrow). After coronary angioplasty (see p. 230), there is good perfusion of the left anterior descending artery, although a residual stenosis is seen (5.25). This can, if necessary, be dealt with electively at a later stage by further angioplasty, stenting or surgery.

5.26 Magnetic resonance cine gradient echo scan (horizontal long axis plane) in dilated cardiomyopathy showing a grossly hypertrophied left ventricle (LV) that contracts poorly. These four frames show extremely poor systolic left ventricular thickening and motion, and a small jet of mitral regurgitation can be seen in the top right image by virtue of loss of signal (black) from the turbulent jet (LV = left ventricle; LA = left atrium; RV = right ventricle; RA = right atrium; Ao = aortic root).
CIRCULATORY FAILURE

Circulatory failure is an extremely common problem with an incidence of 2% at age 50 years, rising to 10% at age 80 years. There is still a high mortality: 10–30% per year.

Circulatory failure occurs when an adequate blood flow to the tissues cannot be maintained. This may be caused by inadequate cardiac output (heart failure) or by a markedly reduced intravascular volume, for example after major haemorrhage, acute dehydration or in septicemic shock.

Heart failure may develop because the heart muscle itself is diseased or because excessive demands are placed on it. The main myocardial disease is ischaemia resulting from atheromatous narrowing of the coronary arteries. Features of heart failure develop when about 40% of the myocardium has been damaged. Other causes include cardiomyopathies and hypertension. Excessive demands on the heart may occur with regurgitant or stenotic valves, atrial fibrillation, outflow tract obstructions and with obstruction caused by cardiac tamponade or constrictive pericarditis. High-output states such as anaemia, thyrotoxicosis, beriberi and Paget’s disease have a similar effect.

When cardiac output is inadequate, compensatory mechanisms develop in an attempt by the body to maintain blood flow. These mechanisms are responsible for many of the signs of heart failure and may have other deleterious effects. Increased sympathetic tone causes tachycardia, and increased aldosterone levels stimulate salt and water retention. The signs of heart failure depend to a great extent on its chronicity. It is conventional to describe heart failure as mainly right-sided or left-sided, but usually features of both are present.

In left ventricular failure, the dominant symptom is dyspnoea, which may be present at rest or after exercise, or may be associated with paroxysmal nocturnal dyspnoea. There may be episodes of acute pulmonary oedema during which the patient coughs up copious volumes of frothy white sputum that may be tinged with blood, and Cheyne–Stokes respiration may also be observed. The clinical signs in the heart vary with the cause of the failure, but most patients have a marked tachycardia and occasionally pulsus alternans and a third heart sound during diastole (gallop rhythm). The basal areas of both lungs may reveal fine moist crepitations.

In right heart failure there is engorgement of the venous tree. This leads to distension of the jugular veins (5.6); distension of the liver, which is enlarged and tender; and retention of fluid, producing dependent oedema of the legs (4.9, 5.7), ascites, hydrothorax and sometimes pericardial effusion. The patient may be deeply cyanosed (4.4).

The degree of failure can be confirmed by chest X-ray (5.15, 5.27). ECG will demonstrate arrhythmia or ischaemia, and echocardiography demonstrates reduced motion of the walls of the failing heart during systole. Doppler echocardiography can demonstrate impaired filling of the ventricles in diastole. Other important investigations include a full blood count to exclude anaemia, urea and electrolytes, thyroid function tests, liver function tests and cardiac enzymes if recent infarction is suspected.

The drug treatment of heart failure is largely concerned with improving or abolishing the unwanted effects of pulmonary congestion and fluid retention. In heart failure, an attempt is also made to increase cardiac output.

Diuretics, nitrates and angiotensin-converting enzyme (ACE) inhibitors reduce cardiac work, while a variety of inotropes can increase cardiac output. Cardiac transplantation should be considered in unresponsive cases, and implantable ‘artificial hearts’ or left ventricular assist devices have a developing role (5.28, 5.29).

5.27 Heart failure following myocardial infarction. The changes are more severe than in 5.15: there is distension of the upper zone vessels, interstitial (Kerley B) lines are present at both bases; and there are some areas of apparent consolidation, indicating alveolar pulmonary oedema.

5.28 & 5.29 A left ventricular assist device implanted in a patient with previously intractable heart failure. The pneumatically driven pump is implanted in the abdomen. Blood flows from the apex of the left ventricle, through a porcine valve into the pump, and from there through an outlet porcine valve to a Dacron conduit attached to the ascending aorta. Electrically driven pumps are also available.
ARRHYTHMIAS

Abnormal heart rhythms may be classified according to the mechanism of origin of the rhythm disturbance, by the site of origin or by their effect on heart rate. Because the mechanisms are often not clear and the precise site is often unknown, this section will classify those rhythms into tachycardias (heart rate greater than 100 bpm) and bradycardias (heart rate less than 60 bpm). The rhythm is usually investigated by a standard 12-lead ECG with a rhythm strip (usually a prolonged section of lead II).

Typical examples of ECG traces in the tachycardias are seen in 5.30–5.44, and typical bradycardia traces are seen in 5.45–5.47.

5.30 Sinus tachycardia – a regular tachycardia in which the beats originate in the sino-atrial node. This may represent a physiological response to exercise, emotion, fear or anxiety; or it may accompany fever, blood loss, thyrotoxicosis, a falling blood pressure or heart failure. Each beat is preceded by a normal P wave, the upper limit of rate is about 180 bpm and, in contrast to paroxysmal tachycardia, the rate tends to fluctuate. Carotid sinus compression usually slows the rate.

5.31 Atrial ectopic beat. The ectopic is arrowed. Its QRS complex is identical to those of normal beats, but the P wave differs slightly in shape and deforms the T wave of the preceding beat. The next sinus beat follows after an interval that is close to the inter-beat interval of the basic sinus rhythm. Like other ectopics, atrial ectopics are caused by an electrical discharge from an irritable focus, but atrial ectopics are usually of little clinical significance.

5.32 5.33 Atrial flutter is always associated with organic heart disease and is characterized by a rapid regular atrial rate between 220 and 360 bpm. There is a fixed or variable degree of atrioventricular block, which results in one, two or three atrial impulses being blocked for each one transmitted. On the ECG the flutter (f) waves produce a ‘saw tooth’ pattern, though some may be buried in the QRS complex. 5.32 shows atrial flutter with 4:1 atrioventricular block. 5.33 shows atrial flutter with 2:1 atrioventricular block. The usual associations are with ischaemic heart disease, rheumatic valvular disease and cor pulmonale. Chronic atrial flutter is usually treated with digoxin.

5.34 & 5.35 Atrial fibrillation. There is chaotic atrial activity at a frequency of 400–600 bpm. There is little or no mechanical activity of the atria and few of the beats are conducted by the atrioventricular node, so the ventricular response is totally irregular and may be slow (5.34) or as rapid as 150 bpm (5.35). The pulse is ‘irregularly irregular’ on palpation and the ECG has absent P waves, which are replaced by rapid irregular waves (f waves). Note the irregularity of the QRS response. This is one of the most common arrhythmias and is found in rheumatic heart disease (especially mitral valve disease), ischaemia, hypertension, cardiomyopathy (especially alcoholic) and thyrotoxicosis. It is also found in about 15% of elderly people who are otherwise symptom-free. Atrial fibrillation of acute onset can often be reversed by DC shock or drug therapy, but in chronic atrial fibrillation, drug therapy may be used to modify the ventricular response. Because of the high incidence of cerebral embolism, a decision must be taken about long-term anticoagulation with warfarin.
5.36 & 5.37 Junctional tachycardias are brought about by re-entry of the cardiac impulse often via an accessory pathway between atria and ventricles. These rhythms are usually paroxysmal, and they may be precipitated by coffee or alcohol. The patient may be aware of palpitations, and the tachycardia may lead to dyspnoea and polyuria. There is usually no major structural heart disease. In atrioventricular re-entry tachycardia (5.36) there is a large circuit comprising the atrioventricular node, the His bundle, the ventricle, an abnormal connection and the atrium. The rhythm is absolutely regular, but the rate may vary from 140 to 280 bpm — in 5.36 it is roughly 150 bpm. In 5.37, the P waves can be clearly seen preceding the QRS complexes. The appearance is that of a regular atrial tachycardia. In 5.37, inverted P waves can be seen buried in the QRST complex (arrowed), so there has been retrograde atrial activation from a focus in the atrioventricular node. These tachycardias may be terminated by vagotonic manoeuvres such as carotid sinus massage, by drug therapy (5.38) or, occasionally, by DC shock. Prophylactic therapy is indicated if the arrhythmias occur frequently or are symptomatically very troublesome. Verapamil, flecainide, propafenone, disopyramide, digoxin and beta-blockers can all be used. Amiodarone may also be effective but should be used only for the most refractory arrhythmias because of its long-term toxic effects. If the arrhythmia does not respond to treatment or there are side effects from the drug therapy, other options to consider are an antitachycardia pacemaker or mapping and ablation of the aberrant pathway. Radio-frequency catheter ablation is being increasingly used in this situation with considerable success.

5.38 Termination of an episode of paroxysmal supraventricular tachycardia by an intravenous bolus of adenosine. A bolus of 3 mg adenosine was given at A. Verapamil may also be used to terminate supraventricular tachycardia in this way.

5.39 Wolff–Parkinson–White (WPW) syndrome. In this congenital condition, there is an abnormal myocardial connection between atrium and ventricle (the bundle of Kent). The activating impulse from the atria can pass down this pathway, as well as across the atrioventricular node, so the ventricles are activated without the usual delay introduced by the atrioventricular node, and the PR interval is short. There is a characteristic wide QRS complex that begins as a slurred part, the ‘delta wave’ (arrowed). WPW may be associated with re-entrant tachycardia or atrial fibrillation. With severe or frequent paroxysmal attacks, patients require treatment, which may involve surgery or electrical ablation of the aberrant pathway.

5.40 Ventricular ectopic beats are beats resulting from an abnormal irritable focus in the ventricle. Occasional ectopics are usually of little clinical significance, but in acute abnormalities such as myocardial infarction they may be the prelude to the ‘coupled’ ectopic beats seen here (where each sinus beat is followed by an ectopic) and to ventricular tachycardia or fibrillation. Coupled beats like this can cause serious disturbance of cardiac performance, as the ectopic beat may contribute little or nothing to cardiac output.
5.41 & 5.42 Ventricular tachycardia. This serious arrhythmia may have a range of appearances and two examples are shown here. The QRS complexes are broad and they merge into one another, and the heart rate is commonly in the range 150–200 bpm. Ventricular tachycardia may be caused by the repetitive discharge of an irritable focus in the ventricles; it may be sustained or end rapidly in ventricular fibrillation. Ventricular tachycardia occurs in ischaemia, rheumatic heart disease, cardiomyopathy and digoxin toxicity, and requires urgent treatment.

5.43 & 5.44 Ventricular fibrillation. This is a terminal rhythm in which coordinated activity of the ventricles ceases. Despite continuing electrical activity, the heart does not pump. The patient rapidly becomes unconscious and pulseless, and emergency treatment for cardiac arrest is essential. The ECG shows irregular, ill-defined waves that vary in size. In 5.43 the fibrillation waves are of good amplitude and there are periods suggestive of ventricular flutter. Defibrillation by DC shock is more likely to be successful with this appearance than with that seen in 5.44, where there are very variable low-voltage waves.

5.45 Sinus bradycardia. The complexes are normal, but the heart rate is below 60 bpm (here about 45 bpm). This may be a normal finding in healthy athletes, but after myocardial infarction it may be more sinister, producing a reduction in coronary blood flow, hypotension and decreased cardiac output. In these circumstances it can be treated with atropine.

5.46 & 5.47 Sinus node disease (the ‘sick sinus syndrome’). This syndrome is caused by ischaemia, infarction or degenerative disease of the sinus node, and is characterized by long intervals between consecutive P waves. These intervals may allow tachycardias to emerge, often resulting in alternating periods of bradycardia and tachycardia (the tachy-brady syndrome). In this patient, extreme sinus bradycardia (5.46) was followed by atrial flutter with 2:1 block (5.47).
Heart block, a failure of conduction, may occur at the atrio-ventricular node (5.48–5.52). When complete, it may need to be treated by cardiac pacing (5.53–5.57). Intraventricular block may be the result of conduction failure in the right or left branches of the His bundle, or in the hemi-branches of the left branch. Left bundle branch block (5.58) and right bundle branch block give typical ECG appearances, but these may often be modified by myocardial infarction or other underlying causes. Bifascicular block (in which any two of the three main intraventricular conduction pathways are wholly or partially blocked) may also occur. The treatment of bundle branch block is usually that of the underlying disease and its haemodynamic complications.

Recurrent tachyarrhythmias which are associated with abnormal conducting pathways in the heart may be identified by cardiac mapping and such pathways may sometimes be destroyed by radio-frequency catheter ablation techniques. When this is not possible, ventricular fibrillation may be detected and reversed in selected patients by an automatic implantable cardioverter-defibrillator (5.59, 5.60).

5.48 & 5.49 First degree atrioventricular block. The PR interval exceeds 0.22 seconds, so there is a delay in atrioventricular conduction, but all impulses pass on and result in a QRS complex and ventricular contraction. In 5.48 the PR interval is easily measured, but in 5.49 the P wave is hidden in the T wave of the preceding beat and could easily be missed.

5.50 & 5.51 Second degree atrioventricular block occurs in two forms. In the first, there is progressive lengthening of the PR interval until finally one P wave is not conducted (the Wenckebach phenomenon, 5.50). In the second form, there is intermittent blockage of P-wave conduction to the ventricles without any preceding lengthening of the PR interval, as in 5.51 which shows regular 2:1 conduction. This type is particularly likely to be followed by complete heart block.

5.52 Third degree atrioventricular block, in which the atria and ventricles beat completely independently of one another and there is no transmission of atrial activity to the ventricles. The ventricular rhythm is usually regular at 40–50 bpm, and the P waves are not always easy to see (they are arrowed here). The most common cause of complete heart block is acute myocardial infarction, but it may occur in a range of other congenital and acquired conditions. Definitive treatment usually requires temporary or permanent cardiac pacing.

5.53 A temporary pacemaker, newly implanted in a patient with heart block following myocardial infarction. Here, the pacemaker wire is introduced via the subclavian vein, and pacing is controlled from an external source.
5.54 A modern permanent cardiac pacemaker unit, together with the pacing wire that leads from the pacemaker to the right ventricle – its bipolar tip is clearly seen (arrow). These pacemakers are small and easily and inconspicuously implantable beneath the skin. They may, however, set off security alarms and are a hazard in the presence of microwaves or MRI equipment. They should be removed before cremation.

5.55 The site of implantation of a permanent pacemaker. The pacemaker is usually implanted in the left pectoral region, but may be placed elsewhere if necessary.

5.56 Chest x-ray showing an implanted pacing system (same patient as 5.55). The pacemaker is in the left pectoral region, and the endocardial pacing wire is positioned at the tip of the right ventricle, in contact with the endocardium.

5.57 Endocardial pacing produces a pacing artefact on the ECG as here, where the patient is being paced with a unipolar electrode at the apex of the right ventricle.

5.58 Left bundle branch block. The QRS complex is widened and notched over the left ventricle as a result of abnormal activation via the right bundle. Repolarization is also abnormal, so the T waves are sharply inverted in these leads. The small Q wave normally seen in V6 is missing, because the septum is no longer activated from the left side.
RISK FACTORS FOR ISCHAEMIC HEART DISEASE (IHD)

Fixed risks
- Male sex
- Family history of IHD
- Increasing age
- Social class V
- Race

Modifiable risks
- Cigarette smoking
- High blood cholesterol level (total and LDL); low HDL
- High blood triglyceride
- Hypertension
- Obesity
- ‘Western’ diet
- Diabetes mellitus
- Physical inactivity
- Use of oral contraceptive pill
- High plasma fibrinogen level
- Unemployment
- Stress
- Personality

Other factors still await identification

5.59, 5.60 An automatic implantable cardioverter-defibrillator (AICD). Modern AICDs can be implanted in a pectoral pocket in the same way as implantable pacemakers (5.59). The AICD is connected to a single transvenous lead which bears two defibrillation coils. On implantation, one coil is in the superior vena cava (right atrium); the other is near the apex of the right ventricle (5.60). The AICD contains a computer which senses the onset of ventricular fibrillation and initiates defibrillation. Function of the device (number of episodes, provoking rhythms, dates of defibrillation, etc) can be interrogated by a non-invasive, external radio device.

ISCHAEMIC HEART DISEASE

Ischaemic heart disease (IHD; also known as coronary heart disease – CHD) is usually caused by structural disorder of the coronary arteries (coronary artery disease – CAD), although disorders of small coronary vessels may occasionally lead to similar symptomatology. IHD is the main cause of death in Western society and is usually a result of a combination of genetic and lifestyle factors (5.61). Cigarette smoking has a major causative effect.

Ischaemic heart disease is characterized by the deposition of plaques of atheroma, a fatty deposit, in the subendothelium of the coronary arteries. Atheroma has a patchy distribution, usually in the proximal parts of the vessels, and the atheromatous plaques narrow the lumen of the arteries, limiting blood flow through them. Further narrowing can result from spasm of the vessel wall near the site of the plaques and from the formation of a platelet-fibrin thrombus on the surface. Symptoms are usually experienced when the cross-sectional area of the artery is reduced by about 75%. Atheromatous plaques may fissure and heal spontaneously or a thrombus may form on the surface of the fissure. Thrombosis usually underlies the development of unstable angina or myocardial infarction.

Ischaemic heart disease produces two main syndromes:
- angina pectoris – stable or unstable
- myocardial infarction.

Cardiac failure may accompany any of these syndromes, and sudden death may result from arrhythmia without the onset of other symptoms.

5.61 Risk factors for ischaemic heart disease (IHD).
ANGINA PECTORIS

Angina is a painful constricting sensation of pressure or weight felt in the centre of the chest, which may radiate to the arms, the throat, back and epigastrium. It is usually provoked by activity that increases heart rate and blood pressure, thereby increasing myocardial oxygen demand, for example exercise, emotion, stress, fear or sexual intercourse. The pain or tightness of ‘stable’ angina typically starts while walking and is relieved in a few minutes by rest or sublingual glyceryl trinitrate.

Patients with stable angina frequently have a normal ECG at rest, but changes may occur during angina attacks (5.62) and an exercise ECG usually shows characteristic changes (5.10–5.12). It is important to consider other possible causes of chest pain (5.63).

<table>
<thead>
<tr>
<th>MAJOR CAUSES OF CHEST PAIN WHICH IS NOT IHD</th>
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<tbody>
<tr>
<td><strong>Cause</strong></td>
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<tr>
<td>Oesophageal/gall bladder/peptic ulcer</td>
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<tr>
<td>Lung/pulmonary embolism</td>
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<tr>
<td>Other cardiac causes</td>
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<tr>
<td>Pericarditis</td>
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<tr>
<td>Mitral valve prolapse</td>
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<tr>
<td>Musculoskeletal</td>
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<td>Functional</td>
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5.62 Angina pectoris associated with ECG changes. During anginal pain, there are usually ST-segment changes on the ECG. This ECG was taken during an episode of exercise-induced angina, and it shows ST-segment depression (4 mm) in leads V4–6, standard leads II and III and lead aVF.

5.63 Major causes of chest pain which is not IHD.
Drug therapy for angina may include nitrates, beta-blockers, calcium antagonists and ACE inhibitors. If optimum drug therapy does not permit a patient to lead a near-normal life, then coronary angiography should be performed to identify the site of atheromatous narrowing or occlusion of the coronary arteries (5.24), as a prelude to possible coronary angioplasty or bypass surgery.

Coronary angioplasty involves dilating a stenosed coronary artery with a balloon-tipped cardiac catheter (usually inserted via the femoral artery); (5.24, 5.25, 5.64-5.67). The technique often relieves angina, but 30% of patients experience recurrent pain within 6 months and need repeated angioplasty or coronary artery surgery. An arterial stent implant may keep the vessel patent for a much longer period.

In coronary artery surgery, the patient's own saphenous vein or internal mammary artery is used to bypass the blocked segment (5.68-5.70). The operation carries a mortality rate of 1-2%. After surgery, almost all patients are free of angina for several years and their life expectancy may also be improved.

**5.64-5.67** Percutaneous transluminal coronary angioplasty of a left anterior descending coronary stricture: 5.64 is the pre-angioplasty coronary arteriogram – a long stricture is arrowed; 5.65 shows the balloon of the angioplasty catheter inflated *in situ* across the stricture; 5.66 shows the coronary arteriogram taken immediately after the angioplasty catheter had been removed. The stricture has been successfully dilated; 5.67 shows the appearance 1 month after angioplasty. There is a slight residual narrowing, which is a normal finding at this stage and does not indicate re-stenosis. The patient's angina was dramatically improved by the manoeuvre.

**5.68 & 5.69** Coronary angiogram before and after saphenous vein grafting in a patient with angina. 5.68 shows the appearance before surgery. There is a significant stenosis in the right coronary artery, but this fills by the normal route. By contrast, the left anterior descending artery (arrowed) fills only by collaterals. The origin of the artery is completely obstructed. 5.69 shows the appearance after surgery. The saphenous vein graft is arrowed, and it fills the left anterior descending artery. The patient's angina was relieved.
**UNSTABLE ANGINA**

Unstable angina is identified when the typical anginal pain becomes more severe and more frequent, comes on with less exertion or occurs at rest, and is not relieved by glyceryl trinitrate. ST-segment changes are present on the ECG. Such patients should be admitted to hospital for adequate analgesia, intravenous infusions of nitrate, intravenous heparin and aspirin. Many patients settle with this but some require immediate bypass surgery.

**MYOCARDIAL INFARCTION**

Myocardial infarction (MI) usually results from the occlusion of one or more coronary arteries by atheroma and subsequent thrombus. It presents with severe central chest pain, having the same site and character as the pain of angina pectoris but usually lasting for more than 30 minutes. Pallor, anxiety, sweating and vomiting are usually present. Occasionally, myocardial infarction occurs without any pain.

Acute ischaemia often provokes changes of rhythm. Ventricular fibrillation (5.43, 5.44) is the most important, as it rapidly leads to death from circulatory arrest. Immediate cardiopulmonary resuscitation is required (5.71-5.77). More rarely, cardiac arrest is due to asystole or there is electromechanical dissociation, in which there is circulatory arrest despite continued coordinated electrical activity in the heart. The details of recommended drug and DC shock therapy differ in these groups.

Acute myocardial infarction produces distinctive ECG patterns. The appearances depend upon the site and the time from the onset of the infarct. Within a few minutes, the T waves become tall, pointed and upright and ST-segment elevation follows rapidly. Within a few hours the T waves invert. With full thickness infarcts, the R-wave voltage diminishes and pathological Q-waves develop (5.78). The ST segment usually returns to normal within a few days. The T wave usually becomes upright within a few weeks, but the pathological Q waves persist as a marker of previous infarction.

The diagnosis of recent infarction can be confirmed by detecting enzymes released from the damaged heart muscle into the blood, especially creatine kinase (CK) and its isoenzyme (CK-MB) (5.79).

Myocardial infarction should usually be managed in hospital, but treatment can begin before admission. Oxygen should be administered and pain relief by morphine or diamorphine is usually necessary. Aspirin should be given immediately, and when the diagnosis has been confirmed by an ECG, a thrombolytic agent should be considered if there are no contraindications (5.80). This may be done en route to hospital by trained staff if a defibrillator is available. Thrombolysis dissolves the thrombus responsible for the occlusion in the coronary artery, improves blood flow to the myocardium, limits left ventricular dysfunction and improves the prognosis (5.81, 5.82). Aspirin
5.72-5.77 Treatment of cardiac arrest.

5.72 The cardiac arrest patient should be placed flat on a hard surface. His head and neck should be extended by lifting the chin with one hand and pressing the forehead with another. The airway may be cleared digitally or with suction if available at this time.

5.73 A firm blow to the sternum may sometimes restart the heart, especially when an arrest has been witnessed.

5.74 Artificial respiration should be started using the mouth-to-mouth technique. The nose is occluded with the thumb and index finger, and the movement of the chest provides an index of the efficacy of ventilation. In this case protection for the operator is provided by a simple plastic sheet with a small mesh-covered vent at the mouth (Laerdal).

5.75 A more efficient way to avoid mouth-to-mouth contact and to ensure adequate respiration is with a Laerdal mask. These should be available in all hospital wards and carried by all members of the resuscitation team. Supplemental oxygen may be added to the inlet port.

5.76 Cardiac massage. The heel of one hand is placed on the lower third of the sternum and the other hand is rested on top of the first with the arms straight. Using a sharp jerky movement, 60-90 strokes per minute are administered, aiming to move the sternum 3-5 cm at each stroke. After each stroke it is important to lift the hands quickly to allow the chest to expand and the heart to fill. An assistant should set up an intravenous line for drug administration, and the patient's ECG should be monitored as soon as possible.

5.77 External DC defibrillation should be performed if the heart has not restarted or the ECG shows ventricular fibrillation, or both. The electrodes must be well separated to avoid a short circuit, electrolyte jelly is necessary for good contact with the skin, and all personnel should stand clear of the patient to avoid receiving an electric shock.
5.78 Acute anterior myocardial infarction extending inferiorly – 3 hours after onset. The changes are those of acute full-thickness infarction, with widespread ST-segment and T-wave changes and Q waves in V1–V4.

5.79 The pattern of serum enzymes after acute myocardial infarction. Creatine kinase (CK), which is muscle specific, rises rapidly after myocardial infarction and before changes in aspartate aminotransferase (AST) or lactate dehydrogenase (LDH). Its rise must be interpreted with some caution as it rises in response to exertion or skeletal muscle injury, for example after an injection or a fall. A more specific marker is the isoenzyme CK-MB, which is expressed as a percentage of the total CK – normally this is less than 5% of the total. Peak levels are usually recorded at 10±2 hours after onset of pain. Other serum markers include myoglobin. The only justification for using AST or LDH is if the patient presents late and the peak of CK (CK-MB) has been missed.

CONTRAINDICATIONS TO THROMBOLYSIS

Recent bleeding from any site
Recent surgery or childbirth
Active duodenal or gastric ulcer or recent gastrointestinal biopsy
Recent stroke (6 months)
Head injury
Severe uncontrolled hypertension
Diabetic retinopathy
Renal or hepatic failure
Congenital bleeding disorders

5.80 Contraindications to thrombolysis.
and heparin may prevent the diseased vessel reoccluding after successful thrombolysis. Further treatment may be needed for arrhythmias.

Other complications of acute myocardial infarction

Cardiac failure and shock
Mild left ventricular failure is a common sequel to acute infarction and the only apparent features are bilateral basal crepitations that respond rapidly to diuretic therapy. More severe heart failure carries a poor prognosis and cardiogenic shock has a mortality of over 90% despite therapy (see also p. 222).

Cardiac rupture
Cardiac rupture is an uncommon feature after infarction and usually occurs about 7–10 days later as the muscle necroses. It may vary from papillary-muscle rupture, producing acute mitral regurgitation, to septal rupture with an acute left-to-right shunt (5.83) or, most severely, to rupture of the left ventricular wall producing acute cardiac tamponade (and rapid death).

Left ventricular thrombosis
Anterior myocardial infarction is associated with an incidence of about 30% of mural thrombus formation. This may be detected by ultrasound (5.84) or ventriculography. Surprisingly, only about 5% of these thrombi throw off clinically significant emboli to the brain, kidneys, mesentery or limbs. Heparin should be given to prevent this complication.

Deep vein thrombosis
Immobility associated with tissue breakdown and cardiac failure produces an incidence of venous thrombosis of 1–2% (see p. 266), and a small number of these thrombi embolize to the lung (see p. 269). These complications may be prevented by low-dose heparin therapy, which should be routinely used after myocardial infarction.

Shoulder–hand syndrome
The cause of shoulder–hand syndrome is unknown, but stiffness of the shoulder and upper arm joints may follow an infarct. Physiotherapy and nonsteroidal anti-inflammatory drugs are useful in treatment.

RESULTS OF SWAN–GANZ CATHETERIZATION

<table>
<thead>
<tr>
<th>Sample from</th>
<th>Oxygen saturation (%)</th>
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<tbody>
<tr>
<td>Superior vena cava</td>
<td>40</td>
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<tr>
<td>Right atrium</td>
<td>42</td>
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<tr>
<td>Right ventricle</td>
<td>84</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>80</td>
</tr>
<tr>
<td>Radial artery</td>
<td>96</td>
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</tbody>
</table>

5.83 Results of Swan–Ganz catheterization, demonstrating a left-to-right shunt in a patient with ventricular septal rupture after myocardial infarction.

5.84 Left ventricular thrombus after myocardial infarction. The diastolic apical four-chamber view shows at least two large thrombi on the apical and anterior walls of the left ventricle (arrowed). Left ventricular thrombosis is common after myocardial infarction, and its incidence, and the risk of embolism, can be dramatically reduced by heparin therapy.
Post-myocardial infarction syndrome (Dressler's syndrome)
Post-myocardial infarction syndrome (Dressler's syndrome) is an autoimmune response to acute myocardial infarction in which autoantibodies are formed and produce a febrile illness with pericarditis and effusion about 10–14 days after the acute episode. Treatment is with nonsteroidal anti-inflammatory agents, or sometimes with a course of systemic steroid therapy.

Left ventricular aneurysm
Death of myocardial fibres and replacement by fibrous tissue may result in a severely weakened left ventricular wall that becomes aneurysmal. This produces persistent ST–T changes on the ECG (5.85) and a typical appearance on chest X-ray (5.86).

Isotope scans (5.87), ultrasound or ventriculography show part of the left ventricle to be noncontractile. Some of these aneurysms can be surgically resected.

Population screening and primary prevention of ischaemic heart disease
Risk factors for IHD can be identified by mass screening projects or by the initiative of individual family or workplace doctors. The cost and logistic implications are massive and most schemes now focus on people who have a high risk, that is those with a family history of premature arterial disease in near relatives, cigarette smokers, hypertensives, diabetics and those with peripheral or cerebral artery disease.

5.85 Left ventricular aneurysm produces a persistence of the pattern of acute myocardial infarction in the ECG. In uncomplicated myocardial infarction, the ST segment has normally returned to the isoelectric line within 3–6 weeks; persistence of ST elevation beyond this time is a pointer to possible aneurysm. This ECG was taken 10 weeks after infarction in a patient who had signs of heart failure. The QRS complexes in all precordial leads show that the patient had an extensive full-thickness infarct.

5.86 Ventricular aneurysm, revealed on chest X-ray 3 weeks after acute myocardial infarction. Note the bulge in the left cardiac border. On screening, this would be found to move paradoxically outwards during systole.

5.87 Technetium blood pool study in a patient with poor left ventricular function after myocardial infarction. Typical diastolic and systolic frames are shown top left and top right, and the contours of the left ventricle are displayed graphically at bottom right. The area of the blood pool at each of 16 frames of the cardiac cycle is plotted bottom left and allows the calculation of the left ventricular ejection fraction, which is very low at 34%. The left ventricular wall movement is best seen kinetically. It was poor at the interventricular septum and there was early aneurysmal dilatation at the apex.
Lifestyle changes must be emphasized, especially stopping smoking, alteration of diet to reduce the amount of saturated fat, an increase in the amount of dietary monounsaturates, roughage and fresh fruit and vegetables. Increased exercise and weight reduction are also beneficial. Drugs to control hypertension and reduce lipid levels have a proven place in management.

Rehabilitation and secondary prevention of ischaemic heart disease
After a few days to stabilize in hospital, most patients with myocardial infarction are fit to return home, but they should be offered a rehabilitation programme of graduated exercise and lifestyle advice. Regular low-dose aspirin and other antiplatelet drugs, beta-blocker and ACE inhibitor therapy may lessen the chances of subsequent infarction. It is usually possible to identify individuals with a poor prognosis after myocardial infarction by exercise ECG, nuclear exercise tests, echocardiography and coronary angiography. When appropriate, coronary artery surgery may improve their prognosis.

All patients with proven coronary disease must be given appropriate lifestyle advice, as reduction of blood cholesterol by diet alteration and drugs, stopping smoking and an exercise programme can improve prognosis, even when coronary artery disease has already developed. There is evidence that these measures may lead to reduction in size (regression) of occluding atheromatous plaques, especially when effective lipid-lowering agents ('statin' drugs) are included in therapy.

RHEUMATIC FEVER

Rheumatic fever is an acute inflammatory disease of connective tissue that is a sequel to infection with Group A streptococci (see p.36) and may involve the heart, skin, CNS and joints. It is now a rare disease in the developed world but is still endemic elsewhere; even in the West there is still a large residue of patients with rheumatic valve disease that has resulted from childhood infection. The differential diagnosis of rheumatic fever includes juvenile rheumatoid arthritis, mixed connective tissue disease, systemic lupus erythematosus and Lyme disease.

The cardinal skin signs are erythema marginatum (5.88) and subcutaneous nodules, which are firm, painless and discrete, about 0.5–1 cm in diameter, and are found mainly over bony prominences and tendons. They resolve after a few weeks.

The arthritis varies from arthralgia to a flitting polyarthritis, mainly affecting the larger joints such as the knees, ankles, wrists and elbows. These joints may become acutely swollen, hot and tender, and the synovial fluid is full of polymorphs.

Carditis is the most important aspect of this disease as it has major long-term implications. Endocarditis, myocarditis and pericarditis are all often present. The diagnosis of carditis requires the finding of
• new cardiac murmurs
• cardiomegaly
• pericarditis
• congestive cardiac failure.

The murmurs may include an apical systolic murmur (caused by mitral regurgitation), a transient apical mid-diastolic (Carey–Coombs) murmur (caused by turbulent flow across the inflamed mitral valve), and a basal diastolic murmur (caused by aortic regurgitation). Other cardiac signs may include tachycardia, pericardial friction rub, muffled heart sounds resulting from pericardial effusion and evidence of heart failure.

Neurological involvement (Sydenham's chorea) is uncommon and develops after a latent period of several weeks. The patient develops rapid purposeless involuntary movements mostly in the limbs and face (see p. 504).

Investigations should include throat-swab culture and the measurement of antibody response to Streptococcus (anti-streptolysin 'O' titre). There is usually a leucocytosis and elevation of the ESR and C-reactive protein levels. X-ray of the chest may show a pericardial effusion and rarely pneumonia or lobar collapse. ECG often shows first degree heartblock (5.48, 5.49).

As an aid to the clinical diagnosis and more accurate classification of rheumatic fever, a range of diagnostic criteria (the Jones criteria) may be used (5.89).

Treatment should be directed towards the elimination of any residual streptococcal infection with penicillin. Aspirin is an effective anti-inflammatory and antipyretic agent for the other features. Prevention of recurrence may be necessary with long-term oral penicillin.

The long-term damage resulting from rheumatic fever may require further lifelong treatment.
CRITERIA FOR THE DIAGNOSIS OF RHEUMATIC FEVER (JONES CRITERIA).

<table>
<thead>
<tr>
<th>Major findings</th>
<th>Minor findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carditis</td>
<td>Arthralgia</td>
</tr>
<tr>
<td>Polyarthritis</td>
<td>Past history of rheumatic fever or rheumatic heart disease</td>
</tr>
<tr>
<td>Sydenham's chorea</td>
<td></td>
</tr>
<tr>
<td>Erythema marginatum</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td><strong>plus</strong> recent evidence of streptococcal infection i.e. ASO titre, antibodies, culture from throat or recent scarlet fever.</td>
<td></td>
</tr>
</tbody>
</table>

5.89 Criteria for the diagnosis of rheumatic fever (Jones criteria). The definitive diagnosis requires two major findings or one major and two minor findings plus evidence of recent infection.

5.90 Arterial embolism causing acute ischaemia of the leg in a patient with mitral stenosis. The patient was in atrial fibrillation, and the source of the embolus was the left atrium (see 5.93). Initial pallor of the leg and foot is followed by cyanosis, and by reactive hyperaemia if a collateral circulation opens up.

5.91 P mitrale. The P wave is bifid and has a duration of 0.12 seconds or more. The appearance results from delayed activation of the enlarged left atrium; the first peak represents right atrial, and the second left atrial activation.

5.92 Arterial embolism causing acute ischaemia of the leg in a patient with mitral stenosis. The patient was in atrial fibrillation, and the source of the embolus was the left atrium (see 5.93). Initial pallor of the leg and foot is followed by cyanosis, and by reactive hyperaemia if a collateral circulation opens up.

5.93 Acute ischaemia of the leg in a patient with mitral stenosis. The patient was in atrial fibrillation, and the source of the embolus was the left atrium (see 5.93). Initial pallor of the leg and foot is followed by cyanosis, and by reactive hyperaemia if a collateral circulation opens up.

ACQUIRED VALVE DISEASES

The most common forms of heart valve disease affect the mitral and aortic valves, causing left heart failure and pulmonary congestion. The valves may fail to open fully (stenosis) or to close (regurgitation or incompetence). Both stenosis and regurgitation can coexist. The effects of both types of lesion are haemodynamic with major implications for cardiac function.

The presence of heart valve disease is suspected from a heart murmur. An ECG and chest X-ray may provide additional clues, but the main diagnostic technique for valve disease is echocardiography. Doppler echocardiography is particularly useful in establishing the severity of valvular stenosis or regurgitation. The diagnosis in adults is usually confirmed by cardiac catheterization and angiography, which also permits evaluation of the coronary arteries.

MITRAL STENOSIS

The most common cause of mitral stenosis is rheumatic fever, and mitral stenosis occurs in about one-half of all patients with chronic rheumatic heart disease. The mitral valve usually narrows slowly and the pulmonary vasculature adapts to the rising pressure of blood within the pulmonary capillaries, pulmonary veins and the left atrium.

The walls of the pulmonary vessels thicken, reducing blood flow and cardiac output but protecting the patient from pulmonary oedema. Patients notice only a gradual decline in exercise tolerance, although they may be aware of a brisk deterioration if their heart rhythm changes from sinus rhythm to atrial fibrillation. Episodes of acute pulmonary oedema occur as the cross-sectional area of the valve diminishes and the patient may have episodes of acute dyspnoea and orthopnoea and paroxysmal nocturnal dyspnoea. As the pulmonary blood pressure rises there are episodes of haemoptysis. Systemic embolism is common from thrombi in the large left atrium, especially in the presence of atrial fibrillation. The common sites for embolism are cerebral (see p. 495), mesenteric, renal and limb arteries (5.90).

Two-thirds of the patients are female. They may have a malar flush (5.4) or central cyanosis; there may be signs of weight loss or peripheral oedema. Jugular venous pulsation becomes obvious only when right heart failure appears. The key cardiac findings are a tapping apex beat, and a rumbling mid-diastolic murmur at the apex (5.9). There may be presystolic accentuation and the murmur may be preceded by an opening snap. Exercise and positioning the patient in the left lateral position will accentuate the murmur. As pulmonary hypertension develops, the pulmonary second sound becomes accentuated and a right ventricular heave becomes apparent. Bilateral basal pulmonary crepitations may herald the onset of left heart failure.

Radiography of the chest shows a generally small heart with an accentuation of its left upper border from the enlarged left atrium and often signs of pulmonary oedema (5.15). The ECG shows a bifid P wave (P mitrale) (5.91) and there may be features of right
ventricular hypertrophy and atrial fibrillation (5.34, 5.35). The diagnosis should be confirmed by echocardiography, which will show the immobility of the mitral valve cusps (5.16, 5.17, 5.92), and may show atrial thrombus (5.93). Cardiac catheterization is usual if surgery is contemplated.

Treatment includes diuretics for heart failure and digoxin for atrial fibrillation. Warfarin reduces the chances of thrombosis in the left atrium and of embolism. In severe cases, the fused cusps may be separated surgically (valvotomy) or the valve can be replaced (1.11).

**Mitral Regurgitation**

There are many causes of mitral regurgitation (5.94). The result of mitral regurgitation is dilatation of the left atrium. Eventually this leads to atrial hypertrophy and pulmonary hypertension and oedema. The same picture may develop acutely with rupture of the chordae tendineae. Infective endocarditis may also occur.

Symptoms may appear only after some time has elapsed; they are usually dyspnoea on exertion (later at rest) and palpitations. With the onset of pulmonary hypertension, there may be symptoms from right heart failure.

Signs are dominated by left ventricular dilatation, with the heaving apex beat displaced to the left, a systolic thrill at the apex and a high-pitched pansystolic murmur at the apex, transmitted to the left axilla (5.9). Later in the disease, there may be a right ventricular heave associated with accentuation of the pulmonary second sound. The diagnosis is confirmed as follows:

- chest X-ray shows enlargement of left ventricle and atrium and sometimes calcification of the mitral valve
- ECG shows left ventricular hypertrophy (5.150), and often atrial fibrillation (5.34, 5.35)
- echocardiography shows the position of the valve leaflets at closure (5.95), and colour-flow Doppler shows the regurgitant jet (5.19, 5.99)
- cardiac catheterization can define the pressure differences between chambers, and ventriculography will confirm the presence of regurgitation
- coronary angiography should be performed in older patients to assess the extent of underlying IHD.

Medical treatment includes prevention of endocarditis, control of heart failure, and anticoagulation to prevent thromboembolism.

Poison prognostic factors include
- poor left ventricular function
- age over 70 years
- New York Heart Association functional grade IV
- myocardial ischaemia
- necessity for emergency surgery.

A severely damaged valve will need surgical replacement with a mechanical valve or bioprosthesis. Rarely, the existing valve can be repaired.

**Causes of Mitral Regurgitation**

- Rheumatic fever in acute phase
- Post-rheumatic fever (with mitral stenosis)
- Mitral valve prolapse
- Ischaemic heart disease (papillary muscle dysfunction)
- Infective endocarditis
- Connective tissue disorders (especially systemic lupus erythematosus)
- Ruptured chordae tendineae
- Myxomatous degeneration

5.94 Causes of mitral regurgitation.
ACQUIRED VALVE DISEASES

5.95 Mitral regurgitation associated with mitral valve prolapse, seen on two-dimensional echocardiography (parasternal long-axis view) in systole. Note the open cusps of the aortic valve. The posterior leaflet of the mitral valve is prolapsing backwards into the left atrium in systole (MVP). This abnormality is fairly common in young women for no obvious cause. It may also be a feature of Marfan’s syndrome (p. 150) and other connective tissue disorders (LA = left atrium; LV = left ventricle; Ao = aorta; RV = right ventricle).

MITRAL VALVE PROLAPSE

Mitral valve prolapse (floppy mitral valve, Barlow’s syndrome) is the second most common valvular disorder after aortic stenosis. It is usually asymptomatic and benign and is often detected clinically at routine medicals or on routine echocardiography. The reported prevalence in women is in the range of 4–17% and in men 2–12%. The range is wide because of differing levels of awareness and the variable availability of routine echocardiography, by which the diagnosis is confirmed (5.18, 5.95).

When symptoms are present they tend to be nonspecific and include vague chest pain, palpitations, syncope and effort intolerance due to breathlessness and general tiredness. The presence of these vague symptoms with valve prolapse is now known as the ‘mitral valve prolapse syndrome’. The character of the pain varies greatly, ranging from an angina-like pain (in quality, duration and site) to a mild left mammary discomfort. In such patients other causes for chest pain often coexist, for example spasm of the oesophagus, peptic ulcer, chest wall pain or coronary artery disease.

Palpitations are reported by about one-half of the patients. This may sometimes be a reflection of heightened awareness in patients in whom the diagnosis has been made. Ambulatory monitoring of the ECG shows a poor correlation between reported symptoms and recorded arrhythmias. Syncope commonly occurs with no change of rhythm.

It has been suggested that mitral valve prolapse may be part of a neuroendocrinopathy in which there is dysautonomia with exaggerated heart rate and blood pressure responses, postural hypotension, hyperresponsiveness to catecholamines, decreased intravascular and intraventricular volume on standing and activation of atrial natriuretic peptide.

Most often a minor degree of mitral prolapse does not interfere in any way with a normal lifestyle. The usual course is benign, but complications may include mitral regurgitation and heart failure, stroke caused by emboli from atrial thrombus, infective endocarditis and ventricular tachyarrhythmias.

Sudden death is rare in mitral valve prolapse and is usually due to sustained ventricular tachycardia or ventricular fibrillation. Patients who survive an arrest should have electrophysiological studies performed in an attempt to identify an alternative conduction pathway, which may then be ablated.

AORTIC STENOSIS

Acquired aortic valve stenosis often results from progressive degeneration and calcification of a congenitally bicuspid valve. Rheumatic fever and arteriosclerotic degeneration are rarer causes. Aortic stenosis leads to left ventricular hypertrophy and relative left ventricular ischaemia, so patients may present with angina, infarction, left ventricular failure or arrhythmias. Ventricular fibrillation is a common cause of sudden death. Calcification around the valve may extend into the conducting tissue, causing heart block and syncope.

The dominant clinical features of aortic stenosis are a low-volume, slow-rising pulse; a forceful apex beat; a systolic thrill at the base of the heart; and a mid-systolic murmur at the aortic area, which radiates to the neck (5.9).

The diagnosis is supported by features of left ventricular hypertrophy on the chest X-ray (5.96) and ECG (5.150).

5.96 Chest X-ray (AP view) in a patient admitted with cardiac failure associated with aortic stenosis. There is gross cardiomegaly, with a bilateral symmetrical increase in bronchovascular markings, especially in the lower zones. Bilateral Kerley B lines are seen, which are consistent with pulmonary oedema.
Echocardiography confirms the diagnosis by showing thickened and calcified valve cusps (5.97). Doppler echocardiography (5.98, 5.99) or cardiac catheterization (5.23), or both, establish the severity of the stenosis, and Doppler echocardiography is extremely valuable in following the course of the disease in individual patients. Ultrasound has removed the need for repeated cardiac catheterization. The peak aortic pressure gradient can be calculated, and it correlates well with the degree of severity of stenosis. Other formulae may be used to measure the aortic valve orifice area.

The valve is usually replaced with a prosthetic valve. Alternatively, the narrowed valve may be stretched by balloon valvuloplasty, although the long-term benefits of this procedure are unclear.

**Aortic Stenosis with Calcification**

5.97 Aortic stenosis with calcification. This M-mode parasternal long-axis view shows the characteristic box shape of valve opening during systole (1). Calcification of the valve and annulus is suggested by the density of whiteness of the tracing (2).

**Doppler Flow Study of the Aortic Valve in Aortic Stenosis**

5.98 Doppler flow study of the aortic valve in aortic stenosis. There is a mosaic pattern at the aortic valve suggesting the valve is narrowed. The velocity of blood flow across the valve is 5 m/s which gives an estimated valve gradient of 100 mmHg by the Bernoulli equation, confirming aortic stenosis.

**Colour Flow Doppler Mapping in Aortic Stenosis**

5.99 Colour flow Doppler mapping in aortic stenosis (same patient as 5.98). The typical jet flow through the stenotic aortic valve is seen (AO ST), and there is also a minor degree of mitral regurgitation (MR) (RV = right ventricle; LV = left ventricle; LA = left atrium).

**Aortic Regurgitation**

Aortic regurgitation occurs if the aortic valve ring dilates, as a result of dissecting aneurysm, ankylosing spondylitis or syphilis for example, or if the valve cusps degenerate, such as after rheumatic fever or endocarditis. Aortic regurgitation leads to hypertrophy of the left ventricle and ultimately left ventricular failure. Clinical symptoms often occur late and the patient may present with significant heart failure or angina. There may have been a preceding history of palpitations, syncope or headaches because of the high systolic blood pressure, especially during exercise.

**Left Ventricular Hypertrophy and Dilatation**

5.100 Left ventricular hypertrophy and dilatation in a patient with severe aortic regurgitation. Left ventricular hypertrophy alters the shape of the heart, making the left heart border more convex than normal, but hypertrophy alone does not increase the size of the heart. The cardiac enlargement seen here is indicative of ventricular dilatation.
ACQUIRED VALVE DISEASES

Many of the physical signs are a reflection of the size of the leak, for example collapsing pulse, capillary pulsation, visible carotid pulsation, head bobbing and the Duroziez's murmur heard over the femoral artery. On examination, there is left ventricular hypertrophy, and an early diastolic murmur down the left side of the sternum, which is best heard by sitting the patient upright, leaning forward in full expiration. A diastolic thrill is rarely felt down the left sternal edge.

Chest X-ray (5.100), ECG (5.150) and echocardiogram show left ventricular enlargement. Aortography (5.101) or colour-flow Doppler (5.102) shows the regurgitant jet.

Medical treatment is directed at managing the angina, correcting the failure and preventing endocarditis. Definitive treatment consists of replacing the valve with a prosthetic one.

TRICUSPID AND PULMONARY VALVE DISEASE

The tricuspid and pulmonary valves are rarely stenosed by rheumatic fever and they may be slightly incompetent in quite healthy individuals. Severe pulmonary regurgitation is usually secondary to left heart failure or lung disease, through the effects of a raised pulmonary arterial pressure, which causes dilatation of the pulmonary artery and stretching of the pulmonary valve annulus. The resultant murmur of pulmonary regurgitation has the same early diastolic characteristics as the murmur of aortic regurgitation, but the characteristic findings in the arterial pulse are absent.

Tricuspid regurgitation usually follows dilatation of the right ventricle. Once it develops, signs of right heart failure become prominent, for example distended jugular veins, enlarged liver, ascites and oedema. A pansystolic murmur may be audible at the lower left sternal border (5.9). Chest X-ray may show right atrial enlargement (5.103). Echocardiography is the most effective method of diagnosing pulmonary and tricuspid valve disease (5.19).

Obstruction to right ventricular outflow may occur above, below or at the level of the pulmonary valve. The clinical problems that result from pulmonary stenosis depend on the severity of the obstruction rather than on the actual site. Patients are usually asymptomatic and symptoms appear only if there is progression of the stenosis. These include fatigue, symptoms of right ventricular failure and syncope. The clinical signs are those of right ventricular hypertrophy (a right ventricular heave) and a loud systolic murmur in the second left intercostal space, with a preceding click if valvular stenosis is responsible. Chest X-ray may show right ventricular enlargement or post-stenotic dilatation. Pulmonary stenosis can be diagnosed by echocardiography and its severity assessed by Doppler. Pulmonary valvuloplasty corrects valvular stenosis.
CONGENITAL HEART DISEASE

Congenital heart disease is found in 8 per 1000 live births. Congenital bicuspid aortic valve is much more common (2% of live births) but usually only becomes a problem when it calcifies. With advances in surgical and medical care, many patients with congenital heart disease now live into adult life.

Congenital lesions may result from a variety of maternal and fetal factors, including maternal alcohol or drug abuse, maternal rubella (diminishing in importance in the developed world), and occasionally single gene mutations. A range of syndromes, that include cardiac abnormalities, are described elsewhere, for example Down’s syndrome (p. 352), Turner’s syndrome (p. 319), Ehlers–Danlos syndrome (p. 150), Friedreich’s ataxia (p. 508) and Noonan’s syndrome (p. 319). Congenital cardiac lesions may also be associated with other, less well defined anomalies (5.104).

Patients with congenital heart disease may present at birth (5.105), with cyanosis or associated symptoms in childhood (5.106, 5.107, 7.169), or sometimes in adult life. They commonly have finger clubbing (5.5).

The most common congenital cardiac anomalies are listed in 5.108. Congenital cardiac anomalies may be divided into two main types:

- communications between cardiac chambers or blood vessels
- lesions that obstruct blood flow.

### The Most Common Forms of Congenital Heart Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defects</td>
<td>33%</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>10%</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>9%</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>6%</td>
</tr>
<tr>
<td>Atrial septal defects</td>
<td>5%</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>4%</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>4%</td>
</tr>
<tr>
<td>Transposition of great vessels</td>
<td>4%</td>
</tr>
<tr>
<td>Others</td>
<td>24%</td>
</tr>
</tbody>
</table>

5.108 The most common forms of congenital heart disease.
Combinations of both types of anomaly may occur, as in Fallot’s tetralogy and other complex congenital conditions.

Communications between the left and right sides of the heart cause blood to flow from the high-pressure left side to the low-pressure right side. This happens when an atrial septal defect or ventricular septal defect is present, or if there is a patent ductus arteriosus causing blood to flow from the aorta to the pulmonary artery. Pulmonary blood flow increases and, in extreme cases, the pulmonary capillaries and arterioles may respond by thickening their walls and narrowing their lumens. This increases the work of the right ventricle, which must raise its systolic pressure to maintain normal cardiac output (pulmonary hypertension). The elevated pressure may then reverse the shunt, causing blood to flow from right to left through the abnormal communication, so that unoxygenated blood bypasses the lungs (Eisenmenger syndrome).

**ATRIAL SEPTAL DEFECT**

Atrial septal defects (ASDs) most commonly occur in the middle of the interatrial septum (a secundum defect), although they may occur in the upper part (sinus venosus defect) or lower part (primum defect) where associated abnormalities of the mitral and tricuspid valves make the condition more serious. The history and findings depend on the age at presentation and the severity of the defect or defects. Children with secundum defects seldom experience symptoms, but in adult life, heart failure and cardiac arrhythmias, usually atrial fibrillation, develop, so the defects should often be closed. If presentation is late, the main features are those of right heart failure. There is usually a marked right ventricular impulse and wide fixed splitting of P2, with a systolic pulmonary ejection murmur resulting from increased flow across the normal pulmonary valve. These findings change as pulmonary vascular resistance increases and a right-to-left shunt appears. The X-ray of the chest may show evidence of right ventricular hypertrophy and dilatation, with a prominent pulmonary artery with pulmonary plethora (5.109). The ECG shows a characteristic right bundle branch block pattern. Echocardiography confirms right ventricular hypertrophy and dilatation of the pulmonary artery and may define the anatomical site and dimensions of the defect (5.110). These findings may be confirmed by cardiac catheterization or by MRI (5.111). Treatment is surgical.
VENTRICULAR SEPTAL DEFECT

Ventricular septal defects (VSDs) are common and the most frequent type is a single opening in the membranous portion of the septum. Noncongenital VSDs may also occur as a complication of septal myocardial infarction. The symptoms and signs are dependent on the size of the defect, the state of the pulmonary vasculature and the presence of other abnormalities. Most congenital defects are small, cause no symptoms and close spontaneously during childhood. Initially, the greater pressure in the left ventricle is associated with a left-to-right shunt that is present throughout systole and is heard as a loud systolic murmur to the left side of the sternum (maladie de Roger). With moderate-sized shunts, fatigue and dyspnoea on exertion may occur, and with larger shunts there may be recurrent pulmonary infections, growth retardation and cardiac failure at an early age. Large defects cause right and left heart failure and, if they are not closed surgically, the Eisenmenger syndrome ensues, with cyanosis, finger clubbing and polycythaemia. Once this has developed survival is poor and lung transplantation is the only possibility.

Clinical signs in these large defects include the signs of right ventricular hypertrophy and pulmonary hypertension. There is cardiomegaly with a forceful apex beat and a prominent systolic thrill at the left sternal edge. The pulmonary second sound is accentuated and there is a characteristic pansystolic murmur best heard at the third and fourth interspaces to the left of the sternum with radiation across the anterior chest wall (5.9). With a small VSD, the chest X-ray and ECG are both normal. With larger defects, the chest X-ray may show an enlarged left atrium, left and right ventricular hypertrophy, a large pulmonary artery and increased pulmonary vascular markings (5.112). The ECG shows evidence of biventricular hypertrophy. The diagnosis can be confirmed by echocardiography (5.113), colour-flow Doppler (5.114) or MRI and cardiac catheterization may be required if the defect is complicated by other pathology. There is a risk of bacterial endocarditis in all VSD patients, especially in those with smaller defects. Surgery is required in all patients with a moderate or large left-to-right shunt.

PATENT DUCTUS ARTERIOSUS

Normal closure of the ductus arteriosus (joining the aorta to the bifurcation of the pulmonary artery) occurs immediately after birth, probably as a result of changes in production of vascular prostaglandins. Patency of the ductus (PDA) may be an isolated lesion or it may be combined with other lesions so that the ductus remains the only route for maintenance of the pulmonary or systemic blood flow. The amount of flow in the ductus is a reflection of its size and of the pulmonary and systemic pressures. The clinical signs depend on the extent of the pathology and its duration. With a large PDA there may be rapid onset of heart failure. Examination often shows a typical thrill at the left sternal edge and, on auscultation, there is a characteristic 'machinery' murmur at the upper left sternal border over the first intercostal
space (5.115). In a large ductus, there is an enhanced differential in pulse pressure, felt as a bounding pulse. The X-ray of the chest may show left ventricular and left atrial enlargement, a prominent aorta and pulmonary artery and pulmonary plethora (appearances similar to 5.112). The ECG and echocardiogram show evidence of left ventricular and atrial hypertrophy and the duct may be seen on echo (5.116). Catheterization of the aorta may be necessary to demonstrate the defect. Heart failure indicates an urgent need for surgical correction.

Coarctation of the aorta is a relatively uncommon lesion, found in 5–10% of patients with congenital heart disease. It is a congenital narrowing of the aorta that can occur at any point in its length but is usually found just after the origin of the left subclavian artery. It is often found in Turner’s syndrome (p. 319) and may be associated with other cardiac and vascular abnormalities. Most children are asymptomatic and the patient is often found to have hypertension in the upper half of the body on routine physical examination. Severe cases may present with intermittent claudication, cold lower limbs or headache and epistaxis from hypertension. The dominant clinical feature is absence, diminution or delay of the pulse at the femoral artery compared with the radial artery. There is also a marked difference between the blood pressure in the upper and lower limbs. In the adult, pulsating collateral vessels may be found in the interscapular area, the axillae and the intercostal spaces. Auscultation of the heart reveals a mid-systolic murmur over the anterior chest and back.

X-ray of the chest may show left ventricular hypertrophy with a dilated ascending aorta. The stenotic area may occasionally be visible. Rib notching caused by dilated collateral vessels is common (5.117). The ECG shows left ventricular hypertrophy (5.150). Aortography is necessary to define accurately the position and length of the coarctation, though MRI can produce elegant results (5.118). Echocardiography and cardiac catheterization may be needed to exclude other lesions, especially bicuspid aortic valve, congenital aortic stenosis and PDA.
AORTIC AND PULMONARY STENOSIS

Aortic stenosis accounts for 2–4% of congenital heart disease. Congenital narrowing of the aortic valve is present from birth, and calcification of the valve may occur later in life (5.97). The signs, investigatory findings and treatment are similar to those in acquired disease (see p. 239). Pulmonary stenosis may also be an isolated congenital lesion (see p. 241) or part of a complex congenital lesion.

FALLOT’S TETRALOGY

Fallot’s tetralogy forms about 10% of all cases of congenital heart disease and is the most common cardiac cause of cyanosis in infants over 1 year of age. The four characteristics of this syndrome are

- ventricular septal defect
- overriding of the aorta over the defect
- pulmonary outflow tract obstruction
- right ventricular hypertrophy resulting from the stenosis.

Affected children are cyanosed from birth (5.105, 7.169) and have dyspnoea on exertion (5.107) (and later at rest), retarded growth, finger clubbing (5.5) and secondary polycythaemia. The cardiac signs are those of right ventricular hypertrophy and dilatation, and a systolic thrill may be felt along the left sternal edge. There is a loud ejection systolic murmur often maximal in the second left interspace as a result of disturbed flow across the stenotic pulmonary outflow tract.

The chest X-ray shows a normal-sized heart that is boot-shaped (coeur-en-sabot) because of prominence of the right ventricle and the small pulmonary arteries (5.119). The ECG shows right ventricular and later right atrial hypertrophy. Echocardiography may show the defect and angiography is necessary to define the extent of the abnormalities (5.120).

Affected children invariably died before the advent of complete surgical repair of both the septal defect and stenosis. Before surgery, patients are cyanosed (5.106, 5.107) and require repeated venesections for polycythaemia. They are susceptible to endocarditis and cerebral abscesses. Total correction of the lesion is required and this may be done in two stages. The first-stage operation is designed to increase pulmonary blood flow and this may involve aortopulmonary or subclavian–pulmonary anastomosis. The second-stage operation – to correct the remaining defects – can then be carried out more safely in adolescence.

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

Complete transposition of the great arteries is a relatively common congenital anomaly (5.105) but few patients survive to adult life. The aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle so that the systemic and pulmonary circulations are quite distinct. Death is inevitable without a communication between the two circulations to oxygenate systemic blood. Fortunately, many patients have an associated ventricular septal defect, and in others an atrial septal defect can be created immediately after birth, by pulling a balloon-tipped cardiac catheter across the interatrial septum. Further surgery is necessary later if life is to be maintained.
PULMONARY HYPERTENSION

Pulmonary hypertension is a common consequence of a variety of lung and heart conditions (5.121). The long-term result is right ventricular and atrial hypertrophy and dilatation. Such patients may present with ischaemic-type chest pain, features of right heart failure, syncope and occasionally hoarseness caused by pressure on the left recurrent laryngeal nerve from the enlarging pulmonary artery. Sudden cardiac death is relatively common and may occur during diagnostic instrumentation. On examination, the clinical picture is that of right heart failure with a prominent right ventricular heave, jugular venous congestion with a prominent A wave, peripheral oedema and hepatic congestion. The pulmonary second sound is accentuated and may be felt. Incompetence of the pulmonary valve may be a late feature.

The chest X-ray usually shows cardiac enlargement with right ventricular and right atrial enlargement and dilatation of the pulmonary arteries. The lung fields may be oligemic. The ECG shows features of right-axis deviation, right ventricular hypertrophy and strain (5.122) and occasionally right bundle branch block. Echocardiography and colour-flow Doppler may show the cause of hypertension, for example atrial or ventricular septal defects or mitral stenosis. Cardiac catheterization is of value to determine the site of the lesion and measure pressures and degree of oxygenation. Treatment is directed at the underlying cause. Diuretics, oxygen, vasodilators and anticoagulants have a place in management, as does heart–lung transplantation as a last resort.

INFECTIVE ENDOCARDITIS

In infective endocarditis, a bacteraemia is complicated by the development of ‘vegetations’ on the endocardium of the heart (endocarditis). Vegetations usually form on aortic and mitral valves that are already damaged from rheumatic fever, but they may be associated with congenital abnormalities such as ventricular and atrial septal defects and coarctation of the aorta (in which they may cause aortitis). The organisms involved are usually commensals of the mouth and pharynx (Streptococcus viridans) or the bowel (Streptococcus faecalis). Rarely, virulent organisms such as Streptococcus pyogenes or Staphylococcus aureus may infect a previously normal heart valve, especially in intravenous drug misusers and in patients with indwelling cannulae and pacing lines. Prosthetic heart valves are more susceptible to endocarditis than normal valves and they may become infected with unusual organisms, such as Staphylococcus epidermidis, Gram-negative organisms and fungi such as Candida albicans, Histoplasma and Aspergillus. Implanted pacemakers and defibrillators may also harbour infection. Although episodes of bacteraemia may apparently occur spontaneously, especially in patients with dental caries and gingivitis (5.104, 5.123), dental procedures, endotracheal intubation and bronchoscopy, genitourinary and colonic endoscopy and surgery are especially likely to provoke bacteraemia. Patients with diseased valves or congenital cardiac abnormalities should therefore be given prophylactic antibiotics before these procedures.

DISEASES ASSOCIATED WITH PULMONARY HYPERTENSION

- Chronic obstructive lung diseases
- Chronic parenchymal lung disease
- Recurrent pulmonary embolism
- Chronic left ventricular failure
- Mitral valve disease
- Congenital heart diseases (VSD, ASD, PDA and pulmonary artery stenosis)
- Idiopathic (primary) pulmonary hypertension
- Connective tissue diseases (SLE, systemic sclerosis, etc.)
- Peripheral arterio-venous shunts
- Left atrial myxoma
- High-altitude living
- Pulmonary veno-occlusive disease

5.121 Diseases associated with pulmonary hypertension.

5.122 Right ventricular hypertrophy in a patient with pulmonary hypertension. Note the tall R wave (7 mm +) in V1, which is taller than the S wave, a combined voltage of R in V1 and S in V6 of 10 mm or more, and the ST depression and T-wave inversion from V1 to V5. Right ventricular hypertrophy may also be manifested as dominant S waves across all the chest leads. P pulmonale (tall, peaked P waves at least 2.5 mm in height) is another common finding, though absent on this trace.
Infected vegetations produce clinical features in four ways:

- They induce febrile symptoms, such as sweating and weight loss.
- They may erode heart valves and rupture chordae tendineae, causing valvular incompetence and heart failure; the infection may extend beyond the valve into the conducting tissue of the heart, causing heart block.
- They can embolize causing stroke, limb ischaemia, renal and splenic infarcts and occasionally myocardial and pulmonary infarction.
- Their presence can stimulate the formation of immune complexes in the blood; these complexes can produce focal glomerulonephritis and vasculitis in the eye and skin.

Untreated endocarditis is usually fatal. Numerous signs are traditionally associated with the disorder, but many are seldom seen in modern medicine. The key features in most patients with infective endocarditis are:

- fever (often low-grade)
- a changing cardiac murmur
- embolic phenomena.

Most patients feel generally unwell, and there may be weight loss, anaemia, haematuria, an enlarged spleen, petechiae and vasculitic lesions under the nails (splinter haemorrhages, 3.33), in the sclerae (5.124), conjunctivae, retinae (Roth spots) (5.125) and in the finger and toe pulps (Osler’s nodes) (5.126). Finger clubbing is now extremely rare, as patients are usually treated before it develops.

When the diagnosis is suspected, an echocardiogram should be performed. Small vegetations are often not identifiable, but large vegetations can be visualized (5.127) and the extent of the

5.123 Severe dental caries and gingivitis predisposes patients to episodes of bacteraemia, and thus to infective endocarditis in the presence of a congenital or acquired cardiac abnormality. Full treatment of caries or appropriate dental extraction should be carried out with antibiotic prophylaxis in all such patients.

5.124 Scleral and conjunctival haemorrhages are a recognized but rare feature in established infective endocarditis. They are probably the result of infected microemboli from cardiac vegetations, but may also be associated with thrombocytopenia.

5.125 A Roth spot in the retina in infective endocarditis. These oval haemorrhagic lesions with white centres are thought to result from septic emboli, but similar appearances may sometimes occur in patients with anaemia or leukaemia.

5.126 Small dermal infarcts in infective endocarditis. When palpable, these are known as Osler’s nodes. These infarcts are usually tender. They may be caused by septic emboli from the cardiac vegetations, but similar appearances may result from vasculitis associated with circulating immune complexes.
valvular incompetence clarified. Vegetations are particularly difficult to identify on prosthetic heart valves and colour-flow or transoesophageal echocardiography may be valuable in these patients and for patients with lesions in the left atrium (5.128). Blood tests often show a normochromic, normocytic anaemia, there may be a polymorph leucocytosis and the ESR and C-reactive proteins are elevated. Circulating immune complexes are found and there is a rise in immunoglobulin levels and a fall in total complement.

Multiple blood cultures are required and sampling should coincide with peaks of fever. This permits identification of the infecting organism, so that appropriate combinations of antibiotics can be given in high dosage intravenously for several weeks (5.129). Less aggressive therapy is usually ineffective. If cultures are negative, other causes of endocarditis should be sought by appropriate serological tests, for example for fungi, Q-fever or psittacosis.

Antibiotics may not eradicate the infection and emergency surgery may be required. The infected valve is removed and replaced with a prosthetic one. Other indications for emergency valve replacement are the development of severe valvular incompetence causing heart failure or a dangerous embolic episode, for example cerebral embolism. The mortality rate associated with emergency valve replacement during endocarditis is higher than for elective surgery involving a sterile valve.

5.127 Echocardiogram in infective endocarditis. This parasternal long-axis view shows a large vegetation on the anterior leaflet of the mitral valve (arrowed). The patient had recently been unwell with diverticulitis and a local intra-abdominal abscess. *Streptococcus faecalis* was grown on blood culture (LA = left atrium; LV = left ventricle).

5.128 Transoesophageal echocardiography is a valuable technique for demonstrating cardiac vegetations in infective endocarditis. Here a vegetation attached to the atrial surface of the mitral valve is clearly seen. This abnormality was not visible on transthoracic echocardiography.

5.129 Prolonged, high-dose antibiotic therapy in infective endocarditis is best given via a central venous line. This patient has a Hickman line, which tunnels under the skin to its entry point into the venous system in the cephalic or axillary vein. The tip of the catheter is in the superior vena cava. This patient's morbilliform rash probably resulted from previous therapy with ampicillin, which also complicated the interpretation of blood cultures.
MYOCARDITIS

Myocarditis is a general term for any inflammatory process involving the heart. It is usually infective but can be caused by chemicals, physical agents or drugs (5.130).

The history depends on the cause. The most common type of myocarditis in the developed world follows a viral infection, typically an upper respiratory tract infection. The onset is usually insidious with features of right and left heart failure, fever and general malaise. There is tachycardia with a low-volume pulse, hypotension, faint heart sounds, a third heart sound and features of pericarditis. The chest X-ray shows cardiomegaly (5.131), sometimes with a pericardial effusion; the ECG may show arrhythmias, diffuse ST-segment and T-wave changes and heart block. Cardiac enzymes are elevated if the acute inflammatory process is ongoing. Serology may show a rising titre of viral antibodies. Treatment involves bed rest and control of failure and arrhythmias. Steroids can be of value.

Myocarditis usually remits but it may progress and behave like a chronic cardiomyopathy.

5.130 Causes of myocarditis.

<table>
<thead>
<tr>
<th>Causes of Myocarditis</th>
<th>Infections</th>
<th>Viruses</th>
<th>Coxsackie</th>
<th>Influenza</th>
<th>Adenoviruses</th>
<th>Echovirus</th>
<th>Rubella</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacteria</td>
<td>Corynebacterium diphtheriae</td>
<td>Chlamydia</td>
<td>Rickettsia</td>
<td>Coxiella burnetii</td>
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<tr>
<td></td>
<td>Protozoa</td>
<td>Trypanosoma cruzi</td>
<td>Toxoplasma gondii</td>
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<tr>
<td></td>
<td>Physical</td>
<td>Radiation</td>
<td>From therapy for breast or lung cancer, lymphoma or thymoma</td>
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<td></td>
<td>Chemical</td>
<td>Lead</td>
<td>Alcohol</td>
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<td></td>
<td>Drugs</td>
<td>Emetine</td>
<td>In treatment of amoebiasis</td>
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<tr>
<td></td>
<td></td>
<td>Chloroquine</td>
<td>In malaria prophylaxis</td>
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</table>

5.131 Acute myocarditis causing marked enlargement of all cardiac chambers and pulmonary venous congestion. The ECG showed generalized T-wave inversion. Serology showed the cause to be a coxsackievirus infection, and the patient made a complete recovery within a few weeks. An identical chest X-ray appearance may be seen in dilated cardiomyopathy.

CARDIOVASCULAR

CARDIOMYOPATHIES

The most common causes of diseased heart muscle are coronary disease, hypertension and heart valve disease. However, the myocardium may also be damaged in other conditions, for example prolonged alcohol abuse, hypothyroidism, acromegaly, phaeochromocytoma, inherited neuromuscular disorders, connective tissue and storage diseases and by some drug therapy (e.g. adriamycin).

Idiopathic cardiomyopathies are primary heart muscle disorders of indeterminate cause. They can be divided into three pathophysiological types that produce distinctive clinical syndromes:

• dilated cardiomyopathy
• hypertrophic cardiomyopathy
• restrictive cardiomyopathy.

DILATED CARDIOMYOPATHY

In dilated cardiomyopathy the heart muscle weakens and the chambers progressively dilate. The aetiology of idiopathic dilated cardiomyopathy is unknown, but previous coxsackievirus infection may be causally related. Patients become breathless and develop signs of right and left heart failure, with pulmonary congestion, cardiomegaly and, sometimes, arrhythmias and emboli. Ventricular dilatation may lead to functional mitral or tricuspid regurgitation.

Chest X-ray (5.131), echocardiography and MRI (5.26) confirm dilated cardiac chambers and inefficient left ventricular wall motion in systole. The ECG may show ST-segment changes and arrhythmias, but has no diagnostic value.
Patients with idiopathic dilated cardiomyopathy may fail to respond to diuretics and vasodilator drugs and the heart failure may progress to death within a few years. Cardiac transplantation is feasible in some younger patients.

**HYPERTROPHIC CARDIOMYOPATHY**

In hypertrophic cardiomyopathy, a localized segment of the heart muscle becomes thickened; the interventricular septum is usually involved and the abnormal muscle restricts filling of the left ventricle during diastole. If it also obstructs the flow of blood from the ventricle to the aorta during systole, the condition is termed 'hypertrophic obstructive cardiomyopathy' (HOCM). The abnormal muscle is a focus for dangerous arrhythmias, especially ventricular tachycardia, which may convert to ventricular fibrillation. Hypertrophic cardiomyopathy is potentially fatal, and patients should avoid strenuous exercise which may provoke arrhythmias. Patients with hypertrophic cardiomyopathy may be asymptomatic. However, some have angina, as their hypertrophied muscle requires more oxygen, even in the absence of coronary disease. Some also have a low cardiac output causing dizziness and syncope. These patients may also develop an ejection systolic murmur, best heard over the left sternal border, caused by the obstruction. As the obstruction develops, it also distorts the mitral valve and a regurgitant murmur may be heard.

The diagnosis is best made by echocardiography (5.132, 5.133). The ECG classically shows a combination of left ventricular hypertrophy and pathological Q waves resulting from hypertrophy of the interventricular septum. Treatment is directed at preventing serious arrhythmias and relieving angina. If there is severe obstruction to left ventricular outflow, surgical removal of the hypertrophied muscle below the aortic valve may be beneficial.

The condition is inherited in about one-half of the reported cases, and family members should be studied by echocardiography to determine whether they have an asymptomatic form of the condition. Long-term follow-up of these family members is required for early diagnosis and treatment of complications.

**RESTRICTIVE CARDIOMYOPATHY**

Restrictive cardiomyopathy is very rare in developed countries. It is associated with a range of conditions, including amyloidosis, sarcoidosis and leukaemic infiltration. Endomyocardial fibrosis is the most common cause in the tropics.

The myocardium is infiltrated by abnormal tissue, which renders the chambers stiff and noncompliant. This is particularly evident in diastole and can be confirmed by Doppler echocardiography. Patients develop congestive cardiac failure, with ascites and ankle swelling. The physical signs are similar to those of constrictive pericarditis (p. 254) with raised jugular venous pressure and cardiac enlargement. The X-ray (5.131) and ECG show cardiac enlargement. The echocardiogram shows the thickening of the myocardium with impaired ventricular filling.

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**5.132 & 5.133 Hypertrophic obstructive cardiomyopathy.** The two-dimensional long-axis parasternal view (5.132) shows the chambers of the heart (LA = left atrium; RV = right ventricle; LV = left ventricle). The left ventricle posterior wall (LVPW) is thickened, and the most striking abnormality is the hypertrophy of the interventricular septum (IVS). Another characteristic feature is a Venturi effect: as blood leaves the left ventricle it sucks the anterior leaflet of the mitral valve forward — systolic anterior motion (SAM). This phenomenon is more clearly shown (SAM) in the parasternal long-axis M-mode echocardiogram (5.133). The massive thickening of the septum is also obvious in the M-mode (IVS).
CARDIOVASCULAR

CARDIAC TUMOURS

Primary cardiac tumours are rare, but secondary deposits are often found incidentally at autopsy, infiltrating the pericardium and, less commonly, the myocardium. Pericardial deposits may produce a pericardial effusion that can constrict the heart and cause death from tamponade.

The most common primary tumour of the heart is an atrial myxoma. It usually grows in the cavity of the left atrium and is attached by a stalk to the left atrial wall just behind the mitral valve. If it obstructs blood flow from the left atrium to the left ventricle, syncope can occur. Portions of the tumour may also become detached and embolize. This association of peripheral emboli with a heart murmur may lead to the mistaken diagnosis of infective endocarditis, but a myxoma is easily demonstrable by echocardiography (5.134) or MRI (5.135). Myxomas can be removed surgically with good long-term results.

Tumours in the myocardium are usually secondaries and the bronchus and breast are the most common primary sites. These malignant deposits may have haemodynamic effects, and they often interfere with the conducting system, causing heart block, or may be a focus for ventricular or supraventricular tachyarrhythmias. Curative treatment is usually impossible.

5.134 Left atrial myxoma. This apical four-chamber echocardiogram shows a circular mass (M) arising in a typical position from the interatrial septum just above the mitral valve (LA = left atrium; LV = left ventricle).

PERICARDIAL DISEASE

Patients with pericardial disease may present in one of three ways: pericarditis, pericardial effusion or constrictive pericarditis.

PERICARDITIS

Causes of pericarditis include
- acute and chronic infections
- myocardial infarction
- metabolic
- connective tissue disorders
- acute rheumatic fever
- malignancy
- radiation
- idiopathic.

The usual clinical presentation is with acute, sharp, central chest pain that may radiate to the neck and shoulders and may be brought on by movement. There is usually associated fever and occasionally myalgia. The most common causes are Coxsackie B virus infection (see p. 20) and acute myocardial infarction (p. 231). A friction rub may be heard. Investigations show leucocytosis and elevation of the ESR, and in the absence of myocardial infarction the ECG shows a typical pattern of ST elevation without QRS changes (5.136). The T wave becomes inverted in most leads after several days. There may also be an increase in levels of cardiac enzymes and echocardiography may show an increase in pericardial fluid. The chest X-ray usually shows a normal cardiac outline, which may enlarge as the amount of pericardial fluid increases. There may also be associated inflammatory lung changes. Analgesia and anti-inflammatory drug treatment are often helpful.

PERICARDIAL EFFUSION

A pericardial effusion is an accumulation of excess fluid within the pericardium, often as a result of acute or chronic pericarditis. There are many possible causes (5.137). The implications for cardiac function depend on the rate at which the fluid accumulates. The first effect is to reduce the venous return to the heart; this is reflected in elevation of the jugular venous
pressure (JVP), hepatic congestion and peripheral oedema. As the amount of pericardial fluid increases, cardiac filling is progressively diminished and cardiac output reduced; thus a vicious circle is established (cardiac tamponade) that leads to declining cardiac function and death. The diagnosis can be made clinically because of the features of heart failure (JVP elevation, peripheral oedema, hepatomegaly) and diminished output (thready 'paradoxical' pulse, central cyanosis, low blood pressure). There may be an increased area of cardiac dullness and the heart sounds may be muffled. Pericardial rub is usually absent.

X-ray of the chest shows an enlarged cardiac shadow (5.138) and may give clues to the underlying cause (5.139). The ECG shows low-voltage complexes, often with T-wave inversion (5.140). Echocardiography shows the size of the effusion (5.141). If there is impairment of cardiac function, urgent aspiration is required (5.142). Examination of the aspirate may give a clue to aetiology and the need for further treatment.

### CAUSES OF PERICARDIAL EFFUSION

- Neoplasia
- Infection — viruses, bacteria, fungi
- Idiopathic
- Myocardial infarction
- Heart failure
- Trauma
- Connective tissue disorders
- Drugs
- Renal failure or nephrotic syndrome

### 5.137 Causes of pericardial effusion (in descending order of frequency).

**5.136 Acute pericarditis.** In the first few days, the ECG shows ST elevation, concave upwards, with upright T waves in most leads. Classically it is more obvious in lead II than in I or III. There are no pathological Q waves, and the widespread distribution of ST–T changes without reciprocal depression, distinguishes acute pericarditis from early myocardial infarction. In the later stages of pericarditis, the T waves become inverted in most leads. The ECG changes in pericarditis are caused by the superficial myocarditis that accompanies it.

**5.138 Pericardial effusion.** The heart shadow appears generally enlarged, but the appearance is not diagnostic. A similar appearance can be seen in cardiac failure, in myocarditis or in dilated cardiomyopathy.

**5.139 Malignant pericardial effusion.** The heart shadow is generally enlarged, but the odd, irregular outline of the enlargement suggests the presence of secondary tumour deposits in the pericardium. This patient had a primary ovarian carcinoma.
clarified by ambulatory blood pressure monitoring (5.152, 5.153).

Proteinuria is an indicator of possible renal disease. Plasma electrolytes, urea and creatinine will show changes if there is renal failure and these and other specific investigations may be required in patients with renal disease (p. 298) and to exclude other causes of secondary hypertension.

Treatment must be decided on an individual basis. This depends on several baseline blood pressure recordings, age, sex and whether complications of hypertension are already present. Patients with diastolic pressure in excess of 105 mmHg are usually treated and those with diastolic pressure between 90 and 105 mmHg may be treated. Many antihypertensive drugs are available and they act in different ways, so drugs may be used in combination. Reduction of blood pressure reduces the risks of stroke, heart failure and renal failure but a significant beneficial effect in reducing mortality from coronary events has not yet been clearly demonstrated.

In those relatively rare patients in whom hypertension is 'secondary' to an identifiable cause, there is the possibility of treatment of the cause, or of curative surgery.

### Causes of Secondary Hypertension

<table>
<thead>
<tr>
<th>Renal disease</th>
<th>Endocrine disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilateral</strong></td>
<td>Conn's syndrome</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>Cushing's syndrome</td>
</tr>
<tr>
<td>Chronic pyelonephritis (reflux nephropathy)</td>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Analgesic nephropathy</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td><strong>Unilateral</strong></td>
<td>Cardiovascular disorders</td>
</tr>
<tr>
<td>Chronic pyelonephritis (reflux nephropathy)</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Pregnancy</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>Pre-eclampsia and eclampsia</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>Drugs</td>
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<tr>
<td>Oral contraceptives</td>
<td>Oral contraceptives</td>
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<tr>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
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<tr>
<td>Carbenoxolone</td>
<td>Carbenoxolone</td>
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<tr>
<td>Monoamine oxidase inhibitors (interaction with tyramine)</td>
<td>Monoamine oxidase inhibitors (interaction with tyramine)</td>
</tr>
</tbody>
</table>

5.149 Causes of secondary hypertension.

5.151 Hypertension. The chest X-ray is usually normal in mild to moderate hypertension, but cardiac enlargement associated with left ventricular hypertrophy (as here) may occur in the later stages. There is no evidence of cardiac failure in this patient.

5.150 Left ventricular hypertrophy in hypertension. This ECG shows severe hypertrophy. Left ventricular hypertrophy (LVH) is present when the R wave in V5 or V6 or the S wave in V1 or V2 exceeds 25 mm in an adult of normal build. This ECG also shows T-wave inversion over the left ventricle (V5–6) and, as the heart is relatively horizontally placed, in I and VL.
PERIPHERAL VASCULAR DISEASE

Peripheral arterial obstruction in the legs is a common problem in the ageing population of the Western world, with a male-female ratio of 10:1. Long-term cigarette smoking is by far the most important underlying cause of peripheral vascular disease (PVD), and atheroma is the major pathological process. Patients often have other arterial manifestations, including IHD, stroke, transient ischaemic attacks and intestinal ischaemia. Ischaemic heart disease is the most common cause of death in these patients. Atheroma usually has a patchy distribution in the aorta and the femoral and popliteal vessels. It is found particularly at the aortic bifurcation and around the origins of smaller vessels. The lesions tend to enlarge slowly and gradually reduce blood flow.

Symptoms usually occur when the arterial obstruction is 50–75%. The most common symptom is a cramp-like pain in the calf and thigh muscles on exercise, which disappears on resting for a few minutes (‘intermittent claudication’). There is often a history of progressive shortening of the distance walked without pain as the disease progresses. The level of the arterial block dictates the muscle group in which pain is felt: for example, an obstructive lesion in the profunda femoris artery will present with buttock, hip and thigh claudication (and impotence).

Patients may also complain of weakness of muscle groups and numbness or paraesthesiae. Ulceration and gangrene may appear with constant pain at rest. Diabetics usually have extensive atheroma and their presentation is more complex as they often also have peripheral neuropathy and small vessel disease, and have lost deep pain sensation and sympathetic tone.

Clinical examination in PVD shows

- atrophy of the skin, loss of hair, trophic nail changes (5.154)
- a cold limb, which may be pallid or cyanosed (5.155, 5.156)
- slow capillary return when finger pressure is released
- loss or diminution of pulses in the affected leg (5.154)

5.154 Peripheral vascular disease. Typical changes in the skin include atrophy, pallor, loss of hair and, in some patients, trophic nail changes. This patient also has early ulceration on the dorsum of three toes. It is important to examine the peripheral pulses. In this patient the dorsalis pedis pulse was impalpable.

5.155 Ischaemic pallor of the patient’s right foot. Note the colour difference between the two feet, which has been accentuated by elevation of the legs.
• a bruit over the affected segment of vessel
• ulceration or gangrene, particularly of the toes (5.157)
• loss of sensation.

Special investigations include measurement of arm and leg systolic blood pressure (normal ankle:brachial pressure index — ABPI — should be >0.9), blood pressure measurement at the ankle after exercise (it falls to very low levels) and arteriography (5.158) to localize the site and extent of the block and the presence of collaterals. The site of block may also be found non-invasively with colour-flow Doppler. Thermography may have a place in determining skin blood flow in patients in whom amputation is being considered (5.159). Other investigations that may be helpful in selected patients include duplex ultrasound measurement of pressure in small arteries, oximetry on the dorsum of the foot, isotope clearance studies, plethysmography and MRI.

Treatment includes lifestyle advice about stopping smoking, weight reduction, cholesterol and blood pressure control, and graded exercises. Sympathectomy may have a place in selected patients. Skilled foot care is important, especially in the diabetic. Drug therapy is generally unsatisfactory. The circulation may be improved by angioplasty (5.160, 5.161) or vessel grafting, but gangrene requires amputation (5.162).
PERIPHERAL VASCULAR DISEASE

5.160 & 5.161 Percutaneous transluminal angioplasty (PTA) may be used in peripheral vascular disease. 5.160 shows a 90% occlusion of the left superficial femoral artery. In 5.161, successful angioplasty is complete. The patient's ankle blood pressure returned to normal. As with coronary angioplasty, recurrence of the lesion may occur.

5.162 Amputation is still often necessary in patients with severe peripheral vascular disease. This patient developed massive gangrene of the leg and foot.

5.163 Digital ischaemia in Buerger's disease. The fingertips are cyanotic, though no irreversible changes have yet occurred. This man continued to smoke, against all advice, and subsequently developed gangrene.

5.164 Digital ischaemia in Buerger's disease often affects the toes. Here the ischaemia is more severe than that seen in 5.163. Again, this progressed to gangrene, and amputation of the toe was necessary to eliminate infection.

THROMBO-ANGIITIS OBLITERANS (BUERGER'S DISEASE)

Thrombo-angiitis obliterans (Buerger's disease) is a disease of young male smokers who develop ulceration and gangrene of their digits, caused by spasm of the digital arteries associated with an intense inflammatory response, which may also involve veins and nerves. There is no evidence of excessive atheroma. The major symptoms are referable to ischaemia of the fingers (5.163) and toes (5.164), but many patients also have intermittent claudication, usually affecting the calf and often the 'instep' of the foot, and also occasionally claudication of the hand. Ultimately, there may be severe rest pain and gangrene. Examination may show cold digits, digital ulcers, a migratory phlebitis of hands and feet and absent foot and hand pulses. Patients should stop all use of tobacco and may be helped by vasodilator drugs. Sympathectomy may be of value, but amputation of digits may become necessary.

ACUTE ISCHAEMIA

Thrombosis on an atheromatous plaque or embolism may produce acute ischaemia very rapidly. The sources of emboli include the left atrium when the mitral or aortic valves are damaged by rheumatic endocarditis (5.93), especially when the rhythm changes from sinus to atrial fibrillation; mural thrombus in the left ventricle after myocardial infarction (5.84); prosthetic valves (1.11); vegetations in infective endocarditis
(5.127, 5.128); and atheromatous plaques or aneurysms in the aorta (5.180). The features are acute onset of pain, pallor of the limb and lack of pulses and capillary return, followed by reactive hyperaemia (5.90) or cyanosis and gangrene (5.155–5.157). The level of the block may be defined by colour-flow Doppler or angiography (5.165). Distal emboli or thrombosis may be treated with a thrombolytic agent. More proximal lesions may be amenable to angioplasty or thrombectomy. Prevention of recurrence requires treatment with aspirin and anticoagulants.

**RAYNAUD’S SYNDROME**

Raynaud’s syndrome affects 5–10% of the adult population worldwide, especially young women, and is characterized by recurrent vasospastic episodes in which one or more fingers becomes white and numb, followed after a few minutes by a blue or purple cyanosis and then by redness caused by reactive arterial dilatation (3.34, 5.166). The toes are rarely affected. The attacks are usually bilateral and symmetrical and may have a familial incidence and follow a benign course. They often start in the early teens and abate at the menopause. These attacks (primary Raynaud’s syndrome) are often precipitated by exposure to cold or by emotion. Most patients have no evidence of any other disease process and are only inconvenienced by the attack. Rarely the signs progress to finger tip ulceration and gangrene (5.167).

Secondary Raynaud’s syndrome implies that the features are a result of an underlying disease (5.168). This is the most likely diagnosis if the condition starts later in life, is seen in a man, or has an abrupt onset with rapid onset of digital ulceration and gangrene. About 20% of patients with Raynaud’s syndrome ultimately develop features of rheumatic disease or a connective tissue disorder. Examination of nailfold capillaries and a serum autoantibody profile, for example anti-double stranded DNA, anti-centromere nucleolar and anti-topoisomerase-1, will predict 95% of those who will subsequently develop systemic sclerosis.

**DISEASES ASSOCIATED WITH SECONDARY RAYNAUD’S SYNDROME**

Connective tissue disorders especially SLE and scleroderma
Drug or chemical associated – especially nicotine, oral contraceptives, beta-blockers, ergot derivatives, bleomycin, cisplatin
Vibration tool associated ('vibration white finger')
Thoracic outlet syndrome/carpal tunnel syndrome
Atherosclerosis
Thrombo-angiitis obliterans
Malignancy
Hyperviscosity syndromes/monoclonal gammopathy
Polycythaemia/cold agglutinin disorders
PERIPHERAL VASCULAR DISEASE

In secondary Raynaud’s, an attempt must be made to identify and treat the underlying condition. Cervical sympathectomy is rarely of value. Treatment with a calcium-channel blocker and transdermal prostacyclin is often effective.

COLD INJURY

Cooling of tissues produces vasoconstriction, increase in plasma and whole blood viscosity, and impairment of oxygen transport. Below freezing point, these changes are compounded by the formation of ice crystals, which produce irreversible cell death.

‘Immersion’ or ‘trench’ foot is a result of wet, cold exposure of the feet over a prolonged period. There are recognizable phases: initially, there is an ischaemic phase when the feet are cold, white and pulseless, followed by a hyperaemic response, when they become painful, red and oedematous. They may eventually recover, but superficial areas of skin gangrene may require grafting. In frostbite, the blood supply is permanently damaged and tissue necrosis occurs in the exposed extremities. The area is usually numb and bloodless. Rewarming is associated with local pain (5.171) and the development of a demarcation zone between viable and nonviable tissues. Gangrene may result (5.172). Chemical or surgical sympathectomy may be of value.

It is important to enquire about cigarette smoking and the use of beta-blocking drugs, oral contraceptives or ergot derivatives, and about the handling of vibrating tools such as drills, chain saws or electric hammers (vibration white finger) (5.169). The position of the arm before the onset of symptoms may suggest a thoracic outlet syndrome (see p. 266).

The extent and severity of Raynaud’s disease may be assessed by thermography (5.170). In the primary form, the prognosis is very good and treatment is directed at prevention of attacks by keeping the hands (and feet) warm. Electrically heated gloves are usually effective. The patient should stop smoking and stop taking any relevant drugs that predispose to the condition. Change of employment is sometimes necessary.
HYPOThERMIA

A fall in the core temperature of the body may result from a variety of illnesses such as myxoedema, Addison's disease, hyperglycaemia, stroke, myocardial infarction and the ingestion of drugs or alcohol. It is especially likely to occur in the elderly. Hypothermia may also occur accidentally in those injured or immersed in snow or icy water or exposed to cold, wet and windy conditions. Often multiple factors play a role, for example the alcoholic lying comatose outside in the winter, or the isolated elderly stroke patient falling in an unheated house. The rate of loss of heat depends on factors such as nutritional status, clothing, recent alcohol or drug ingestion and the ambient temperature.

The clinical features depend on the core temperature. Mild hypothermia (core temperature 35-37°C) usually only causes discomfort: the patient feels cold and shivers, but remains mentally alert and is often able to take appropriate action to reverse the decline in temperature. Below this level there is progressive impairment of higher cerebral function with loss of coordination, judgement and eventually loss of consciousness. Below a temperature of 32°C there is an exponential rise in mortality.

Patients usually appear cold and pale, with bradycardia, hypotension, slow respiration and an appearance of rigor mortis. Laboratory investigations show acidosis, haemoconcentration and renal impairment. There is peripheral hypoxia as the low temperature drives the oxygen dissociation curve to the left – there is decreased unloading of oxygen in the periphery. Central nervous reflexes (e.g. pupillary responses) become progressively impaired. Ventricular arrhythmias (tachycardia or fibrillation) are the common cause of death, but a variety of changes may be found on the ECG, for example bradycardia, slow atrial fibrillation and a characteristic J wave (5.173).

Treatment of minor degrees of hypothermia can be achieved by gradual rewarming in a heated room or bed, use of a 'space blanket' (5.174) and general supportive measures. Most patients with temperatures over 32°C respond to these simple measures. In severe hypothermia the patient should also be well oxygenated and attention should be paid to correction of the fluid and metabolic disturbance. External warming with an electric blanket is contraindicated, but intravenous fluids and peritoneal dialysis fluid (if needed for renal failure) should be warmed. Antibiotics should be given, as these patients are likely to develop pneumonia.

5.173 Hypothermia. The characteristic finding is the J wave (Osborne wave), a positive wave occurring on the down slope of the QRS complex. It is seen in most leads and broadens and increases its size as the body temperature drops.

5.174 Treatment of hypothermia. A 'space blanket' is useful for slow rewarming. A constant-reading digital electronic rectal thermometer is in place. An intravenous infusion and a central venous pressure line are established, so that any hypotension caused by vasodilatation as warming occurs can be safely corrected.

AORTIC DISEASES

ANEURYSMS

An aneurysm is an abnormal widening of an artery that involves all four coats. In the aorta they may occur in the thoracic and abdominal segments.

Abdominal aneurysms

Abdominal aneurysms are most common in men aged over 50 years whose vessels are arteriosclerotic. They may be found by chance on routine abdominal palpation or on X-ray.
The diagnosis may be made (often coincidentally) on plain X-ray (5.175), but ultrasound (5.176) is the diagnostic method of choice, and may be used for screening purposes. CT scan (5.177) and (occasionally) angiography (5.178) may be used for presurgical assessment or before insertion of a stent. Elective surgery carries a mortality of 5–10% and emergency surgery has a mortality of over 50%.

**Thoracic aneurysms**

Thoracic aneurysms are historically associated with the long-term complications of syphilitic aortitis (1.245) and may involve the ascending or descending thoracic aorta or the arch. Aneurysms of the ascending aorta may involve the ostia of the coronary arteries and the aortic valve, so that diastolic filling of the coronary arteries is defective and the patient has angina pectoris. Massive enlargement may lead to a pulsatile painful mass in the anterior chest wall as the ribs and sternum are eroded. Aneurysmal dilatation of the arch may compress the left main bronchus to produce respiratory difficulty from atelectasis, a 'brassy' cough, a tracheal tug and paralysis of the left recurrent laryngeal nerve, and occasionally a left-sided Horner's syndrome. Compression of the oesophagus may cause dysphagia, and rupture may occur into the oesophagus, bronchus or externally. The diagnosis of syphilis should be confirmed serologically and treated with an appropriate antibiotic regime. These aneurysms are now extremely rare in the developed
world, but nonsyphilitic aneurysms of the descending thoracic aorta may be found at routine X-ray examination (5.179) and are often symptomless. They may be further investigated by CT (5.180) or MRI.

Other aneurysms
Aneurysms may develop in many other situations in the arterial tree.
- berry aneurysms in the circle of Willis result from genetic weakness at the bifurcation of vessels and probably represent developmental defects in the media and elastic fibres; the aneurysmal sac gradually enlarges, and rupture may occur with extravasation of blood into the subarachnoid space (see p. 499)
- mycotic aneurysms may form in any part of the arterial tree, but they are found most commonly in the cerebral circulation; they are associated with damage to the arterial wall caused by sepsis, which may be embolic in nature; they are rare in developed countries
- polyarteritis nodosa may be associated with the formation of multiple microaneurysms (see p. 144, 198, 292)
- Kawasaki syndrome is probably an infectious disease caused by an unknown agent, which causes arteritis and aneurysms of the coronary arteries (see p. 74).

DISSECTING ANEURYSM OF AORTA
Dissection of the aorta often begins with an intimal tear that allows blood to dissect into the media, forming a 'false channel' which may re-enter the lumen at a point farther down. About one-half of the cases involve the ascending aorta, one-third the arch and the rest are found in the descending aorta. The initial tear may occur spontaneously in patients with defects in the aortic wall (as seen in Marfan's syndrome, Ehlers-Danlos syndrome and cystic medial necrosis), in patients with coarctation of the aorta and in patients with hypertension; alternatively, it may be iatrogenic, after angiography or coronary artery surgery.

The clinical presentation is usually a sudden onset of severe pain in the chest, abdomen or back. Ascending aortic dissection may involve the coronary ostia and the aortic valve, which may become acutely incompetent, and the patient may present with acute left ventricular failure or with acute myocardial infarction. Dissection of the arch may involve the arteries to the brain and upper limbs with hemiplegia or an ischaemic arm. Rupture may occur into the pericardium, mediastinum, left pleural cavity or abdomen.

The diagnosis can often be made clinically by the finding of absent or diminished pulses with differences in blood pressure, and it may be confirmed by X-ray (5.181). Transoesophageal echocardiography (5.182) is now the method of choice for diagnosing aortic root dissection, but the extent of dissecting aneurysms may also be investigated by angiography, CT scan.
AORTIC DISEASE

Echocardiography and normal serum enzyme levels exclude acute infarction. The high mortality varies with the site and length of dissection. Surgery is the only treatment and involves replacement or repair of the damaged wall if possible.

AORTIC ARCH SYNDROME

Aortic arch syndrome is a general term given to diseases of the aortic arch that interfere with blood flow in the major vessels of the arch, the innominate artery, the left common carotid artery and the left subclavian artery. A range of pathologies may produce this effect (5.185). The usual presentations result from cerebral ischaemia and impairment of upper arm circulation but sometimes the presenting features may relate to vascular disease elsewhere (5.186).

CAUSES OF AORTIC ARCH SYNDROME

Atherosclerosis
Dissecting aneurysm
Takayasu's disease
Syphilis (aortitis and aneurysm)
Mycotic aneurysm
Relapsing polychondritis
Giant cell aortitis
Ankylosing spondylitis
Kawasaki syndrome

5.186 Takayasu's disease is a form of arteritis that mainly affects the aorta and its large branches and the pulmonary arteries, although this patient presented with unstable angina due to arteritic involvement of the coronary arteries. This digital subtraction angiogram shows the origin of four vessels from the aortic arch. From left to right in this view they are the innominate, left common carotid, an anomalous origin of the left vertebral and the left subclavian artery. The vertebral and subclavian arteries have discrete stenoses near their origins. The cause of Takayasu's disease is unknown. It may respond to systemic steroid therapy, but surgical treatment may also be necessary when major cerebral or other impairment is present.
CARDIOVASCULAR

Isolated proximal occlusion of the subclavian artery may be associated with the ‘subclavian steal’ syndrome, in which the distal subclavian artery is perfused by retrograde flow through the ipsilateral vertebral artery (5.187, 5.188). The ‘steal’ of blood via the circle of Willis may result in symptoms and signs of cerebral ischaemia when the arm is used.

THORACIC OUTLET SYNDROMES

The neurovascular bundle that supplies the upper limb lies in the angle between the scalenus anterior muscle and the first rib. An extra rib (‘cervical rib’), or a fibrous band equivalent to it, may compress the lower trunk of the brachial plexus (C8, T1) and the subclavian artery when the shoulder is ab ducted. Patients are often aware of the association between symptoms of paresthesiae, numbness and blanching of the fingers and arm position and their immediate disappearance when the arm is returned to the side. Eventually aneurysmal dilatation of the artery occurs, which may be associated with peripheral ischaemic episodes, Raynaud’s phenomenon and emboli.

The diagnosis is made clinically by abducting the arm to 90° and rotating it externally. This leads to disappearance of the radial pulse, a bruit over the subclavian artery and the appearance of symptoms. The scalene manoeuvre (Adson’s test) consists of rotating and hyperextending the neck. This produces subclavian compression and similar symptoms and signs. X-ray of the thoracic inlet may show unilateral or bilateral cervical ribs or a rudimentary cervical rib, which is often associated with a fibrous band (5.189). Treatment is surgical removal of the rib(s).

VENOUS THROMBOSIS AND PULMONARY EMBOLISM

One of the most common causes of preventable death in developed countries is pulmonary embolism after deep vein thrombosis. Autopsies carried out in hospitalized patients show that up to 25% of all deaths are associated with pulmonary embolism, and it is estimated that in over one-half of these deaths venous thrombosis and pulmonary embolism were the main cause. 1% of all hospitalized patients may die from pulmonary embolism. Most emboli originate in the deep veins of the legs; only a small number originate from the pelvis and the inferior vena cava. The types of patients who are at risk of deep vein thrombosis are shown in 5.190 and these risks are important when considering patients for prophylaxis, which has now been shown to prevent deep vein thrombosis and pulmonary embolism without significant side effects in most patients. The appropriate pharmacological prophylaxis in most patients is low-dose heparin or low molecular weight heparin. This should be given by deep subcutaneous injection in the anterior abdominal wall (5.191), and may sometimes lead to multiple local haematomas (5.192). Prophylaxis also prevents the development of the post-phlebitic limb, which is estimated to affect about 5% of the population.

DEEP VEIN THROMBOSIS

Deep vein thrombosis (DVT) is common, but its clinical history and signs are very unreliable. Up to one-half of the patient group may have no leg symptoms or signs before presenting with a pulmonary embolism and even leg symptoms are nonspecific (5.193). A high index of suspicion is essential, especially in the ‘at risk’ patients listed in 5.190. The patient may be aware of changes in skin colour, from normal to a dusky blue or a waxy white, and this is usually associated with swelling. Signs may be present (5.194), but are nonspecific and always require further investigation.
### RISK FACTORS FOR THROMBOEMBOLIC COMPLICATIONS

- Over 40 years old
- Obesity
- Malignancy
- Infection/inflammation
- Previous thromboembolism
- Family history of thromboembolism
- Some haematological and biochemical abnormalities, e.g. polycythaemia, thrombophilias
- Heart failure
- Varicose veins
- Trauma
- Re-operation
- Oestrogen therapy
- Renal transplant recipients
- Paralysis/immobility
- Types of surgery:
  - Knee surgery
  - Hip fracture surgery
  - Elective hip surgery
  - Retropubic prostatectomy
  - General abdominal surgery
  - Gynaecological surgery
  - Neurosurgery

### POSSIBLE SYMPTOMS IN DEEP VEIN THROMBOSIS

- Cramping pains in the calf or thigh (usually in one leg)
- Tenderness to touch or movement
- Swelling and tightness
- Discoloration, ranging from white to deep purple
- No symptoms in the legs:
  - Presentation with pulmonary embolism
  - Sudden death
  - Detected in a screening test

### SIGNS THAT MAY INDICATE DEEP VEIN THROMBOSIS (DVT), BUT ARE NONSPECIFIC.

- Swelling with some pitting oedema on the dorsum of the foot or ankle
- Pain in the calf on gentle compression, in the popliteal fossa and along the line of the femoral vein
- Colour changes
- Increased temperature that tends to be generalized in the whole limb
- Dilatation of superficial veins, particularly around the ankles
- Signs of pulmonary embolism
- No apparent signs – the patient has been diagnosed by a screening test because of a high-risk situation

### Thromboprophylaxis

5.191 Thromboprophylaxis with subcutaneous heparin (or low molecular weight heparin) is effective in reducing the risk of deep vein thrombosis in medical and surgical settings. The injections should be given subcutaneously into the anterior abdominal wall.

5.192 Multiple abdominal wall haematomas resulting from regular prophylactic subcutaneous heparin injections. Though relatively common, this complication is usually harmless and is not a contraindication to the continuation of prophylaxis. The appearance may, however, alarm inexperienced staff.

### Possible symptoms in deep vein thrombosis.

5.193 Possible symptoms in deep vein thrombosis.
5.195 Deep vein thrombosis, presenting as an acutely swollen left leg. Note the dilatation of the superficial veins. The leg was hot to the touch, and palpation along the line of the left popliteal and femoral veins caused pain. Less than 50% of DVTs present in this way, and other conditions may mimic DVT, so further investigation is always indicated. Note the coincidental psoriatic lesion below the patient’s right knee.

5.197 Phlegmasia cerulea dolens. The painful, swollen, blue leg results from vascular stasis caused by massive venous thrombosis, and it may lead to venous gangrene unless the resulting high tissue pressure is relieved by thrombectomy. This is a relatively rare presentation of deep vein thrombosis. Most patients have few, if any, signs.

5.198 Deep vein thrombosis in the iliac vein. Venography is still the ‘gold standard’ in the diagnosis of deep vein thrombosis (DVT). All DVTs are potentially dangerous, but this example seems particularly likely to embolize as it is not obviously attached to the wall of the vein.

Treatment of DVT is with heparin followed by warfarin for at least 3–6 months. Analgesics, support stockings, and occasionally surgery or fibrinolytic therapy may also be of value. Prevention of DVT should be considered in all hospitalized patients at medium to high risk and this involves the use of support stockings and low doses of heparin or related compounds (5.191).

DVT is very uncommon in the upper limbs. When it does occur, there may be a history of recent physical activity or of rest or coma in which the arms may have been held in an unusual position or compressed. Underlying malignant disease is another important cause (9.80). The presenting features are similar to those in the lower limb, but there are rarely any significant sequelae. Treatment is with a short course of anticoagulants.
VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Post-phlebitic syndrome

Thrombosis in the leg veins is usually centred around venous valve cusps. Resolution of the thrombus often leaves the valve leaflets damaged and incompetent; retrograde flow occurs, and this increased venous pressure distends the distal veins and makes the blood follow different pathways, especially after prolonged standing and after exercise. The long-term result is varicose veins that are under increased pressure (5.196). Recurrent minor haemorrhages lead to deposition of iron in the skin, which becomes brown-stained and firm from the deposition of fibrous tissue. Local anoxia and oedema lead to ulceration, often around the medial malleolus, which tends to be resistant to healing (5.200). Treatment should be directed at reduction of the hydrostatic pressure by the use of support hose and healing of the ulcer by elevation of the limb and, if necessary, by plastic surgery.

PULMONARY EMBOLISM

Acute pulmonary embolism is the impaction of one or more emboli in the pulmonary circulation. It is usually the sequel of venous thrombosis in the legs, is a major cause of morbidity and causes significant avoidable mortality. The clinical presentation is often dramatic, with the sudden death of a patient who was expected to recover uneventfully from major surgery. Sometimes there are preceding symptoms, such as chest discomfort, wheeze, cough or syncopal attacks. These result from small emboli (‘herald’ emboli), but the symptoms are often ignored. Often there are no specific symptoms or signs, and it is the suspicious mind of the vigilant clinician that will trigger the appropriate investigations.

Symptoms that may be present in established embolism include dyspnoea, pleuritic chest pain, cough, apprehension, haemoptysis, sweating and syncope. Signs are not specific, but may include increased respiratory rate (>20/min), pulmonary crackles, an accentuated pulmonary second sound, a rapid pulse rate (>100 bpm), fever, phlebitis, sweating, pleural friction rub and cyanosis. A range of abnormalities is usually present in the ECG, reflecting the sudden increase in right ventricular strain (e.g. arrhythmias, axis deviation and right bundle branch block, acute cor pulmonale (S1, Q3, T3), the development of P pulmonale and T-wave abnormalities – 5.201). The plain X-ray of the chest may be totally normal or, in a minority of cases, may show an infiltrate or consolidation, a high hemidiaphragm, pleural effusion, atelectasis or focal oligemia (5.202).

The diagnosis depends on a ventilation/perfusion γ-scan of the lungs (V/Q) using radioactive xenon gas for the ventilation part and technetium-labelled macroaggregates of human serum albumin for the perfusion part (4.48, 4.49, 5.203). The ‘gold standard’ test is pulmonary angiography (5.204), but this is invasive and carries a small morbidity and mortality. The legs should also be examined and an ultrasound scan may define the source of the emboli. Treatment is with anticoagulant doses of heparin followed by warfarin for at least 3–6 months. Fibrinolytic agents may be used in the acute stage and emergency surgery to remove a massive embolus is occasionally life-saving.
5.201 Acute pulmonary embolism. The classic changes are seen in the ECG. They include tachycardia, right-axis deviation, the appearance of an S wave in lead I and a Q wave in lead III, T-wave inversion in III and over the right ventricle, and right ventricular conduction delay. The changes are often slight and easily overlooked. More major changes may occur in massive pulmonary embolism.

5.202 Pulmonary embolism. The chest X-ray is rarely diagnostic. In this patient it showed a raised right hemidiaphragm, some right basal shadowing and blunting of the right costophrenic angle. The diagnosis is unclear, but the combination of a history of right-sided chest pain and slight haemoptysis with these findings was an indication to proceed to lung scanning (5.203).

5.204 Acute massive pulmonary embolism. This pulmonary angiogram shows some filling of the left upper and lower segmental vessels only. The remaining vessels show near-total embolic occlusion. This patient responded well to streptokinase infusion.

5.203 Pulmonary embolism. Ventilation and perfusion scintigrams in pulmonary embolism. There are multiple perfusion defects with normal ventilation in the same areas. This combination gives a high probability of a diagnosis of pulmonary embolism (RPO = right posterior oblique view; RAO = right anterior oblique view).
DISORDERS OF PERIPHERAL LYMPHATICS

LYMPHANGITIS

Lymphangitis is an acute inflammation of peripheral lymphatic vessels in which a focus of infection, usually on the skin and usually caused by streptococci, drains to the regional lymph nodes and causes an acute inflammatory reaction, with redness, swelling, oedema and pain in the lymphatic vessels and nodes (see p. 37).

LYMPHOEDEMA

Oedema that results from blockage of the lymphatic drainage of a limb is termed lymphoedema. It may be secondary or primary. Secondary causes are more common and include infiltration with neoplasm, parasitic infiltration (1.204, 1.205), and surgical operations or radiotherapy that remove or damage lymphatics. Primary disorders result from a hereditary abnormality in the formation of the lymphatics (5.205). The most common of these is Milroy's disease but lymphoedema may also be found in ovarian dysgenesis, Noonan's syndrome and other genetic disorders.

The onset of the condition varies according to the cause. Oedema is usually easily pitted, but as the disease becomes more chronic, the limb becomes hard and woody and the skin thickened and wrinkled. The diagnosis is made on isotope lymphangiography (5.206) or lymphangiography (5.207).

Lymphoedema is a difficult condition to treat adequately, but elevation of the limb or compression bandages may help. Surgery has little to offer.
HISTORY

A full medical history is important in any patient with suspected renal disease. Remember that the kidney has endocrine as well as excretory functions.

Specific questions should be asked about current features and symptoms, including

- Urine volume: high in diabetes mellitus, diabetes insipidus or with loss of renal concentration; low in advanced renal failure or urinary tract obstruction
- Frequency of micturition or presence of nocturia, or both: high frequency associated with high urine volume or urinary infection
- Urine appearance and colour — may be affected by a range of disorders or ingested substances (6.1); painless haematuria may be a sign of urological malignancy and requires urgent investigation
- Pain: in loins, back, abdomen, suprapubic area? Constant or intermittent? Related to micturition? Pain may result from infection, stones, tumour or inherited renal or urinary tract disorders
- Nonspecific symptoms associated with renal failure, including fatigue, nausea, weight loss, pallor, easy bruising and symptoms associated with heart failure (see p. 222).

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Cause</th>
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<tbody>
<tr>
<td>Milky</td>
<td>Acid urine: urate crystals</td>
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<td></td>
<td>Alkaline urine: insoluble phosphates</td>
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<td></td>
<td>Infection: pus</td>
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<tr>
<td></td>
<td>Spermatozoa</td>
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<td></td>
<td>Chyluria</td>
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<tr>
<td>Smoky pink</td>
<td>Haematuria (&gt;0.54 ml blood/litre urine)</td>
</tr>
<tr>
<td>Foamy</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>Blue or green</td>
<td>Pseudomonas urinary tract infection</td>
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<tr>
<td></td>
<td>Bilirubin</td>
</tr>
<tr>
<td></td>
<td>Methylene blue</td>
</tr>
<tr>
<td>Pink or red</td>
<td>Aniline dyes in sweets</td>
</tr>
<tr>
<td></td>
<td>Porphyrins (on standing)</td>
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<tr>
<td></td>
<td>Blood, haemoglobin, myoglobin</td>
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<tr>
<td></td>
<td>Drugs, for example phenindione, phenolphthalein</td>
</tr>
<tr>
<td></td>
<td>Anthocyaninuria (beetroot — ‘beeturia’)</td>
</tr>
<tr>
<td>Orange</td>
<td>Drugs: anthraquinones (laxatives), rifampicin</td>
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<tr>
<td></td>
<td>Urobilinogenuria</td>
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<tr>
<td>Yellow</td>
<td>Mecaprine</td>
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<td></td>
<td>Conjugated bilirubin</td>
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<tr>
<td></td>
<td>Phenacetin</td>
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<tr>
<td></td>
<td>Riboflavin</td>
</tr>
<tr>
<td>Brown or black</td>
<td>Melanin (on standing)</td>
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<tr>
<td></td>
<td>Myoglobin (on standing)</td>
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<tr>
<td></td>
<td>Alkaptonuria</td>
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<tr>
<td>Green or black</td>
<td>Phenol</td>
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<tr>
<td></td>
<td>Lysol</td>
</tr>
<tr>
<td>Brown</td>
<td>Drugs: phenazopyridine, furazolidone, L-dopa, niridazole</td>
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<tr>
<td></td>
<td>Haemoglobin and myoglobin (on standing)</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
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6.1 Macroscopic appearance of the urine.
EXAMINATION

On general examination, there may be few, if any, abnormal findings in patients with urinary infections, renal calculi or other uncomplicated renal disorders; even some patients with acute renal failure may appear physically normal.

In acute nephritis, the patient (often a child) develops acute facial puffiness (6.2) and hypertension in association with haematuria, proteinuria and oliguria; whereas in the nephrotic syndrome, there is usually severe oedema and ascites (6.3).

Chronic renal failure (CRF) is usually associated with a wide range of signs (6.4–6.6).

Where renal disease is part of a multisystem disorder (diabetes mellitus, systemic lupus erythematosus (SLE), etc.), there may be other signs of the primary disease.

6.2 Acute nephritis. The generalized facial puffiness and the erythematous periorbital oedema are typical, and this boy also had ankle oedema and hypertension.

6.3 Nephrotic syndrome in a young boy. Note the severe generalized facial and body oedema. The facial oedema gives him a cushingoid appearance, but this picture was taken before he started on steroid therapy. He also had ascites.

6.4 Uraemic facies. Note the pale, sallow, yellow-brown appearance of the skin and the anaemic pallor of the sclera.

6.5 Chronic renal failure: common symptoms and signs.

6.6 The nail in chronic renal failure. Various nail changes may be observed, including those seen here: discoloration of the distal nail, pallor of the proximal nail and lunula and pigmentation of the skin at the base of the nail.
Investigations in renal disease have three main purposes:
- To establish a diagnosis
- To assess the complications of impaired renal function
- To monitor the progress of the disease or its response to therapy, or both; the ideal sequence of investigations depends upon the clinical picture, but a widely applicable approach is summarized in 6.7.

### INVESTIGATIONS IN RENAL DISEASE

<table>
<thead>
<tr>
<th>Initial investigations</th>
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<tbody>
<tr>
<td>Urine stick test:</td>
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<tr>
<td>specific gravity</td>
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<tr>
<td>blood</td>
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<tr>
<td>protein</td>
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<td>glucose</td>
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<td>crystals</td>
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<tr>
<td>epithelial cells</td>
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<tr>
<td>parasites</td>
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<tr>
<td>Midstream urine for culture</td>
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<td>Plasma:</td>
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<tr>
<td>urea</td>
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<tr>
<td>creatinine</td>
</tr>
<tr>
<td>electrolytes: sodium, potassium, chloride, bicarbonate, calcium, phosphate</td>
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<tr>
<td>Haematology:</td>
</tr>
<tr>
<td>full blood count</td>
</tr>
</tbody>
</table>

**Investigations used selectively**

| 24-hour urine collection: |
| creatinine clearance |
| protein excretion       |
| Ultrasound              |
| Plain X-ray of renal tract: |
| kidney                  |
| ureter                  |
| bladder (KUB)           |
| Intravenous urogram (IVU) |

**Specialized investigations**

- Further radiology, including CT and MRI
- Isotope scans
- Specialized renal tubule function tests
- Biopsy
- Endoscopy
- Tests for multisystem diseases

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INVESTIGATIONS ON URINE AND BLOOD

- Urine test sticks (6.8, 6.9) should, as a minimum, test for pH, glucose, blood and protein, and usually also for ketones, bilirubin, urobilinogen and nitrites; the nitrite test is a simple screening test for the presence of infection, as many urinary pathogens convert dietary nitrates to nitrites; a positive nitrite test is an indication for urine culture.

6.8 A typical urine test stick, which provides instant measurement of a range of possible abnormalities in the urine.

6.9 A positive result for blood (arrowed) occurred when this reddish-brown urine was tested with a standard stick.

6.7 The investigation of patients with suspected renal disease.
• Urine microscopy, including phase-contrast microscopy, may identify red cells (6.10), white cells, casts (6.11), crystals, urinary tract epithelial cells or parasites
• Urine culture. In women, urine culture samples must be collected with care to avoid contamination — usually in midstream after washing the external genitalia; urine may be cultured on a plate or on a dip-slide impregnated with culture medium (6.12); if there is a suspicion of urinary tract tuberculosis, three early-morning samples may be required for concentration and culture
• Plasma biochemistry provides an initial assessment of renal function; as most laboratories now use automated systems, the urea, creatinine, sodium, potassium, chloride and bicarbonate levels are usually accompanied by calcium, phosphate and alkaline phosphatase results and the albumin level, which allows correction of the calcium value; complement (C3, C4) values may be helpful; cholesterol elevation is found in nephrotic syndrome, and may be associated with premature vascular disease
• Haematology profile – a fall in haemoglobin is invariable, as renal function and the production of endogenous erythropoietin decline; a normochromic normocytic anaemia may be complicated by acute episodes of haemolysis (microangiopathic haemolytic anaemia, MAHA) or by iron deficiency; elevation of the white cell count is a good indicator of renal tract infection, and a decline reflects the response to antibiotic therapy; thrombocytopenia is found in the consumption coagulopathies associated with haemolytic uraemic syndrome
• Urine biochemistry is used selectively to measure 24-hour

6.10 Phase-contrast microscopy of urine sediment, showing a wide range of dysmorphic red cells. In fresh urine, dysmorphic red cells imply glomerular bleeding. In lower urinary tract bleeding, the red cells appear similar to one another (isomorphic). Patients with isomorphic red cells in the urine require further detailed urological investigation, whereas patients with dysmorphic red cells require further investigation for possible renal disease.

6.11 A red-cell cast, seen on direct microscopy of urine from a patient with the acute nephritic syndrome. The presence and nature of casts in the urine provide clues to the nature of the underlying renal disease: for example, red-cell casts imply bleeding at the glomerular level, whereas white-cell casts are seen most commonly in acute bacterial pyelonephritis.

6.12 A dip-slide coated with culture medium (CLED – green; MacConkey – brown) may be used to start urine culture away from the laboratory, in general practice or in the clinic.
excretion of creatinine, and thus calculate the creatinine clearance; the 'selectivity' of proteinuria can also be assessed. Electrophoresis may show the presence of kappa or lambda light chains and suggest a diagnosis of multiple myeloma (see p. 466).

- Passage of a stone or 'gravel' may reflect a metabolic abnormality and all such materials passed should be analysed (see p. 304).

IMAGING

- Ultrasound is a cheap, noninvasive and repeatable technique which determines kidney size, shape and position and the presence or absence of obstruction or space-occupying lesions; it is an ideal tool for screening relatives of patients with polycystic kidneys (6.13). Enlargement of the prostate may be further investigated by transrectal ultrasound. This allows repeated examination of patients with prostatic carcinoma to assess the presence and extent of local invasion (6.116); it is also used as guidance for prostatic biopsy. Ultrasound is of limited value in assessment of renal calculi and nephrocalcinosis

- Plain X-ray of kidney, ureter and bladder (KUB) is a preliminary to specialized imaging. It is of value in detecting and following calcification in the kidney or stone in the renal tract (6.14) and may reveal other abnormalities

- Intravenous urogram or pyelogram (IVU, IVP) requires the injection of a radio-opaque contrast medium; serial pictures reveal a nephrogram phase that shows lesions in the parenchyma and a pyelogram phase that outlines the renal collecting systems, ureters and bladder (6.15, 6.16). In...
patients with diminished renal function, films taken many hours later may still show contrast, but tomography may be necessary to visualize the kidneys (6.17). The IVU is the investigation of choice in acute renal colic.  
* Renal arteriography allows precise anatomical demonstration of the branches of the renal arteries; this is of value in detecting stenosis (6.92), aneurysms (6.72) or a tumour circulation (6.18), although it is now rarely used in diagnosis or assessment of tumours. The quality of arteriography is enhanced by modern digital subtraction techniques (6.19) and in some circumstances adequate images may be obtained using an intravenous contrast medium bolus.

- Renal vein venography allows the anatomy of the renal vein to be seen and samples of blood to be collected for assays (e.g. of renin in the investigation of suspected renovascular hypertension).
- Retrograde pyelography is carried out in conjunction with cystoscopy; a ureteric catheter is threaded into the lower end of the ureter and contrast medium injected; retrograde pyelography can usually define the site and cause of obstruction (6.20).
- CT scanning is valuable in defining retroperitoneal lesions and urinary tract obstruction; it is especially valuable in locating and staging tumours (6.113) and will also show abnormalities such as polycystic kidneys (6.21); modern spiral CT

6.17 Tomography was necessary to reveal the left kidney in this patient's intravenous urogram. The grossly hydronephrotic right kidney was visible on a normal film, but the nephrogram, which reveals a large left kidney, can be seen only on tomography.

6.18 Renal arteriography (aortography). This 'flood' film, in which contrast is allowed to enter both kidneys simultaneously from the aorta, demonstrates a normal arterial circulation in the left kidney and an abnormal tumour circulation in the right kidney. Selective arteriography can also be performed by catheterizing individual renal arteries, and digital subtraction imaging (6.19) allows further detailed assessment.

6.19 Aortogram (digital subtraction technique) showing bilateral renal artery stenosis. The appearances are typical of stenosis caused by fibromuscular hyperplasia rather than atheroma, and the stenosis is more marked on the right (arrow). The stenoses were successfully treated by balloon angioplasty.

6.20 Retrograde pyelogram revealing a large filling defect in the left ureter caused by a transitional cell carcinoma. The technique is particularly useful in defining the nature and site of ureteric obstruction.
also provides excellent demonstration of the renal arteries
- Micturating cystogram is used to demonstrate reflux of urine
  from the bladder to the ureter(s) during emptying of the
  bladder; the bladder is catheterized and filled with contrast
  medium, and films are then taken during and after mictura-
  tion (6.22)
- Radionuclide scans are of value in both static and dynamic
  imaging; 99m Tc-DMSA provides static images of the renal
  parenchyma, particularly valuable in assessing the presence
  and extent of scarring in reflux nephropathy (6.23, 6.95);
  99m Tc-DTPA (6.24, 6.25) or -MAG3 is used for dynamic
  renography, which provides information about vascularity of
  the kidneys and may be used to screen for renal artery steno-
  sis (6.90, 6.91). Renography is also useful in assessing sus-
  pected upper tract obstruction, and both renography and
  DMSA scans permit quantitation of divided renal function
- MRI will undoubtedly increase in importance; at present it
  is used especially in the assessment of prostatic carcinoma,
  but local and distant spread of tumours, including the extent
  of tumour thrombus in the inferior vena cava and right
  atrium in renal cell carcinoma, also show up well. Magnetic
  resonance angiography can provide high-quality images of
  the renal arteries without any contrast medium or other inva-
  sive technique.

6.22 Micturating cystogram, showing bilateral ureteric reflux. Reflux is
categorized in three grades: grade I, in which contrast medium enters the ureter
only; grade II, in which the pelvicalyceal system is filled with dye; grade III, in which
dilatation of the calyces and ureter also occurs. In this patient, there is some ureteric
dilatation and early calyceal clubbing, so there is grade III reflux.

6.23 A 99m Tc-DMSA scintigram, showing defects in the right kidney. The two largest
defects are arrowed, but other defects are also evident. The most common cause of this
appearance is reflux nephropathy, in which recurrent pyelonephritis results in scarring. This
was confirmed by micturating cystogram in this patient.

6.24 99m Tc-DTPA diuretic renogram in a patient with left-sided obstructive uropathy. The patient
was given intravenous frusemide (furosemide) at 20 minutes. Note the similar perfusion scans in both
kidneys, followed by accumulation of isotope in the urine in the renal collecting systems. Isotope persists in
the left kidney for much longer than in the normal right kidney. The results can be quantitatively displayed as a
plot of counts over the kidney against time (6.25).
Interventional radiological techniques play a major role in urinary tract disease; these include CT and ultrasound-guided biopsy, nephrostomy, abscess drainage, ureteric stenting and percutaneous access for stone extraction; in renovascular disease, renal angioplasty is of major importance; embolization of renal tumours is practised much less widely than a few years ago, but it may still have a role in very vascular tumours as a prelude to surgery or in inoperable disease.

OTHER INVESTIGATIONS

Renal biopsy can be performed percutaneously, usually with ultrasound guidance, in patients who can cooperate and hold their breath, have normal coagulation, have two kidneys, have a reasonably controlled blood pressure and have a haemoglobin greater than 8 g/dl (6.26). Open biopsy is advisable if these criteria are not met. Contraindications to percutaneous renal biopsy include a bleeding diathesis that cannot be corrected, uncontrolled hypertension, renal or urinary tract infections (UTIs), very small kidneys, a single functioning kidney and ureteric obstruction. Transjugular biopsy may be used in the presence of a bleeding diathesis.

Significant complications of renal biopsy are rare. Haematuria follows in 5–10% of patients, and local haematomas in about 1%. Blood loss requiring transfusion, and death, are rare complications.

Renal biopsy is valuable in patients with nephrotic syndrome, nephritic syndrome and unexplained renal failure. Light microscopy with special stains will often lead to a diagnosis but may be complemented by immunofluorescence and electron microscopy.

Electron microscopy of glomeruli from patients with glomerulonephritis determines the location of electron-dense deposits in relation to the glomerular basement membrane (subepithelial, intramembranous, subendothelial) or mesangium. Immunofluorescence microscopy, using cryostat sections treated with fluorescein-labelled antiserum, determines the pattern of deposition (granular, linear, mesangial) of different classes of immunoglobulin and complement within glomeruli.

Cystoscopy allows for direct vision and biopsy of bladder wall pathology (1.221, 6.27) and the insertion of ureteral catheters for retrograde pyelography or the direct removal of ureteric stones.

Tests for systemic disease may be needed, including a search for infection elsewhere (throat swab, ASO-titre, hepatitis B markers, syphilis serology, etc.), an autoantibody screen, including antinuclear factor, rheumatoid factor, anti-ds-DNA antibody, cryoglobulins, anti-neutrophil cytoplasmic antibody (ANCA) and anti-glomerular basement membrane antibody (6.68), and investigations into diabetes mellitus or other underlying disorders.

6.25 99m Tc-DTPA renogram. Activity over the kidney is measured after initial injection of the isotope and plotted against time. Typical results in normal subjects and in patients with acute tubular necrosis, obstruction and renal artery stenosis are shown here.

6.26 A Trucut biopsy needle, of the type commonly used for percutaneous renal biopsy (and for other biopsies, including liver and prostate). Renal biopsy is an important technique in the assessment of many patients with renal, especially glomerular, disease.

6.27 Cystoscopy revealing a transitional cell carcinoma of the bladder. The patient presented with painless haematuria.
CLINICAL PRESENTATIONS OF RENAL DISEASE

ACUTE RENAL FAILURE

Acute renal failure is defined as a recent rapid and profound decline in renal function, whereas rapidly progressive renal failure refers to renal failure developing over weeks rather than days. These disorders, therefore, can be diagnosed only by serial observations of serum creatinine levels and urine flow rates.

Patients commonly present because of oliguria, but more than 25% of patients with acute renal failure are nonoliguric (urine volumes remain greater than 400 ml per day). There are no characteristic clinical signs, but physical features on examination may include peripheral and pulmonary oedema, pleural effusions, pericarditis, acidic respiration and a depressed conscious level.

The causes of acute renal failure are usually considered in three groups (prerenal, renal or postrenal), depending on whether the main component of the initiating event is renal hypoperfusion, intrinsic renal disease or urinary outflow obstruction (6.28). Prerenal failure may be prevented from evolving to established acute renal failure by correction of hypovolaemia or impaired cardiac output. Prerenal failure is likely to be present if urinary concentrating ability (urine to plasma osmolality >1.7) or urinary sodium retention (urinary sodium concentration >20 mmol/litre) are demonstrated.

Established acute renal failure that is caused by nephrotoxins (myoglobinuria, haemoglobinuria, aminoglycosides, organic solvents, contrast material), ischaemia (hypovolaemia or cardiac failure), septicaemia, surgery or obstetric complications is potentially reversible and acute tubular necrosis is usually found if the kidneys are examined morphologically.

In these forms of reversible acute renal failure, a diuretic phase usually begins spontaneously during the second or third week after the onset of renal failure and the functional and histological abnormalities may completely resolve. Acute renal failure caused by glomerular lesions is less likely to recover without specific treatment and renal biopsy should be performed promptly in suspected cases. Postrenal failure is potentially reversible, so obstruction should be excluded in all cases of acute renal failure.

The causes of acute renal failure can usually be identified from a full history, examination, urinalysis, urine microscopy and renal ultrasound. It is important to exclude the possibility of pre-existing CRF, because patients with CRF may present acutely.

The management of established acute renal failure requires careful attention to fluid and dietary intake, dialysis to correct and thereafter prevent hyperkalaemia (6.29), fluid overload, acidosis or uncontrolled uraemia; and treatment of the underlying cause if possible (6.30). Immunosuppressive therapy is often needed in patients with rapidly progressive or acute renal failure caused by biopsy-proven glomerular, interstitial, vasculitic or multisystem disease.

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**COMMON CAUSES OF ACUTE RENAL FAILURE**

<table>
<thead>
<tr>
<th>Pre-renal failure</th>
<th>Intrinsic renal failure</th>
<th>Post-renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia</td>
<td>Rhabdomyolysis</td>
<td>Obstructive uropathy</td>
</tr>
<tr>
<td>Low cardiac output</td>
<td>Haemolysis</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Drugs or nephrotoxins</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>Glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multisystem diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignant hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arterial occlusion</td>
<td></td>
</tr>
</tbody>
</table>

6.28 Common causes of acute renal failure.

6.29 Severe hyperkalaemia is a common complication of acute renal failure and can be diagnosed on ECG, which shows peaked and symmetrical T waves. Hyperkalaemia is an indication for urgent dialysis; other indications include pulmonary oedema, severe acidosis and pericarditis.

6.30 Patients with acute renal failure are often severely ill. They may require both ventilation and haemodialysis. The percentage survival of patients with acute renal failure has not improved significantly over the past decade, but this may be explained, at least in part, by an increasing proportion of patients with multiorgan failure surviving to a stage at which they develop renal failure.
CHRONIC RENAL FAILURE

CRF is defined as a progressive decline in renal function for at least 3 months. Loss of functioning nephrons in chronic renal disease often results in an exponential rise in serum creatinine as end-stage renal failure is approached. Consequently, the decline in renal function is frequently linear when the reciprocal of serum creatinine is plotted against time (6.31). Progressive impairment of the excretory, homeostatic, metabolic and humoral functions of the kidneys produces a range of nonspecific symptoms and signs (6.4, 6.31), so CRF may be diagnosed only after biochemical investigation. The syndrome of advanced uraemia includes anaemia, osteodystrophy (see p. 157), metabolic acidosis, pruritus, nausea and vomiting, pericarditis (see p. 252) and fluid overload. When renal disease progresses insidiously, patients may not present until they develop end-stage renal failure (6.5, 6.32). Long-standing pre-existing renal disease may be suspected in such patients by the presence of anaemia or evidence of hyperparathyroidism (see p. 155) and confirmed radiologically by the presence of bilateral shrunken kidneys (6.33). CRF may result from a range of primary diseases (6.34).

![Graph showing the typical progressive onset of nonspecific symptoms and signs of chronic renal failure.](image1)

6.31 The typical progressive onset of the nonspecific symptoms and signs of chronic renal failure.

![Intravenous urogram demonstrating two small contracted kidneys.](image2)

6.33 Intravenous urogram demonstrating two small contracted kidneys. The cortical scarring and calyceal dilatation and deformity, seen especially in the left upper pole, are features of reflux nephropathy (chronic pyelonephritis) (see also 6.100), but shrunken kidneys without these appearances may also occur in end-stage glomerular or interstitial disease.

![Uraemic facies. Another patient demonstrating slatow brown pigmentation, pallor and facial puffiness associated with long-standing renal failure.](image3)

6.32 Uraemic facies. Another patient (see 6.4) demonstrating slatow brown pigmentation, pallor and facial puffiness associated with long-standing renal failure.

<table>
<thead>
<tr>
<th>MAJOR CAUSES OF END-STAGE CRF</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Pyelonephritis or reflux nephropathy</td>
<td>10</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>10</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>5</td>
</tr>
<tr>
<td>Obstruction</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous or unknown</td>
<td>12</td>
</tr>
</tbody>
</table>

6.34 Major causes of end-stage chronic renal failure, with approximate percentage figures for prevalence in the UK and most other developed countries.
A number of factors may exacerbate CRF. These include infections, heart failure, acute fluid loss from diarrhoea and vomiting, hypercalcaemia, urinary tract obstruction and some drug therapy. Progression of CRF can be arrested when there is treatable urinary tract obstruction, UTI, hypertension or dehydration.

In the absence of reversible factors or effective therapy for the primary renal disease, conservative management of CRF requires restriction of dietary protein and potassium intake, maintenance of correct fluid and sodium balance, and the use of phosphate-binding agents and active metabolites of vitamin D to control hyperparathyroidism. Anaemia in CRF results mainly from inappropriately low production of erythropoietin by the diseased kidneys but other factors, such as iron or folate deficiency, chronic blood loss, aluminium toxicity or hyperparathyroidism, may also often contribute. Renal anaemia can now be corrected by the regular administration of human recombinant erythropoietin and treatment of any coexisting causal factors.

Renal replacement therapy
Most patients with CRF require renal replacement therapy when renal function declines to approximately 5% of the normal expected for age, usually with a creatinine clearance of 5–10 ml/min. The requirement in the UK for renal replacement therapy is approximately 70–80/million population.

The treatment options for patients with end-stage renal failure are hospital or home haemodialysis, continuous ambulatory peritoneal dialysis (CAPD) or renal transplantation.

**Haemodialysis**
Most patients on regular haemodialysis have an arteriovenous fistula created for vascular access (6.35) and require approximately 12 hours dialysis per week, usually divided into three treatment periods. This may be carried out in hospital (6.36) or in the patient’s home. Even with this regimen, patients still need to follow dietary and fluid restriction.

**Continuous ambulatory peritoneal dialysis**
 Patients on a standard CAPD regime perform exchanges of 2-litre volumes of dialysis solution through a permanent indwelling peritoneal catheter (6.37, 6.38) usually four times every day using an aseptic technique. CAPD is less restricting than haemodialysis and may be carried out at home. Patients do not usually need to restrict their dietary or fluid intake.

6.35 Vascular access for long-term haemodialysis is usually provided through a surgically created arteriovenous fistula. Blood leaves the patient through the distal needle to pass through the dialyser before returning to the patient through the proximal needle. Patients usually become adept at inserting their own needles.

6.36 Typical patient with chronic renal failure undergoing haemodialysis in a hospital setting. In some countries, including the UK, many patients carry out this treatment on a long-term basis in a specially converted room at home.

6.37 Continuous ambulatory peritoneal dialysis (CAPD) is a simpler and less restricting technique than haemodialysis, and is compatible with a virtually normal lifestyle. Bags need only be connected to the peritoneal catheter four times per day during exchanges of fluid.

6.38 The Tenckhoff peritoneal dialysis catheter remains implanted in the CAPD patient, but it can be simply strapped to the abdominal wall when not in use for fluid exchanges.
Renal transplantation

Haemodialysis and CAPD are both associated with significant physical and psychological demands on the patient and his or her family. Almost normal renal function and much improved quality of life can result from successful renal transplantation (6.39, 6.40) and recent improvements in immunosuppression protocols have increased the percentage of functioning grafts in the long term.

Most patients with CRF are keen to undergo transplantation, but the feasibility of this approach is limited in most countries by the supply of kidneys for transplantation.

6.39 Renal transplant - typical surface markings. The kidney is usually implanted extraperitoneally in either the right or left iliac fossa, and it can be easily palpated. Percutaneous biopsy is also simple when necessary.

6.40 Normal renal transplant in situ. This digital subtraction angiogram shows the normal site for a renal transplant. The renal artery has been anastomosed to the right external iliac artery.

ACUTE NEPHRITIC SYNDROME

In the acute nephritic syndrome (acute nephritis) there is an abrupt onset of haematuria and proteinuria accompanied by evidence of salt and water retention and reduced renal function. The clinical features are periorbital puffiness (6.2), ankle oedema, brown or cola-coloured urine (6.9) and hypertension. Sometimes the patient or his or her parents may also notice a reduction in urine volume. All patients have haematuria and proteinuria on urinalysis, but the degree of renal impairment is variable. Glomerular bleeding in patients with nephritis can be confirmed by demonstrating red-cell casts in the urinary sediment (6.11).

Acute nephritis may result from:

- Infection: poststreptococcal glomerulonephritis, infective endocarditis or shunt nephritis
- Multisystem disease: SLE, Henoch–Schönlein disease, vasculitis or Goodpasture's syndrome
- Primary glomerulonephritis: mesangiocapillary glomerulonephritis, IgA nephropathy or crescentic glomerulonephritis.

Evidence of infection or extrarenal involvement should therefore be sought in all patients with acute nephritis. It is important to establish the underlying cause of the nephritic syndrome as soon as possible, as renal outcome can be improved when specific therapy is started promptly.

NEPHROTIC SYNDROME

The nephrotic syndrome is characterized by the combination of heavy proteinuria, hypoalbuminaemia and oedema (1.193, 6.3, 6.41, 6.42, 6.43) and is a common mode of presentation in a variety of glomerular diseases. Prolonged proteinuria leads to hypoalbuminaemia, decreased plasma oncotic pressure, hypovolaemia, subsequent retention of sodium and water by the kidney caused by activation of the renin–angiotensin–aldosterone axis and accumulation of fluid in the extravascular space. Hypercholesterolaemia is frequently present and may be a consequence of increased hepatic synthesis of cholesterol as well as albumin. Prolonged hypercholesterolaemia may lead to premature corneal arcus (6.44) and vascular disease. Serious complications of the nephrotic syndrome include bacterial infections, particularly cellulitis and peritonitis, and arterial and venous thrombotic episodes.

The major causes of the nephrotic syndrome are listed in 6.45. No systemic cause is evident in 80% of cases and renal biopsy in such patients shows a variety of primary glomerular diseases (minimal change glomerulonephritis, focal and segmental glomerulosclerosis, membranous glomerulonephritis, mesangiocapillary glomerulonephritis and mesangial proliferative glomerulonephritis). Almost 20% of cases of nephrotic syndrome are caused by renal involvement from systemic disease (e.g. diabetes mellitus, amyloidosis, SLE) and the remainder are caused by drugs, neoplasia or rare heredofamilial disorders.

The nonspecific treatment of the nephrotic syndrome involves fluid and dietary sodium restriction, high protein intake
and judicious use of diuretics. A mild degree of ankle oedema late in the day while on treatment is desirable, in order to avoid complications from hypovolaemia. Infusions of albumin should be reserved for patients with gross hypovolaemia or refractory oedema. Renal outcome is dependent on the underlying cause of the nephrotic syndrome. Corticosteroid treatment is of value in patients with minimal change glomerular lesions (see p. 286), and may have a role in some other forms of glomerulonephritis; however high-dose steroid therapy may produce cushingoid features (6.46) and its use should be carefully controlled.

6.41 Nephrotic syndrome – a typical adult patient. He is breathless as a result of pulmonary oedema and has oedema of the ankles, calves, scrotum and penis. He has abdominal swelling as a result of oedema of the abdominal wall, and ascites.

6.42 Nephrotic syndrome in childhood. Note the gross facial and periorbital oedema, which was associated with gross proteinuria.

6.43 Nephrotic syndrome – gross pitting oedema of the abdominal wall, secondary to severe hypoalbuminaemia.

6.44 Premature corneal arcus in a 15-year-old boy with chronic nephrotic syndrome. This was associated with hypercholesterolaemia, and is indicative of a risk of premature vascular disease. Treatment of the hypercholesterolaemia may be indicated in these circumstances (see p. 340).

6.45 Causes of nephrotic syndrome.

<table>
<thead>
<tr>
<th>CAUSES OF NEPHROTIC SYNDROME</th>
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<tbody>
<tr>
<td>Glomerulonephritis</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Multisystem disease</td>
</tr>
<tr>
<td>Drugs: gold, penicillamine, heroin, captopril</td>
</tr>
<tr>
<td>Neoplasia</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Heredofamilial disorders</td>
</tr>
</tbody>
</table>

6.46 Gross cushingoid features (see also p. 314) in a 7-year-old girl with the nephrotic syndrome who was treated with corticosteroids. Although steroid treatment is of value in children with minimal change glomerular lesions, such gross features of steroid excess should be avoided if possible by careful planning of dosage and timing of therapy.
ASYMPTOMATIC PROTEINURIA

Screening investigations in apparently healthy patients may show persistent asymptomatic proteinuria (6.47) or microscopic haematuria, or both, which may be the only evidence of underlying renal disease. The presence of urinary abnormalities in patients with hypertension strongly suggests that they are suffering from renal disease. Asymptomatic proteinuria always requires further investigation to exclude treatable causes of progressive renal disease.

GLOMERULAR DISEASES

Glomerular diseases may be classified on a three-tier basis:
• Clinical syndromes
• Histological appearances
• Aetiology.

Glomerular disease may lead to a variety of clinical syndromes, including asymptomatic proteinuria, haematuria, acute nephritis, nephrotic syndrome and slowly or rapidly progressive renal failure.

There is a degree of correlation between the histological appearance of the glomeruli (6.48) and the clinical presentation (6.49). The histological appearance often provides a valuable guide to prognosis and likely response to therapy.

In primary glomerular disease, the aetiology is usually unclear; but ‘aetiological’ classification is useful in secondary glomerulopathies (6.50).

Investigations in glomerular disease should usually include the ‘initial’ investigations listed in 6.7, together with renal ultrasound or an IVU, serum complement levels, autoantibodies and appropriate tests for multisystem disorders. In adults, these will usually be followed by renal biopsy, with assessment of light-microscopic (6.51) and, often, electron-microscopic (6.52) and immunofluorescence-microscopic appearances.

In children, biopsy may often be postponed until after a trial of steroid therapy.

PRIMARY GLOMERULOPATHIES

Minimal change glomerulonephritis
The nephrotic syndrome (see p. 284) is the clinical presentation in almost all cases of minimal change glomerulonephritis, but occasionally asymptomatic proteinuria may be the only abnormality. Hypertension and haematuria are both rare. The disease is the underlying cause in more than 80% of children and almost 20% of adults with the nephrotic syndrome.
Autoantibody and complement studies are normal and proteinuria is usually highly selective (high urinary transferrin to IgG ratio). On renal biopsy, the glomeruli are normal (6.53) except for the presence of epithelial foot process fusion on electron microscopy (6.54), which is found with all causes of proteinuria of glomerular origin.

As remission of proteinuria can be induced in virtually all cases by a course of prednisolone, this is usually prescribed to all childhood nephrotics without first performing a renal biopsy. Renal biopsy is reserved for children with steroid-resistant or frequently relapsing nephrotic syndrome. In adults, minimal change glomerulonephritis is a less frequent cause of nephrotic

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**SYSTEMIC DISORDERS**

- Diabetes mellitus
- Systemic lupus erythematosus (SLE)
- Rheumatoid arthritis
- Ankylosing spondylitis
- Multiple myeloma
- Amyloidosis
- Vasculitis
- Sarcoidosis
- Neoplasia

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6.50 Systemic disorders that may be associated with secondary glomerular disease.

6.51 A normal glomerulus. (PAS x352).

6.52 The ultrastructure of the normal glomerulus as seen on electron microscopy: 1 = capillary lumen; 2 = epithelial cell; 3 = basement membrane; 4 = red blood cell; 5 = epithelial foot processes; 6 = endothelial cell; 7 = mesangial matrix; 8 = mesangial cell.

6.53 Minimal change glomerulonephritis showing a normal glomerulus on light microscopy of a renal biopsy (MSB x224). The appearance is identical to that seen in 6.51, but here the red cells are stained yellow with MSB.

6.54 Minimal change glomerulonephritis. Electron micrograph showing fusion of the epithelial foot processes (arrowed) and absence of electron-dense deposits (magnification x10750); 2 = epithelial cytoplasm; 3 = basement membrane; 4 = red blood cell in capillary lumen; 6 = endothelial cell.
syndrome and a biopsy is indicated in all cases. When relapses are frequent or unacceptable steroid side effects develop, an 8-week course of cyclophosphamide (2 mg/kg) may produce prolonged remission. On rare occasions, the disease is associated with lymphoma, and remission is usually induced on successful treatment of the underlying disease. Renal prognosis in this condition is very good, even though a few patients may develop acute renal failure as a result of overuse of diuretics.

**Focal and segmental glomerulosclerosis**

Patients with focal and segmental glomerulosclerosis most commonly present with nephrotic syndrome; this disease is the underlying cause in almost 10% of child nephrotics. Autoantibodies and complement studies are normal. Renal biopsy shows segmental areas of sclerosis, initially only in the juxtamedullary glomeruli, without evidence of cellular proliferation or necrosis (6.55). Immunofluorescence microscopy often shows deposition of IgM and C3 in affected glomeruli.

As glomerular involvement is at first focal, early cases may be indistinguishable from minimal change glomerulonephritis, even on renal biopsy. This disease may be suspected if the nephrotic syndrome in childhood is resistant to steroid therapy or runs a relapsing and remitting course. Cyclophosphamide or cyclosporin may induce partial or complete remission of proteinuria, but in more than 50% of patients renal function declines progressively and 20–40% of patients reach end-stage renal failure after 10 years. The long-term renal prognosis may be further compromised by recurrence of the disease in around one-third of patients after renal transplantation.

**Membranous glomerulonephritis**

Membranous glomerulonephritis is the most common cause of adult-onset nephrotic syndrome, but is rare in childhood. Microscopic haematuria is common and hypertension is present in around one-third of patients at presentation. The diagnosis is confirmed by the presence of diffuse uniform thickening

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6.55 Focal and segmental glomerulosclerosis. The segmental sclerosis is clearly seen on light microscopy of a renal biopsy (PAS x330).

6.56 Membranous glomerulonephritis. The renal biopsy shows uniform thickening of the capillary basement membranes (arrow). Compare with 6.51 and 6.53 (MSB x224).

6.57 Membranous glomerulonephritis. Electron micrograph showing markedly thickened basement membrane with electron-dense deposits (arrowed) representing deposits of antigen–antibody complexes located subepithelially, that is beneath the fused epithelial cell foot processes. 3 = basement membrane; 5 = epithelial cell foot processes; 6 = endothelial cell; 13 = mesangium (Magnification x10 750).
of the glomerular capillary wall in all glomeruli (6.56), associated with subepithelial electron-dense deposits on electron microscopy (6.57) and diffuse granular capillary-loop IgG on immunofluorescence microscopy (6.58). Most cases are idiopathic, but it is important to exclude associated infection (syphilis, hepatitis B), neoplasia, SLE or drug therapy (gold, penicillamine, captopril). Renal outcome in the secondary type depends on the underlying cause. If untreated, 20% of the idiopathic group remit spontaneously and up to 30% reach end-stage renal failure after 10 years. Corticosteroids are of no benefit. Recent clinical studies in nephrotic patients have shown reduction in proteinuria and improvement in renal function after treatment with combined courses of prednisolone and chlorambucil.

6.58 Membranous glomerulo-nephritis. Immunofluorescence microscopy showing diffuse granular deposition of IgG in the capillary loops (x300).

Mesangiocapillary glomerulonephritis
The mode of presentation of mesangiocapillary glomerulonephritis is variable: 20% of patients have the acute nephritic syndrome, whereas all of the remaining patients have proteinuria; 50% have hypertension, 50% have renal failure and 30% have haematuria. The disease mainly affects school-age children and young adults and is more common in females. Its frequency is falling in the developed world. Serum C3 levels are reduced transiently in Type 1 and are persistently low in Type 2. These are differentiated from each other on renal biopsy. The histological feature common to both types of disease is a combination of mesangial cell proliferation and thickening of the glomerular capillary wall on light microscopy (6.59). In the subendothelial type (Type 1) there is interposition of mesangial matrix between the endothelial cells and glomerular basement membrane, subendothelial deposits on electron microscopy (6.60) and granular deposition of IgG and C3 on immunofluorescence microscopy. In the dense-deposit type (Type 2) there are linear dense intramembranous deposits on electron microscopy (6.61), and only deposition of C3 on immunofluorescence microscopy. There is no specific therapy.
for this form of glomerulonephritis and the renal prognosis is relatively poor: more than 50% of patients reach end-stage renal failure after 10 years. Type 2 mesangiocapillary glomerulonephritis may recur in patients after renal transplantation.

**Mesangial proliferative glomerulonephritis**

Recurrent macroscopic haematuria, often within 2 days of an upper respiratory tract infection, was the most common mode of presentation of this disorder; however, as a result of routine urinalysis many patients are now detected with microscopic haematuria or asymptomatic proteinuria, or both. Peak incidence is in young adults, and men are more commonly affected. Renal failure at presentation is uncommon. Autoantibodies and complement studies are usually normal, unless the disorder is a manifestation of SLE. Serum IgA levels may be elevated in Henoch–Schönlein disease. Renal biopsy shows increased mesangial cells and mesangial matrix (6.62). These light-microscopic appearances are associated with the presence of mesangial deposits on electron microscopy (6.63) and commonly with mesangial deposition of IgA on immunofluorescence microscopy (6.64), so-called IgA nephropathy (Berger’s disease). Less frequently, immunofluorescence microscopy shows mesangial deposition of either IgG or IgM. The electron and immunofluorescence microscopy appearances of IgA nephropathy are indistinguishable from those of Henoch–Schönlein nephritis. The latter is usually associated with purpura (2.133), abdominal pain or arthropathy, is more common in children, and is more likely to present with the nephritic syndrome and to have glomeruli containing crescents on biopsy.

There is no specific treatment for either IgA nephropathy or Henoch–Schönlein nephritis, but the overall prognosis is good. Only 5–10% of patients with IgA nephropathy reach end-stage renal failure after 10 years, and progressive renal failure is more likely in patients with hypertension or nephrotic syndrome at presentation.

**Diffuse endocapillary proliferative glomerulonephritis**

Patients with diffuse endocapillary proliferative glomerulonephritis usually present with acute nephritis, although not all features may be evident. The condition is more frequent in children and young adults. In some patients, the onset of renal disease is associated with an extrarenal infection 10–14 days earlier, but most cases are idiopathic.

Classically, this disease is preceded by a nephritogenic group A streptococcal infection, usually of the throat or skin.

6.62 Mesangial proliferative glomerulonephritis. Light microscopy of a glomerulus from a patient with microscopic haematuria and asymptomatic proteinuria showing an increase in mesangial cells and matrix (H & E).

6.63 Mesangial proliferative glomerulonephritis. Electron micrograph showing electron-dense deposits distributed within the mesangium (arrows) (Magnification x13 200).

6.64 Mesangial proliferative glomerulonephritis. Immunofluorescence microscopy from the same patient as in 6.63 showing mesangial deposition of IgA, indicating that this patient has IgA nephropathy (Berger’s disease).
However, the frequency of isolating streptococcus from the presumed site of infection, or demonstrating a rise in antibody titre to streptococcal antigens (anti-streptolysin O titre), is relatively low. Autoantibodies are negative and serum C3 levels are usually transiently decreased. Renal biopsy is characterized by hypercellularity in all of the glomeruli (6.65), not infrequently associated with crescent formation (6.66). Electron microscopy in the acute stage shows large subepithelial electron-dense deposits (6.67) and immunofluorescence microscopy shows granular staining of IgG and C3 within the glomeruli. The prognosis in poststreptococcal glomerulonephritis is generally good, and the only specific treatment recommended is a 7-day course of penicillin. Complete recovery is common, and less than 5% of patients reach end-stage renal failure after 10 years. The latter is more likely in adult patients with persistent hypertension or nephrotic syndrome, and in patients with rapid progressive renal failure. The long-term outcome for the larger idiopathic group is less well defined, but is again generally good if there is early regression of features of renal disease.

SECONDARY GLOMERULOPATHIES

Anti-glomerular basement membrane disease

Anti-glomerular basement membrane disease (anti-GBM disease) usually presents with rapidly progressive renal failure, haematuria and proteinuria. The haematuria may be macroscopic and, if associated with haemoptysis, is termed Goodpasture's syndrome (see p. 200). The disease has a peak incidence in young adults, and is more common in men. There is often an association with recent infection or exposure to hydrocarbons at the onset or before relapses of the disease. The disease is mediated by an anti-glomerular basement membrane antibody present in the serum, and the antibody titre is used for diagnostic purposes and to assess the adequacy of treatment. Other autoantibodies and complement levels are usually normal. The diagnostic feature on renal biopsy is linear deposition of IgG and occasionally C3 along the capillary loops of the glomeruli (6.68). Light microscopy usually shows a focal necrotizing glomerulitis with crescent formation (6.69).
The prognosis is dependent on the degree of renal failure at the time of diagnosis and on whether pulmonary haemorrhage is present. Two major features of the natural history of the disease determine treatment strategies: pulmonary haemorrhage is almost invariably fatal if untreated, and recovery of renal function is rare if the patient is already dialysis dependent when immunosuppressive therapy is begun. Consequently, immunosuppression with pulsed intravenous methylprednisolone, oral prednisolone, cyclophosphamide and plasma exchange is reserved for patients with Goodpasture’s syndrome or patients not yet receiving dialysis. The risks of intensive immunosuppression in patients already requiring dialysis and without pulmonary haemorrhage outweigh the small chance of improvement in renal function.

Renal vasculitides
The renal vasculitides should be suspected in patients with symptoms and signs of multisystem disease in addition to renal disease. The clinical features depend to some extent on the type of vasculitis. Weight loss, anaemia, malaise, fever, high ESR and raised C-reactive protein are found in most cases. Peak incidence is in the middle-aged or elderly and patients are more often male. The more common forms of renal vasculitis can be conveniently classified according to the size of the vessels involved, the presence or absence of granulomata, and whether there is evidence of either gastrointestinal or respiratory tract disease (6.70). Churg–Strauss syndrome (allergic granulomatosis, see p. 198) is relatively rare, and renal disease is usually associated with asthma and eosinophilia. Evidence of vasculitis may also be found histologically in patients with severe renal disease caused by SLE or Henoch–Schönlein disease.

Polyarteritis nodosa
In polyarteritis nodosa (classic polyarteritis) there is segmental necrosis and fibrinoid change within the walls of medium-sized arteries, often associated with intraluminal thrombosis (6.71). Ischaemia distal to occluded vessels may produce infarcts in virtually any organ. The clinical features depend on the extent and location of the lesions (see p. 144). Mesenteric, splenic, myocardial, cerebral or renal infarction are common modes of acute presentation. Renal infarcts, often multiple, may lead to the development of loin pain, macroscopic haematuria and hypertension. The diagnosis is best confirmed by selective renal arteriography, which may show both aneurysms of the intrarenal vessels and renal infarcts (6.72). The prognosis without treatment is poor, and less than one-half of untreated patients survive more than 1 year. Treatment with high doses of prednisolone and cyclophosphamide produces rapid symptomatic improvement and appears to improve patient survival.

**Microscopic polyarteritis**
Microscopic polyarteritis (hypersensitivity angiitis) involves mainly the arterioles and capillaries. Many organs may be involved, but the kidneys, skin and lungs are most often affected. Patients with renal disease commonly present with rapidly progressive renal failure associated with microscopic haematuria and proteinuria. Serological investigations may show positive titres for rheumatoid factor and antinuclear factor in up to one-third of patients. Serum from patients with microscopic polyarteritis may also be positive for ANCA, showing a perinuclear staining pattern. Renal biopsy shows diffuse proliferation and focal fibrinoid necrosis in the glomeruli (6.73), often associated with crescent formation. Electron and immunofluorescence microscopy usually show absence of deposits. Arteriolitis or capillaritis is seen in only a minority of renal biopsies, but may be demonstrated on biopsy of skin lesions. Prognosis is poor without treatment and is worst in patients who are already oliguric at presentation, or who have more than 70% crescent formation in the glomeruli on renal biopsy. Treatment with pulsed intravenous methylprednisolone, oral prednisolone and cyclophosphamide has significantly improved both patient and renal survival. Some centres also
perform short-term daily plasma exchange in patients who are already dialysis dependent when therapy is started.

**Wegener's granulomatosis**
The presence of nasal symptoms, haemoptysis, pleurisy or deafness combined with renal disease is highly suggestive of Wegener's granulomatosis (see pp. 145, 198). In many cases renal involvement is detected only during the course of investigation of either the respiratory tract or ear and nasal symptoms. Renal disease in this disorder commonly manifests itself as rapidly progressive renal failure associated with haematuria and proteinuria. Serum is usually positive for ANCA and the diagnosis can be confirmed by nasal mucosa or renal biopsy. The latter may show similar histological appearances to microscopic polyarteritis, with features of necrotizing glomerulitis, crescent formation and arteritis. Granulomata are present only in the minority of renal biopsy specimens (6.74), but may be found on biopsy of the nasal mucosa. Indirect immunofluorescence microscopy for ANCA shows a cytoplasmic pattern in Wegener's granulomatosis. This test may prove helpful in differentiating Wegener's granulomatosis from microscopic poly-arteritis. Patient and renal survival in this condition have improved considerably since the introduction of treatment with pulsed methylprednisolone, cyclophosphamide and prednisolone. Long-term immunosuppression with cyclophosphamide or azathioprine is required, as clinical relapse is common on withdrawing cytotoxic agents.
Renal systemic lupus erythematosus
Renal involvement is evident in up to 75% of patients with other features of SLE (see p. 139), and some patients may present with renal disease before the onset of extrarenal symptoms of SLE. The severity of renal disease varies greatly: some patients may have only asymptomatic proteinuria or microscopic haematuria, whereas others may develop nephrotic syndrome or rapidly progressive renal failure. The diagnosis is confirmed serologically by the presence of serum antibodies to double-stranded DNA and a reduced concentration of C3 in the serum.

Several histological types of renal disease are evident on renal biopsy. Mesangial proliferative and membranous glomerulonephritis in SLE patients have clinical and histological features akin to idiopathic types of these disorders (see p. 288, 290).

SLE patients with nephrotic syndrome or renal failure often have a diffuse proliferative glomerulonephritis (6.75) with subepithelial, intramembranous and subendothelial deposits on electron microscopy (6.76) and peripheral deposition of IgG and complement components on immunofluorescence microscopy. Patients with this form of glomerulonephritis who have more severe renal impairment may also show evidence of crescent formation (6.77), vasculitis and interstitial fibrosis on renal biopsy.

Treatment depends on the severity of renal disease and the histological findings on renal biopsy. Patients with mesangial proliferative glomerulonephritis usually have mild renal disease, and treatment is required only for extrarenal involvement. Patients with membranous glomerulonephritis often improve with prednisolone alone, and the prognosis for renal function is good. Evolution to end-stage renal failure is relatively common in diffuse proliferative glomerulonephritis, and treatment with azathioprine or cyclophosphamide in addition to prednisolone is usually necessary. Female patients with SLE should be warned that renal function may worsen with use of the oral contraceptive pill or post partum.

Renal amyloidosis
The most common mode of presentation of amyloidosis in the kidney is the nephrotic syndrome associated with renal failure. Even in advanced renal failure, the kidneys may remain relatively large because of the deposition of amyloid. Clinically evident renal disease is more frequent in primary than secondary amyloidosis. Congestive cardiomyopathy, hepatosplenomegaly, peripheral neuropathy and malabsorption may result from systemic deposition of amyloid.

6.75 Systemic lupus erythematosus. This renal biopsy shows proliferative changes within three glomeruli (H&E x143).

6.76 Systemic lupus erythematosus with the nephrotic syndrome. This electron micrograph shows both subendothelial deposits (small arrows) and subepithelial deposits (large arrows). The subepithelial deposits show classic ‘fingerprinting’ (Magnification x5200).

6.77 Systemic lupus erythematosus. This renal biopsy shows proliferative change and crescent formation in both glomeruli (HV x110).

6.78 Renal amyloidosis. The glomerulus shows amyloid deposition, stained by Congo Red, in the glomerular capillaries (x330).
At the ultrastructural level, amyloid consists of protein fibrils and a glycoprotein known as amyloid P component. Two forms of fibril protein are found: amyloid light-chain (AL) proteins are found in myeloma-associated and primary amyloidosis, and amyloid A (AA) fibril proteins are found in amyloidosis secondary to chronic infections, rheumatoid arthritis or familial Mediterranean fever. Rectal or renal biopsy confirms the diagnosis. Renal biopsy sections stained with Congo Red show pink-red deposition within the glomeruli and blood vessel walls (6.78), which under polarized light exhibits apple-green birefringence (6.79). Electron microscopy of the amyloid deposits shows a characteristic arrangement of fibrils, and immunofluorescence microscopy for immunoglobulin and complement is negative. Monoclonal antibodies can be used to differentiate amyloid light-chain and amyloid A proteins.

There is no specific treatment for amyloidosis, although renal function may stabilize after chemotherapy in patients with myeloma-associated amyloidosis, or colchicine in patients with familial Mediterranean fever. The prognosis for renal function in most cases is poor, and more than 50% of patients with biopsy-proven amyloidosis reach end-stage renal failure within 1 year.

Renal disease is evident in around 40% of patients 20 years after developing insulin-dependent diabetes mellitus (IDDM, see p. 329) and, until recently, was a major cause of death in diabetic patients. The aetiology of diabetic nephropathy is multifactorial; both metabolic and genetic factors appear to be important, as more than 40% of patients with IDDM do not develop microvasculopathy in spite of the presence of long-term hyperglycaemia. Renal involvement in IDDM usually evolves through a number of stages.

- **Stage I**: at diagnosis, the glomerular filtration rate is increased, because of poor metabolic control
- **Stage II**: with improved glycaemic control, renal function remains within the normal range, and urinary albumin excretion (UAE) is normal
- **Stage III**: within the first 10 years after onset of diabetes, a proportion of patients develop microalbuminuria, defined as a persistent elevation in the urinary albumin excretion rate to greater than 20 μg/min but without evidence of proteinuria on urinalysis
- **Stage IV**: most patients with microalbuminuria progress to overt nephropathy, which is characterized by the onset of clinical proteinuria and hypertension and is usually associated with retinopathy; the nephrotic syndrome commonly develops at this stage
- **Stage V**: renal impairment from stage IV almost invariably progresses to end-stage renal failure.

The evolution of renal disease in noninsulin-dependent diabetes mellitus (NIDDM) is less well defined, because of difficulty in ascertaining the exact time of onset of diabetes in this group.

In patients with suggestive clinical features and associated retinopathy, diabetic retinopathy is usually assumed without performing a renal biopsy. The latter is performed only if renal disease unrelated to diabetes is suspected. The most common feature on renal biopsy is diffuse glomerulosclerosis (6.80), which may be associated with the classic lesions of diabetic nephropathy (6.81, 6.82). Electron microscopy in diabetic
nephropathy shows thickening of the glomerular membrane in all patients. It is important to exclude other urological diseases associated with diabetes, such as renal papillary necrosis (6.83), UTI, perinephric abscess or pyonephrosis and neurogenic bladder.

Progression of renal failure in patients with overt proteinuria can be retarded by achieving good control of hypertension, but the benefits of good glycaemic control and low-protein diets in this group remain to be confirmed. The efficacy of maintenance of normal blood pressure levels and optimal glycaemic control are currently undergoing assessment in patients with microalbuminuria. Early aggressive control of blood pressure, using angiotensin-converting enzyme inhibitors, has demonstrated a reduction in microalbuminuria in patients with incipient nephropathy, and a decrease in proteinuria and improvement in renal function in patients with clinical nephropathy in preliminary trials. These therapeutic strategies, introduced at an early stage of diabetic nephropathy, may help prevent progression of renal failure in future.

Once CRF develops, patients almost inevitably require renal replacement therapy, unless reversible factors such as UTI or obstruction are present. CAPD has been preferred to haemodialysis for most diabetic patients, as it provides steady-state control of biochemistry and fluid balance, and stable blood pressure, and avoids the need for either vascular access or heparin. Quality of life and patient survival are better with renal transplantation than with either mode of dialysis.

**TUBULOINTERSTITIAL DISEASES**

The generic term tubulo-interstitial diseases refers to all diseases of the interstitium and tubules with little or no evidence of concomitant glomerular disease.

**ACUTE INTERSTITIAL NEPHRITIS**

Acute interstitial nephritis frequently manifests itself as acute renal failure and may be idiopathic, associated with infection or drug-induced (antibiotics, nonsteroidal anti-inflammatory drugs, diuretics). Acute renal failure is frequently accompanied by the presence of fever, rash, eosinophilia, non-nephrotic range proteinuria and microhaematuria. On renal biopsy, there is interstitial infiltration with lymphocytes, plasma cells, polymorphs and eosinophils, interstitial oedema and variable degrees of damage to the renal tubules (6.84). Renal function usually recovers on withdrawal of the putative drug or treatment of the associated infection. Treatment with prednisolone induces recovery of renal function in the idiopathic cases.
CHRONIC INTERSTITIAL NEPHRITIS

Chronic interstitial nephritis usually presents with CRF associated with non-nephrotic range proteinuria and evidence of tubular dysfunction. Polyuria, renal salt wasting, hypokalaemia and renal tubular acidosis are common, but there may be a surprising lack of symptoms even in the presence of severely impaired renal function. Renal biopsy in long-standing cases shows interstitial fibrosis, tubular atrophy and a variable degree of interstitial infiltration (6.85). A search for an underlying cause may reveal analgesic abuse, chronic pyelonephritis, radiation nephritis, Sjögren's syndrome, gout, sickle-cell disease or heavy metal exposure, but many cases are idiopathic. Control of fluid and electrolyte balance may require sodium, potassium or bicarbonate supplementation.

ANALGESIC NEPHROPATHY

Analgesic nephropathy results from the long-term ingestion of large quantities of analgesic drugs, such as phenacetin combined with aspirin. Analgesic abuse is a common cause of CRF in Australia and Switzerland, and is more common in women than men. Tubulointerstitial damage occurs along with papillary necrosis. Patients may present with CRF, sterile pyuria, haematuria, renal colic resulting from ureteric obstruction by a fragment of necrotic tissue, or hypertension. Anaemia is often more severe than expected for the degree of chronic renal impairment. On IVU, the kidneys are usually bilaterally shrunken with deformed calyces and the appearance of a 'ring sign' on the pyelogram, representing a sloughed papilla within a dilated calyx, is typical of this disorder (6.86). The main therapeutic endeavour is in convincing the patient to stop ingesting analgesics, as continued intake invariably leads to end-stage renal failure.

MYELOMA KIDNEY

Myeloma kidney is the most common cause of renal failure in patients with multiple myeloma (see p. 466), and is more frequent in patients with Bence–Jones proteinuria. Renal failure in such patients is almost invariably associated with anaemia, and the diagnosis can usually be established by serum and urine electrophoresis, bone marrow examination and skeletal survey. Histologically, myeloma kidney is characterized by eosinophilic intraluminal casts, atrophic renal tubules and multinucleated giant cells within the tubule walls or interstitium (6.87). Renal failure in myeloma may also be caused by amyloid light-chain amyloidosis, light-chain nephropathy, hypercalcaemia, or

6.85 Chronic interstitial nephritis. The renal biopsy shows a diffuse lymphocytic infiltrate and fibrosis in the interstitium with focal tubular atrophy and periglomerular scarring (arrow) (H&E x80).

6.86 Analgesic nephropathy. This intravenous urogram shows bilaterally shrunken kidneys with typical calyceal distortions – the classic 'ring sign' plus the appearance of 'horns' and 'egg in cup'.

6.87 Myeloma kidney. There are prominent casts in the renal tubules, and a giant cell reaction is seen (bottom right) (MB x330).
hyperuricaemia, or it may follow dehydration or intravenous urography. Management of renal impairment in myeloma includes maintaining hydration, bicarbonate supplementation to improve solubility of light chains in the urine, and allopurinol to prevent hyperuricaemia after chemotherapy.

RENAL TUBULAR DISORDERS

Most patients with renal disease have some abnormality in renal tubular function, but other manifestations of renal disease usually dominate the clinical picture. In some patients, however, renal tubular dysfunction occurs in isolation and results in clinical disorder.

There are many rare inherited and acquired disorders of renal tubular function. Their classification and management is a specialized field. The main categories of renal tubular disorders are summarized in 6.88.

HYPERTENSION AND THE KIDNEY

RENAL HYPERTENSION

Renal disease is the most common cause of secondary hypertension and should be excluded in all young hypertensive patients (see also p. 254). Causes of renal-mediated hypertension can be classified into vascular diseases and parenchymal diseases (6.89).

The clinical features associated with hypertension depend on the underlying disease. Renal artery stenosis may be caused by atheroma or fibromuscular hyperplasia.

- Atheromatous renal artery stenosis should be suspected in patients with severe hypertension presenting in middle age or later without other evidence of renal disease; often these patients are heavy smokers and there is evidence of widespread atherosclerosis. This is now a relatively common problem in elderly patients, who may present with acute renal failure, CRF or end-stage renal failure requiring dialysis at presentation.

- Fibromuscular hyperplasia is more common in women, appears most often in the third or fourth decades, and is frequently bilateral.

A bruit may be heard over the flank, and biochemical investigation often reveals evidence of secondary hyperaldosteronism. Screening for unilateral renal artery stenosis is best performed by ultrasound, which may show unequal-sized kidneys, and the diagnosis can be confirmed noninvasively by a DTPA isotope renogram, before and after captopril. The renogram shows delayed perfusion, delayed uptake, and a reduced rate of excretion of isotope from the affected kidney (6.89, 6.90), which is further accentuated after captopril. Identification of renal artery stenosis can then be accomplished by arteriography (6.91, 6.92). Hypertension caused by fibromuscular disease is cured in more than 90% of patients after renovascular surgery. In patients with atherosclerotic disease, the failure rate after either surgery or angioplasty is much higher and corrective procedures are often restricted to patients who have severe renal failure or poorly controlled hypertension on medical therapy.

Renal disease may ultimately develop in about one-half of patients with systemic sclerosis (see p. 141), often with the sudden onset of severe hypertension and progression to end-stage renal failure within months. Renal biopsy shows gross intimal thickening and reduction in the lumen of the interlobular arteries. Control of hypertension may be difficult and, if renal failure develops, recovery of renal function is unlikely.

The other causes of renal hypertension are described elsewhere in this chapter.
HYPERTENSIVE NEPHROPATHY

In hypertensive nephropathy, renal failure results from inadequately treated hypertension in the absence of primary renal disease. Long-standing moderate hypertension in itself can lead to hyaline thickening of the intrarenal arterial walls, patchy ischaemic atrophy and glomerulosclerosis. Patients with benign hypertensive nephrosclerosis usually present with CRF and mild proteinuria, without haematuria or other evidence of glomerulonephritis. Renal impairment often stabilizes if adequate, long-term control of hypertension is achieved.

Accelerated nephrosclerosis is a dramatic complication of malignant hypertension, which commonly caused progressive or acute renal failure before effective antihypertensive drugs were available. The two essential clinical features are the presence of severe hypertension and grade IV retinopathy (5.148). Cardiac failure, hypertensive encephalopathy, renal failure, secondary hyperaldosteronism and microangiopathic haemolytic anaemia may accompany the onset of malignant hypertension. The malignant phase may complicate essential and all forms of secondary hypertension. Renal biopsy may be required to determine whether there is underlying renal disease or whether renal failure is a direct consequence of severe hypertension. The histological features of malignant hypertension are fibrinoid necrosis of the afferent arterioles, and endarteritis of the interlobular and arcuate arteries that results in ischaemic atrophy or infarction distal to the abnormal vessels (6.93).

High blood pressure should be lowered gradually, to lessen the risk of a sudden drop in blood pressure either precipitating cerebral infarction or worsening renal function. In many patients, renal function may recover or at least stabilize once blood pressure is controlled and the prognosis depends on whether or not there are cardiac or cerebral complications.

FAMILIAL DISORDERS

There are many inherited disorders of renal structure and function. Some gross structural disorders, such as unilateral or bilateral duplex kidneys and ureters or a single horseshoe kidney, may predispose patients to ureteric reflex or obstruction and to recurrent UTIs, with a long-term risk of renal failure. Others, such as polycystic kidneys, may lead more directly to renal failure, by reducing the volume of functional renal tissue.

Inherited disorders may also cause both glomerular disease and tubular disorders.

Two inherited conditions are particularly important causes of CRF: adult polycystic kidney disease and Alport’s syndrome.

ADULT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) or adult-type polycystic kidney disease may be detected during the investigation of hypertension, loin pain or haematuria in young adults. Patients without these symptoms may not present until they develop CRF when middle-aged or older. These cases represent up to 10% of all cases coming to dialysis or transplantation. The condition is inherited as an autosomal dominant with high penetrance, and many patients are now diagnosed during screening of the proband’s family. The prevalence in the UK is 1 in 2500, and the measured prevalence is rising because of increased ultrasound screening. The kidneys are almost invariably symmetrically enlarged because of the presence of multiple cysts. They may often be palpable clinically (6.94) and the diagnosis is best confirmed by ultrasound (6.13), or by CT scan (6.21, 9.57), both of which may also demonstrate cysts in the liver and pancreas. IVU may show

6.90, 6.91 99mTc-DTPA renogram in a patient with left renal artery stenosis. The minute 4 static renogram (6.90) shows the right kidney clearly, but the outline of the left kidney is not seen. The dynamic renogram (6.91) shows a very low count over the left kidney, which remains more or less constant, whereas the count over the right kidney shows a normal peak and decline (see also 6.25). These appearances are typical of unilateral renal artery stenosis.

6.92 Renal artery stenosis. There is an atheromatous stricture of the left renal artery with slight poststenotic dilatation and a reduction in left renal size.

6.93 Malignant hypertension. The renal biopsy shows fibrinoid necrosis in the arterial and glomerular capillaries (red) and haemorrhage into the renal tubules (yellow) (MSB x132).
characteristic stretching and distortion of the calyces but is a less sensitive test than ultrasound. Cysts may also be demonstrated by radionuclide scan (6.95). Haemorrhage or infection in a cyst, haematuria leading to clot colic, UTI and renal calculi are not uncommon. Hypertension develops in more than 75% of patients, and renal function usually declines slowly until end-stage renal failure is reached from middle age onwards. Patients with end-stage renal failure caused by ADPKD tend to be less anaemic than patients with renal failure resulting from other disorders. The enlargement of the kidneys does not usually lead to problems in performing peritoneal dialysis or renal transplantation.

By use of linkage analysis the ADPKD gene was located on the short arm of chromosome 16; a second locus is on the long arm of chromosome 4. This second defect is associated with less severe disease, and with later onset of renal cysts, hypertension and end-stage disease, although the renal and other abnormalities appear the same. Genetic counselling is an important aspect of patient management, especially in families undergoing screening. Detection of carriers has now become possible with a gene probe.

In autosomal recessive polycystic kidney disease (ARPKD), the renal cysts arise from collecting tubules and the clinical features appear in childhood. There is an association with congenital hepatic fibrosis, which results from intrahepatic dilatation of bile ducts. No gene abnormality has yet been detected.

**ALPORT'S SYNDROME**

Alport's syndrome is characterized by hereditary glomerulonephritis and nerve deafness (6.96). In about 40% of cases there are also eye abnormalities such as spherophakia, cataracts and macular and perimacular flecks. It is now appreciated that there are various pathogeneses. In some families there is diffuse leiomyomatosis involving the oesophagus, trachea and genital tracts. In the kidney the prime defect is in the glomerular basement membrane and its type IV collagen. In 80% of cases there is a dominant X-linked inheritance. Men tend to be more severely affected. It is uncommon for women to be symptomatic before the age of 40 years, whereas most men have reached terminal renal failure by the age of 30 years. Most male patients present with recurrent or persistent haematuria in childhood, non-nephrotic range proteinuria, hypertension and CRF. Renal biopsy shows proliferative glomerulonephritis which on electron microscopy shows characteristic splitting and lamellation of the glomerular basement membrane. Renal failure is uncommon in women, but affected men usually require renal replacement therapy when adolescents or young adults.

In the 20% who are not X-linked there is a dominant or recessive autosomal trait that presents as renal disease of similar severity in both sexes.

The various genetic abnormalities have been localized to the X chromosome and chromosomes 2 and 13.
URINARY TRACT INFECTION

UTI is defined as the presence of microorganisms within the urinary tract with or without symptoms or signs of inflammation. Symptomatic urinary infection is a very common problem, accounting for 3–4% of consultations in general practice in the UK.

Bacteriuria is considered significant if the numbers of bacteria in urine voided per urethram exceed 100,000 colony-forming units/ml in a properly collected specimen. Dip-slide urine culture (6.12) should be performed if delay is anticipated in a midstream urine specimen reaching the laboratory. A suprapubic aspiration may be needed to obtain a urine sample in infants, and any growth of bacteria from a suprapubic specimen of urine signifies the presence of infection.

The organisms that commonly cause UTI are listed in 6.97, and E. coli is numerically most important. The organisms are thought usually to come from the patient’s bowel, probably by direct spread from the anus, to colonize the urethra and then ascend to the bladder and kidney. Women are thought to be more likely to have UTIs because of the short length of the urethra. An important local defence against ascending infection is the hydrokinetic effect of passage of urine from the bladder. The clinical relevance of this is the increased incidence of UTIs in prostatic obstruction in men or in the presence of urinary stasis associated with a urinary diverticulum or urinary tract dilatation. Predisposing factors for urinary infection are listed in 6.98.

UTI is important because of its frequency and its association with reflux nephropathy. In the female the incidence of UTI increases with age, and approximately 5% of adult women will, at some time, develop infection. In the male, there is a high incidence in the neonatal period, associated with developmental anomalies of the lower urinary tract, a low incidence in childhood and adult life, and an increase with advancing age. Investigation of the structure of the urinary tract is indicated in children of both sexes and adult men found to have a symptomatic or asymptomatic UTI. Women with recurrent infection also merit investigation (6.98).

UTI is usually adequately treated with a course of antibiotics but long-term prophylaxis may be required in patients with structural abnormalities or recurrent infections.

CHRONIC PYELONEPHRITIS (REFLUX NEPHROPATHY)

Chronic interstitial nephritis that is thought to result from bacterial infection of the kidney has been termed chronic pyelonephritis. It may occur in patients with predisposing urological abnormalities (vesico-ureteric reflux, obstruction or neurogenic bladder) or in patients with apparently normal

### ORGANISMS THAT CAUSE UTI

- **Escherichia coli**
- **Klebsiella sp.**
- **Proteus mirabilis** (and other sp.)
- **Streptococcus faecalis**
- **Pseudomonas aeruginosa**
- Coagulase-negative **Staphylococcus** (esp. *saprophyticus*)
- **Staphylococcus aureus**
- **Corynebacterium sp.**
- **Haemophilus influenzae**
- **Gardnerella vaginalis**

The urinary tract may also be infected by **Mycobacterium tuberculosis** (see p. 302) and by **Schistosoma haematobium** (see p. 72).

### PREDISPOSING FACTORS IN UTI

- Vesico-ureteric reflux
- Obstructive uropathy
- Calculi
- Neurogenic bladder
- Structural urinary tract abnormality (e.g. vesical fistula)
- Pregnancy
- Diabetes mellitus
- Immunocompromised patient
- Recent instrumentation or catheterization of urinary tract
- Diaphragm use with or without spermicidal creams
- Postmenopausal lack of oestrogen
- Energetic sexual intercourse (especially in women)

6.97 Organisms that commonly cause urinary tract infection.
6.98 Predisposing factors in urinary tract infection.
urinary tracts. The pathogenesis of pyelonephritic renal scarring in children is attributed to both parenchymal damage and impaired renal growth, which result from intrarenal reflux of infected urine. A history of recurrent UTI during childhood and evidence of vesico-ureteric reflux are therefore risk factors for the development of focal cortical scars.

During micturating cystography, reflux of contrast from the bladder may be limited to the ureter (grade I), reach the kidney but not distend the calyces (grade II) or reach the kidney and cause calyceal distension (grade III) (6.22, 6.99). Vesico-ureteric reflux is present in 85% of patients with coarse scarred kidneys and 35% of children with symptomatic UTIs.

Reimplantation of the ureters to correct reflux and long-term antibiotic prophylaxis to prevent infection have been the main interventions utilized to try to prevent development of chronic pyelonephritis in children, but studies have shown no proven benefit from operative treatment of reflux when compared with antibiotic prophylaxis alone. Surgery to correct reflux is therefore now reserved for patients who have urinary infection despite antibiotic prophylaxis. Further renal scarring is unlikely after 7 years of age, so children with vesico-ureteric reflux and UTIs are often treated with prophylactic antibiotics until they reach this age and are encouraged to keep up a liberal fluid intake and practise double voiding.

Chronic pyelonephritis may be unilateral or bilateral and the characteristic appearance on IVU is clubbing of the calyces with overlying cortical scars, most commonly in the upper poles but ultimately generalized (6.15, 6.100). Scarring of the renal outline may also be demonstrated by DMSA isotope scan, and unilateral scarring is not uncommon (6.23). Chronic pyelonephritis may be detected during the investigation of patients with nonspecific ill health, recurrent UTIs, hypertension or CRF. End-stage renal failure may develop in patients with bilateral renal scarring (6.34), even when hypertension is treated and further UTI prevented.

Renal tuberculosis is uncommon, but should be considered in all patients with sterile pyuria. The most common symptoms are fever, dysuria, haematuria, weight loss and general malaise (see p. 43 for a general account of tuberculosis). At least three early-morning urine samples should be sent for culture of Mycobacterium tuberculosis and IVU may show calyceal changes (6.101), hydronephrosis, a contracted bladder or calcification at any point in the renal tract (6.102). Treatment with antituberculous drugs should continue for at least 6 months and surgery may be required in some cases to relieve obstruction or to remove a nonfunctioning kidney.
OBSTRUCTIVE UROPATHY

Obstruction to the flow of urine results in increased urinary tract pressure and is a common cause of acute or chronic renal failure. Early relief of obstruction can allow renal function to recover completely, but chronic obstruction may produce cortical atrophy and permanent renal dysfunction. Obstructive uropathy should therefore be excluded promptly in all patients with acute or chronic renal failure of no established cause. Obstruction to urine flow may result from intrinsic or extrinsic mechanical blockade at any level of the urinary tract from the renal calyces to the external urethral meatus. Obstruction at or below the level of the bladder usually produces bilateral dilatation of the ureter (hydro-ureter) and renal pelvis and calyces (hydronephrosis), whereas obstruction may be unilateral if the site of blockage is above the level of the bladder. Mechanical causes of obstruction may be congenital (posterior urethral valves, ureterocele or pelviureteric stricture), acquired intrinsic defects (calculi, tumour, blood clot, sloughed papilla, stricture) or extrinsic defects (retroperitoneal fibrosis, fibroids, retroperitoneal or pelvic tumour). Functional impairment of urinary flow, caused by neurogenic bladder, may also cause obstruction. The most common cause of urinary obstruction in men is benign prostatic hypertrophy (BPH).

Patients with acute obstruction may present with loin or suprapubic pain, renal colic, oliguria or anuria. Chronic obstruction, on the other hand, may progress insidiously, but on direct questioning patients often admit to having polyuria and nocturia as a result of impaired renal concentrating ability. Hesitancy, postvoiding dribbling, urinary frequency and overflow incontinence are common in patients with obstruction at or below the level of the bladder. The possibility of obstructive uropathy should always be considered in patients with unexplained UTI or calculi. Dilatation of the urinary tract may be demonstrated by ultrasound (6.103) and functional obstruction confirmed by DTPA renography (6.24, 6.25). Intravenous urography can be used to demonstrate obstruction anatomically and functionally, provided that the patient does not have significant renal failure (6.16, 6.17), and retrograde pyelography may be needed in some cases (6.104, 6.105).

Treatment depends on the site of obstruction and the underlying cause. The renal prognosis after relief of obstruction depends largely upon the degree of irreversible renal damage that has already occurred. Prerenal failure may develop because of a postobstructive diuresis, which not uncommonly occurs after relief of bilateral diuresis, which not uncommonly occurs after relief of bilateral urinary tract obstruction. Such patients may require intravenous fluids temporarily.

BENIGN PROSTATIC HYPERPLASIA

The most common cause of BPH is benign nodular hyperplasia (BNH) which is an inevitable consequence of ageing in men. Changes in the gland histology start at the age of 40 years.
and progress so that most men have symptoms by the age of 70 years. The diagnosis is made by eliciting a classic history (6.106), by rectal examination that shows an enlarged gland, by the finding of a normal prostate-specific antigen (PSA) and by confirmatory transrectal ultrasound (see also p. 306).

Traditional treatment is surgical, and transurethral prostatectomy (TUR) has largely replaced open prostatectomy. In addition, techniques such as laser ablation, balloon inflation and stent insertion have been attempted. Medical treatment for BPH is also available. Prostatic tissue contains an enzyme, 5α-reductase, that metabolizes testosterone to dihydrotestosterone, a more potent androgen which is implicated in the hypertrophy. Finasteride is a testosterone analogue that blocks production of dihydrotestosterone. This leads to a reduction in gland size and significantly reduces clinical symptoms.

Clinical presentation is often dramatic, with the sudden onset of acute colicky pain resulting from impaction of the stone in the kidney, the ureter, bladder or urethra. There may also be haematuria and obstruction to urine flow. Passage of the stone produces instant relief, but if it obstructs either ureter or urethra it may cause progressive dull back pain. Infection is common (see p. 301) and may produce a pyonephrosis when combined with obstruction.

The diagnosis is usually suggested clinically and is confirmed by a plain X-ray of the abdomen (6.14, 6.108, 6.109, 6.110), an IVU (6.111), ultrasound or retrograde pyelography. Urine should be cultured and examined microscopically for blood. Treatment of the pain is the overriding necessity and an anti-spasmodic may be of value. UTI requires an appropriate antibiotic. Stones less than 5 mm in diameter will usually pass spontaneously. Surgical intervention or lithotripsy may be required for larger stones. In extracorporeal shock wave lithotripsy (ESWL) a shock wave is generated by piezoelectric crystals outside the body and focused on the renal stone(s). Such shocks are administered as short pulses up to 500–2000 times. The stone disintegrates sufficiently for the particles to be passed down the ureter. Stones of any size may be treated.

### CLINICAL FEATURES OF BPH

<table>
<thead>
<tr>
<th>Urinary obstruction</th>
<th>Irritative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor flow and or dribbling</td>
<td>Dysuria</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>Urgency</td>
</tr>
<tr>
<td>Increased frequency</td>
<td>Nocturia</td>
</tr>
<tr>
<td>Impaired bladder emptying</td>
<td></td>
</tr>
</tbody>
</table>

6.106 Clinical features of benign prostatic hypertrophy.

### RENAL CALCULI

Renal calculi are relatively common, affecting 1–5% of the population in the UK; they are more common in warm, dry countries and are composed of a mixture of chemicals, most commonly calcium oxalate alone or in combination with hydroxyapatite or calcium phosphate. Rarely, they may contain only uric acid or cystine. (Uric acid stones are radiolucent.) About 20–40% of patients with calcium-containing stones have hypercalciuria (6.107) and a small number have hypercalcaemia, which should be investigated and treated (see p. 155). In the others, a search should be made for a cause of increased calcium absorption, for example vitamin D intoxication or renal tubular acidosis.

6.107 Causes of hypercalciuria.

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### CAUSES OF HYPERCALCIURIA

- Hyperparathyroidism
- Immobilization
- Bone metastases
- Sarcoidosis
- Distal renal tubular acidosis

6.107 Causes of hypercalciuria.

6.108 A single calculus in the renal pelvis is demonstrated on this plain (KUB) X-ray. The X-ray was performed to investigate an episode of renal colic.

6.109 Large bilateral staghorn calculi are shown on this plain (KUB) X-ray. The patient presented with recurrent urinary infections.
Occasionally staghorn calculi may need to be disintegrated percutaneously before ESWL, as may stones in the lower calyces. Uric acid and cystine stones tend to be harder and more difficult to break down. Ureteric stones in the upper two-thirds of the ureter may also be treated with ESWL. The success rate of ESWL is about 60–70%.

Renal and urinary tract calcification may occur in renal tuberculosis (see p. 302) and in medullary sponge kidney, a condition in which cystic change occurs in the collecting ducts in the renal papillae, with accompanying stone formation. This most commonly presents as haematuria or renal colic, or with UTI. Nephrocalcinosis, the deposition of calcium within the body of the kidneys, may also occur in conditions associated with hypercalcaemia, including sarcoidosis, hyperparathyroidism, myeloma, malignancy and Paget’s disease, and in idiopathic hypercalciuria.

Bladder stones may grow to a massive size before presentation and need to be removed surgically. They may arise from stones formed in the kidneys that have migrated, from foreign bodies in the bladder (e.g. sutures) or from the same biochemical abnormalities as in renal stones.

**RENAL TUMOURS**

Neoplasms may develop at any point in the urinary tract, but they occur most commonly in the kidney or bladder and they should be excluded in all patients presenting with painless macroscopic or microscopic haematuria. Renal cell carcinoma (hypernephroma, adenocarcinoma of kidney) is the most common renal neoplasm and is of tubular epithelial origin. Patients may present with systemic symptoms (weight loss, malaise, fever) or urinary tract symptoms (haematuria, loin pain, abdominal mass), or both. Renal cell carcinoma may be demonstrated by ultrasound, intravenous urography (6.112), abdominal CT scan (6.113) or renal arteriography (6.18). Metastases are common and, once the diagnosis is established, patients should be investigated to evaluate whether pulmonary (4.32), bone (3.160), hepatic (9.59) or cerebral (11.61) metastases are present. The prognosis depends largely upon the extent of tumour involvement at the time of diagnosis. The standard approach to treatment in patients without evidence of metastases is radical nephrectomy; in this group, the survival rate at 5 years approaches 65%. However, many patients have
metastatic disease at the time of diagnosis and have a much poorer prognosis despite treatment with chemotherapy and radiotherapy.

Nephroblastoma (Wilms’ tumour) is the second most common malignant tumour of the kidney and is the most common malignancy of the urinary tract in children, with a peak incidence between the ages of 2 and 4 years (6.114, 6.115). Aggressive treatment with nephrectomy, preoperative or postoperative radiotherapy and postoperative chemotherapy have improved the prognosis and 5-year survival now exceeds 75%.

Neoplasms of the renal pelvis, ureter and bladder, derived from transitional urothelium, are relatively common and often occur or recur at multiple sites in the lower urinary tract. There is an increased incidence of bladder cancer in workers exposed to various aromatic amines employed in chemical, rubber or dye industries. Haematuria is the most common presentation and the site and extent of involvement is usually determined by a combination of cystoscopy (6.27) with biopsy, and intravenous urography (6.20). The prognosis is dependent upon the extent of local invasion and degree of anaplasia at the time of diagnosis. Treatments include cystoscopic removal, cystectomy and local radiotherapy. Patients with urothelial tumours of the renal pelvis or ureter usually require nephro-ureterectomy.

Diffuse infiltration of the kidneys by neoplastic cells in lymphomas or leukemias may result in renal enlargement or renal failure. Retroperitoneal lymphoma may also cause renal failure as a result of bilateral ureteric obstruction.

**PROSTATE CANCER**

Prostate cancer is the fifth most common type of cancer in men in the UK. Its incidence rises with advancing years and it occurs in 1 in 10 in the men living to the age of 70 years. Early clinical features are indistinguishable from those of BPH (see p. 304) and the gland may feel normal on digital examination. The PSA may be elevated (>4 ng/ml). As the tumour grows locally it may produce bladder neck obstruction, obstruct the ureters and rapidly lead to renal impairment. In late disease rectal examination shows the prostate to be large, hard and irregular. Rectal ultrasound may show the spread of the cancer (6.116) and this should also be used for directing needle or aspiration biopsy. Prostatic biopsy is important in giving prognostic information—the prognosis being poorer with poorly differentiated tumours.

Distant spread via lymphatics and blood leads to bony metastases, which are often sclerotic in nature (3.159, 6.117).

Therapy depends on staging. Early disease is treated with local radiotherapy and more advanced disease by orchidectomy and hormone therapy with oestrogen.

It has been suggested that all men over the age of 50 years should be screened by rectal examination, transrectal ultrasound and PSA measurement. However, such techniques may reveal large numbers of patients with small, clinically silent tumours for which optimal management has not been established, so there is continuing debate about the role of screening.
HISTORY, EXAMINATION AND INVESTIGATION

The presentations of endocrine disease are diverse, and the findings in the history and on examination of the patient reflect this. Although multiple endocrine disorders may occur in the same patient, most have abnormalities of a single hormonal system, and the symptoms, signs and necessary investigations relate closely to those abnormalities.

A full history and examination is essential in any patient with a suspected endocrine disorder. Common presentations that should raise the possibility of endocrine disease are listed in 7.1, and 7.2 emphasizes the common importance of aspects of the patient's previous medical and family history.

Necessary investigations depend upon the patient's clinical presentation and may include many different tests on blood and urine and imaging by radiological, nuclear or magnetic resonance techniques.

The diagnosis of endocrine diseases has been advanced by techniques that can measure low concentrations of hormones in body fluid by sensitive radiochemical means. As most hormones are produced in characteristic patterns, it is important to take appropriate samples at the relevant times; for example some hormones have a circadian rhythm with higher levels in the morning. Some hormones, especially the gonadotrophins, are produced intermittently. The pattern of release may vary with sex and with advancing age, with stress, diet and concurrent medication. Urine collections over a 24-hour period are of value for some hormones in measuring total output of the gland and overcoming the problems of rhythmic variations in level.

7.1 Common presenting complaints in endocrine disease.

<table>
<thead>
<tr>
<th>COMMON PRESENTING COMPLAINTS IN ENDOCRINE DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body size and shape</strong></td>
</tr>
<tr>
<td>Short stature</td>
</tr>
<tr>
<td>Tall stature</td>
</tr>
<tr>
<td>Excessive weight or weight gain</td>
</tr>
<tr>
<td>Loss of weight</td>
</tr>
<tr>
<td><strong>Metabolic effects</strong></td>
</tr>
<tr>
<td>Tiredness</td>
</tr>
<tr>
<td>Weakness</td>
</tr>
<tr>
<td>Increased appetite</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Polydipsia or thirst</td>
</tr>
<tr>
<td>Polyuria or nocturia</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Palpitation</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td><strong>Local effects</strong></td>
</tr>
<tr>
<td>Swelling in the neck</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Bone or muscle pain</td>
</tr>
<tr>
<td>Protrusion of eyes</td>
</tr>
<tr>
<td>Visual loss (acuity or fields, or both)</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td><strong>Reproduction or sex</strong></td>
</tr>
<tr>
<td>Loss or absence of libido</td>
</tr>
<tr>
<td>Impotence</td>
</tr>
<tr>
<td>Oligomenorrhoea or amenorrhoea</td>
</tr>
<tr>
<td>Subfertility</td>
</tr>
<tr>
<td>Galactorrhoea</td>
</tr>
<tr>
<td>Gynaecomastia</td>
</tr>
<tr>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Precocious puberty</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>Hirsutes</td>
</tr>
<tr>
<td>Hair thinning</td>
</tr>
<tr>
<td>Pigmentation</td>
</tr>
<tr>
<td>Dry skin</td>
</tr>
<tr>
<td>Excess sweating</td>
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</tbody>
</table>

7.2 Endocrine disease - past and family histories.

<table>
<thead>
<tr>
<th>ENDOCRINE DISEASE - PAST AND FAMILY HISTORIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous medical history</strong></td>
</tr>
<tr>
<td>Previous pregnancies (ease of conception, postpartum haemorrhage)</td>
</tr>
<tr>
<td>Relevant surgery (e.g. thyroidectomy, orchidopexy)</td>
</tr>
<tr>
<td>Radiation (e.g. to neck, gonads, thyroid)</td>
</tr>
<tr>
<td>Drug exposure (e.g. chemotherapy, sex hormones, oral contraceptives)</td>
</tr>
<tr>
<td>In utero, complications of pregnancy</td>
</tr>
<tr>
<td>At birth, weight and length</td>
</tr>
<tr>
<td>In childhood, developmental milestones</td>
</tr>
</tbody>
</table>

| **Family history**                             |
| Family history of:                            |
| Autoimmune disease                            |
| Endocrine disease                             |
| Essential hypertension                        |

| **Family details of:**                         |
| Height                                         |
| Weight                                         |
| Body habitus                                   |
| Hair growth                                     |
| Age of sexual development                     |

7.2 Endocrine disease - past and family histories.
In addition to these static tests, it is often important to determine the response of a gland to stimulation and suppression.

- Stimulation tests assess the ability of the gland to increase its hormonal output; the response is diminished if the cells are structurally or functionally damaged.
- Suppression tests use the administration of purified hormone to test the negative feedback loop; hormone production is normally suppressed in these tests, but persists if there is autonomy or a functional endocrine tumour.

Although isolated endocrine abnormalities are common, many are potentially related to abnormalities of the hypothalamic–pituitary axis, so initial investigations may lead on to a need for further tests.

### DISORDERS OF THE PITUITARY AND HYPOTHALAMUS

The pituitary gland consists of an anterior and a posterior lobe. It lies at the base of the brain, in the sella turcica, within the sphenoid bone, and has a close anatomical and physiological relationship to the hypothalamus. Its anatomical relationship to the optic chiasma is important, as pituitary tumours often affect the visual fields. The hypothalamus has a major role in integrating and coordinating pituitary function, body temperature, water, mineral and calorie balance, and sexual and reproductive behaviour. This is achieved through the hypothalamo–hypophyseal portal system. The hypothalamus controls the secretion of the anterior pituitary hormones by secreting a number of regulatory factors (releasing or inhibitory hormones).

The posterior pituitary also functionally includes various hypothalamic areas. Oxytocin is released here. Antidiuretic hormone (ADH) is secreted by the supra-optic and paraventricular nuclei; it passes down the neurohypophyseal tract to be linked with neurophysin and is stored in the posterior lobe, from which it is secreted into the general circulation.

Pituitary lesions may declare themselves by

- Local space-occupying effects
- Hypopituitarism
- Hypersecretion of a pituitary hormone
- An incidental radiological finding.

Both neuroradiological and endocrinological investigations are important in diagnosis and management.

Dynamic tests of pituitary hormonal reserve are summarized in 7.3.

Space-occupying effects are caused by large tumours that commonly grow upwards, compressing the optic chiasma, which is only 1 cm above the pituitary fossa (see also p. 491). The most common visual defects are a bitemporal upper quadrantic defect or a hemianopia (11.7). The patient may not notice the deterioration in eyesight until the central fields are affected. Expansion of the pituitary fossa is seen on a lateral skull radiograph in 90% of patients. Other important features are thinning and undercutting of the anterior and posterior clinoid processes and asymmetry of the fossa floor (7.4, 7.5). The extent of a pituitary tumour can be demonstrated by CT scan (7.6) or by MRI (7.7, 7.8).

Less common effects of growth outside the pituitary fossa include

- Diplopia (cranial nerve palsies with extra-ocular muscle dysfunction, 7.9, 11.14).
- Papilloedema (7.10) from raised intracranial pressure is very rare, as is optic atrophy from long-standing suprasellar extension with compression of the optic pathways (7.11).
- Personality changes, focal hemispheric neurological signs and epilepsy.
- Pituitary apoplexy (acute enlargement of a tumour caused by haemorrhagic infarction), resulting in depressed consciousness, sudden loss of vision, other focal signs and often meningism.

### DYNAMIC TESTS OF PITUITARY HORMONAL RESERVE

<table>
<thead>
<tr>
<th>Stimulation tests</th>
<th>Hormones stimulated</th>
<th>Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin hypoglaemia</td>
<td>ACTH, GH</td>
<td>ACTH, GH, cortisol</td>
</tr>
<tr>
<td>Glucagon</td>
<td>ACTH, GH</td>
<td>ACTH, GH, blood glucose</td>
</tr>
<tr>
<td>Thyrotrophin-releasing hormone (TRH)</td>
<td>TSH</td>
<td>TSH, T3, T4, prolactin, GH</td>
</tr>
<tr>
<td>Gonadotrophin-releasing hormone (GnRH)</td>
<td>LH, FSH</td>
<td>FSH, LH, spermatogenesis, ovulation, GH</td>
</tr>
<tr>
<td>Growth hormone-releasing hormone (GHRH)</td>
<td>GH</td>
<td>GH</td>
</tr>
<tr>
<td>Corticotrophin-releasing hormone (CRH)</td>
<td>ACTH</td>
<td>ACTH, cortisol</td>
</tr>
<tr>
<td>Fluid deprivation/desmopressin</td>
<td>ADH</td>
<td>Urine/plasma osmolality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suppression tests</th>
<th>Hormones suppressed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin (GHRH)</td>
<td>GH, TSH, insulin, glucagon, gastrin, VIP</td>
<td></td>
</tr>
<tr>
<td>(analogue is octreotide)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 7.3 Dynamic tests of pituitary hormonal reserve.

#### 7.4 Enlargement of the pituitary fossa resulting from a chromophobe adenoma. The patient had a 3-year history of headache and a bitemporal visual field defect, but no clinical features of pituitary dysfunction.
7.5 Pituitary fossa enlargement with a double floor (arrowed) on lateral X-ray. The enlargement is less marked than in 7.4, but the double floor is typical. This patient had an acidophil tumour, with symptoms and signs of acromegaly.

7.6 CT scan demonstrating a pituitary tumour with suprasellar extension (arrowed). This transverse cut shows the size and position of the tumour at a level at which pituitary tissue would not normally be seen.

7.7 & 7.8 Pituitary macroadenoma. A large tumour is demonstrated on sagittal and coronal T1-weighted MR images. Areas of high signal represent patchy haemorrhage. The tumour extends above the sella, distorting the optic chiasma, and laterally into the right cavernous sinus.

7.9 Sixth nerve palsy with lack of abduction of the right eye in a patient with a pituitary tumour. Invasion of the cavernous sinus by a pituitary tumour usually affects the sixth nerve first, because it is more medial than the third and fourth cranial nerves.

7.10 Early papilloedema in a patient with a pituitary tumour. There is hyperaemia of the optic disc, with blurring of the inferonasal margin. Papilloedema is a rare complication of pituitary tumours.

7.11 Optic atrophy in a patient with acromegaly. The flat, pale optic disc has a well defined margin and the appearance of 'primary' optic atrophy. This type of optic atrophy results from compression of the optic pathways by the tumour, and is not a consequence of long-term papilloedema.
HYPOPITUITARISM

Most lesions of the pituitary cause destruction of the anterior pituitary or the hypothalamus. The pattern of deficiencies depends on the nature of the lesion and its rate of progress. The clinical picture depends on the cause, the pattern of hormone loss and local effects of the pathology within the sella. Postpartum pituitary necrosis (Sheehan’s syndrome, 7.12, 7.13, 7.14) was formerly the most common cause, but with improved obstetric practice this is now much less common. The main causes are peripituitary tumours, that is chromophobe adenomas in adults and craniopharyngiomas in children, and iatrogenic hypopituitarism after surgical or radiotherapeutic damage. Trauma, infection and infiltration in sarcoidosis, histiocytosis X and haemochromatosis are other rare causes.

Partial degrees of pituitary damage can occur, but symptoms are uncommon before at least 70% of the gland is destroyed.

The development of hypopituitarism often results in a progressive loss of function, starting with growth hormone (GH): this is important in children but probably not in adults. Gonadotrophin failure — initially luteinizing hormone (LH) then follicle-stimulating hormone (FSH) — also occurs early and impotence in the male and amenorrhoea in the female are common symptoms. The clinical features in adults include fine wrinkling of the skin around the mouth with loss of facial and body hair (7.12), and atrophy of the genitalia in both sexes (7.15). In childhood, gonadotrophin failure leads to delayed puberty and short stature (7.16). Isolated gonadotrophin deficiency associated with anosmia is seen in Kallman’s syndrome (discussed later).
Next to be lost is adrenocorticotrophic hormone (ACTH). The features of this deficiency are asthenia, nausea, vomiting, postural hypotension, hypoglycaemia, collapse and coma, pallor of the skin and reduced sun-tanning ability. Thyroid-stimulating hormone (TSH) is eventually lost, giving rise to features similar to those seen in primary hypothyroidism, although the skin is not dry and coarse. In childhood, TSH deficiency contributes to growth retardation. Finally, in large tumours, vasopressin production may be lost, leading to polyuria and polydipsia as patients are unable to concentrate their urine and they may pass 5–20 litres of dilute urine per day. Prolactin deficiency causes failure of lactation. A more common effect in hypopituitarism is hyperprolactinaemia, which occurs if a tumour prevents the prolactin inhibitor, dopamine, from reaching the pituitary by stalk compression.

Cranial diabetes insipidus (CDI) occurs uncommonly in pituitary disease and results from ADH (vasopressin) deficiency (or rarely, renal resistance to the hormone occurs in the nephrogenic form, NDI). It is most frequently associated with craniopharyngioma, which may cause destruction of the posterior pituitary. There may be other hypothalamic disturbances, such as sleep disorders, hyperphagia, disturbed thermoregulation and emotional lability. The main investigation is the water deprivation test. Treatment is with desmopressin by intranasal spray.

Pituitary hypofunction can be confirmed by ‘basal’ blood samples for cortisol, thyroxine, testosterone or oestriadiol, and pituitary hormones, followed by a pituitary stress test.

Treatment of panhypopituitarism is by hormone replacement. GH is replaced by biosynthetic (recombinant) GH therapy during childhood (its use in adults is under investigation). Cortisol is normally replaced by hydrocortisone, given in the morning and evening to mimic the normal diurnal pattern. Thyroxine and either testosterone or oestrogen, usually with progestogen, are prescribed to restore libido and prevent osteoporosis.

### DISEASES ASSOCIATED WITH HYPERSECRETION OF PITUITARY HORMONES

#### Acromegaly and gigantism

The excessive secretion of GH is almost invariably caused by a pituitary tumour. If this occurs before fusion of the epiphyses, it leads to gigantism (7.17); after fusion, it produces the features of acromegaly.

Acromegaly is an uncommon condition with a prevalence of approximately three new cases/million people per year. Some patients with multiple endocrine adenomatosis (MEA Type 1) may present this way. Some tumours are mixed and produce both prolactin or TSH and GH. The disease should be suspected on the finding of clinical features that include thickening of the soft tissues and skin, broadening of the nose, increased prominence of supraorbital and nuchal ridges, and prognathism, which leads to separation of the teeth (7.18–7.20).
Excessive sweating and acne (7.18) are common symptoms of acromegaly, and on examination large 'spade-like' hands are obvious (7.21, 7.22). There is enlargement of the tongue (7.23) and all other viscera such as liver and spleen. Cardiomegaly, heart failure (7.24) and malignancy are major causes of death.

Diagnosis is based on demonstrating that GH is not suppressed during an oral glucose tolerance test. Imaging by X-ray (7.4, 7.5), CT (7.6) and MRI (7.7, 7.8) defines the size and local impact of the pituitary adenoma.

Treatment is often difficult. Surgical removal of the tumour (trans-sphenoidal route) may reverse the disease, but complete removal without recurrence is rare and external radiotherapy to the pituitary fossa is indicated postoperatively. Radiotherapy alone leads to only a slow clinical improvement, causing GH to fall over 1–10 years. Surgery with or without radiotherapy often causes hypopituitarism; this should always be assessed and treated accordingly. Medical treatment is less effective in long-term management. Dopaminergic compounds lower GH in acromegaly, and 75% of acromegalic patients respond to bromocriptine. Somatostatin lowers GH; although its action is too brief to be therapeutically useful, synthetic analogues have been developed that are long-acting and appear to offer a therapeutic option.

7.21 Spade-like hands are often an obvious abnormality in acromegaly. Compare the acromegalic hands on the right with the normal hand on the left. Overgrowth of the soft tissues may also cause compression of the median nerve at the wrist (carpal tunnel syndrome – see p. 515).

7.23 Enlargement of the tongue in acromegaly is obvious in this patient, who also shows other facial signs, and has classic changes in her hands.

7.24 Acromegaly. The chest X-ray shows generalized cardiac enlargement (cardiothoracic ratio >50%). Heart failure is a major cause of morbidity and mortality in acromegaly.
Hyperprolactinaemia

Sleep, stress, nipple stimulation, coitus, pregnancy and suckling are all associated with physiological elevation of circulating prolactin levels. Hyperprolactinaemia is associated with hypogonadism, either from pathological, physiological or iatrogenic causes. Therefore, the woman who breast feeds is often infertile and amenorrhoeic, and patients on drugs that raise prolactin may have infrequent periods (in women) or impotence (in men). Hyperprolactinaemia in childhood may lead to delayed onset of puberty. Pituitary tumours secreting prolactin are four times more common than GH-producing tumours, and very much more common than those producing ACTH. Some non-functioning tumours may produce moderate elevations in prolactin by pituitary stalk compression. There are no specific signs of hyperprolactinaemia except hypogonadism, although galactorrhoea (inappropriate lactation; 7.25) should always arouse suspicion. It should always be remembered, however, that galactorrhoea may result from other causes, especially from malignant tumours producing prolactin or oestrogen, or from drug therapy with phenothiazines, antidepressants, haloperidol, methyldopa, metoclopramide or oral contraceptives.

Prolactinomas are usually microadenomas in women and macroadenomas in men. Clinical features are related to tumour size and function. In women the clinical features relate mainly to excess production of prolactin, which causes amenorrhoea, infertility and hirsutism. In men excess prolactin causes galactorrhoea, loss of libido and impotence, and with larger tumours there may be headache, visual field defects and nerve palsies. Similar pressure-related features may develop in women during pregnancy, at which time microadenomas often enlarge markedly.

Diagnosis of a prolactinoma is made from elevated prolactin levels above 4000 mU/litre (upper limit of normal on most assays is 360 mU/litre). Smaller tumours give lower levels. CT or MRI may show the presence of an adenoma (7.26), and it is important to note that these may undergo considerable expansion during pregnancy.

Treatment by a long-acting dopamine agonist such as bromocriptine will inhibit prolactin production and produce shrinkage of 80% of tumours, thus relieving pressure symptoms particularly on the optic chiasma. Fertility is regained and, although the drug is not teratogenic, once pregnancy has been established it is usually stopped; visual fields must be monitored regularly. Patients with macroadenomas are best advised to have surgery or radiotherapy at least 3 months before attempts at conception, as these tumours may expand rapidly during pregnancy.

Cushing’s syndrome

The term Cushing’s syndrome is often used to describe the combination of symptoms and signs which results from persistent elevation of circulating glucocorticosteroid levels. The most common cause of Cushing’s syndrome is prolonged therapy with systemic glucocorticosteroids. The term Cushing’s disease is used to describe patients in whom the syndrome results from excessive ACTH production by the pituitary; this is the most common cause of spontaneous Cushing’s syndrome (60%). Other causes are ectopic ACTH production (15%), adrenal adenomata (15%) and carcinomata (10%). Cushing’s disease is usually caused by a basophilic pituitary microadenoma (90%) and occurs more frequently in women, with a female : male sex ratio of approximately 10:1.
The clinical features of the syndrome that are of greatest discriminatory importance include thinning of the skin, easy bruising and bright purple striae (7.27-7.30), proximal muscle weakness and myopathy (7.30), facial plethora (6.46, 7.31), hirsutism (7.31, see also p. 108), acne and loss of scalp hair. Weight gain and obesity are the most common presenting features. The distribution of fat is central, involving the trunk and abdomen (7.32, 7.33). This, together with the kyphosis that is often caused by osteoporosis (see p. 152), results in a ‘buffalo hump’, with a ‘moon face’ and relatively thin limbs.

7.27 Cushing’s syndrome is associated with typical thin skin and fragile blood vessels. Bruising commonly results from very minor trauma.

7.29 Cushing’s syndrome. This patient has typical purple striae on the breast and arm, associated with thinning of the skin.

7.31 The typical facial features of Cushing’s syndrome. The patient has a moon face with erythema and hirsutes. Identical appearances may result from corticosteroid therapy (see 6.46).

7.28 Thin, fragile skin in Cushing’s syndrome and blood vessel fragility has resulted in extensive purpura.

7.30 Proximal muscle wasting is common in Cushing’s syndrome and leads to great difficulty in rising from the sitting position. Note the presence of striae on both thighs.

7.32 & 7.33 Cushing’s syndrome results in central rather than peripheral obesity. This patient also has typical facial features and a ‘buffalo hump’.
Pigmentation may occur, but this is more common in ectopic ACTH production (from a malignant bronchial tumour, for example) or in Nelson’s syndrome, in which ACTH levels are very high. Nelson’s syndrome may follow bilateral adrenalectomy for Cushing’s disease if excessive ACTH production continues (7.34); expansion of the pituitary fossa may occur. Pigmentation is most marked in areas exposed to sunlight and friction, and in scars. Psychiatric symptoms, hypertension, glucose intolerance, diabetes and gonadal dysfunction (oligomenorrhea and impotence) are all common.

Adrenal tumours may secrete cortisol and cause classic Cushing’s syndrome. However, the concomitant secretion of adrenal androgens may cause more virilization, particularly in the case of carcinomas. Ectopic ACTH from highly malignant tumours causes gross elevations of cortisol; patients may present with fewer classic signs but with an illness of rapid onset with weight loss, profound proximal myopathy, pigmentation and a severe hypokalaemic alkalosis. Carcinoid tumours and other relatively benign sources of ectopic ACTH are clinically indistinguishable from other causes of Cushing’s syndrome.

Diagnosis of Cushing’s syndrome can be made by the detection of increased 24-hour urinary free-cortisol, by the loss of the normal circadian rhythm of cortisol at 24.00 hours or by use of a 48-hour low-dose dexamethasone suppression test. The differentiation between adrenal tumour, pituitary Cushing’s disease and ectopic ACTH needs to be made with care. If plasma ACTH is consistently undetectable, the condition is usually caused by an adrenal tumour. Diagnosis is established by ultrasound or CT scan of the adrenals (7.35) and carcinomas often show local invasion. Patients with adrenal tumours also show no suppression of serum cortisol with high-dose dexamethasone, and no response to the CRH test.

Plasma cortisol and ACTH are often grossly elevated in malignant tumours. Plasma potassium is almost always subnormal in patients with ectopic ACTH, so a hypokalaemic alkalosis is a pointer to this diagnosis. The high-dose dexamethasone suppression test is valuable in about 80% of cases. Patients with pituitary-dependent Cushing’s disease show significant suppression of their cortisol to less than 50% of the basal value at 48 hours, whereas those with adrenal tumours and ectopic ACTH do not show cortisol suppression. Some ectopic tumours behave as though there were a pituitary-dependent cause, but significant suppression is associated with a high probability (>50:1) that the condition is Cushing’s disease. The CRF test provides further help in the differentiation.

Chest X-rays may reveal a bronchial carcinoma (see p. 207), and CT scans of the pituitary in Cushing’s disease may be helpful, as may scans of the lung fields, mediastinum, liver, pancreas and adrenals for detecting small carcinoids.

The treatment of choice for adrenal tumours is surgery, but metyrapone or mitotane may be necessary to achieve a clinical remission preoperatively. In Cushing’s disease, trans-sphenoidal surgery is the treatment of choice, achieving a biochemical cure in 75% of cases. Pituitary irradiation is now restricted to cases in which surgery has been unsuccessful and, as it takes several years to be effective, it needs to be combined with medical therapy. Ectopic ACTH production should be treated by eradicating the source if possible; bilateral adrenalectomy is an alternative, but is now rarely used, as the loss of feedback results in pigmentation and the development of pituitary adenomas in 20% of patients. If used, bilateral adrenalectomy should be combined with pituitary irradiation.

Overproduction of other pituitary hormones

Tumours that secrete TSH and produce hyperthyroidism are rare. Most tumours that secrete gonadotrophins are large, and they often do not produce a clinical syndrome (especially in menopausal women), although testicular enlargement in men has been described. Some tumours secrete the biologically inactive alpha subunit that is common to FSH, LH and TSH. About 30% of all pituitary tumours are nonfunctioning.
ENDOCRINE, METABOLIC AND NUTRITIONAL

DISORDERS OF THE ADRENAL GLANDS

The adrenal glands are made up of cortex and medulla, which have separate embryological origins and different physiological functions.

ADRENAL CORTEX

The cortex secretes glucocorticoids, mineralocorticoids and androgens.

Glucocorticoid-related disorders

- Glucocorticoid excess causes Cushing's syndrome (see p. 313)
- Primary adrenocorticoid insufficiency or Addison's disease is very uncommon and is usually caused by an autoimmune process or, more rarely, by destruction of the cells by tuberculosis, other granulomatous disease, or infiltration by metastases
- Acute adrenal failure follows withdrawal of suppressive doses of systemic steroids or haemorrhage into the gland in the Waterhouse-Friderichsen syndrome or during anticoagulant therapy.

The main clinical features of hypoadrenalism include tiredness, weight loss, gastrointestinal disturbances, hypoglycaemia and depression. The loss of negative feedback on the pituitary causes massive elevation in ACTH production with associated pigmentation. This is particularly seen in skin folds, areas of friction, light-exposed areas, the buccal mucosa and often in scars (7.36-7.41). Aldosterone deficiency results in muscle cramps, dehydration and postural hypotension with the

7.36 A patient with Addison's disease. Note the generalized increase in pigmentation, especially marked over the extensor surface of the knees.

7.37 Facial appearance in Addison's disease. Note the generalized increase in pigmentation.

7.39 Addison's disease produces a similar increase in skin pigmentation in the skin creases of the palmar surface of the hands.

7.40 Buccal pigmentation in Addison's disease. There is a fairly general increase in mucous membrane pigmentation, and, in addition, there are some areas of much darker pigmentation. Both features are commonly seen in patients with Addison's disease.

7.38 Addison's disease produces a generalized pigmentation of the hands, which - on the extensor surfaces - is often most marked over the knuckles.
classic electrolyte disturbances of low serum levels of sodium and glucose and high potassium and urea. Androgen deficiency may lead to hair loss from the scalp and axillary and pubic regions in women. Associated vitiligo (see p. 105) may produce a striking contrast to the hyperpigmentation seen in other areas. The diagnosis is established by the short Synacthen test. Other investigations may reveal the underlying cause, for example adrenal autoantibodies or adrenal calcification may be found (7.42).

Acute adrenal crisis in Addison's disease may be precipitated by infection or stress such as trauma or a surgical operation. Treatment in the acute crisis is intravenous hydrocortisone and 0.9% saline, with the addition of dextrose if hypoglycaemia is present. Long-term replacement is by oral hydrocortisone and fludrocortisone, and the dose should be increased at times of physiological or pathological stress.

Synthesis of adrenal steroids is dependent on a number of enzymatically regulated stages. Congenital deficiencies exist in six specific enzymes that can lead to congenital adrenal hyperplasias. The clinical features depend on where the block occurs, as biosynthesis is diverted down alternative metabolic pathways with effects predominantly on sexual development, or on mineralocorticoid or glucocorticoid balance.

**Mineralocorticoid-related disorders**
Primary aldosteronism is caused by an adrenal adenoma (Conn's syndrome) in 70% of cases. In the remaining 30% there is bilateral adrenal hyperplasia. Patients present with hypertension and hypokalaemia (<3.5 mmol/litre) (7.43) and few if any symptoms. The characteristic biochemistry is a hypokalaemic alkalosis with a plasma sodium of 140–150 mmol/litre, increased plasma aldosterone, suppressed plasma renin activity and an inappropriately high urinary potassium excretion. Differentiation between adenomas and hyperplasia is based on the effects of salt loading with fludrocortisone, adrenal CT scans (7.44), iodocholesterol radionuclide scanning and adrenal venous sampling. Treatment of adenomas should be surgical: 60% of patients are cured of hypertension postoperatively and a further 20% improved. In hyperplasia, the treatment of choice is spironolactone or amiloride.
ADRENAL MEDULLA

Most phaeochromocytomas (80–90%) are found in the adrenal glands; 10% are malignant and 25% multiple. Their characteristic symptoms relate to catecholamine release. Symptoms include sustained or intermittent hypertension, tachycardia, palpitations and paroxysmal attacks of blanching and sweating. Diabetes and neuroectodermal diseases, such as neurofibromatosis, are commonly associated. Diagnosis is based on clinical suspicion and the measurement of urinary metabolites of catecholamines such as vanillylmandelic acid. The tumour may be localized by selective venous sampling of catecholamines or by scanning techniques, or both. Usually the tumours are large and can be localized by CT scan (appearance similar to the right adrenal in 7.35), ultrasound (7.45), radioisotope scanning (7.46) and MRI (7.47, 7.48). Treatment should be surgical removal with preoperative alpha and beta blockade.

7.45, 7.46, 7.47, 7.48 Four images of a right-sided phaeochromocytoma in the same patient, a 52-year-old man who presented with labile hypertension. 7.45 shows the initial ultrasound identification of the adrenal tumour, which was found to have a maximum diameter of 3.72 cm (RK = right kidney). 7.46 is a radioisotope scan with MIBG (metaiodobenzylguanidine), which is taken up by the neuronal uptake system in the adrenal medulla and other tissues with rich sympathetic innervation, as it is structurally related to noradrenaline. Some MIBG can also be seen in the liver and the bladder. 7.47 is an MR image, showing the close relationship of the adrenal phaeochromocytoma (arrowed) to the right kidney. 7.48 is a coronal turboflash MR image, in which the tumour is clearly seen as a bright circular abnormality, adjacent to the liver.
MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

Multiple endocrine neoplasia syndromes (MEN1-3) are characterized by multiple endocrine hyperfunction due to hyperplasia, adenomas or carcinomas.

MEN-1 (Wermer's syndrome) is the familial occurrence of tumours of the anterior pituitary, parathyroid glands and pancreatic islet cells. This is associated with an increased incidence of peptic ulcer. There may also be hyperfunction of the adrenal and thyroid. Clinical features often become apparent in middle age - most patients presenting with hypercalcaemia, peptic ulcer, hypoglycaemia or pituitary dysfunction. Because of genetic transmission (autosomal dominant), first and second degree relatives should also be investigated when the diagnosis is made.

MEN-2 (Sipple's syndrome) is characterized by medullary carcinoma of the thyroid, phaeochromocytoma, and parathyroid hyperplasia. In addition, there is an associated incidence of glial tumours and meningiomas. Clinical presentation is protean and the difficulty in diagnosis is compounded by the secretion of a range of other biologically active substances and hormones that are not produced by the normal tissues - these include ACTH, prolactin, serotonin, prostanoids, and vasoactive intestinal peptides. First and second degree family members should be screened.

MEN-3 (mucosal neuroma syndrome) is similar to MEN-2 but there may also be neuromas of the lips, tongue and buccal mucosa, and neurofibromata with café-au-lait spots on the skin. These patients tend to be tall and thin and may be mistaken for patients with Marfan's syndrome.

Management of patients with MEN must be directed to the tumour(s) causing significant clinical problems.

DISORDERS OF GROWTH AND SEXUAL DEVELOPMENT

Growth assessment is an accurate and sensitive guide to child health. Growth velocity represents the dynamics of growth much better than a single measurement of stature. A healthy, adequately nourished and emotionally secure child grows normally. A slowly growing child has a disorder requiring diagnosis and, if possible, treatment.

Growth charts relating height to age are used to indicate the rate of growth in comparison with a reference population (7.49). From the fifth month of fetal life, rapid growth begins to decelerate markedly over 3-4 years; there is a slight acceleration at 6-8 years, the midchildhood growth spurt, and a pubertal growth spurt. There is a 4-year difference between when the earliest and latest 3% of normal children enter puberty. Abnormal height cannot be defined absolutely, but a child is usually considered abnormally short if height is below the 3rd centile, or too tall if above the 97th centile. Skeletal maturity is assessed by computing the maturation of bones in the wrist. This may be useful in predicting final height and puberty timing. Final height is also contributed to by the child's parents: 95% of the children of given parents will have a height prognosis within approximately 8.5 cm of the midparental centile.

SHORT STATURE

Short stature is a diagnostic challenge. A small child with normal growth velocity will be expected to achieve a normal final height, but may have growth delay, previous poor growth as a result of illness or short parents. Children with impaired growth velocity require careful examination for underlying disorders. Investigations include urinalysis, blood count, ESR, chromosome analysis, bone age and endocrine status - particularly GH, thyroxine and TSH, and sex steroids.

7.49 A growth chart, showing the normal age percentiles for boys aged from 2 to 18 years. The growth of an individual child should be plotted on such a chart and response to therapy can be monitored in the same way. Superimposed on the percentile chart is the growth chart of a child with severe asthma. When first diagnosed the child was on the 10th centile (A). His uncontrolled asthma was subsequently treated with a prolonged course of oral prednisolone therapy, during which his growth was significantly impaired (B). Later he was weaned onto inhaled steroid therapy while maintaining control of his asthma (C). At this stage catch-up growth was seen, and he reached the 50th centile.
It is convenient to separate short children into those with normal proportions and those with abnormal proportions. Those with normal proportions form the largest group. There is a wide variety of causes of short stature.

- Any cause of intrauterine growth retardation and low birth weight leads to short stature.
- Numerous rare congenital syndromes lead to poor growth; these include the Silver–Russell syndrome (triangular facies, clinodactyly, facial and limb length asymmetry), the Prader–Willi syndrome, Cornelia de Lange syndrome, progeria, Hallermann–Streiff syndrome, Seckel's syndrome, Ollier's disease, Aarskog's syndrome, Williams' syndrome and the mucopolysaccharidoses (see p. 352).
- Nutritional and emotional deprivation leads to short growth as does systemic disease.
- GH deficiency may be congenital or acquired; it leads to short, plump children with immature facies and genitalia, and delicate extremities (7.50).
- Hypothyroidism should always be considered; the earlier the onset, the more severe the delay in growth, particularly in skeletal maturity.
- Cushing's syndrome delays growth, particularly when associated with precocious puberty.

The 'fat' short child is likely to have an endocrine cause for his short stature and obesity. The underlying endocrine condition should be treated and the growth response will be a good sign of clinical response. In GH deficiency, treatment with recombinant GH should continue throughout puberty.

Studies are under way to determine the benefits of accelerating the growth in 'short normal' children and in children with Turner's syndrome and Noonan's syndrome. Turner's syndrome (karyotype 45X0) and its many chromosomal variants (e.g. XO/XY mosaic in Noonan's syndrome) are always associated with impaired sexual development and short stature (7.51, 7.52). The combination of sex steroids and GH appears to increase the final height slightly.

Of the causes of short stature with abnormal proportions, achondroplasia, an autosomal dominant condition, is the most familiar with a frequency of 1 in 40,000 births (7.53, 7.54). There are many other forms of short limb and short trunk dwarfism.

TALL STATURE

Tall stature is a much less common problem than short stature.

- Gigantism caused by GH excess precedes acromegaly and is investigated and treated as described on p. 308.
- Marfan's syndrome is a relatively common inherited cause of tall stature (see p. 150).
- Rarer causes include generalized lipodystrophy, Soto's syndrome and eunuchoidism.
At puberty, the growth of genitalia accelerates, secondary sexual characteristics develop and there is a general growth spurt. These changes are induced by pulsatile secretion of gonadotrophin-releasing hormone (GnRH) which augments pituitary gonadotrophin output and promotes gonadal maturation and steroidogenesis.

Pubertal onset varies widely in different parts of the world, but in the UK the mean age of onset is 11.5 years for boys, and 10.5 years for girls with menarche occurring 2 years later. Delayed puberty in the UK for a boy is defined as a testicular volume below 4 ml by 14 years old, and for girls no breast development by 13.2 years of age. The most common cause is constitutional delayed puberty (‘late developers’).

The clinical features of hypogonadism depend on whether androgen secretion is impaired, and on the age of onset of the deficiency.

- With fetal onset, differentiation of the external genitalia along male lines is androgen dependent within the first trimester of gestation; if testosterone fails to act, pseudohermaphroditism occurs, as is seen in testicular feminization syndrome in which XY males have an X-linked deficiency of androgen receptors (7.55); the testes, which may be found in the labia or inguinal canals, are hyperactive, producing high levels of testosterone and oestrogens; as negative feedback is ineffective, the LH levels are high; in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, the female child presents at birth with ambiguous genitalia, clitoral hypertrophy and partial or complete fusion of the labioscrotal folds (7.56) caused by the excess of androgenic cortisol precursors produced.
- Prepubertal onset of androgen deficiency leads to eunuchoidism as in Kallman’s syndrome (hypogonadal hypogonadism, GnRH deficiency, anosmia, colour blindness, midline facial deformities) and Klinefelter’s syndrome (7.57).
Diagnosis of hypogonadal states requires evaluation of visual fields and detection of anosmia, chromosome analysis, measurement of testosterone or oestradiol, LH and FSH. Stimulation tests with GnRH or clomiphene and pituitary stress testing may be required. Treatment depends on cause; primary gonadal failure requires either cyclical oral oestrogen and progesterone preparations or intramuscular testosterone every month. This treatment will produce secondary sexual characteristics and prevent osteoporosis, but fertility can be produced only in secondary gonadal failure by the complex administration of human chorionic gonadotrophin (HCG), FSH or pulsatile GnRH in hypothalamic lesions.

Precocious puberty in boys is generally defined as pubertal development before 10 years of age. 40% of cases have no detectable organic disease, but there are rare associations with hypothyroidism, hepatoblastomas and cerebral tumours that affect the hypothalamus. In girls, the definition of precocious puberty is defined as sexual maturation before the age of 8 years; 80% of girls have no detectable organic disease.

Secondary amenorrhea and infertility are common postpubertal presentations of gonadal failure. They may be caused by hypothalamic–pituitary axis disorders (see p. 308–312), and hyperprolactinaemia is common. Weight loss is the underlying cause in 20% of cases, although when severe, as in anorexia nervosa, the gonadotrophin secretion reverts to a prepubertal pattern. Ovarian failure with a premature menopause often has an autoimmune basis and is associated with other autoimmune diseases such as Addison's disease (see p. 316).

Patients with polycystic ovary syndrome (PCO) commonly present in their mid-20s with menstrual irregularity (usually amenorrhoea or oligomenorrhoea), hyperandrogenization (hirsutism, greasy skin and acne (7.58, 7.59), infertility and often obesity. The classic triad of amenorrhoea, obesity and hirsutism, (Stein–Leventhal syndrome) is at the extreme end of the spectrum of clinical presentation. Use of high resolution ultrasound suggests that up to 20% of women have polycystic ovaries but have no features of disease. However, later weight gain may be associated with some of the clinical features of PCO. Typical laboratory findings in PCO are a raised serum LH and slightly raised testosterone with normal FSH, prolactin and TSH. The ovaries contain multiple cysts which are easily detected by pelvic ultrasound (7.60). Other conditions, such as adrenal and ovarian tumours and late onset adrenal hyperplasia, present with virilization (frontal baldness, deepening of the voice, breast atrophy, clitoral hypertrophy and masculine habitus), but in these conditions the testosterone concentration is in the normal male range. Management is of the primary problem, but in PCO hirsutism is treated with oestrogenic oral contraceptives or antiandrogens, such as cyproterone acetate. Regular menstruation or artificially induced bleeding is necessary to prevent endomenstrual hyperplasia. Weight loss is important as an increased body mass index (BMI) is closely correlated with an increased rate of hirsutism, cycle disturbance and infertility and the BMI may be improved by weight reduction. Effective treatment may take 12–18 months, during which time cosmetic treatments, shaving and electrolysis are required. Surgical removal of a wedge of ovarian tissue may be of value and lead to a return of ovulation. Also laparoscopic ovarian diathermy of the cysts may lead to ovulation and a fall in LH levels.
THYROID DISORDERS

The thyroid secretes thyroxine (T4) and a small amount of triiodothyronine (T3). Approximately 85% of the biologically more active circulating triiodothyronine is converted from thyroxine in the tissues (liver, muscle and kidney). The hormones are transported in the plasma almost entirely bound to thyroxine-binding globulin (TGB), prealbumin and albumin. Production is stimulated by TSH in response to thyrotrophin-releasing hormone (TRH), and free thyroxine (FT4) has a negative feedback effect on TSH release. The thyroid parafollicular C-cells release calcitonin in response to an elevation in serum calcium. Enlargement of the thyroid gland from any cause is known as goitre.

HYPERTHYROIDISM

Hyperthyroidism is caused by excess circulating thyroxine or triiodothyronine. It is a common condition with a prevalence of about 20 per 1000 in females and 2 per 1000 in males, respectively. Over 90% of cases are caused by either Graves’ disease, toxic multinodular goitre or toxic solitary goitre. Graves’ disease is the most common cause. The onset of the disease may be insidious. Atrial fibrillation is rare in young patients, but occurs in almost 50% of male patients over 60 years of age.

Graves’ disease results from IgG antibodies against the TSH-receptor which bind and stimulate the gland via the adenylcyclase-cAMP system. These antibodies are termed thyroid-stimulating antibodies (TSAb). They may be responsible in part for thyroid enlargement in Graves’ disease, but they do not appear to be responsible for the ophthalmopathy and pretibial myxoedema.

The cardinal signs of Graves’ disease include a diffuse goitre, over which a vascular bruit can be heard, and with eye signs, including exophthalmos, lid retraction, lid lag on downward eye movement, periorbital puffiness, grittiness, increased lacrimation, chemosis and reddening of the sclera.

7.61 Graves’ disease. This usually affects women between the ages of 20 and 40 years. This patient presented classically with a diffuse goitre over which a vascular bruit could be heard, and with eye signs.

7.62 Pretibial myxoedema in Graves’ disease. When this sign occurs, it may be combined with thyroid acropachy, in which there is oedema of the nail folds, producing a condition resembling clubbing.

7.63 Exophthalmos (proptosis) in Graves’ disease. This results from enlargement of the muscles, and fat within the orbit as a result of mucopolysaccharide infiltration.

7.64 Lid retraction is a common eye sign in Graves’ disease, which can be recognized when the sclera is visible between the lower margin of the upper lid and the cornea. Lid retraction is usually bilateral, but may be unilateral.

7.65 Periorbital swelling may be associated with other eye signs, giving an erythematous and oedematous appearance to the eyelids. Note that this patient also has chemosis, seen as reddening of the sclera.
chemosis (7.65), conjunctival oedema and ulceration (7.66), ophthalmoplegia (7.67), diplopia, papilloedema and loss of visual acuity. Symptoms of ophthalmopathy may include pain, lacrimation, photophobia, blurred vision and diplopia. Rapid correction of thyrotoxicosis is necessary but may not reverse the associated ophthalmopathy. Other measures, including oral steroid or cyclosporin therapy or radiotherapy, may reduce the volume of the orbital contents. Surgical decompression of the orbit, by removal of one or more orbital walls, may also be necessary.

Eye signs may be absent in thyrotoxicosis, especially in the elderly in whom ‘masked’ or ‘apathetic’ thyrotoxicosis is common. Atrial fibrillation, heart failure and weight loss may be the only signs in this group (7.68).

The diagnosis is made clinically, with confirmation by detecting biochemically raised triiodothyronine and thyroxine, and undetectable TSH levels. Where a toxic multinodular goitre or a single toxic nodule (a toxic adenoma) in the thyroid is suspected clinically, a thyroid scan may provide useful information (7.69, 7.70).

Treatment options in thyrotoxicosis include:
- Antithyroid drugs – carbimazole or methimazole, followed by propylthiouracil
- Beta-blocking drugs in the initial stages of management
- Subtotal thyroidectomy
- Radioactive iodine therapy.

The choice of therapy depends upon a number of factors, especially the age and previous history of the patient.

7.67 Ophthalmoplegia in Graves’ disease. This is not caused by nerve palsy, but is the long-term result of swelling and infiltration of the extrinsic muscles of the eye. In this case, there is impaired upward and outward gaze in the patient’s right eye. Ophthalmoplegia is usually accompanied by other eye signs. Note the presence of lid retraction. This patient also has marked corneal arcus.

7.68 ‘Masked’ hyperthyroidism. In the elderly, hyperthyroidism is commonly caused by a toxic multinodular goitre, but this does not necessarily result in significant thyroid enlargement. Because the patient does not have Graves’ disease, the other signs associated with that condition are lacking. The clinical diagnosis is thus much less obvious, being suggested by a combination of tachycardia or atrial fibrillation, or both, heart failure and weight loss in a patient over the age of 60 years.

7.69 Toxic adenoma causing hyperthyroidism. This patient had a partial thyroidectomy 20 years previously, and a toxic nodule has now recurred. This was confirmed by isotope scanning.

7.70 Toxic adenoma in the right thyroid (a hot nodule), demonstrated using 99mTc-pertechnetate scanning. The remainder of the gland does not take up significant amounts of isotope.
HYPOTHYROIDISM

Hypothyroidism (myxoedema) is the clinical syndrome that results from deficiency of the hormones triiodothyronine (T3) and thyroxine (T4). Its prevalence in the UK is about 15 per 1000 in females and 1 per 1000 in males.

Primary hypothyroidism is caused by an intrinsic disorder of the thyroid gland and is associated with raised TSH. Spontaneous atrophic hypothyroidism and thyroid failure after surgery, radioactive iodine or Hashimoto's autoimmune thyroiditis account for over 90% of cases.

Secondary hypothyroidism is much less common and is caused by pituitary disease, in which absence of TSH leads to atrophy of the gland.

Hypothyroidism affects all the systems of the body, but the wide range of clinical features means that the diagnosis will be missed if it is not positively considered. In children, the dominant features are a reduction in growth velocity and arrest of pubertal development. In adults, the presentation may vary from biochemical evidence with no clinical signs, to the insidious onset over many years of myxoedematous changes in the tissues with infiltration of mucopolysaccharides, hyaluronic acid and chondroitin sulphate (7.71, 7.72). Dermal infiltration gives rise to nonpitting oedema, most marked on the skin of the eyelids and hands. This is often associated with loss of scalp (7.73) and eyebrow hair. Dryness of the skin, and reduced body hair are other common features and infiltration of the median nerve may lead to the carpal tunnel syndrome (see p. 512). Patients are often very sensitive to cold weather and may wear excessive clothing or use excessive bedclothes. Systemic effects including pericardial and pleural effusions, ascites, cardiac dilatation, bradycardia and hypothermia may be life-threatening (see p. 262). There is an association with pernicious anaemia (see p. 432). Secondary hyperlipoproteinaemia is an invariable consequence of hypothyroidism and is a positive risk factor for the development of premature arterial disease, especially myocardial infarction. Treatment with thyroxine usually results in lowering of lipid levels.

Diagnosis is based on clinical suspicion - prolonged relaxation time of peripheral reflexes and a low-voltage ECG may be helpful - biochemical estimation of thyroxine and TSH and an assessment of thyroid antibodies. Antibodies to thyroid microsomes or thyroglobulin, or both, are present in the serum of 90% of patients with Hashimoto's thyroiditis.

Hashimoto's disease is the most common form of goitrous hypothyroidism in the world. It usually manifests itself in the sixth decade, and women are affected 15 times more frequently than men. The gland characteristically feels firm and rubbery and may range in size from being scarcely palpable to many times enlarged (7.74).

7.72 Gross clinical hypothyroidism produces characteristic nonpitting oedematous changes in the skin of the face, giving rise to a characteristic clinical appearance. Note the dry, puffy facial appearance and the coarse hair. This patient was admitted with hypothermia. Her skin was cold and she showed mental apathy.

7.73 Hair loss is a common feature of hypothyroidism, as in this 48-year-old woman.
Spontaneous atrophic hypothyroidism is the most common form of nongoitrous hypothyroidism in the UK, with a prevalence of 10 in 1000 people and an incidence that increases with age. Women are affected six times more commonly than men. This is also an autoimmune condition: many patients have TSH-receptor blocking antibodies and some have a history of Graves' disease treated successfully with drugs or radioiodine many years previously. These patients may also have other autoimmune diseases such as pernicious anaemia, diabetes mellitus, Addison's disease or vitiligo.

Drugs may induce hypothyroidism. Lithium carbonate, which like iodide inhibits the release of thyroid hormones, may result in a TSH-induced goitre; and prolonged administration of iodine, as in cough mixtures or in amiodarone given for the treatment of dysrhythmias, also occasionally induces goitrous hypothyroidism.

In certain parts of the world where there is iodine deficiency, such as the Andes, central Africa and the Himalayas, thyroid enlargement is common, affecting 5–15% of the population (endemic goitre, 7.75). Although most patients are euthyroid and have normal or only slightly raised TSH, the greater the iodine deficiency or the greater the demands (as in pregnancy), the greater the incidence of hypothyroidism.

Dys hormonogenesis is an unusual autosomal recessive defect in hormone synthesis. The most common form results from a deficiency in peroxidase enzyme (Pendred's syndrome: goitre, hypothyroidism, deaf mutism and mental retardation). Homozygotes present with congenital hypothyroidism, which needs to be distinguished from athyreosis or hypoplasia of the thyroid, the most common causes of neonatal hypothyroidism.

Neonatal hypothyroidism (1 in 4000 live births) is screened for by TSH measurement 5–7 days after delivery. If it is undetected, cretinism results. Prompt treatment with thyroxine has been shown to result in normal development, except in the rare cases of thyroid agenesis and impaired brain development caused by intrauterine hypothyroidism.

Treatment in all cases of hypothyroidism is with thyroxine. In patients with ischaemic heart disease, sudden introduction of thyroxine can cause myocardial infarction and therefore thyroxine is started in low doses (25 µg) and the dose increased very slowly every 4–6 weeks with intensified management of anti-anginal therapy. ‘Myxoedema coma’ is severe hypothyroidism in an elderly patient. Its presenting features may include hypothermia, cardiac failure, an altered conscious state often with convulsions, high CSF fluid pressure and protein content, hypotension, alveolar hypoventilation, intercurrent chest infection and dilutional hyponatraemia. Mortality is around 50% and careful management is required.

**7.74 Hashimoto's disease** is the most common cause of goitrous hypothyroidism in the world and is much more common in women than men. This teenage patient has a marked goitre but few obvious signs of hypothyroidism. She is rather unusual, as the condition is much more common in older women.

**7.75 Endemic goitre.** Large goitres like this are not unusual in areas of iodine deficiency, but they are not always associated with hypothyroidism. This African patient was euthyroid.

**7.76 Multinodular goitre.** The patient was euthyroid, but surgical treatment was ultimately required because of retrosternal extension with tracheal compression.
THYROID NODULES AND THYROID CANCER

A thyroid nodule is any discrete intrathyroidal lesion and nodules may be solitary or multiple. Palpable nodules can be found in 5–10% of European and North American adults, and the incidence increases with age. In iodine-deficient parts of the world, the prevalence is much greater. Clinically undiagnosed (occult) cases of thyroid cancer are found in up to 18% of routine autopsies. These are usually small (<1 cm) papillary carcinomas without evidence of local invasion or metastases.

Thyroid nodules may be caused by involutional or degenerative changes, discrete inflammatory lesions or neoplasms. Colloid or adenomatous nodules are the most common type and consist of thyroglobulin-containing follicles. These are often multiple and may present as a multinodular goitre (7.76) or a simple nontoxic goitre. They are most common in women, and require no treatment unless they are cosmetically disfiguring or cause pressure effects such as tracheal compression.

Single thyroid nodules may be benign or malignant. The chance of a nodule being benign is at least 95%, and most thyroid cancers have a mortality rate similar to skin cancer and are not immediately life threatening. Malignancy may be suspected if there is a history of previous exposure to ionizing radiation — especially external irradiation in childhood. Other suggestive features on examination include asymmetry, unusual location of the swelling, firmness, lymphadenopathy, a rapid painful increase in size, which may be caused by haemorrhage, hoarseness of the voice and fixation to skin and underlying tissues. The investigation of choice is a fine-needle aspiration (FNA), which allows immediate identification of cysts and microscopic examination of the aspirated cells (7.77). Ultrasonography is the most sensitive method available for delineating nodules and identifying cysts (7.78) but it will not distinguish benign from malignant. Radionuclide scanning may also give valuable information (7.79).

The prognosis and management of thyroid carcinomas varies according to the histological type: papillary, follicular, medullary and anaplastic.

Most thyroid carcinomas are the papillary type, which may be multifocal and spread to regional lymph nodes and to lungs and bone (3.158). Most occur in women aged less than 50 years with a tumour size less than 4 cm in diameter. Treatment is by total thyroidectomy; radioiodine ablation is needed postoperatively, as the metastases and any remaining thyroid take up iodine under TSH-drive after thyroidectomy. Thereafter the patients are treated with a sufficiently high dose of thyroxine to suppress TSH completely. Papillary carcinoma carries a good prognosis.

Follicular carcinoma is more aggressive. It is usually unifocal and rarely spreads to lymph nodes, but spreads via the blood to lungs and bone. Treatment is similar to that for papillary carcinoma.

Medullary carcinoma is derived from the parafollicular C-cells of the thyroid. When sporadic it is usually unifocal, but when familial it is typically bilateral and multicentric and may form part of the MEN syndromes. In MEN-2, it is associated with phaeochromocytoma and parathyroid adenoma. In MEN-3, it is associated with a marfanoid habitus, mucosal neuromas of lips, eyelids and tongue, proximal myopathy and ganglioneuromatosis of the bowel. Medullary carcinoma metastasizes as above and is treated in the same way, but it produces calcitonin which can be used as a tumour marker.

Anaplastic carcinoma is very aggressive and may be inoperable at presentation.

7.78 Ultrasound is the imaging technique of choice in the initial investigation of thyroid nodules. In this patient, one large and several smaller lesions are seen. Further investigation is indicated, and aspiration biopsy is likely to provide a definitive cellular diagnosis.

7.77 Fine-needle aspiration of a thyroid nodule is the investigation of choice in a patient with a solitary nodule of the thyroid, as it is very successful in obtaining cells for cytological examination and thus in the diagnosis of thyroid carcinoma. It can usually be performed under local anaesthesia. This patient had a recurrent nodule after previous partial thyroidectomy for thyrotoxicosis.

7.79 A large ‘cold’ nodule in the right lobe of the thyroid, demonstrated using 99mTc-pertechnetate scanning. A cold nodule could be malignant, and fine-needle or open biopsy is always indicated.
HYPERPARATHYROIDISM

For a discussion of hyperparathyroidism, see p. 155.

HYPOPARATHYROIDISM

Failure of parathyroid hormone (PTH) secretion is rare; the major causes are neonatal, severe magnesium depletion, postsurgical or idiopathic hypoparathyroidism. The clinical features are mainly caused by hypocalcaemia. They include tetany, which is characterized by carpopedal spasm (7.80) and paraesthesia. Idiopathic hypoparathyroidism may be sporadic or familial and is often associated with autoimmune diseases such as Addison's disease. Candidiasis, together with impaired nail and dental development, is common. Cataracts and calcification of the basal ganglia are common, but parkinsonism features are rare.

Pseudohypoparathyroidism is caused by a defect at the PTH-receptor level. In addition to the characteristic biochemical profile of hypoparathyroidism (low serum calcium, raised inorganic phosphorus and usually normal alkaline phosphatase), these patients have a raised PTH and they exhibit somatic features. They have short stature, mental retardation, a round face and short neck, abnormal dentition and shortening of some of the metatarsals and metacarpals (usually the third, fourth and fifth, 7.81, 7.82). A few families have these somatic features without the biochemical abnormalities; this condition is known as pseudo-pseudo-hypoparathyroidism.

Treatment of tetany is with intravenous calcium and, as oral calcium is rarely adequate alone, an active metabolite of vitamin D is prescribed to normalize the serum calcium levels.
GASTROINTESTINAL HORMONE ABNORMALITIES

A number of rare syndromes are associated with abnormalities in gastrointestinal hormones. These are summarized on p. 391.

DIABETES MELLITUS

Diabetes mellitus is a disease characterized by a chronically elevated blood glucose concentration, often accompanied by other clinical and biochemical abnormalities. The hyperglycaemia of diabetes results from an inadequate action of insulin, caused by low or absent insulin secretion, the presence of antagonists to the peripheral action of insulin or a combination of these factors.

The effects of the disease may be acute or chronic, involving many organs, including the eye, the kidney, peripheral nerves and large arteries. Primary diabetes mellitus is traditionally divided into either insulin dependent (IDDM or Type 1) or noninsulin dependent (NIDDM or Type 2). The classification is important because of the different genetic backgrounds, clinical presentations, metabolic effects, treatment and consequences of the two types. Diabetes may also be secondary to other disorders (7.83).

Diabetes is defined biochemically by the following criteria:
- A fasting venous plasma glucose level greater than 7.8 mmol/litre (140 mg/dl) on more than one occasion; or
- A 2-hour (plus one other) venous plasma glucose level in excess of 11.1 mmol/litre (200 mg/dl) in a formal 75 g oral glucose tolerance test (GTT).

IMPAIRED GLUCOSE TOLERANCE

Impaired glucose tolerance (IGT) is often classified as 'chemical', 'borderline' or 'latent' diabetes. It is defined as the finding of a fasting venous plasma glucose level below 7.8 mmol/litre, and a 2-hour sample, after an oral GTT, with levels between 7.8 and 11.1 mmol/litre. Annually, about 2–4% of these patients develop diabetes. IGT carries the same risk of atherosclerotic vascular complications as diabetes, although the risk of retinopathy 10 years after diagnosis is negligible. Management of patients with IGT should be aimed at diminishing the risk of metabolic and physical deterioration, by reducing obesity, hypertension, physical inactivity and hyperlipidaemia, and by stopping smoking. In pregnancy, IGT should be taken seriously and treated as gestational diabetes.

PRIMARY DIABETES MELLITUS

Primary diabetes is either IDDM (Type 1) or NIDDM (Type 2). The prevalence of diabetes in industrialized countries is approximately 3–4% and about 10% have IDDM. Some communities, such as the Pima Indians, have a diabetes prevalence of over 30%, mainly obese NIDDM.

IDDM patients are ketosis prone and C-peptide negative. They have an absolute requirement for insulin from diagnosis. IDDM is believed to be an autoimmune condition, in which environmental factors trigger the diabetogenic process via islet cell antibodies in genetically susceptible individuals. Most patients presenting under the age of 25 years have IDDM.

NIDDM generally occurs over the age of 40 years in patients with resistance to insulin and abnormal beta cell function. An underlying genetic susceptibility is even more important than in IDDM and most patients are obese. The onset of the disease is insidious and biochemical evidence of diabetes may be present for several years before symptoms or complications lead to the diagnosis. These patients are not dependent on insulin for treatment but may require it temporarily for glycaemic control under stress.

MALNUTRITION-RELATED DIABETES MELLITUS

The World Health Organization has recognized malnutrition-related diabetes (MRDM) with two subtypes—fibrocalcaneous pancreatic diabetes (FCPD) and protein-deficient pancreatic disease (PDPD). MRDM has a high prevalence in certain tropical developing countries, where it manifests itself with severe symptoms but without ketosis in young people. Pancreatic calcification is common in the FCPD subtype.

7.83 A classification of diabetes mellitus.
SECONDARY DIABETES MELLITUS

Diabetes may be secondary to pancreatic disease (e.g. haemochromatosis, chronic pancreatitis), other endocrine disorders (e.g. Cushing’s syndrome, acromegaly, phaeochromocytoma), drug therapy (e.g. thiazides, steroids, phenothiazides), insulin-receptor abnormalities (lipodystrophy, 7.84) and various inherited disorders (e.g. Type 1 collagen diseases, Prader–Willi syndrome, diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) syndrome).

PRESENTING FEATURES OF DIABETES

Patients with diabetes may be detected by a range of presentations which include:

- Acute: the typical presentation of the young patient with IDDM; features include polyuria, polydipsia and weight loss of short duration, often associated with, or apparently precipitated by, a viral infection; if these symptoms have been neglected there may be visual disturbance or impairment of the conscious level associated with severe ketoacidosis
- Chronic: the typical presentation of a patient with NIDDM; the symptoms have usually been present for some months and often include weight loss, thirst, excess urine volume, genital infection with *Candida albicans* and skin infections, often with *Staphylococcus aureus*
- Coincidental discovery: routine screening for urine or blood glucose as part of a pre-employment medical, during pregnancy or in local campaigns
- Complications: the patient may present with visual disturbance or overt retinopathy, neuropathy, nephropathy or after major thrombotic events such as premature stroke or myocardial infarction
- Drug-related diabetes may develop in patients on long-term steroids or thiazide diuretics
- Disease-related as in acromegaly, Cushing’s syndrome, phaeochromocytoma, thyrotoxicosis, pancreatitis, haemochromatosis, cystic fibrosis, carcinoma or surgical removal of the pancreas
- Gestational: pregnancy may unmask diabetes in a woman who is predisposed.

A full history and clinical examination are essential to detect any of the causative diseases and document the consequences.

INVESTIGATIONS

Investigations are required for screening, diagnosis, monitoring of control and the early detection of degenerative changes.

- Urine testing for glucose is still widely used, but glucose will be found in the urine only when it rises above the renal threshold (usually about 10 mmol/litre); urine tests are simple and cheap; enzyme strip tests are specific for glucose.
- Urine testing for ketone bodies is also simple; the presence of ketones suggests loss of control.
- Urine testing for ketone bodies is also simple; the presence of ketones suggests loss of control.
- Proteinuria is a reflection of the development of renal complications and is an early indicator of diabetic renal disease. Multiple test strips allow rapid testing for all these substances in urine (6.8).
- Blood glucose is the key to diagnosis in diabetes (see p. 329); careful attention to detail is required in skin preparation, blood collection and monitoring the reaction. The colour change may be recorded visually but is better recorded electronically, and meters are available for home use (7.85-7.87). If the patient is to read the strips visually it is important to check colour vision. Noninvasive percutaneous glucose sensors are also becoming available (7.88).
- GTT is of value if random blood glucose results are equivocal; it defines the response to a 75 g oral glucose load; blood and urine are monitored before and for 2.5 hours after the glucose drink; the renal threshold for glucose can be determined, as can the presence of diabetes (capillary glucose ≥11.1 mmol/litre) or IGT (capillary glucose 7.8-11.1 mmol/litre).
- Glycosylated haemoglobin and other proteins: measurement of these proteins reflects the degree of diabetic control in the previous 4-6 weeks and is of value in long-term management and control (7.89).
- Microalbuminuria is a very sensitive marker of early and potentially reversible renal impairment; it is the term given to the presence of protein below the level of detection with the stick methods, that is 200 mg/litre.
- Serum electrolytes, blood gases, osmolality and anion gap are all of value in metabolic crises if there is loss of water, sodium and potassium and acidosis is developing, or if there is a hyperosmolar state.

7.84 Lipodystrophy is a rare cause of secondary diabetes. The atrophy of adipose tissue occurs throughout the body, and is well seen here, especially in the gluteal region. Nonketotic insulin resistance is combined with severe hyperlipidaemia with subcutaneous xanthomas and hepatosplenomegaly.
Lipid profile: elevations in serum cholesterol are common, and elevation of serum triglycerides is a reflection of poor glycaemic control, which usually reverts to normal when euglycaemia is achieved.

PRINCIPLES OF MANAGEMENT

The aim of management is to control symptoms, prevent acute metabolic complications of ketoacidosis and hypoglycaemia, encourage self-reliance and self-care, prevent or treat complications early and prevent the increased morbidity and mortality associated with poorly managed diabetes.

In IDDM, glycaemic control is achieved by subcutaneous insulin administration two or more times a day, using modified insulins with differing absorption characteristics to provide an insulin profile that controls the glycaemia around meals and provides a background level for basic metabolic functions. Glycaemic control is best assessed by blood glucose monitoring. Dietary modification is essential, and involves eliminating simple sugars and eating a low-fat, high-fibre diet with 50% of the calories from carbohydrate, 30% from fats (mainly polyunsaturated) and 20% from protein.

In NIDDM the main form of treatment is dietary, with the emphasis on avoiding simple sugars and calorie restriction. Weight reduction is important in most patients with NIDDM, and only if this cannot be achieved and the patients are unacceptably hyperglycaemic, should oral hypoglycaemic agents be added. Sulphonylureas are first-line treatment in nonobese NIDDM patients, whereas biguanides have a particular role in the obese diabetic. Hyperlipidaemia in patients with diabetes may require further investigation, and control of hyperlipidaemia should always be an aim of therapy in diabetes (see p. 340).

7.85-7.88 Electronic measurement of capillary blood sugar allows immediate monitoring in the clinic and at home. 7.85 shows a meter that measures blood glucose by coupling a biochemical reaction to an electronic response, together with the enzyme-containing test strip (sealed and unwrapped) and the stylet used for obtaining a finger-prick sample of blood. The test strip is inserted in the meter and a drop of blood applied to it (7.86). The blood glucose level appears on the meter within seconds (7.87). Other meters are available, that measure colour changes in test sticks by reflectance methods. Non-invasive measurements of blood glucose are also becoming available. The sensor shown in 7.88 measures glucose levels non-invasively by beaming infra-red light through the skin.

7.89 Glycosylated haemoglobin levels provide valuable evidence of the degree of control achieved in patients with diabetes. The equipment required for automated measurement is commonly installed ‘near to patient’ in the diabetic clinic. The result is obtained within 6 minutes; the investigation can therefore be performed immediately before the patient is seen for follow-up.
The most important acute complications of diabetes are metabolic: diabetic ketoacidosis (7.90), hypoglycaemia (7.91), lactic acidosis and nonketotic hyperosmolar coma.

Other acute complications include insulin allergy, acute infections and acute neuropathy.

Insulin allergy (7.92) is becoming very rare with the increasing use of highly purified animal insulins or genetically engineered human insulin.

Acute infections may be the presenting complaint in NIDDM. They may include

- Candidal infections, presenting in the genital region as balanitis or vulvitis (1.177), in the finger nails (2.62) or as intertrigo beneath the breasts (2.61)
- Carbuncles (1.99), boils (2.50) and other staphylococcal skin infections
- Osteomyelitis, urinary infections, pneumonia, tuberculosis and other systemic bacterial infections
- In the diagnosed diabetic, finger pulp infections caused by nonsterile finger pricks (7.93)

Acute motor or sensory neuropathy may be seen in various guises during or after a period of poor metabolic control. The most typical are mononeuritis multiplex, often affecting the

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7.90 Diabetic ketoacidosis. There is evidence of marked dehydration, and the patient's eyeballs were lax to pressure. The patient was hyperventilating and confused, though not (yet) comatose. The smell of ketones on the breath allowed an instant probable diagnosis.

7.91 Hypoglycaemic coma in diabetes. Coma resulted from self-administration of an excessive insulin dose by an alcoholic patient who did not subsequently eat any food. When the patient is comatose, hypoglycaemia is more immediately dangerous than hyperglycaemia. This patient died.

7.92 Local allergy to insulin injections is less common when purified preparations are used, but may still occur. The usual manifestations are erythema and sometimes urticaria at injection sites. The areas are itchy and hot to the touch.

7.93 Septic finger pulp in diabetes. This young diabetic girl had been using the finger-prick method to test her own blood sugar level, but the finger had become infected.
third, sixth or seventh cranial nerves (7.94) and diabetic amyotrophy caused by a proximal radiculopathy. Pain and skin tenderness with weakness and wasting of the upper thigh muscles is the most common presentation of amyotrophy (7.95). With improved glycaemic control (often with insulin), these complications may resolve.

The chronic complications of diabetes are summarized in 7.96.

Insulin lipodystrophy results from frequent injections into the same injection sites, particularly in girls. Hypertrophy (7.97) is caused by hypertrophied fat cells, and fat cell atrophy may also occur (7.98).

Most chronic complications result from disease of either the large blood vessels (macroangiopathy) or the small blood vessels (microangiopathy).

Macroangiopathy is responsible for a high prevalence of coronary, peripheral and cerebral artery disease in diabetics. Hypertension coexists with diabetes in about 50% of patients. Accelerated atherosclerosis occurs at a young age and runs an aggressive course in diabetics, especially in women. It accounts for most deaths from diabetes, particularly in NIDDM.

Microangiopathy is a generalized microvascular (capillary) disorder that is specific to diabetes and clinically most apparent in the eyes, kidneys and nerves. It is characterized by capillary

7.94 Mononeuritis multiplex in diabetes, affecting the right sixth and seventh facial nerves in a mild diabetic. The presenting symptoms were facial weakness and double vision. The right side of the face is palsied, as seen in this attempt to smile by the patient. He also had double vision on looking to the right, because a right sixth nerve palsy prevented lateral gaze in the right eye.

7.95 Diabetic amyotrophy, causing wasting of the thigh muscles. Adequate control of diabetes may lead to partial or total resolution of diabetic neuropathy.

7.96 Long-term complications of diabetes mellitus

7.97 Lipohyperatrophy at the site of repeated insulin injections in the lower abdomen in a young female diabetic.

7.98 Lipoatrophy in the legs of a diabetic patient, resulting from repeated insulin injections in these sites.
basement membrane thickening, endothelial cell dysfunction, platelet aggregation, impaired fibrinolysis and a prothrombotic tendency, and results in microvascular occlusion and tissue ischaemia. The sequence of events in microangiopathy is best seen in the retina (see p. 336-339).

Diabetic renal disease is an important cause of morbidity and mortality, especially in IDDM. Its diagnosis and management are discussed on p. 295.

Chronic diabetic neuropathy may have a microvascular component in its aetiology, but intraneural metabolic derangement caused by alternative pathways of glucose metabolism is also implicated.

- Sensory neuropathy usually presents in the feet as a painless trophic ulcer (7.99) or as a neuropathic arthropathy, that is a Charcot joint (7.100); stiffness of the joints is a common feature best demonstrated by the 'prayer sign' (7.101)
- Motor neuropathy may lead to interosseous muscle wasting in the hands and feet (7.102)
- Autonomic neuropathy may cause postural hypotension, impaired cardiovascular reflexes, gastroparesis, atonic bladder, impotence and disturbance of sweating (7.103).

Care of the feet is an important part of the management of diabetes and patients or their relatives should be educated in the need for daily examination of the skin of the feet. The common combination of neuropathy and peripheral vascular disease often results in peripheral gangrene in the foot (7.104). Sometimes patients have good peripheral pulses, the ischaemic damage being secondary to small vessel occlusion. Infection of ulcers on the foot may lead to chronic sepsis with osteomyelitis (3.154). As in other peripheral vascular diseases (see p. 257), gangrene usually requires treatment by amputation.

7.99 Painless trophic ulceration of the sole of the foot is a common presenting feature of sensory neuropathy in diabetes. Diabetic ulcers are commonly complicated by infection (see 3.152) and, if peripheral vascular disease is present, gangrene may also develop.

7.100 Charcot joint in diabetes. Sensory neuropathy has led to derangement of the left forefoot and ankle. Note the distortion and swelling. The derangement was painless, and there was little functional disability. On examination, the patient had loss of sensation and reflexes in the left ankle and foot.

7.101 The 'prayer sign' in diabetes. Joint movement is limited, and the patient is unable to bring together the palms of the hands as in prayer. Note also the 'waxy' changes in the skin. Both these features are associated with diabetic microangiopathy.

7.102 Ulnar mononeuropathy in a diabetic patient, causing wasting of the small muscles of the hand.

7.103 Autonomic neuropathy has led to gustatory sweating in this diabetic patient. Spicy food and cheese provokes sweating in an area on the right side of the head and trunk, as outlined with iodine in this picture. Autonomic neuropathy is an important and irreversible chronic complication of diabetes.
Dermatological manifestations of diabetes include acanthosis nigricans (2.90), necrobiosis lipoidica (2.138), granuloma annulare (2.137) and candidal and staphylococcal infections (1.99, 2.50). Xanthomata are common as a result of hyperlipidaemia (see p. 339).

Diabetes in pregnancy poses special problems, but the outlook for the fetus is greatly improved by good diabetic control. Even so, the typical baby born to a diabetic mother is overweight and prone to neonatal complications (7.105) that can, however, usually be overcome by intensive care in the neonatal period. Congenital abnormalities are more common in babies born to diabetic mothers. Counselling of known diabetics before conception is helpful.

7.104 Gangrene of the foot is a common complication of chronic diabetes. In this patient ‘wet’ gangrene has developed in the hallux of the left foot, and dry gangrene in the second toe of the right foot. Ulceration and gangrene of the foot are commonly the result of a combination of diabetic neuropathy with large or small vessel disease, or both.

7.105 A baby born to a diabetic mother at 38 weeks' gestation. The baby was large, oedematous and plethoric. Management in a special-care baby unit is advisable to overcome the risks of respiratory distress, but the overall outcome is now much better than in the past.

7.106 The ocular manifestations of diabetes mellitus.

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<tr>
<th>Eyelids:</th>
<th>xanthelasmata caused by hyperlipidaemia (7.127)</th>
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<td>Conjunctiva:</td>
<td>microaneurysms, venous dilatation</td>
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<tr>
<td>Extra-ocular muscles:</td>
<td>palsy with diplopia caused by third, fourth or sixth cranial nerve involvement (7.94)</td>
</tr>
<tr>
<td>Orbit:</td>
<td>mucormycosis – a potential complication of severe diabetic acidosis</td>
</tr>
<tr>
<td>Iris:</td>
<td>neovascularization of the anterior surface (rubeosis iridis, 7.108)</td>
</tr>
<tr>
<td>Glaucoma:</td>
<td>neovascular glaucoma, chronic open angle glaucoma</td>
</tr>
<tr>
<td>Pupil:</td>
<td>poor dilatation caused by rubeosis iridis, Argyll Robertson pupil (11.8)</td>
</tr>
<tr>
<td>Lens:</td>
<td>cataract (7.107), refractive errors</td>
</tr>
<tr>
<td>Vitreous body:</td>
<td>vitreous haemorrhage (7.120), asteroid hyalosis</td>
</tr>
<tr>
<td>Retina:</td>
<td>diabetic retinopathy (7.110–7.123), retinal vein occlusion (7.122), lipaemia retinalis (7.109)</td>
</tr>
<tr>
<td>Optic nerve:</td>
<td>ischaemic papillitis, optic atrophy</td>
</tr>
</tbody>
</table>

Diabetes and the eye

Diabetes mellitus is a leading cause of blindness in the developed world, and diabetes has numerous effects on the eye (7.106). Up to 20% of patients with NIDDM have retinal changes at presentation, but it is essential that all patients with diabetes enter a programme of eye surveillance. Routine eye examinations should include visual acuity testing and fundoscopy after mydriatic drops.
'Senile' cataract (7.107) occurs at a younger age in diabetics than in other patients, and rarer conditions such as rubeosis iridis (7.108) may also affect the anterior parts of the eye.

Extreme hypertriglyceridaemia may be visible in the retinal vessels as lipaemia retinalis (7.109).

The major retinal changes in diabetes are a reflection of microangiopathy, and their progress gives valuable information on the likely effect of the diabetes on other organs (especially the kidney), as well as on the retina itself.

The characteristic early lesions are microaneurysms associated with exudates and venous dilatation (7.110). These early changes are best visualized by fluorescein angiograms (7.111) and are designated early background retinopathy (7.112, 7.113). They are common, occurring in 80% of patients who have had diabetes for 20 years. They do not always threaten sight and need no specific treatment, but must be monitored because exudates around the macula with associated oedema are a common cause of diabetic blindness (7.114, 7.115). Cotton wool spots (7.116) are retinal infarcts and are a bad prognostic sign, as the retina responds to ischaemia by capillary proliferation. The formation of new vessels (7.117, 7.118) is a serious form of retinopathy as they give rise to vitreous haemorrhages and blindness. New vessels may form on the disc (7.118) or in the periphery (7.119), and they tend to extend forward into the vitreous leading to haemorrhage (7.119, 7.120) and fibrosis.

Diabetic retinopathy may be complicated by the presence of hypertension (7.121) or by thrombosis in the retinal veins (7.122).

Proliferative retinopathy and maculopathy can often be treated by laser photocoagulation which may prevent blindness by producing an iatrogenic choroidoretinitis (7.123).

7.108 Rubeosis iridis. New vessels develop on the anterior surface of the iris in response to severe ocular ischaemia. Resulting obstruction to aqueous drainage may lead to glaucoma. Rubeosis iridis is most commonly a complication of diabetes, but may also occur in patients with carotid stenosis, longstanding retinal detachments, central retinal vein occlusion or ocular tumours.

7.109 Lipaemia retinalis is a reflection of severe hypertriglyceridaemia. The retinal vessels appear white as a result of the 'milky' chylomicron-rich plasma within them. Lipaemia retinalis is commonly seen in acute uncontrolled diabetes.

7.110 Background diabetic retinopathy. Note the presence of multiple microaneurysms and some small areas of haemorrhage.
**7.112 Background diabetic retinopathy.** The arrow points to a soft exudate. This represents an area of retinal infarction. Small haemorrhages are also present, and there is evidence of deterioration in the retinal microcirculation.

**7.111 Fluorescein angiogram in background diabetic retinopathy,** showing the presence of multiple microaneurysms.

**7.113 Background diabetic retinopathy** with microaneurysms (dots), retinal haemorrhages (blots) and hard yellow exudates. Despite the appearance, the patient's visual acuity is usually unaffected at this stage.

**7.115 Fluorescein angiogram of diabetic retinopathy with macular involvement and blindness.** Note the widespread capillary microaneurysms and the extensive capillary leakage in the two areas arrowed.

**7.114 Macular involvement in diabetic retinopathy is a common cause of diabetic blindness.** Note the presence of multiple exudates and the blurring caused by macular oedema – the most common cause of visual impairment in macular disease.

**7.116 Cotton wool spots in diabetic retinopathy.** These are retinal infarcts resulting from arterial occlusion. They are a bad prognostic sign, because they are likely to herald capillary proliferation.
7.117 Proliferative diabetic retinopathy. Fronds of new vessels (arrowed) can be seen emerging from the disc and elsewhere.

7.119 Proliferative diabetic retinopathy. Some new vessels have grown forwards into the vitreous, and haemorrhage has occurred into the retina and the vitreous (arrow).

7.118 Fluorescein angiogram in diabetic retinopathy showing dark ischaemic areas in which capillaries are abnormally absent (C), microaneurysms (M) and leakage from new vessels on the optic disc (L).

7.120 Vitreous haemorrhage resulting from proliferative retinopathy in diabetes. These haemorrhages appear as a haze or a red or black reflex through the ophthalmoscope as in the curvilinear accumulation of blood seen here. This patient's proliferative retinopathy has been treated by laser photocoagulation, which has left typical circular scars.

7.121 Diabetic retinopathy in a hypertensive patient. Note the presence of hypertensive vessel changes (silver-wiring, arrowed) and a macular subhyaloid haemorrhage. Hypertension adds to the risk of haemorrhage in diabetic retinopathy.
HYPOGLYCAEMIA

Hypoglycaemia is defined as a blood glucose level below the lower limit of the normal range, and may be associated with clinical features below a blood glucose level of about 3 mmol/litre.

Causes of hypoglycaemia include
- Drug induced in diabetes (insulin and sulphonylureas), often associated with not eating (7.91)
- Deliberate inappropriate insulin injection
- Other drugs — salicylates in children, propranolol, trimethoprim, pentamidine and quinine
- Excess alcohol intake
- Insulinoma (7.124)
- A range of other tumours
- Malnutrition or starvation.

The clinical presentation of hypoglycaemia is often due to endogenous catecholamine release, which provokes anxiety, weakness, a feeling of hunger, sweating, shakiness and palpitations. There may also be confusion, irritability, reduced higher cerebral function, convulsions, coma and death, which relate directly to the effects of hypoglycaemia on the brain.

Intravenous glucose or concentrated oral glucose (7.125) should be given to patients with suspected hypoglycaemia as soon as blood has been taken for glucose estimation. Even if the diagnosis is proved incorrect no harm will be done and prompt treatment will reduce the duration of hypoglycaemia and the risk of death or serious complications.

7.124 Insulinoma demonstrated by 123I-octreotide scanning. This technique images tumours that have somatostatin receptors. The picture shows some radioactivity in the gall bladder, bowel and kidneys. The abnormal uptake in the insulinoma is arrowed. The patient had presented with symptoms suggesting hypoglycaemia, which had been confirmed by a blood glucose of 1.8 mmol/litre. Surgical removal was successful.

7.125 Concentrated oral glucose gel can be administered by mouth to patients with suspected hypoglycaemia who can swallow. This should be done with the patient in the recovery position to minimize the risk of pulmonary aspiration. The response to oral or intravenous glucose in hypoglycaemia is rapid.

7.123 Photocoagulation is usually the treatment of choice for proliferative diabetic retinopathy. Here it has resulted in numerous typical scars in the peripheral retina, many of which reveal the black pigmentation of the choroid beneath the destroyed retinal cells.
HYPERLIPIDAEMIA

Hyperlipidaemia may be classified on the basis of laboratory findings, disease entities and genetic or environmental causes. All such classifications are complex and potentially confusing.

The importance of hyperlipidaemia relates mainly to its association with atheromatous vascular disease. There is clear evidence that elevation of the level of cholesterol and triglycerides is important in the premature development of atheroma and thrombotic events, such as myocardial infarction, thrombotic stroke and peripheral gangrene. There is also evidence at population and individual patient levels that a lowering in total blood cholesterol (specifically in the LDL fraction) leads to a decrease in the risk of cardiovascular morbidity and mortality.

In many patients, lipid abnormalities are now identified in screening programmes, but a number of clinical signs may give clues, especially in patients with gross hyperlipidaemia. These include

- Premature arcus cornealis (6.44, 7.67, 7.126, 7.127, 8.2)
- Xanthelasmata (7.127, 9.5, 9.36)
- Skin xanthomata (7.128, 7.129, 9.6)
- Tendon xanthomata (7.130, 7.131)
- Lipaemia retinalis (7.109).

The diagnosis of hyperlipidaemia is easily made on a fasting blood sample. In Western countries, counselling and treatment can often be based on cholesterol and triglyceride levels alone, but the measurement of LDL and HDL cholesterol may be useful in some patients. It is important to identify or exclude causes of secondary hyperlipidaemia (7.132).

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7.126 Corneal arcus is a normal phenomenon associated with ageing (arcus senilis), but its occurrence in patients under the age of 50 years suggests the possibility of underlying hyperlipidaemia. The ring represents deposits of phospholipid and cholesterol in the corneal stroma.

7.127 Corneal arcus and xanthelasmata in the same patient. This combination is strongly suggestive of underlying hyperlipidaemia, and the presence of xanthelasmata alone is an indication for investigation of lipid status.

7.128 Eruptive xanthomas may be quite widespread in the skin, but they are most commonly found over the buttocks. They are strongly suggestive of underlying hyperlipidaemia.

7.129 Tuberous xanthomata on the knee, occurring in a patient with familial hypercholesterolaemia. Massive xanthomata may sometimes require surgical removal.
It is essential that any recommendations for dietary modification or drug therapy are made in the context of an overall assessment of the patient's cardiovascular risk profile. Other risk factors (smoking, hypertension, etc., see p. 228) should be identified and treated at the same time, and the patient's family history should be investigated so that other at-risk family members can be identified, especially if a familial disorder is suspected.

A number of international working parties have recommended levels at which treatment should be instigated for hyperlipidaemia, and a consensus view is summarized in 7.133. Treatment of hyperlipidaemia starts with a diet low in saturated fats, and rich in fibre, complex carbohydrates and polyunsaturated or monounsaturated oils and fish. If this is unsuccessful over a 3–6-month period, a range of lipid-lowering drugs is available. Lipid-lowering statin drugs have been shown to be effective in the primary and secondary prevention of coronary artery disease. In secondary prevention, for example, a 10% reduction in total cholesterol has been shown to reduce the risk of a further coronary event by 25%.

Therapy for hypercholesterolaemia may involve the use of a bile acid sequestrant resin, a fibrate, a nicotinic acid derivative or an HMG-CoA reductase inhibitor. A fibrate or nicotinic acid derivative can be used to lower triglyceride when diet has proved ineffective.

**7.131 Tendon xanthomata** are characteristically found over the tendons and extensor surfaces of joints. They are particularly common over the patellar and Achilles tendons. This patient had familial hypercholesterolaemia.

**7.130 Tendon xanthomata** were the first clue to the diagnosis in this patient with familial hypercholesterolaemia and premature coronary heart disease.

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**SECONDARY CAUSES OF RAISED CHOLESTEROL AND TRIGLYCERIDE**

<table>
<thead>
<tr>
<th>Raised cholesterol</th>
<th>Raised triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Obesity</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Poorly controlled diabetes</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Alcohol excess</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>High-carbohydrate diet</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Renal failure</td>
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<td></td>
<td>Oestrogen therapy</td>
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**ACTION LEVELS FOR TREATMENT OF HYPERLIPIDAEMIA**

<table>
<thead>
<tr>
<th>CHOLESTEROL</th>
<th>TRIGLYCERIDE</th>
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</thead>
<tbody>
<tr>
<td>&lt;5.2 mmol/l</td>
<td>&lt;3.0 mmol/l</td>
</tr>
<tr>
<td>5.2–6.5 mmol/l</td>
<td>3.0–6.0 mmol/l</td>
</tr>
<tr>
<td>6.5–7.8 mmol/l</td>
<td>&gt;6.0 mmol/l</td>
</tr>
<tr>
<td>&gt;7.8 mmol/l</td>
<td>&gt;6.0 mmol/l</td>
</tr>
</tbody>
</table>

- Satisfactory: no action
- Moderately elevated: diet and counselling on other risk factors; repeat in 3 months
- High: diet first; consider drugs only if diet fails and other risk factors are present
- Very high: diet, assess other risk factors, other family members; if diet fails use drugs
- Satisfactory: no action
- High: check HDL; weight loss; diet; counsel on other risk factors; consider drugs if diet fails, especially if HDL is <1.0 mmol/l.
- Very high: check HDL; weight loss; diet; drugs are indicated to prevent coronary heart disease and pancreatitis.

**7.132 Secondary causes of raised cholesterol and triglyceride.**

**7.133 Action levels for treatment of hyperlipidaemia found on screening.** Lipid lowering drug therapy should be started at all levels of hyperlipidaemia in all patients who have already experienced a thrombotic vascular occlusion.
NUTRITIONAL DISORDERS

OBESITY

Storage of lipids in excess of daily requirements results in obesity—an excess of adipose tissue that is associated with a health risk. Obesity is defined as a 20% excess over ideal body weight and in many Western populations 30–40% of individuals are obese. Most obese individuals ingest excess calories that are then stored. The reasons for overeating are not clear, but they may involve psychosocial factors that modulate the activity of the satiety centre; this may be coupled with reduced caloric expenditure resulting from a sedentary existence, or with alterations of thermogenesis. In a small number of cases, obesity is secondary to diseases such as hypothyroidism, Cushing’s syndrome and extremely rare disorders such as insulinoma, Fröhlich’s syndrome and the Prader–Willi syndrome.

The end result of excessive calorie intake is an increase in fat deposition around the internal organs and muscles, and in subcutaneous sites such as abdomen, buttocks, breasts, thighs, face and upper arms (7.134–7.136). Such obesity is associated with insulin resistance and glucose intolerance, hyperlipidaemia, hypertension and an increased incidence of thrombotic arterial and venous disease and of degenerative joint diseases. Weight reduction towards the norm is associated with improved life expectancy.

Tables of desirable weights are available for age, sex and height. A more acceptable and accurate assessment method is to use the Body Mass Index (BMI), which is calculated as weight in kilograms divided by height in metres squared. BMI values of 19–24 in women and 20–25 in men are associated with the longest life expectancy. Values over 30 (obese) and over 35 (morbidly obese) are associated with significant reduction of life expectancy. The problem is that BMI does not differentiate between upper and lower body fat distribution.

Measurement of skin-fold thickness over the upper arm and back (7.137) provides a measure of subcutaneous fat and is better for use in elderly patients who have lost muscle bulk and also in younger heavily muscled subjects. It is difficult to obtain reproducible measurements. It is probable that more information of predictive value is obtained from the waist: hip circumference ratio (WHR). Upper body obesity is defined as a WHR >0.83 in women and WHR >0.95 in men. The waist is measured midway between the lower rib margin and the iliac crest and the hips over the great trochanters.

Higher mortality from ischaemic heart disease, stroke and death from all causes is associated with higher BMI, skin-fold thickness and WHR.

Treatment of obesity is by calorie restriction, which must be permanent and represent a real change in lifestyle. Patients should also be encouraged to exercise. Adherence to a diet providing 800–1200 calories per day results in weight loss. A waist cord may encourage the patient to maintain the lower weight.

Attempts may also be made to stop patients eating by wiring the jaws, using an inflated balloon to fill the stomach or by surgery to create a jejunoileal bypass. All these procedures may have major complications and are used only as a last resort.
PROTEIN-ENERGY MALNUTRITION

In protein-energy malnutrition (PEM) there is a loss of adipose tissue and lean body mass, usually as a result of deficient quantitative and qualitative food intake in the developing countries, or of malabsorption or organic disease (usually malignancy) in developed countries. PEM is of insidious onset, and up to one-quarter of the world’s population lives on the verge of insufficiency of protein and calorie intake.

The group most commonly affected is children. Their growth is stunted, and they may show evidence of loss of muscle mass with spindly arms and legs, and with a bloated abdomen, caused partly by ascites. There is usually little or no subcutaneous fat. Most internal organs are also affected. There is a small heart with reduced cardiac output, atrophy of endocrine glands producing hypofunction, atrophy of the intestinal wall that may lead to rectal prolapse, atrophy of muscle and an increased risk of infection because of reduced immune function; the liver may be enlarged as a result of fatty infiltration. The terms ‘kwashiorkor’ and ‘marasmus’ are descriptive terms of the extent of the PEM. In marasmus, there is a deficiency in total food intake; the child is apathetic, withdrawn, and stunted in growth with spindly arms and legs. In kwashiorkor, the major deficiency is in protein intake; the child has a swollen abdomen with dependent oedema of the legs, often with skin and eye infections, a large fatty liver, and a reddish-yellow tinge to the hair. The two conditions are part of a spectrum and may coexist in the same community (7.138).

In the adult, weight loss is the most common feature of the disease. Often these people are old, poor or reclusive; they may have alcoholism or psychiatric disease and take an extremely deficient diet. There may be evidence of chronic infections (e.g. tuberculosis), malignancy, previous surgery (particularly alimentary) or diseases of kidneys or liver. The appearances are typical, with obvious major weight loss so that the person looks skeletal with significant loss of adipose tissue, skin hanging in folds, wasted limbs, ascites, dependent oedema, dry flaky skin and depigmentation (7.139). The blood pressure is reduced, the pulse slow, and central core temperature may be reduced. The triceps skin-fold thickness and muscle bulk are reduced. There may also be other features of vitamin or trace element deficiency.

The diagnosis is usually made clinically, but investigations show anaemia that may be caused by deficiency of iron or folate, or both; biochemistry shows the extent of the protein deficiency, with low serum albumin and transferrin. There may also be impairment of renal and liver function. Immunity is also depressed, with cutaneous energy and lymphopenia. Death is often caused by infection.

7.137 Skin-fold thickness, using special calipers, provides an objective measure of body fat. Here, the ‘triceps’ skin-fold thickness is being measured halfway between the acromial and olecranon processes. If this measurement is accompanied by other measurements over the biceps, the subscapular region and the suprailliac region, the sum of the four thicknesses can then be used to assess the patient’s degree of obesity.

7.138 Kwashiorkor and marasmus in brothers. The younger brother, on the left, has kwashiorkor with generalized oedema, skin changes, pale reddish-yellow hair and a miserable expression. The older child, on the right, has marasmus, with generalized wasting, spindly arms and legs and an apathetic expression.

7.139 Malnutrition has resulted in severe weight loss. Underlying malignant disease, chronic infection or malabsorption is the most likely cause, but occasionally the condition may result simply from self-neglect and inadequate food intake.
Treatment is with a diet of normal calorie content and constituents. This should be implemented slowly and young children may require nasogastric feeding. Hypothermia and infections require treatment. Supplements of vitamins and minerals should also be given.

PEM is probably the most common cause of death worldwide. The mortality of severe cases is 50–75%, and there is a massive morbidity resulting from physical and mental stunting.

**ANOREXIA AND BULIMIA NERVOSA**

Anorexia nervosa usually occurs in white adolescent girls. It results in severe weight loss as a result of ‘voluntary’ starvation. There is often a history of obesity in childhood; there may have been psychological trauma with teasing at school, which has produced an intense desire to alter the body image and there may be associated psychosexual problems. Patients often deny hunger or weight loss. They become devious about avoidance of eating and may vomit up a meal surreptitiously if they have been forced to eat. The desire to lose weight may also involve the use of purgatives, diuretics and violent programmes of exercise. The clinical features include

- Onset before age 25 years in a female
- Loss of >25% of body weight — absence of body fat
- Secondary amenorrhoea
- Presence of lanugo hair over body
- Preservation of breast tissue
- Parotid enlargement
- Dependent oedema caused by low serum albumin
- Low blood pressure with bradycardia.

Patients may also have diarrhoea as a result of laxative abuse or eroded teeth due to the repeated vomiting of acid stomach contents (7.140), or both; they may show features of depression or anxiety. The facial and bodily appearances are recognizable, but not in themselves diagnostic (7.141, 7.142).

There is no diagnostic laboratory test, but there may be anaemia and leucopenia, and the serum albumin may be low. There is often a disturbance of glucose tolerance. Many patients show disturbance of other endocrine functions and biochemical abnormalities may include high levels of cortisol, low potassium with metabolic alkalosis secondary to vomiting, low zinc levels and elevated triiodothyronine levels.

Treatment is often difficult, but includes psychological and physical support.

Bulimia nervosa is a related condition in which binge eating is associated with self-induced vomiting. It is often seen in women in their mid-20s.

Both conditions have a mortality rate of 5–10% from the disease itself or from suicide. Osteoporosis is a long-term complication of chronic eating disorder.
ARTIFICIAL NUTRITIONAL SUPPORT

In a hospital population, artificial nutritional support improves morbidity and mortality in patients with a range of intestinal disorders and in those with swallowing difficulties.

It is indicated when a patient has
• Continuing weight loss greater than 10% of original body weight
• Inability to increase normal oral intake
• Active disease that cannot be controlled and will lead to either of the above criteria.

Consideration must be given to nutritional requirements of total energy, fluid intake, proteins, electrolytes, trace elements and vitamins. Balanced oral and parenteral feeds are available.

If intestinal function is otherwise normal, enteral feeding is suitable. In the hospital setting, enteral tube feeding must be considered for those who have swallowing difficulties due to stroke, prolonged coma or severe burns, and for those who do not eat because of nausea associated with chronic sepsis, renal failure, malignancy or brain disease. In the presence of intestinal failure (e.g. ileus, fistulae, obstruction, active Crohn’s disease), the parenteral route should be used. Increasingly, these nutritional support systems may be used in the community.

Enteral nutrition can be effectively carried out by the use of a fine-bore naso-ental feeding tube (7.143) or by percutaneous endoscopic gastrostomy (PEG) (7.144, 7.145). The PEG tube system should be used if it is predicted that nutritional support will be required for more than 3 weeks. The advantages are the increased comfort of the patient and reduction of the possibilities of aspiration.

Parenteral access has until recently concentrated on catheter placement into the central veins. However, this has been associated with a significant incidence of local venous and intracardiac thrombosis, and with generalized infection. The result is failure in about 20% of cases. In addition, there is a significant morbidity when inserting the catheter into the subclavian or internal jugular veins (e.g. pneumothorax or arterial cannulation in error). If the requirement is clearly for a prolonged period, a ‘Hickman—Broviac’ line may be used. This is a silicone catheter with a Dacron cuff, which is placed in a central site via a subcutaneous tunnel (7.146). The cuff allows fibrous tissue to grow into it to anchor the catheter and to reduce the risk of infection. Such catheters may also be used for long-term administration of chemotherapy (4.108). Peripheral catheters may be used for parenteral nutrition, especially when the anticipated need is relatively short term (7.147). Infection and local thrombosis are potential complications of all venous cannulae.

7.143 Enteral nutrition in a hospital patient with swallowing difficulties following stroke. A fine-bore polyurethane tube is passed via the nose into the stomach or duodenum, and the administration of the feed can be controlled by an automated pump. Such naso-ental tubes are usually well tolerated. Mucosal ulceration rarely occurs, but aspiration pneumonia is a possible complication. With practice, the tube may be reinserted at home if necessary by the patient or his family.

7.144, 7.145 A newly inserted percutaneous endoscopic gastrostomy (PEG) tube seen endoscopically in the stomach wall (7.144) and exteriorly (7.145). A cannula is inserted from the exterior abdominal wall to the stomach under endoscopic control; a guide suture is inserted through this cannula, which is then caught by an endoscopic snare and pulled up the oesophagus to the mouth. Finally, the PEG tube is attached to this suture and is pulled down via the mouth and the oesophagus to the stomach and the exterior. When the PEG tube is finally positioned, only a retaining collar and its orifice remain in the stomach. The tube is held in place on the exterior abdominal wall by a special fixation device.

7.146 Intravenous catheter for the long-term administration of parenteral nutrition (‘Hickman—Broviac line’). The line passes through a subcutaneous tunnel and has a Dacron cuff before entering the venous system. These features minimize the risks of displacement and tracking infection.
7.147 Peripheral intravenous catheter for parenteral nutrition. There has recently been a move back to appropriate peripheral intravenous cannulae for parenteral nutrition. The risk of serious complications may be lower than with central catheterization.

VITAMINS AND DISEASE

Vitamin A (Retinol)
In the human diet, vitamin A is found mainly in dairy products (milk, butter, eggs and cheese) and in liver and is added to various foods, especially margarine, as beta-carotene, the immediate precursor. A normal balanced diet provides 750–1000 µg per day — sufficient to maintain the liver stores of this vitamin.

Vitamin A is necessary for the normal function of most cell lines but particularly for function of the retinal cells (especially the rods), and for the integrity of the conjunctival epithelium and the skin generally. Dietary deficiency may be found worldwide, particularly among rice-eating populations and those suffering from PEM. In the West it is found in patients with malabsorption, especially after surgical removal of portions of the small intestine.

Deficiency of vitamin A leads rapidly to night blindness because of failure of rhodopsin regeneration in the rods. Alterations to the conjunctival and corneal epithelium and the tear glands produce dryness and roughness with loss of sensation, followed by erosions and local inflammation (xerophthalmia). Bitot’s spots are frothy, waxy, white accumulations of desquamated epithelium on the exposed conjunctiva at the corneal edge (7.148). The end result may be visual impairment and blindness as the erosions enlarge, become infected and allow prolapse of the iris and lens (keratomalacia).

The skin is also generally affected, with loss of sebaceous gland function as the glands become covered with keratin.

The diagnosis is clinical, but the plasma vitamin A may be measured, as may the visual fields in different light intensities. Fluorescein angiography is of value in defining the retinal changes.

Treatment is with vitamin A. This may require health education and dietary change for a community. Those with features of deficiency will readily respond to vitamin A given orally, or by injection when there is malabsorption.

Intoxication with vitamin A is rare and may present acutely with nausea, vomiting and headache as a result of a rise in intracranial pressure. Chronic overdosage results in changes in the skeleton as a result of painful periosteal proliferation. Hypercalcaemia may also be found. Stopping the excessive vitamin intake results in rapid healing of the lesions.

Excess ingestion of beta-carotene-containing foods, that is carrot juice, carrots, or dark green leafy vegetables, may lead to pigmentation of the skin (7.149).

Niacin
Niacin is the generic name for nicotinic acid and related compounds that are widely available in the diet and can be synthesized in the body from tryptophan. The daily requirement is of the order of 20 mg and, if absent from the diet, clinical features of deficiency (pellagra) appear in about 1 month. Pellagra is found particularly in populations who eat maize as their staple diet, as tryptophan is absent from maize proteins and niacin is present in an unavailable form. It may also be found in general malnutrition, as in chronic alcoholism or malabsorption syndrome, with low protein diets and in certain genetic disorders. Use of isoniazid for treatment of tuberculosis may induce deficiency.

The typical clinical presentation of pellagra is that of a chronic wasting disease associated with the triad of dermatitis, dementia and diarrhoea. The skin lesions are symmetrical, often, but not exclusively, on skin exposed to sunlight (7.150). The features of dementia are associated with peripheral neuropathy. Diarrhoea is associated with mucosal changes that may also manifest as glossitis, proctitis and vaginitis.

Diagnosis is purely clinical and is confirmed by a rapid response to therapy with niacin or tryptophan.
7.149 Carotenaemia has resulted in an orangey pigmentation of the skin in this patient. The condition can be distinguished from jaundice by examination of the sclerae, which remain white. This rare condition is usually the result of excessive ingestion of carrots or other carotene-containing foods. It is benign and usually subsides after withdrawal of the source.

7.150 Pellagra. The skin changes begin as an erythema with pruritus and burning. Bullae may form and rupture. At the slightly later stage shown here, the skin becomes hard, rough, cracked, blackish and brittle; with more severe involvement, extensive exfoliation may occur. Here only sun-exposed areas are affected, but any part of the body may become involved.

7.151 Wet beriberi. The patient has generalized oedema and signs of pulmonary congestion resulting from left heart failure. Peripheral neuropathy was also demonstrable.

7.152 Dry beriberi. This patient has chronic polyneuritis, with wrist drop and foot drop. In dry beriberi, there is also loss of tendon reflexes, joint position sense and vibration sense, tenderness in the calf muscles on pressure, anaesthesia of the skin, especially over the tibia, paraesthesia in the legs and arms, and motor weakness.

Thiamine
Thiamine is found extensively in vegetable products and in animal tissues. There may be major losses during preparation of food (e.g. machine milling of rice) and also during cooking above 100°C. The absorption and metabolism of thiamine are affected by factors such as pregnancy, alcoholism and coincidental diarrhoeal disease. Storage in the body is minimal and deficiency develops rapidly on a diet containing under 1 mg thiamine per day. Two rather different syndromes may result.

- Wet beriberi is characterized by peripheral vasodilatation with a hyperkinetic circulation, heart failure and retention of fluid, with oedema of the legs, ascites, hepatomegaly and pulmonary congestion (7.151); peripheral neuropathy is a common accompaniment.

- Dry beriberi is manifest as peripheral neuropathy with symmetrical loss of sensation, and loss of motor function (7.152), encephalopathy with cranial nerve palsies, ataxia, confusion, coma and death; the Wernicke-Korsakoff syndrome is usually associated with thiamine deficiency in alcoholic patients; it consists of retrograde amnesia and confusion in association with other features of dry beriberi. The diagnosis is often made on clinical grounds, as there is usually evidence of cause (e.g. alcoholism, inadequate diet or famine). A range of biochemical tests is available in specialized laboratories, including blood thiamine, pyruvate, lactate and red cell transketolase. Clinical response to added thiamine can be dramatic, with reversal of heart failure, spontaneous diuresis and improvement of neurological signs, but only about one-half of the patients with severe deficiencies recover full neurological function.
**Riboflavin**

Riboflavin is found in vegetables and meat. The daily requirement is about 1.5 mg, and deficiency is most commonly seen in association with deficiencies of other vitamins and minerals. The clinical picture is that of mucocutaneous changes which are known as the oro-oculo-genital syndrome. There are extensive changes in the mouth and pharynx with glossitis, cheilosis (7.153), angular stomatitis and oedema of the pharyngeal and oral mucosa. There may also be marrow depression with a normochromic normocytic anaemia and widespread seborrhoeic dermatitis involving the scrotum or perineum.

**Pyridoxine (vitamin B6)**

Pyridoxine and related vitamin B6 molecules are found widely in meats, vegetables and grains and an intake of about 2 mg is required per day. Dietary deficiency is rare, but may be found as part of a more generalized deficiency in patients with malabsorption syndromes or chronic alcoholism. The most common presentation now results from B6 antagonism by drug therapy with penicillamine, cycloserine or isoniazid.

The clinical features of deficiency are seborrhoeic dermatitis and glossitis (9.47). The diagnosis may be made by measurement of tryptophan metabolites and deficiency rapidly responds to dietary supplementation with pyridoxine.

Also described are a range of pyridoxine-responsive disorders that include a genetic liability to epilepsy and brain damage, chronic anaemia with ringed sideroblasts, cystathioninuria and xanthurenic aciduria.

**Biotin**

Biotin deficiency is exceptionally rare and is found only in food faddists. The clinical features may include dermatitis, fatigue, depression and mucosal changes in the mouth and intestine.

**Vitamin E**

Vitamin E deficiency is rare in humans, but has been associated with haemolysis. Recent work suggests that the vitamin also has a role as an antioxidant and may prove to be of long-term value in the prevention of atheroma formation.

**Other vitamins**

Diseases related to deficiencies or excess of other vitamins are included elsewhere in this book:
- Folic acid: pp. 372, 427
- Vitamin B12: pp. 372, 427
- Ascorbic acid: 8.22, p. 459
- Vitamin D: pp. 154, 372

**TRACE ELEMENTS IN NUTRITION**

A large number of inorganic ions are essential for the maintenance of health. These include iron, iodine, copper, zinc, cobalt, selenium, chromium and tin. Deficiencies of iron and iodine are discussed on p. 429 and p. 323, respectively. Identifiable clinical syndromes have also been described in zinc and copper deficiency.

Deficiency of zinc in the diet may lead to retarded growth, retarded sexual development, hyperkeratotic dermatitis (7.154), loss of hair and anaemia. Supplementation of the diet with zinc produces a growth sprint and correction of anaemia.

Acrodermatitis enteropathica is an inherited disorder of zinc absorption in which patients present with chronic diarrhoea and growth retardation, weight loss, dermatitis, and perianal ulceration, often caused by candidal infections. It responds dramatically to zinc therapy.

Deficiency of copper in the diet is rare and is usually associated with other deficiencies, especially of protein and vitamins. Anaemia and leucopenia are the usual manifestations and these respond to normalization of the diet. Menke’s kinky hair syndrome results from an extremely rare disorder of intestinal copper absorption. Death results from CNS and arterial degeneration.

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7.153 Cheilosis is one manifestation of riboflavin deficiency, and may also occur with deficiency of iron and other vitamins. It is characterized by vertical fissuring, which is later complicated by redness, swelling and ulceration of the lips. Angular stomatitis may also be present, as here; many patients with riboflavin deficiency also have widespread seborrhoeic dermatitis involving the scrotum or perineum.

7.154 Zinc deficiency leads to a characteristic erythematous, hyperkeratotic skin rash. This 24-year-old woman had generalized malnutrition, associated with severe Crohn’s disease. Note the wasting of the thigh muscles. She was managed by prolonged parenteral nutrition, and the skin rash responded well to zinc supplementation.
THE PORPHYRIAS

The porphyrias are a heterogeneous group of inborn errors of metabolism in which there is an overproduction of various intermediate compounds (porphyrins) in the biosynthesis of haem. Their classification is summarized in 7.155. The acute hepatic porphyrias are the result of partial enzyme blocks in the biosynthetic pathway for haem.

Acute intermittent porphyria

Acute intermittent porphyria is an autosomal dominant genetic disorder of metabolism in which exposure to various drugs, including alcohol, may trigger a life-threatening crisis (a pharmacogenetic disorder). The condition results from a deficiency in porphobilinogen deaminase. It presents acutely in early adulthood with fever, abdominal pain and vomiting, which may be mistaken for an acute abdomen, but is caused by autonomic neuropathy. There may also be a history of acute onset of peripheral neuropathy with limb paralysis and loss of sensation, often associated with depression or anxiety. The diagnosis is often missed, and the symptoms may be attributed to hysteria. The clues lie in a positive family history and in examination of the urine, which turns dark red-brown on standing. Attacks may be precipitated by alcohol or by drugs such as anticonvulsants and oral contraceptives, and they may be associated with a rise in pulse rate and blood pressure. Between attacks there may be no clinical features.

During the acute attacks, there may be a polymorphonuclear leucocytosis, which may be misinterpreted as an indicator of infection. There may also be hyponatraemia, hypomagnesaemia and uraemia. The best screening test is to find porphobilinogen in the urine. On standing, the urine darkens, as a result of the formation of uroporphyrin and porphobilin, and fluoresces in ultraviolet light (7.156). After treatment with Ehrlich’s aldehyde, it develops a pink coloration. The level of delta aminolaevulinic acid in the blood is also raised.

Treatment is supportive, with avoidance of drugs known to precipitate the acute attack.

Variegate porphyria

Variegate porphyria combines the acute features of acute intermittent porphyria with chronic skin sensitivity to sunlight and trauma. The inheritance is autosomal dominant, and the enzyme defect is in protoporphyrinogen oxidase. The clinical presentation is often similar to that of acute intermittent porphyria, but it occurs on a background of pigmentation of the skin, associated with bullae, ulceration, atrophy and hypertrichosis (7.157). The diagnosis is made by finding excess protoporphyrin in the urine at all times and a positive test for porphobilinogen during acute attacks. Important aspects of management include the avoidance of direct sunlight and the wearing of adequate protective clothing.
Porphyria cutanea tarda
Porphyria cutanea tarda is the most common type of porphyria and is characterized by chronic skin lesions and chronic liver disease, often associated with alcoholism and sometimes with hepatic siderosis. The enzyme defect is in uroporphyrinogen decarboxylase. The clinical features are similar to the chronic features of variegate porphyria (7.158). The incidence of diabetes mellitus is increased and there is an association with a range of autoimmune diseases. As the disease is caused by an inherited deficiency of uroporphyrinogen decarboxylase, there is an increased excretion of uroporphyrin in the urine, which may be pink or brown.

A similar clinical picture may be found in people poisoned with a range of polychlorinated hydrocarbons and with primary and secondary liver neoplasia.

Erythropoietic protoporphyria
Erythropoietic protoporphyria is a very rare genetic disorder of porphyrin metabolism in which the transmission is autosomal recessive. The usual clinical presentation is with solar urticaria without blistering, scarring or hyperpigmentation. Occasionally, patients may develop cirrhosis of the liver, splenomegaly, gallstones and anaemia. A characteristic feature is red pigmentation of the teeth (erythrodontia, 7.159). The chemical defect is in the enzyme ferrochelatase, which promotes the incorporation of ferrous iron into protoporphyrin. As a result, there is excessive protoporphyrin in many tissues, especially in haemopoietic cells, liver and skin. The diagnosis is made by demonstrating the red fluorescence of protoporphyrin in red cells in a blood film.

DISORDERS OF AMINO ACID METABOLISM
Alkaptonuria
Alkaptonuria is a hereditary disorder caused by the absence of the enzyme homogentisic acid oxidase. The result of this defect is that homogentisic acid produced by degradation of phenylalanine and tyrosine cannot be further metabolized and therefore accumulates in the body. It is excreted in the urine and may manifest itself in childhood, through the brown colour that develops in nappies (diapers). This is caused by a reduction product of the colourless homogentisic acid. Homogentisic acid tends to pigment cartilage and other connective tissue, including the sclera (ochronosis) (7.160), and eventually causes a degenerative arthropathy (7.161). No prophylactic or curative treatment is available. Gene therapy may prove possible in the future.
Phenylketonuria
Phenylketonuria is an autosomal recessive disorder that produces deficiency of the enzyme (phenylalanine hydroxylase) responsible for the conversion of phenylalanine to tyrosine, with resultant high levels of phenylalanine and its metabolites in the blood and body tissues. This results in progressive mental retardation and epilepsy. There is usually fair, sparse hair and eczema. Neonatal screening is routinely available (the Guthrie test), and should enable most affected individuals to be detected early and dietary restrictions to be imposed.

Homocystinurias
The homocystinurias are transmitted as autosomal recessives and are caused by at least three enzyme defects that allow the accumulation of homocystine in the body. There is progressive mental impairment with epilepsy, subluxation of the lens (7.162), arachnodactyly and a likelihood of arterial and venous thrombosis.

Cystinosis
Cystinosis is an autosomal recessive disorder in which cystine accumulates in the tissues, especially the cornea, bone marrow, liver and spleen and kidneys. A range of disorders results. In childhood, the kidney is particularly affected and renal failure may develop (Fanconi syndrome); in the adult, the cornea is particularly affected (7.163). There are intermediate varieties. The diagnosis is made by finding typical cystine crystals in biopsy material or in the cornea by slit-lamp examination.

LYSOSOMAL STORAGE DISEASES
Deficiencies of lysosomal enzymes may result in the accumulation of substrates or abnormal metabolites in all the tissues of the body. At least 30 separate enzyme deficiencies have been characterized and these produce different clinical syndromes of which only the most common are described here.

Lipoidoses
Gaucher's disease is an autosomal recessive disease in which deficiency of the enzyme glucosylceramidase results in the accumulation of glucocerebrosidase in the body. The disease is found especially in Ashkenazi Jews, and patients present in a wide variety of ways, especially with hepatosplenomegaly (7.164) with neurological involvement (epilepsy and mental retardation) in children, and involvement of liver and spleen, bone marrow, bone, lung and eye in adults. The diagnosis is made by finding the characteristic Gaucher cell in biopsy tissue (e.g. bone marrow or spleen biopsy). Enzyme replacement therapy and gene therapy are now becoming feasible.

Niemann–Pick disease is an autosomal recessive disease in which a deficiency of sphingomyelinase results in accumulation of sphingomyelin in the tissues, especially in the CNS, liver and spleen and bone marrow. The clinical presentation varies according to the subtype of the disease. The common presentation in childhood is with mental retardation and hepatosplenomegaly. In Type A disease, there is often a cherry-red spot in the retina (7.165). The diagnosis is made by finding...
the characteristic lipid-laden sea-blue histiocyte in biopsy material. Adults with Type E disease present with hepatosplenomegaly but no neurological abnormalities.

Tay–Sachs disease (familial amaurotic idiocy) is an autosomal recessive disorder in which a deficiency of hexosaminidase A and B results in the accumulation of GM2 gangliosides in the brain and peripheral nerves. The result is mental retardation and epilepsy. There is usually a cherry-red spot on the retina (7.165). Programmes of antenatal detection are available.

Fabry’s disease is an X-linked recessive disease that is caused by deficiency of alpha-galactosidase A resulting in accumulation of a trihexoside in body tissues. Typical features include punctate angiomatosus lesions on the skin, corneal dystrophy, progressive renal failure and liability to thrombotic arterial disease. There may also be mental retardation, epilepsy and peripheral neuropathy.

**Mucopolysaccharidoses**

There are seven disorders in this group of metabolic defects, with very similar presentations.

Hurler’s syndrome is an autosomal recessive disorder caused by a defect in the breakdown of complex carbohydrates. The glycosaminoglycans chondroitin, dermatan and heparan sulphate accumulate in subcutaneous tissues, bone, brain and liver leading to characteristic physical and mental changes. The appearances are typical with coarse facies (7.166), hepatosplenomegaly, corneal opacities and multiple bone abnormalities causing stunting of growth (dysostosis multiplex). There is severe mental retardation and a typical life expectancy of 10 years as a result of cardiorespiratory problems.

**LAURENCE–MOON–BIEDEL SYNDROME**

This is an autosomal recessive disorder that is associated with mental retardation, polydactyly (7.167), retinitis pigmentosa, hypogonadism and obesity.

**DOWN’S SYNDROME**

Down’s syndrome accounts for up to one-third of children with severe learning difficulties. The degree of disability ranges from mild to severe. The physical features are typical and include a small head with a flat occiput, up-slanting palpebral fissures, epicanthic folds, small nose with a poorly developed bridge and small ears (7.168–7.170). Grey-white areas of depigmentation
are seen in the iris (Brushfield spots, 7.171); the mouth is often held open and the tongue protrudes. The hands are broad with a single transverse palmar crease (7.172), and the fifth finger shows clinodactyly (7.168). Congenital heart lesions are common (7.169). Adult stature tends to be small and there is a significant incidence of leukaemia in the older patients.

At maternal age 25 years the chance of bearing a child with Down's syndrome is 1 in 1400; at age 30 years, 1 in 800; at 40 years, 1 in 110; and at 45 years, 1 in 30. As these children tend to be born to older mothers, it is important to offer amniocentesis or chorionic villous sampling to this group in early preg-
nancy, to look for trisomy or translocation of chromosome 21.

Maternal blood tests have also now become available for women of all ages and have a place in screening (in combination with ultrasound). These include alpha fetoprotein, unconjugated oestriol (uE3), human chorionic gonadotrophin (HCG) and neutrophil alkaline phosphatase. These tests are claimed to give a 60–80% diagnostic rate, and ultrasound scanning detects early evidence of heart defects. Such screening must be accompanied by skilled counselling on the possibility of termination of pregnancy if the fetus is found to be affected.

7.170 Down's syndrome in a young adult showing the characteristic adult facies. Note the prominent epicanthic folds and the small nose and ears.

7.171 Brushfield spots are a common feature of Down's syndrome and may be seen in the newborn baby, as here. They are tiny, whitish areas of depigmentation on the iris.

7.172 Single palmar crease is a classic feature of Down's syndrome, but it is important to remember that it can occur with other chromosomal abnormalities, and as a normal variant. It is diagnostic of Down's syndrome only when associated with the other features of the condition.
Patients with gastrointestinal disease present with a variety of symptoms (8.1). These may indicate a specific disease, but patients often have alimentary disease without specific symptoms, so the clinician must be alert to clinical signs.

### 8.1 Common gastrointestinal symptoms.

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>Heartburn</td>
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<tr>
<td>Chest pain</td>
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<tr>
<td>Dysphagia</td>
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<tr>
<td>Anorexia</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Diarrhoea</td>
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<tr>
<td>Gastrointestinal bleeding</td>
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<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Jaundice</td>
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<tr>
<td>Ascites</td>
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</tbody>
</table>

General inspection is of particular importance. Muscle wasting, together with the more obvious depletion of fat stores, is indicative of malnutrition (4.1, 7.139, 8.2). Pallor of the mucous membranes is indicative of anaemia (p. 424 and 8.3, 10.2, 10.3) and koilonychia is found with prolonged iron deficiency (2.103, 10.6, 10.21). Finger clubbing accompanies malabsorption, small intestinal disease and cirrhosis (2.104, 2.105). Palmar erythema occurs in chronic liver disease and such patients may also have jaundice, spider naevi, ascites, and, in male patients, gynaecomastia and testicular atrophy (see p. 393). Skin rashes such as erythema nodosum (2.45) may accompany inflammatory bowel disease and these patients sometimes also suffer from arthritis. Inspection of the mouth and tongue may reveal evidence of candidiasis (1.35, 1.175, 1.176) or aphthous ulcers (8.4) that may be associated with intestinal disease.

Patients with upper gastrointestinal bleeding may present with frank haematemesis (vomiting of fresh blood), with vomiting of altered blood (‘coffee ground’ vomit; 1.61), with passage of altered blood in the stool (melena), or silently as anaemia. Those with lower intestinal bleeding may present with the passage of fresh blood or clot per rectum (8.5), with frank blood-streaking of the stool, or silently with anaemia (and occult blood in the stool on testing). The many possible causes of gastrointestinal bleeding are summarized in 8.6.
### Causes of Gastrointestinal Bleeding

#### Common causes

<table>
<thead>
<tr>
<th>Location</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>Mallory-Weiss tear</td>
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<tr>
<td></td>
<td>Reflux oesophagitis</td>
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<tr>
<td></td>
<td>Carcinoma</td>
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<tr>
<td></td>
<td>Varices</td>
</tr>
<tr>
<td>Stomach</td>
<td>Erosions or gastritis</td>
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<tr>
<td></td>
<td>(alcohol/aspirin/NSAIDs)</td>
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<tr>
<td></td>
<td>Gastric ulcer</td>
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<tr>
<td></td>
<td>Carcinoma</td>
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<tr>
<td></td>
<td>Other tumours</td>
</tr>
<tr>
<td></td>
<td>(polyps/lymphoma/leiomyoma/haemangioma)</td>
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<tr>
<td></td>
<td>Varices</td>
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<tr>
<td>Duodenum</td>
<td>Erosions</td>
</tr>
<tr>
<td></td>
<td>Duodenal ulcer</td>
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<tr>
<td>Lower</td>
<td>Haemorrhoids</td>
</tr>
<tr>
<td>gastrointestinal tract</td>
<td>Anal fissure</td>
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<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>(ulcerative colitis/Crohn's disease)</td>
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<tr>
<td></td>
<td>Diverticulitis</td>
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<tr>
<td></td>
<td>Colonic carcinoma</td>
</tr>
<tr>
<td></td>
<td>Intussusception</td>
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</tbody>
</table>

#### Unusual causes

- Arteriovenous fistulae
- Hereditary haemorrhagic telangiectasia
- Angiodysplasia
- Vasculitis
- Amyloidosis
- Meckel's diverticulum
- Blood disorders – haemophilia, thrombocytopenia
- Rupture into bowel of aortic aneurysm

### 8.4 Aphthous ulcers

Commonly occur in isolation, but they may be an indication of an underlying intestinal disease, such as gluten enteropathy or inflammatory bowel disease.

### 8.5 Massive lower gastrointestinal bleeding

The patient passed a large bloody stool. When teased apart, this was found to be a blood-clot cast of much of the colon. The unusual cause of bleeding here was erosion and rupture of an abdominal aortic aneurysm into the bowel.

### 8.6 Causes of gastrointestinal bleeding

8.7 Typical steatorrhoea. The stool is pale, with the consistency of pale clay. It often floats in the lavatory (because of its high air and fat content) and is difficult to flush away.

8.8 Left-sided supraclavicular lymphadenopathy (Virchow's node) may result from lymphatic spread of a gastric or pancreatic neoplasm via the thoracic duct. This may be the first sign of malignancy, as in this patient. The node mass was biopsied 1 month before this picture was taken, and has regrown since then. Histology revealed adenocarcinoma cells. The primary tumour was in the stomach.
The stools should be examined for blood and colour. In steatorrhoea, they are usually the colour and consistency of soft clay (8.7) and have a particularly unpleasant odour. Diarrhoea is common in gastroenteritis, and in cholera and some forms of *Escherichia coli* gastroenteritis typical 'rice water' stools are passed (1.145). Some other forms of gastroenteritis, dysentery and acute ulcerative colitis are associated with the passage of bloody diarrhoea. Parasitic worms may be seen in the stool (see p. 387).

Examination of the regional lymph nodes is important: patients with gastric carcinoma sometimes have left-sided supraclavicular lymphadenopathy (8.8), and posterior cervical lymphadenopathy may occur in pharyngeal carcinoma. General lymphadenopathy is a feature of Whipple's disease. Abdominal examination may reveal enlargement of the spleen or liver, or the liver may be small or craggy. Ascites (8.9, 9.13), detected by shifting dullness, most commonly reflects cirrhosis or malignancy. Abdominal masses suggest colonic or other malignancy, or an inflammatory disease of the bowel such as Crohn's disease or diverticulitis.

Rectal examination provides important clues. Haemorrhoids cannot be felt but may be seen externally (10.23) or on proctoscopy. Perianal skin tags denote thrombosed haemorrhoids. In Crohn's colitis, they may be associated with fistula-in-ano. Perianal condylomata (8.10) may be mistaken for anal carcinoma; they are most commonly found in homosexual men.

INVESTIGATIONS

Investigations of both structure and function may be needed, including endoscopy, radiology, nuclear medicine, histopathology, tests on blood and stool, and manometry.

The video or fibreoptic endoscope allows direct inspection and biopsy of lesions as well as therapeutic intervention.

- Upper alimentary endoscopy with the forward viewing endoscope, performed in the fasting patient, usually under light sedation, facilitates the demonstration of oesophageal disorders (8.11), the dilatation of oesophageal strictures, the removal of foreign bodies and the injection of oesophageal varices; gastric lesions (8.12) and duodenal lesions (8.13) are readily seen and biopsied, and haemorrhage can be arrested by the use of a laser beam or heater probe passed down the biopsy channel.

- The side-viewing endoscope placed in the second part of the duodenum, permits cannulation of the ampulla of Vater and retrograde radiological examination of the pancreas and biliary tree (endoscopic retrograde cholangiopancreatography, ERCP — see p. 399).
The flexible sigmoidoscope and colonoscope are used to examine the distal and entire colon; sigmoidoscopy or colonoscopy, or both, are indicated for the diagnosis and staging of inflammatory bowel disease and for the investigation of colonic symptoms, particularly rectal bleeding; when polyps are found, they can often be removed with a diathermy snare (8.14).

Radiological investigations are important. Endoscopy has reduced the need for the barium meal and the barium enema, but double-contrast techniques can still provide valuable information (8.15, 8.16); and small bowel meals or enemas are still important for the identification of structural disease of the jejunum and ileum such as Crohn's disease (8.17). Plain abdominal radiographs are important for the recognition of toxic dilatation in colitis and to confirm clinical suspicions of intestinal obstruction (8.18). Angiography is occasionally helpful in the investigation of gastrointestinal bleeding of obscure cause or of suspected mesenteric ischaemia.

Ultrasound and CT scanning are especially useful in the investigation of the liver, pancreas and biliary tract (see p. 400), but also have a useful role in generalized abdominal disease (8.19).

Nuclear medicine has been used extensively for structural imaging of the liver and biliary tract, and can also be applied to the assessment of intestinal function. Oesophageal dysmotility and gastric emptying can both be assessed by reference to the pattern and time of transit of swallowed isotope, measured by the gamma camera. Radiolabelled (99mTc) red blood cells (from the patient) may be used to investigate the site of chronic gastrointestinal blood loss when this is not revealed by other means (8.20).

8.12 Endoscopic view of the gastric mucosa showing several gastric polyps. One has just been biopsied via the endoscope and is bleeding. Multiple gastric polyps are usually benign and, unlike polyps in the large bowel, most should not be regarded as premalignant lesions. Histological examination is essential, however.

8.13 A large duodenal ulcer, seen via a videoendoscope. Duodenal ulcers are almost invariably benign, so histological examination is not usually required to exclude malignancy. Antral biopsies may, however, be taken to investigate the probability of underlying infection with Helicobacter pylori.

8.14 Colonoscopic polypectomy. A wire snare has been introduced through the colonoscope. It will be looped over the pedunculated colonic polyp, tightened around its stalk, and diathermy will then be applied via the snare to sever the stalk without bleeding.

8.15 Double-contrast barium meal, showing a small duodenal ulcer crater (arrow). In expert hands, this technique has a diagnostic accuracy similar to that of endoscopy for many lesions of the stomach and duodenum; nevertheless, biopsy is not possible with radiology alone and most lesions of the stomach require biopsy.
8.16 Double-contrast barium enema in a patient with familial polyposis coli. This close-up view shows multiple small, sessile colonic polyps, appearing as small, rounded, dark patches. The surface of polyps is poorly coated with barium, whereas their edges and the rest of the colonic wall retain more contrast medium. The radiological appearance of the polyps corresponds to their colonscopic appearance (see 8.115). Familial polyposis is a premalignant condition and prophylactic colectomy is indicated.

8.17 A small bowel meal demonstrates a typical feature of Crohn's disease - a long stricture of the terminal ileum. Strictures may also be caused by tuberculosis and lymphoma, but the 'cobblestone' appearance (arrow) is strongly suggestive of Crohn's disease.

8.18 Plain abdominal X-ray, taken in the erect position, demonstrating multiple fluid levels in the bowel. In combination with a supine film, this appearance shows apparent obstruction to the gut at the distal end of the small bowel. It is important to remember that similar appearances may occur in paralytic ileus, peritonitis, gastroenteritis and coeliac disease. The films must always be interpreted in their clinical context.

8.19 CT scan demonstrating a large abdominal tumour (arrowed). CT-guided biopsy showed this to be a leiomyosarcoma, which originated in the duodenum.

8.20 A bleeding site in the colon, revealed by scanning after intravenous administration of some of the patient's red blood cells that had been labelled with $^{99}$mTc. This 10 minute film shows two 'hot spots' in the colon, but films at other times showed that the high count at the splenic flexure (arrow) was consistent (the other 'hot spot' here is the result of retrograde flow of blood in the colonic lumen). No abnormality had been seen on colonoscopy or barium enema, but a small angioma was found on re-endoscopy and removed at subsequent surgery.
The glycocholate breath test utilizes the ability of bacteria to deconjugate bile acids to investigate bacterial overgrowth in the small intestine. The patient is given $^{14}$C-glycine glycocholic acid. Deconjugation leads to the rapid absorption of glycine, which is metabolized, and the measured exhaled $^{14}$CO$_2$ indicates the extent of deconjugation. A similar principle is applied to the measurement of fat malabsorption using the triglyceride glyceryl-$^{14}$C-triolein. The $^{13}$C and $^{14}$C breath test is helpful in the diagnosis of Helicobacter pylori infection.

The urease test (see p.367) may be carried out on gastric antral biopsies to investigate the possibility of H. pylori infection.

The absorption of vitamin B$_12$ can be investigated by measuring the urinary excretion of the labelled vitamin, which is administered by mouth after saturating the body stores with an intramuscular injection (see p. 427).

Histopathology is important for the confirmation and staging of tumours, the recognition of different types of bowel inflammation such as Crohn's disease, and the identification of small bowel disease such as gluten enteropathy and its response to a gluten-free diet. Biopsy samples may be obtained on endoscopy (8.61) or using a Crosby capsule (8.75). H. pylori may be identified by appropriate staining of biopsies of the gastric antrum in many patients with peptic ulceration and gastritis (8.51).

Blood tests provide evidence of malabsorption (macrocytic or hypochromic microcytic anaemia), malnutrition (low transferrin, fibronectin and lymphocyte count) and liver dysfunction. Serology for H. pylori infection is helpful in diagnosis and management.

Faecal occult blood testing may point to intestinal blood loss; faecal fat measurement aids the assessment of malabsorption.

Microbiological investigation is important. The need for microscopy of stool or jejunal aspirate to identify protozoa such as Giardia (8.21) is often overlooked. Gastric biopsies may be cultured for H. pylori.

Manometry is increasingly used to investigate motility disorders.

Laparoscopy has an increasing role in the investigation of intra-abdominal disease (9.23).

### MOUTH AND TONGUE

Important information may be gained from the inspection of the mouth.

- The lips and tongue are blue in conditions associated with central cyanosis (4.4).
- Angular stomatitis (7.153, 10.2) is common in iron deficiency and in the edentulous elderly.
- Aphthous ulcers occur anywhere in the oral cavity (8.4); they may be found in otherwise healthy people, especially women, but are associated with poor dental hygiene, haematocin deficiency, gluten enteropathy and inflammatory bowel disease. Large deep ulcers are sometimes found as part of Behçet’s syndrome (3.102).
- The gums may bleed where there is periodontal disease, and in patients with monocytic leukaemia or scurvy (8.22, 10.75).
- Hypertrophied gums are a recognized complication of prolonged treatment with phenytoin (8.23), cyclosporin and calcium antagonists.
- A blue line is found at the margin of the gum and teeth in lead poisoning (8.24).
- Yellow–brown staining of the teeth may occur if tetracycline was administered during childhood or fetal life (8.25).
- Candidal infection (1.35, 1.175, 1.176) is common in debilitated and immunosuppressed patients, and under ill-fitting dentures.
- The tongue may be smooth and sore in patients with haematocin and B-vitamin deficiencies (9.47, 10.35) and in various other conditions (8.26); enlarged in patients with acromegaly (7.23), myxoedema and amyloidosis; and small and spastic in motor neuron disease; inspection may reveal evidence of hereditary haemorrhagic telangiectasia (10.113).
- Leukoplakia (2.127, 8.27) is a premalignant condition and can lead to carcinoma (8.28); hairy leukoplakia may occur in patients with HIV infection (1.136).
- Patients with conditions as varied as herpes simplex (1.77), lichen planus (2.70), Peutz-Jeghers syndrome (2.88) and scleroderma (3.81, 3.82) may present with oral or perioral lesions.
- In the burning mouth syndrome, the patient (usually an elderly woman) complains that her mouth feels 'on fire'; no abnormalities are usually found on examination, but underlying features may include ill-fitting dentures, anaemia, depression, diabetes mellitus and fear of cancer; reassurance is usually appropriate.
8.22 The gums in scurvy. Vitamin C deficiency characteristically leads to gingivitis. The gingival papillae are swollen and fragile, with a purplish coloration. In this patient, grossly neglected oral hygiene with resulting caries has compounded the problem.

8.24 Lead poisoning produces a blue line at the margin of the gum and teeth. This patient's employment involved the dismantling of car batteries. He presented with colicky abdominal pain.

8.25 Tetracycline staining of the teeth occurs when tetracycline is administered during the period of tooth formation, either via the mother in fetal life, or to the child up to the age of 12 years. In this patient, there is generalized staining without any hypoplasia of the tooth substance. Hypoplasia often occurs, but this may frequently result from the underlying condition for which the tetracycline was administered, rather than from the tetracycline itself. There are almost always satisfactory alternatives to tetracycline therapy during pregnancy and childhood.

8.26 Causes of sore tongue.

<table>
<thead>
<tr>
<th>Local irritation</th>
<th>Smoking</th>
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<tbody>
<tr>
<td>Fractured tooth</td>
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<tr>
<td>Ill-fitting dentures/crowns</td>
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<tr>
<td>Candidiasis</td>
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<td>Dry mouth</td>
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<table>
<thead>
<tr>
<th>Systemic diseases</th>
<th>Folate/vitamin B₁₂ deficiency</th>
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<tr>
<td></td>
<td>Iron deficiency</td>
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<tr>
<td></td>
<td>Collagen-vascular disorders</td>
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<tr>
<td></td>
<td>Diabetes</td>
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</tbody>
</table>

8.27 Leukoplakia of the tongue. The aetiology in this 83-year-old patient was unclear. Characteristically, leukoplakia cannot be wiped off, and it shows a nonspecific histological appearance, which excludes other diagnoses. Leukoplakia sometimes has no consequences, but should always be regarded as a potentially premalignant condition.
8.28 Carcinoma of the tongue. There is an extensive squamous cell carcinoma on the left side of the tongue. Note also the patch of leukoplakia on the right border of the tongue posteriorly.

8.29 A hiatus hernia may first be revealed on chest X-ray, especially when chest pain is the presenting feature. The presence of a fluid level crossing the midline behind the heart (arrows) is virtually diagnostic of hiatus hernia or achalasia. This patient has also had a previous right mastectomy for carcinoma of the breast and has an osteolytic secondary in the head of the right humerus.

8.30 Rolling hiatus hernia on double-contrast barium meal. The fundus of the stomach has herniated into the thorax alongside the oesophagus. The constriction in the stomach marks the level of the diaphragm, and the gastro-oesophageal junction is still beneath it. By contrast, in a sliding hernia, the gastro-oesophageal junction (cardia) slides into the chest.

OESOPHAGUS

PEPTIC OESOPHAGITIS

A lax oesophageal sphincter permits the reflux of corrosive gastric contents, containing acid pepsin and sometimes bile acids, into the oesophagus. The tendency to gastro-oesophageal reflux disease (GORD) may be compounded by the intrathoracic position of the gastro-oesophageal junction in patients with a hiatus hernia (8.29, 8.30), by increased abdominal pressure in the obese and pregnant, and by the consumption of fatty meals, alcohol, caffeine and tobacco, all of which relax the sphincter. The refluxed gastric content damages the squamous oesophageal mucosa and may impair the underlying muscle function leading to delayed oesophageal clearance which exacerbates the problem.

The patient complains of heartburn and acid reflux, which is worse after meals and at night when recumbent. Other symptoms of GORD may include eructation, dysphagia, nausea and epigastric pain. The diagnosis of oesophagitis is confirmed by endoscopy (8.31, 8.32).

Complications of oesophagitis include stricture formation (8.32, 8.33), which causes dysphagia; oesophageal ulcer, characterized by severe pain and dysphagia; bleeding; and Barrett's syndrome, in which chronic reflux leads to the replacement of the squamous epithelium by metaplastic columnar epithelium, with a risk of ulceration and carcinoma (8.34). Aspiration pneumonia may occur.

8.31 Peptic oesophagitis. This endoscopic view of moderate disease shows typical flame-like areas of shallow ulceration that are coated with yellow slough. These bleed readily when touched by the endoscope. Normal mucosa is present between these patches.

8.32 Severe peptic oesophagitis. Here the lower oesophagus is extensively ulcerated. The ulcer surface is friable. The lower oesophagus is narrowed as a result of early stricture formation.
Treatment depends on the severity of the symptoms and mucosal damage. For mild disease, advice about diet, that is losing excess weight and avoiding late, large and fatty meals, and coffee and alcohol; stopping smoking; and avoiding sleeping flat; together with symptomatic or regular use of a protective alginate preparation, may be sufficient. More severe disease requires acid suppression with an H$_2$ antagonist or a proton-pump inhibitor. The efficacy of such treatment can be enhanced by prokinetic drugs, such as domperidone and cisapride, which increase gastric emptying and oesophageal sphincter tone.

Oesophageal stenosis is usually amenable to endoscopic dilatation using balloons or other dilators (8.37, 8.47).

**INFECTIVE OESOPHAGITIS**

Oesophageal candidiasis occurs in debilitated patients who have received broad-spectrum antibiotics. It is also found in patients infected with the HIV virus (in whom it is diagnostic of AIDS). The radiological appearances of oesophageal candidiasis are shown in 1.43, and the diagnosis should be confirmed endoscopically (8.35). Patients without AIDS may respond to topical treatment with nystatin, but those with AIDS require a systemically active agent such as ketoconazole.

Patients with AIDS may also develop oesophageal infections with herpes simplex (8.36) and cytomegalovirus, and HIV itself may cause oesophagitis.

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**8.33 Benign oesophageal stricture, seen on barium swallow.** The stricture is smooth with a tapering (or funnelling) upper end that narrows gradually from normal oesophagus. The most common cause of such a benign stricture is chronic reflux oesophagitis.

**8.34 Barrett’s oesophagus.** In this condition, the junction between oesophageal (squamous) and gastric (columnar) epithelium is higher in the oesophagus than normal. The columnar epithelium is a deeper pink than the normal oesophageal squamous epithelium. There is an increased risk of dysplasia and adenocarcinoma in columnar epithelium in the oesophagus. This patient has an ulcer at the junction between the two types of epithelium, which must be biopsied to exclude malignant change.

**8.35 Oesophageal candidiasis in a patient with AIDS.** The multiple small white plaques of Candida on the background of abnormally reddened oesophageal mucosa correspond to the radiological appearance in 1.43. Patients with oesophageal candidiasis may also present with a smaller number of plaques, or with a more or less confluent white coating of the mucosa (which must not be confused with a coating of barium if the patient has recently undergone a barium study).

**8.36 Herpes simplex ulceration of the lower oesophagus in a patient with AIDS.** Note the multiple shallow ulcers in the lower part of the oesophagus. This appearance is not diagnostic of herpes simplex infection, as a similar appearance may be seen with other causes of ulceration, including some drugs (such as potassium supplements). The presence of vesicles in the mucosa (not shown here) is virtually diagnostic of herpes simplex. Treatment with high-dose intravenous acyclovir may be helpful.
GASTROINTESTINAL

OESOPHAGEAL STRICTURES

Oesophageal strictures may develop as a consequence of oesophagitis (8.32, 8.33), in response to the ingestion of corrosives or after radiotherapy. Such strictures are usually benign, but may require dilatation (8.37) or surgery to relieve dysphagia.

The Plummer–Vinson or Patterson–Brown–Kelly syndrome is the association of iron-deficiency anaemia (with koilonychia) with angular stomatitis, glossitis and atrophy of the oesophageal mucosa in the postcricoid region, which forms an obstructing postcricoid web (8.38 and p. 430). Iron therapy may reverse the process, but there is a risk of malignant change.

Oesophageal rings may also occur at or near the gastro-oesophageal junction (8.39). Their cause is unknown, but they are often associated with oesophageal motility disorders, and may be associated with dysphagia. Dilatation may be helpful.

OESOPHAGEAL CARCINOMA

Patients with oesophageal carcinoma present with progressive dysphagia for solids, and subsequently for liquids as the luminal stenosis progresses. Weight loss may be obvious.

The diagnosis is confirmed by the typical radiological and

8.37 Oesophageal dilators. These semirigid Celestin dilators may be used to dilate benign oesophageal strictures. The stricture is viewed endoscopically, and the guide wire (shown here in the lower dilator) is passed via the operating channel of the endoscope through the stricture. The endoscope is then withdrawn, leaving the wire in place. The dilator is threaded over the wire and passed down into the stricture. A series of dilatations may be necessary to relieve tight strictures. Other types of oesophageal dilator may be used in a similar way.

8.39 A lower oesophageal ring. This ring is at the squamo-columnar junction at the lower end of the oesophagus (a Schatzki ring). It is benign, but dilatation may be required for symptomatic relief.

8.38 Oesophageal web in the Plummer–Vinson syndrome. The postcricoid web is arrowed on this barium swallow, and the element of oesophageal obstruction is obvious. The patient was a postmenopausal woman, and she showed other signs of severe iron-deficiency anaemia.

8.40 Oesophageal carcinoma. The patient had a 6-week history of dysphagia and weight loss. Note the abrupt change from normal oesophagus to the area of the tumour (cf. 8.33). The barium spicules (arrows) represent areas of ulceration in the tumour. There is, as yet, no dilatation of the proximal oesophagus.
endoscopic features (8.40, 8.41, 8.42). CT scan and endoscopic ultrasound examination (8.43) are valuable in assessing the extent of the tumour. Surgical resection offers the only curative treatment, but is frequently not feasible. Palliation can be achieved by the endoscopic insertion of a prosthetic tube (8.44, 8.45), or by endoscopic laser therapy. Other tumours, including leiomyomas, lymphomas and Kaposi's sarcoma, may be found in the oesophagus, but are rare.

OESOPHAGEAL MOTILITY DISORDERS

Achalasia, a relatively uncommon disorder, is seen mainly in the age group 40–70 years. It is characterized by the failure of the lower oesophageal sphincter to relax and impaired peristalsis of the oesophagus. This results in dysphagia and ultimately the retention of food debris in a dilated oesophagus (8.46). Aspiration pneumonia is a common complication (see p. 193).
The diagnosis may be suspected from a chest X-ray that may show widening of the mediastinum, or gas/fluid levels behind the heart (8.29), or both. Barium swallow may show absence of peristaltic waves and later in the disease a dilated oesophagus (8.46). Endoscopy is essential to exclude oesophageal carcinoma.

Manometry is the investigation of choice and shows a sphincter which has a high resting tone and relaxes only partially.

Calcium antagonists or nitrates, or both, may be of some benefit, but definitive treatment is by balloon dilatation (8.47) or surgical myotomy. Chagas' disease may produce a similar motility disorder (see p. 67).

Diffuse oesophageal spasm is another cause of chest pain and dysphagia, in which there are multiple high-pressure incoordinate waves. Barium examination demonstrates abnormal contractions known as tertiary waves. This disorder may complicate gastro-oesophageal reflux. Other patients may suffer severe chest pain with no demonstrable radiological abnormality but manometric studies may show that occasional peristaltic waves generate very high pressures.

There is reduced oesophageal motility in patients with systemic sclerosis (3.88).

Coughing or retching, especially in alcoholic patients, may lead to an acute tear at the gastro-oesophageal junction (a Mallory-Weiss tear) with resulting upper gastrointestinal bleeding. Most patients heal spontaneously, but a few require surgery. Oesophageal varices are another cause of major lower oesophageal bleeding (see p. 402).

FOREIGN BODIES IN THE GUT

Ingestion of foreign bodies is extremely common in children, in those who are mentally disturbed and accidentally during eating (foreign bodies in food, broken teeth, dentures, etc.). Those with oesophageal strictures or carcinoma may also present with impaction of food or drug tablets in the oesophagus.

Small, blunt, nontoxic foreign bodies may often be allowed to pass through the gut, but sharp or toxic bodies must be removed, and larger bodies may become impacted in the oesophagus.

The patient is usually aware of swallowing the foreign body and of its impaction in the oesophagus. There is often pain at the site and retching or vomiting may be stimulated.

Such foreign bodies may be seen on X-ray (if radio-opaque) and may often be removed endoscopically (8.48, 8.49).
STOMACH

HELICOBACTER PYLORI INFECTION

Chronic infection with the spiral Gram-negative bacterium Helicobacter pylori is now known to be a common underlying factor in most of the major disorders of the stomach and duodenum. The organism is found in 30–75% of the total populations that have been studied, and infection is more common in socially deprived families. It has been identified in saliva, in dental scrapings and in faeces, but is most universally found attached to gastric epithelial cells, especially in the antrum. It is thought to be transmitted by the faecal-oral and oral-oral routes.

There is evidence that some strains are not pathogenic, but there is a close association with duodenal ulcer (100% infected in some series) and gastric ulcer (80% infected) and a lesser association with duodenitis and gastritis. The organism produces large amounts of the enzyme urease, which breaks down urea into ammonia and carbon dioxide. Gastrin is secreted in excess as a result, and this leads to excess acid production, which provokes gastritis, mucosal atrophy, ulceration and intestinal dysplasia. There is also an enhanced risk of gastric cancer and mucosal-associated lymphoid tissue (MALT) lymphoma of the stomach. A recent study suggests that chronic infection with H. pylori may even be associated with myocardial infarction as the chronic inflammation of H. pylori infection raises both the white cell count and fibrinogen levels.

Diagnosis of H. pylori infection may be made by
- Endoscopy and biopsy
  - part of the biopsy material is used for a rapid urease test (CLO test) that detects the enzyme urease by the colour change of an indicator induced by ammonia production; this has a 95% specificity (8.50)
  - another part of the biopsy is stained to show H. pylori (8.51) and determine its resistance to antibiotics
  - a third part of the biopsy may be used to culture H. pylori
- Serology
  - IgG antibodies against H. pylori may be detected using a simple serology kit test; this has an 85% specificity; repeat testing after eradication should be performed at 6 months
- $^{13}$C and $^{14}$C breath test
  - this involves the administration orally of labelled urea and the detection of labelled CO$_2$ in the breath, the implication being that active H. pylori infection is necessary for the urea breakdown; this test has a 95% specificity.

Treatment of proven infection is with an acid secretion inhibitor such as omeprazole, ranitidine or cimetidine, in combination with other drugs. Triple therapy with colloidal bismuth, metronidazole and tetracycline is very effective (90% of patients free of H. pylori within 1 month), and other effective combinations include omeprazole (or ranitidine) with amoxicillin, tinidazole and clarithromycin. Dual therapy with omeprazole and amoxicillin is slightly less effective but associated with fewer adverse events and higher compliance than triple therapy. Further treatment regimens are under investigation.

GASTRITIS

Gastritis is a common problem and its incidence is increasing. It is best defined as 'an inflammatory response to gastric mucosal injury'. Various previous classifications have been superseded by the Sydney system, which takes account of the aetiological role of Helicobacter pylori and integrates the clinical presentation, endoscopic findings, histological appearance and anatomical involvement of different regions of the stomach.

There is little association between symptoms, endoscopic
abnormality, histological abnormality, anatomical distribution of any abnormalities found, and the presence or absence of *H. pylori* infection or other causative factors. Endoscopy alone is not diagnostic of any particular form of gastritis, though various abnormalities may be seen including erythema, erosions and haemorrhage. Gastritis is now best classified as follows.

- Acute gastritis caused by viruses or bacteria: vomiting is a common clinical presentation after infection with rotavirus, Norwalk agent and type-specific *Escherichia coli*; acute infection with *H. pylori* is associated with epigastric pain, nausea, vomiting and a feeling of fullness; *H. pylori* is easy to identify on appropriately stained biopsy samples.
- Acute gastritis caused by drugs or chemicals: aspirin (and other nonsteroidal anti-inflammatory drugs – NSAIDs) and alcohol are the most common agents to cause acute gastritis; they have a synergistic effect on the gastric mucosa; aspirin inhibits local prostaglandin production and removes its cytoprotective effects, whereas alcohol produces local reduction of mucosal blood flow; the end result is acute erosions, which may bleed (8.52, 8.53).
- Chronic gastritis is found in an asymptomatic form in the elderly and is often associated with *H. pylori* infection; other causes include drugs, alcohol and gastroduodenal reflux of bile.

- Atrophic gastritis: a few patients have autoimmune gastritis, with a positive test for parietal cell antibodies; these patients fail to secrete acid and intrinsic factor, and may eventually develop a deficiency of vitamin B12, (see p. 432).

Ménétrier's disease (giant hypertrophic gastritis) is a rare, possibly premalignant condition, in which there is thickening and enlargement of the gastric mucosal folds. It may affect the entire upper gut (8.54), and may then be associated with protein loss (protein-losing enteropathy).

### GASTRIC ULCERS

Gastric ulcers are most common in the elderly. NSAIDs are often an important factor in their genesis, and both acid and gastroduodenal bile reflux may also have a role.

Gastric ulcers present with epigastric pain or anaemia, or both. Bleeding is usually chronic, but acute haemorrhage can occur; it is a major threat in elderly patients.

Gastric ulcers cannot be distinguished on clinical grounds from duodenal ulcers or gastric cancers. Barium studies may demonstrate an ulcer and give strong clues to its benign nature (8.55), but definitive diagnosis requires endoscopy with brush cytology and biopsy (8.56–8.58).
Gastric ulcers usually respond to acid secretion inhibitors (though more slowly than duodenal ulcers), but a number of other drugs may also be used, especially when *Helicobacter pylori* infection is demonstrated. Follow-up to confirm healing is wise.

**GASTRIC TUMOURS**

The most common gastric tumour is adenocarcinoma. There is a high incidence of this tumour (with a 2:1 male:female ratio) in some parts of the world, especially Japan, but generally it is becoming less common in developed countries. Predisposing factors may include a high salt consumption, aflatoxins, living in regions with a high nitrate content in the soil, and perhaps chronic infection with *Helicobacter pylori* interacting with other factors. Also implicated are smoking, a diet deficient in fresh fruit and vegetables and a diet deficient in selenium. There is an increased incidence in patients who have undergone gastric surgery, and those with atrophic gastritis. Factors that encourage bacterial overgrowth may favour nitrosation of luminal amines to form carcinogens.

Unfortunately, symptoms do not usually occur until the disease is advanced; then, patients complain of anorexia and weight loss. The tumour often ulcerates, leading to dyspeptic symptoms and iron-deficiency anaemia. Dyspepsia occurring for the first time in a patient over the age of 50 years is an indication for endoscopy, as is progressive iron-deficiency anaemia. Occlusion of the pylorus or cardia respectively may cause vomiting and dysphagia. Spread to the liver and lymph nodes is often present at diagnosis. Left-sided supraclavicular lymphadenopathy may be evident (8.8). Careful palpation of the epigastrium may reveal a mass. Obstruction of the pylorus may lead to a succussion splash, epigastric distension and visible peristalsis. Hepatic metastases, ascites, ovarian secondaries and secondaries in the pouch of Douglas all indicate advanced terminal disease.

Diagnosis is best confirmed at endoscopy, which reveals an ulcer or tumour mass (8.59, 8.60) and permits biopsy and histological examination (8.61). Sometimes the size of the tumour and its extension are best appreciated by a barium meal examination (8.62, 8.63). Liver metastases may be identified by ultrasound (9.59) or CT scan (9.21), and peritoneal metastases by laparoscopy.

The only effective treatment is surgery. This can be curative in early gastric cancer when the 5-year survival is 90%, but by the time lymph node spread occurs this figure falls to 10%.

Other tumours that may be found in the stomach include benign polyps (8.12), leiomyoma (8.64), leiomyosarcoma (8.9), lymphoma, and Kaposi’s sarcoma.
8.59 Malignant gastric ulcer. The endoscopic appearance is not conclusive, but malignancy was confirmed by biopsy.

8.60 Carcinoma of the stomach. This ulcerated mass is situated between the incisura and the pylorus. The patient was an 80-year-old lady who presented with a 2-month history of dyspepsia and melaena.

8.61 Endoscopic biopsy of an ulcerating mass in the stomach wall. The forceps are being advanced towards the lesion.

8.62 Carcinoma of the stomach. The barium meal demonstrates a large fungating mass in the gastric fundus. The patient presented with severe weight loss and iron-deficiency anaemia (8.2).

8.63 Linitis plastica of the stomach. In this form of gastric carcinoma, there is widespread submucosal invasion giving a rigid and immobile appearance on screening during the barium meal.

8.64 Gastric leiomyoma is a benign tumour of smooth muscle. In this patient, the barium meal shows a huge mass in the stomach. Patients with leiomyomas present with dyspeptic symptoms or with bleeding, which may be occult and lead to iron-deficiency anaemia. Surgical resection is usually possible and curative.
8.68 Duodenal ulcer with a scarred duodenal cap shown in a double-contrast barium meal.

Note the ulcer crater, and the radiating barium spicules representing folds in the scarred mucosa.

DUODENUM

DUODENAL ULCERATION

Duodenal ulceration is very common in the developed world, affecting about 1 per 1000 population, but the cause of duodenal ulcer diathesis remains unknown. Recent attention has focused on the potential role of *Helicobacter pylori*, which is found in at least 95% of cases (see p. 367). NSAIDs may also play a role in some patients. Multiple and resistant ulcers should prompt investigation for a gastrinoma (see p. 391).

Features suggestive of peptic ulceration include
- intermittent epigastric pain related to eating
- epigastric pain causing nocturnal wakening
- relief of pain by certain bland foods and alkalis
- a close relationship of pain to cigarette smoking
- response to H$_2$ and proton-pump inhibitors.

Many patients, however, do not have symptoms, and become aware of their ulcers only when complications occur. Suspected ulcers are best investigated by endoscopy (8.13, 8.65, 8.66), although high-quality barium meal examination can still provide useful information (8.15, 8.67, 8.68). Antral biopsy during endoscopy is helpful to confirm the presence or absence of *Helicobacter* infection.

Complications of duodenal ulceration include haemorrhage (8.69), pyloric stenosis caused by scarring, and perforation, leading to acute peritonitis and pneumoperitoneum (8.70).

Duodenal ulcers usually respond to treatment with H$_2$-receptor antagonists (e.g. cimetidine, ranitidine) or proton-pump inhibitors (e.g. omeprazole). Other drugs, including bismuth...
8.69 Haemorrhage is one of the most common complications of peptic ulceration. Urgent endoscopy often yields a rather poor view, because of the presence of altered blood and food residues, but this view clearly shows adherent blood clot on a large duodenal ulcer, providing evidence of recent bleeding.

8.70 Pneumoperitoneum in a patient with a rigid abdomen caused by a perforated duodenal ulcer. The onset of his pain and rigidity was abrupt. Note the upper edge of the liver (1), and the air under both diaphragms.

PEPTIC ULCERATION AT OTHER SITES

Peptic ulceration may occur in the oesophagus (see p. 362), at or near the stoma after gastric surgery, or in the ectopic gastric mucosa in a Meckel's diverticulum.

ZOLLINGER–ELLISON SYNDROME

Zollinger–Ellison syndrome results from a gastrin-producing tumour, which is often located in the pancreas, but occasionally is elsewhere in the small intestine or in the gastric antrum. The clinical features are of severe recurrent peptic ulceration (especially multiple ulceration – 8.66), which has a high incidence of bleeding and perforation. There may also be diarrhoea with malabsorption, and there may be other endocrine neoplasms as part of the multiple endocrine neoplasia syndrome (see p. 391).

The diagnosis is made by finding a high gastrin level and a high basal secretion. The tumour may be localized by CT or MRI scanning or by selective venous catheterization.

Treatment is with a proton-pump inhibitor to block acid secretion and surgery to remove the tumour if it has not already metastasized.

SMALL INTESTINE

MALABSORPTION

Malabsorption is the most common presenting feature of small intestinal disease and is characterized by failure to digest or absorb, or both, nutrients from the intestinal tract. Important causes are summarized in 8.71.

Patients may present with pale offensive stools that float and are difficult to flush away (8.7), and they may exhibit features of nutrient deficiency (8.2, 8.72, 8.73) in addition to those that characterize the underlying disease process.

Investigations (8.74) are undertaken with three objectives:
• to confirm impaired absorption, for example faecal fat collection and the Schilling test
• to identify specific deficiencies, for example anthropometric measurements, blood count, iron, transferrin, folate, vitamin B₁₂, prothrombin and related vitamin K-dependent clotting factors and vitamin D levels
• to establish the mechanism and cause of malabsorption; this may include a search for bacterial overgrowth, testing pancreatic exocrine function, and aspiration or biopsy of the proximal small bowel (8.75) to look for evidence of giardiasis (8.21) or gluten enteropathy (8.76, 8.77).

Gluten enteropathy (coeliac disease)

Patients with gluten enteropathy develop an immunological response to gluten which damages the small intestinal mucosa, resulting in partial or subtotal villous atrophy. The prevalence of gluten enteropathy in Europe is 1 per 1000 population. Gluten is a protein found predominantly in wheat, but also in rye, barley and (to a lesser extent) oats. The degradation of gluten in the intestinal lumen means that the proximal small intestine is maximally affected. Those who have more severe involvement develop steatorrhoea. The characteristic presentation is chronic diarrhoea, steatorrhoea, abdominal distension
8.71 Causes of malabsorption.

**CAUSES OF MALABSORPTION.**

<table>
<thead>
<tr>
<th>Level</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Stomach</td>
<td>Post-gastrectomy dumping</td>
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<td></td>
<td>Zollinger-Ellison syndrome</td>
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<td></td>
<td>Pernicious anaemia</td>
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<td>Hepatic/biliary tree</td>
<td>Biliary obstruction/cholestasis</td>
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<td>Pancreas</td>
<td>Cystic fibrosis</td>
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<td>Pancreatitis</td>
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<td>Pancreatic carcinoma</td>
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<td>Small bowel</td>
<td>Coeliac disease</td>
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<td>Crohn's disease</td>
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<td>Surgery and removal of small bowel</td>
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<td>Fistulae/blind loops</td>
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<td></td>
<td>Infection - bacterial, parasitic</td>
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<td>Radiation</td>
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<td>Lymphoma</td>
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<td>Drugs e.g. neomycin, cholestyramine</td>
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<td></td>
<td>Specific enzyme defects of brush border</td>
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<td>Whipple's disease</td>
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8.74 General investigations of value in malabsorption.

| Blood                       | Full blood count, film                        |
|                            | Serum B₁₂ and folate                          |
|                            | ESR, plasma viscosity, C-reactive protein     |
| Biochemistry                | Calcium                                        |
|                            | Zinc                                           |
|                            | Albumin                                        |
|                            | Faecal fat excretion                           |
|                            | Schilling test                                 |
|                            | Pancreatic function tests                      |
|                            | Bile salt absorption                           |
| Bacteriology               | Faecal culture                                 |
|                            | Microscopy for ova, cysts or parasites         |
|                            | Small bowel culture                            |
|                            | Glucose breath test                            |
|                            | ¹⁴C xylose test                                |
| Radiological               | Barium meal and follow-through                 |
|                            | CT scan of abdomen                             |
|                            | Endoscopic retrograde cholangiopancre-         |
|                            | atography                                      |
| Histology                  | Small bowel biopsy                            |

8.75 The Crosby capsule, seen here dismantled, is designed to obtain small samples of jejunal mucosa. After assembly it is swallowed by the patient and it passes through the stomach and duodenum into the jejunum, where its position is checked radiologically. The application of suction to the tube leading to the capsule pulls a small piece of mucosa into the port of the capsule, and triggers the cutting mechanism, which slices off a thin mucosa sample. The capsule is then withdrawn through the mouth.

8.72 & 8.73 Malabsorption in coeliac disease may remain undiagnosed for many years. This woman was diagnosed at the age of 32 years, but her height—5 feet (1.52 m)—was less than all other members of her family, suggesting that her malabsorption dated from childhood. On presentation she weighed 40 kg (88 lbs), she had marked steatorhoea and she was pale and anaemic. Small bowel biopsy showed villous atrophy. A gluten-free diet relieved her steatorhoea and reversed the changes in her jejunal mucosa. She rapidly gained weight, but should probably remain on a gluten-free diet for life.
and failure to thrive in childhood. Presentation in adult life is often more obscure with megaloblastic anaemia, intermittent diarrhoea and vague abdominal symptoms.

The diagnosis is confirmed by proximal small bowel biopsy, either endoscopically or with the Crosby capsule (8.75–8.79); or by sequential biopsies with an improved and subsequently deteriorated appearance of the mucosa, on introduction of a gluten-free diet followed by a gluten challenge. Barium follow-through may also provide useful information (8.80).

A gluten-free diet relieves symptoms and reverses the biopsy appearances in most patients. Small intestinal lymphoma and carcinoma are more common in patients with coeliac disease than in the general population; extra-gastrointestinal cancers are also more common. The effect of a gluten-free diet on the risk of these complications is unclear.

In dermatitis herpetiformis, a gluten-sensitive enteropathy is accompanied by a bullous skin eruption (2.72, 2.73). Both may respond to a gluten-free diet, though treatment with dapsone may also be needed for the skin eruption.

8.76 & 8.77 Jejunal biopsies from normal and coeliac patients, seen here under the dissecting microscope immediately after removal from the Crosby capsule. Normal mucosa (8.76) shows a normal pattern and number of jejunal villi, whereas the abnormal mucosa (8.77) shows complete flattening – the characteristic appearance of gluten-sensitive enteropathy.

8.78 & 8.79 Microscopic sections of jejunal biopsies from normal and coeliac patients. The sections correspond to the appearance seen in 8.76 and 8.77, respectively. The normal microscopic appearance of the jejunal mucosa is seen in 8.78, whereas 8.79 shows the jejenum of a previously undiagnosed patient with gluten-sensitive enteropathy on a normal diet. The normal intestinal villi are absent, the mucosa is flattened and there is hyperplasia of the intestinal crypts. There is lymphocytic infiltration, and the surface mucosa is cuboidal rather than columnar.

8.80 Barium follow-through in coeliac disease in a 26-year-old man. The film shows dilatation of the small bowel with 'simplification' of the mucosal pattern. The transverse folds are straight in appearance, rather than 'feathery' as they would be in a normal film. Flocculation of barium used to be described as a classic sign of coeliac disease, but the additives in modern barium prevent this sign from appearing. Nevertheless, the diagnosis is clearly suggested by the film.
BACTERIAL OVERGROWTH

Small intestinal bacterial overgrowth commonly accompanies the reduction of gastric acidity by drugs or surgery, blind loops (8.81) and motility disorders. It is an important consideration in the elderly. Diagnosis is supported with a glycocholate or hydrogen breath test (see p. 360).

TUMOURS OF THE SMALL INTESTINE

Small intestinal tumours account for only 1% of gastrointestinal neoplasms. In descending order of frequency they comprise adenocarcinomas, carcinoids, lymphomas and leiomyosarcomas. Kaposi's sarcoma of the intestine may occur in patients with HIV infection.

Adenocarcinomas may complicate Crohn's disease, particularly in a bypassed segment, and coeliac disease. Almost one-half occur in the duodenum. Presentation is with pain and vomiting, anaemia and, in the case of periampullary tumours, jaundice. Diagnosis is often made by a small bowel barium study (8.82).

If the carcinoma involves the ampulla of Vater, the patient usually presents with obstruction of the pancreatic and biliary tracts and biochemical evidence of obstruction (high alkaline phosphatase and bilirubin) and later with clinical evidence of jaundice. There may also be steatorrhoea and positive faecal occult blood. These features may be intermittent as the tumour necroses. The diagnosis should be made endoscopically (8.83) and a stent may sometimes be inserted to relieve obstruction (8.84).
Intestinal lymphomas also occur more commonly than expected in patients with coeliac disease (8.85). The lymphoma is often located in the distal small intestine, whereas the proximal intestine bears the brunt of the damage from gluten. Lymphomas also occur in patients who are immunosuppressed after organ transplantation or by HIV infection. Patients develop diarrhoea and pain and lose weight.

Most small intestinal carcinoid tumours arise in the ileum. The clinical features are determined by local growth that can lead to intestinal obstruction, and by their secretion of humoral agents that become systemically active after metastases have developed in the liver. The characteristic syndrome of flushing (8.86) with diarrhoea, bronchospasm and congestive cardiac failure is well known. Patients may even develop pellagra caused by nicotinic acid deficiency as a result of disturbed tryptophan metabolism.

Tumours and vascular malformations may present with recurrent gastrointestinal bleeding of obscure cause. As with Meckel’s diverticulum, the diagnosis may be made on mesenteric angiography, or – for slow bleeding – by a technetium-labelled red cell scan (8.20).

**INFLAMMATORY BOWEL DISEASE**

Inflammatory bowel disease is a term that encompasses two main conditions: ulcerative colitis and Crohn’s disease.

**CROHN’S DISEASE**

Crohn’s disease is a chronic granulomatous inflammatory disease of unknown cause, which is becoming more common. The prevalence in the UK is about 3 per 100000. The terminal ileum and colon are principally involved, but the disease may affect any part of the intestinal tract, often with discontinuous patches of inflammation of all the bowel wall structures (’skip’ lesions). Initially, aphthoid ulcers may be seen at endoscopic examination with macroscopically normal intervening mucosa (8.87). Subsequently, more severe inflammation leads to more extensive ulceration and oedema of the mucosa (8.88-8.90) and ultimately fibrosis can cause bowel strictures (8.17, 8.91, 8.92). Inflamed bowel may adhere to surrounding structures and

**8.85 Intestinal lymphoma in a patient with coeliac disease** that had been well controlled on a gluten-free diet for the past 13 years. An irregular shouldered stricture (1) is seen on barium follow-through. Radiologically, the appearance suggests lymphoma or carcinoma, and at operation a lymphoma was found. Even with surgery followed by radiotherapy or chemotherapy, the prognosis is poor.

**8.86 Facial flush in carcinoid.** This is usually seen only when hepatic secondaries are present, although it may occur with primary tumours that drain directly into the systemic circulation (in the lung, testis or ovary). Other symptoms resulting from the release of vasoactive substances by these tumours may include abdominal pain, diarrhoea, bronchospasm and congestive cardiac failure.

**8.87 Crohn’s proctitis.** In this colonoscopic view, there are multiple small ulcers but the adjacent mucosa looks normal. This is a common endoscopic appearance in the rectum and colon in early Crohn’s disease, though initially the ulcers may be fewer in number or even single.
INFLAMMATORY BOWEL DISEASE

8.88 Crohn's colitis on double-contrast barium enema. Many ulcers can be seen in this view of the transverse colon, by their retention of barium, but the remaining mucosa appears normal.

8.89 Severe ileal Crohn's disease. There is extensive boggy, inflammatory, oedema of the mucosa, leading to partial obstruction of the ileum. The 29-year-old patient had severe abdominal pain and weight loss.

8.90 Crohn's disease in the colon. Multiple oedematous inflammatory polyps give a 'cobblestone' appearance to the mucosa. Similar changes may be seen in ulcerative colitis.

8.91 Crohn's disease in the duodenum. This videoendoscopic view shows 'bridging' lesions in the mucosa. Ulceration and healing leads to these isolated bridges of mucosa. In other parts of the bowel, such fibrosis often leads to obstruction.

8.92 Crohn's disease of the small intestine revealed on barium follow-through X-ray. Four strictures of the small intestine are clearly seen, and the dilated segments of bowel appear between the strictures. These 'skip lesions' are characteristic of Crohn's disease, and similar appearances may be seen in the colon when there is colonic involvement.

8.93 Enterocutaneous fistulae in Crohn's disease are most common, as here, in patients who have undergone bowel resection, but they may also occur in unoperated cases. Sinography may be used to demonstrate communication with the affected bowel.
Crohn's lesions shows inflammation of all layers of the bowel wall, and giant cell granulomas are commonly found (8.95).

The clinical presentation is varied depending upon the region, extent, and manner of the intestinal involvement. Common features include diarrhoea, abdominal pain, anorexia, weight loss and pyrexia. Childhood Crohn's disease may present with growth retardation and delayed puberty. Eventually the patient may suffer from intestinal obstruction and intestinal failure, with malnutrition, often including zinc deficiency (7.154).

Patients with Crohn's disease may develop diarrhoea for numerous reasons. These include extensive intestinal inflammation, partial obstruction, small intestinal bacterial overgrowth, bile-acid malabsorption caused by terminal ileal disease or excision, entero-enteral fistulae, short-bowel syndrome, amyloidosis and intestinal infections. It is important that the true cause is identified and treated.

Extra-intestinal manifestations of Crohn's disease are similar to those experienced by patients with ulcerative colitis and may include sclerosing cholangitis (8.96), arthritis, uveitis, deep vein thrombosis and skin rashes such as pyoderma gangrenosum (2.135) and erythema nodosum (2.45). Most patients with Crohn's disease who develop right hypochondrial pain and jaundice do not have sclerosing cholangitis, however: the majority have gall stones.

Crohn's disease can be controlled in most patients with short-term courses of corticosteroids, and azathioprine is useful in resistant patients. Other drugs which may be helpful include 5-aminosalicylic acid, cyclosporin and interferon. Surgery is required for the relief of obstruction and the correction of fistulae. Nutritional support, either enteral or parenteral, corrects malnutrition thus making a major contribution to the patient's wellbeing (see p. 345).

**ULCERATIVE COLITIS**

Ulcerative colitis has a stable incidence and prevalence of 6 and 100 per 100000, respectively, in the UK. It is primarily a mucosal disease that extends for a variable distance and in a continuous fashion, around the colon from the rectum, which is always involved.

Symptoms depend on the extent and severity of colonic involvement. Patients in whom the disease is confined to the rectum experience rectal bleeding and tenesmus, but the stool is formed and constipation may be a problem. Diarrhoea is the predominant symptom with more extensive disease, and severe attacks are accompanied by abdominal pain, pyrexia and tachycardia.
Endoscopy reveals the severity of the disease (8.97–8.100) and allows biopsy (8.101), which may show goblet cell depletion, crypt abscesses, distortion of the architecture with little submucosal inflammation and no granulomas (in contrast to Crohn's disease; 8.102). Barium enema may show characteristic findings (8.103, 8.104). Other important investigations include FBC, erythrocyte sedimentation rate (ESR) or C-reactive protein, serum albumin and stool microscopy and culture to exclude an infective or parasitic cause for symptoms.

The differential diagnosis of ulcerative colitis includes Crohn's disease, gastrointestinal infections, pseudomembranous colitis, ischaemic colitis, radiation-induced enteritis and drug-induced colitis.

Extra-intestinal manifestations of ulcerative colitis may include skin rashes, erythema nodosum (2.45) and pyoderma gangrenosum (2.135), hepatobiliary disease, especially sclerosing cholangitis (8.96) and arthritis. Inflammation involving the peripheral joints reflects the activity of the intestinal disease, but this does not apply if patients have sacroiliitis or ankylosing spondylitis.

Complications of acute disease include colonic dilatation (8.105) which may lead to perforation and haemorrhage and is suggested by features of an acute abdomen. Chronic disease may also produce anaemia, and carries an increasing risk of colonic carcinoma in patients with extensive disease of more than 10 years' duration (8.106). Colonoscopic surveillance every 2 years facilitates the detection of premalignant dysplasia in the mucosa, allowing timely surgical intervention.

Medical treatment involves the control of disease activity with short courses of corticosteroids or azathioprine, or both, the maintenance of remission with sulphasalazine or one of the preparations designed to deliver 5-aminosalicylic acid to the colon (mesalazine or olsalazine) and the correction of anaemia. Surgery is required if medical management fails, and to prevent acute and chronic complications such as perforation or carcinoma. Pan-proctocolectomy with a permanent ileostomy is usually necessary, although pouch procedures involving ileoanal anastomoses are currently fashionable. Maintenance of good nutrition is essential (see p. 345).
Inflammation of the colon may occur as an indirect consequence of antibiotic administration (pseudomembranous colitis—see p. 386), or as the result of treatment with non-steroidal anti-inflammatory analgesics. Some, such as mefenamic acid, are particularly prone to cause diarrhoea with an associated colitis.

**8.102 Ulcerative colitis histopathology.** In contrast to Crohn's disease, the inflammatory process in ulcerative colitis is usually confined to the mucosal layer of the bowel wall and granulomas are not seen. In active disease, as here, there is an increase in the number of lymphocytes, plasma cells and neutrophils in the lamina propria (beneath the epithelium). The epithelium shows patchy or continuous ulceration, and large numbers of neutrophils migrate through the walls of the glands to form 'crypt abscesses'. Three crypt abscesses are seen in this view.

**8.103 Ulcerative colitis.** This double-contrast barium enema shows typical chronic changes throughout the colon. There is loss of the normal haustral pattern, giving the colon a smooth tubular appearance. Deep, penetrating ulcers can be seen, especially in the barium-filled splenic flexure, and there are many pseudopolyps, best seen in the transverse colon.

**8.104 Ulcerative colitis with multiple inflammatory polyps ('pseudopolyps').** The double-contrast barium enema technique demonstrates the appearance well in the descending colon, and this correlates with the endoscopic view (8.100). Note the area of deep ulceration (arrow). On screening, this area showed a lack of movement that raised the suspicion of carcinomatous change.

**8.105 Colonic dilatation in ulcerative colitis ('toxic megacolon').** This complication of acute ulcerative colitis requires urgent intensive management, including fluid replacement and steroid therapy. The patient presents with a tender, swollen abdomen, which is tympanitic, due to the amount of gas in the colon. Fever and signs of shock are common accompaniments. It is important to auscultate the abdomen, as bowel sounds are usually absent.

**8.106 Carcinoma of the colon has developed as a complication of long-standing ulcerative colitis** in this patient with a 17-year history of the disease. The blood in this view results from biopsy of the lesion. Regular colonoscopic surveillance should allow identification of this complication at an earlier stage.
RADIATION ENTEROCOLITIS

Radiation enterocolitis is a sequel to radiotherapy for pelvic and abdominal malignancy. The safety margin between therapeutic effect and damage to surrounding structures is narrow and factors such as previous surgery may enhance intestinal damage by fixing loops of bowel within the field of exposure.

Early changes after exposure include increased crypt cell death and loss of villus height, and the extensive loss of intestinal function may lead to fluid and electrolyte imbalance. However, the initial clinical features of nausea, vomiting and diarrhoea, frequently with rectal bleeding, may settle.

Late complications develop from endarteritis obliterans, which leads to intestinal ischaemia. After a period that varies from a few months to many years, ischaemic strictures and fistulae may develop, and patients may suffer from subacute obstruction and chronic malabsorption (8.107). Sometimes, damage to the enteric nerves causes a pseudo-obstruction. The colonic symptoms can resemble idiopathic ulcerative colitis, but endoscopy reveals the typical picture of an atrophic mucosa with telangiectasia.

Medical therapy is limited in scope. Antibiotics are useful for the treatment of secondary bacterial overgrowth, cholestyramine may be helpful with bile-acid malabsorption when the terminal ileum is affected, and topical steroids or mesalazine should be given to patients with proctitis. Some patients with intestinal failure need prolonged parenteral nutrition. Surgery is required for perforation, stricture and fistulae, but the morbidity of operative intervention is considerable.

ISCHAEMIC DISORDERS

Intestinal ischaemia may be acute or chronic, and it may affect the small or large intestine.

- Acute mesenteric ischaemia usually occurs in patients with generalized atheroma, but it may be embolic; rarely, it is caused by venous occlusion in patients who are taking oral contraceptives or who have antithrombin-III deficiency; the initial presentation with diarrhoea, vomiting and vague abdominal pain, is rapidly followed by increasing pain and shock; early laparotomy and resection of the affected segment offers the only prospect of survival.

- Chronic mesenteric insufficiency causes intestinal angina, a postprandial abdominal pain that usually prompts an initial search for peptic ulcer or biliary disease.

- Colonic ischaemia is more common than mesenteric ischaemia and usually affects the splenic flexure; the patient complains of abdominal pain and diarrhoea; after a few hours the diarrhoea contains fresh blood; at this stage, the diagnosis may be suspected from plain abdominal X-ray in which 'thumb-printing' is evident (8.108); infection with Escherichia coli 0157 may produce a similar clinical picture (see p. 385); occasionally, the affected segment perforates, but usually the features subside; fibrosis may lead to stenosis causing alteration of bowel habit or chronic intestinal obstruction (8.109).
GASTROINTESTINAL

8.109 Colonic ischaemia

This single-contrast barium enema shows gross ischaemic changes throughout the descending colon. There is narrowing of the lumen, accompanied by typical 'rose-thorn' ulcers (1) and some 'thumb-printing' (2) in the sigmoid colon, where a partial stricture has formed. The apparent stricture at the hepatic flexure disappeared on screening. The patient also had symptomatic coronary heart disease and peripheral vascular disease.

8.110 Diverticular disease of the colon

This barium enema shows typical changes, with multiple diverticula outlined by the double-contrast technique. The patient presented with a change in bowel habit and abdominal pain, and although this could be caused by the diverticular disease itself, it is important to exclude the possibility of coexistent colonic carcinoma in these circumstances. This is best done by colonoscopy.

8.111 Diverticular disease of the colon with sinus formation

This patient with known diverticular disease was reinvestigated for right iliac fossa pain and tenderness. The barium enema shows the presence of multiple diverticula, and a communicating sinus is clearly seen (arrow). This appearance is diagnostic of local abscess formation.

8.112 Severe diverticular disease viewed through the colonoscope

Wide-mouthed openings to diverticula are present, and these were seen throughout the sigmoid colon in this patient. Colonoscopy may be difficult and hazardous when diverticula are large enough to admit the tip of the scope.

COLON AND RECTUM

DIVERTICULAR DISEASE

Diverticula are acquired pouches of the colonic mucosa that have herniated through the muscular layers of the colon. They are present in about one-half of the population over the age of 65 years in the developed world, and are often found by chance in barium enemas that have been carried out for other purposes. The most common site is the sigmoid colon, where they are usually multiple. The cause is unclear, but they may result from an increased pressure within the lumen in the sigmoid colon. They are most common in patients in whom dietary fibre intake is low.

Many patients have no symptoms, but some have recurrent lower abdominal pain, particularly in the left iliac fossa, associated with flatulence and constipation or, sometimes, diarrhoea. Pain follows a meal and is often relieved by passing gas or by defaecation. Bleeding and localized abscess formation (diverticulitis) may occur. Diverticulitis is associated with severe localized pain in the abdomen, fever and localized guarding. Septicaemia may result, and other complications include fistulas, colonic obstruction and generalized peritonitis.

The diagnosis is made on barium enema (8.110, 8.111) or colonoscopy (8.112). Most symptoms settle with conservative treatment, and patients should be given a high-fibre diet. Surgery may be required for complications and anaemia may require iron therapy or blood transfusion.

PNEUMATOSIS OF THE COLON

Pneumatosis of the colon is an unusual condition of unknown aetiology in which gas-filled cysts are found within the wall of the sigmoid or descending colon. There is an association with chronic obstructive pulmonary disease and pneumatosis may also follow colonoscopy or a double-contrast barium enema. Pneumatosis is often found incidentally at colonoscopy or even
on a plain X-ray of the abdomen (gas in wall as well as lumen). Occasionally there may be symptoms such as colicky lower-abdominal pain, diarrhoea and blood and mucus on the stools. The appearance at endoscopy is typical (8.113). No specific treatment is available.

8.113 Pneumatosis of the colon (pneumatosis cystoides intestinales). Multiple gas-filled cysts are present in the submucosa and subserosa of the colon. The cause is obscure, but it is possible that gas may track down from the pleural space in patients with chronic obstructive pulmonary disease, or that mucosal perforation during endoscopy or contrast radiography may occur. Biopsy of a cyst is often accompanied by a loud 'pop'.

LARGE BOWEL CANCER

Large bowel (colorectal) cancer is predominantly found in Western societies. It is the most common gastrointestinal malignancy in the UK, with 28000 new registrations each year and is responsible for approximately 20000 deaths each year. The population risk of dying of large bowel cancer is 3 per 100 population. High-fat, low-fibre diets have been blamed for supporting bacterial flora that result in the formation of carcinogens from intestinal contents, including bile acids, an effect compounded by a delayed transit time.

Most cancers develop from benign adenomas. There is a low risk of malignancy in single polyps that are less than 1 cm in diameter, but a much higher risk when the diameter exceeds 2 cm (8.14, 8.114) or the polyps are multiple. The histological type is also important, as malignancy is much more common in villous (40%) than tubular (5%) adenomas.

Patients with familial polyposis coli (8.16, 8.115) almost invariably develop bowel cancer, so they are advised to undergo prophylactic colectomy. Patients at risk include the family members with familial polyposis, those who have previously developed polyps, patients over 40 years of age with first degree relatives with colonic cancer, those with long-standing extensive ulcerative colitis, and possibly patients who have undergone cholecystectomy.

Patients with colonic cancer may present with alteration of bowel habit, rectal bleeding, abdominal pain, anaemia or symptoms of disseminated disease.

8.114 A single colonic polyp, beautifully revealed by double-contrast barium enema. Its pedunculated nature should mean that it can be successfully removed by snare diathermy performed through the colonoscope (see 8.14). If the excision is histologically complete, no further treatment is required for this polyp; however the patient should have a full-length colonic examination at the time of colonoscopy and any further polyps should be similarly treated. Because of the risk of recurrence of the polyp at the same or a different site, follow-up colonoscopy is usually recommended.

8.115 Familial polyposis coli. Multiple sessile polyps are seen in this colonoscopic view. Histologically, the lesions are adenomatous polyps, but there is a high risk of malignant change in this dominant condition, which usually presents in the second decade of life with diarrhoea, rectal bleeding and, sometimes, abdominal pain. Multiple polyps can usually also be seen on double-contrast barium enema examination (8.16) Prophylactic colectomy is usually advised.
The diagnosis is established by a barium enema examination (8.116, 8.117), which should be preceded by sigmoidoscopy. When the barium examination fails to provide conclusive information, or when polyps are found, colonoscopy is required to detect lesions missed on the barium films and to allow biopsy of suspect areas and the removal of polyps (8.14, 8.106, 8.118). Investigations are also needed to determine the effects of the disease, for example a blood count and film to look for iron deficiency, and a CT scan or ultrasound examination of the abdominal nodes and liver to search for metastatic disease (9.21).

Colonic cancer may be prevented by the identification and removal of polyps (8.119). The established tumour is treated by surgical resection, a right or left hemicolectomy or abdomino-

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**DUKES’ CLASSIFICATION OF LARGE BOWEL CANCER.**

<table>
<thead>
<tr>
<th>Dukes’ stage</th>
<th>% (at presentation)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cancer confined to bowel wall</td>
<td>&lt;5</td>
</tr>
<tr>
<td>B</td>
<td>Extension through serosa into pericolic tissue</td>
<td>60</td>
</tr>
<tr>
<td>C</td>
<td>Spread into adjacent lymph nodes</td>
<td>25</td>
</tr>
<tr>
<td>D</td>
<td>Distant metastases</td>
<td>10</td>
</tr>
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First degree relatives of patients with large bowel cancer are at increased risk of developing the disease (1 in 6 risk if two first degree relatives are affected). Screening of relatives may be helpful, but there is no general agreement on whether such screening should be based on occult blood testing, sigmoidoscopy or colonoscopy.
**GASTROINTESTINAL INFECTIONS**

Infection may occur at any level in the gut. Infection of the mouth and oesophagus are important causes of local symptoms (see pp. 49, 357 and 360). *Helicobacter pylori* infection plays a role in the genesis of gastritis and peptic ulceration (see pp. 362 and 366).

Intestinal tuberculosis is rare in the developed world but still relatively common elsewhere. It usually affects the terminal ileum, where it may produce symptoms and a barium X-ray appearance similar to those of Crohn's disease (8.17).

Management is usually medical (see p. 43). Gastroenteritis is a common problem throughout the world. The most common symptom is diarrhoea, and it is important to distinguish infective from other causes (8.121).

Secretory diarrhoea may be caused by *Vibrio cholerae* (p. 50), *Campylobacter jejuni* and many strains of *Escherichia coli* and *Salmonella*. Typically, there are copious fluid stools, and dehydration is the most important clinical problem.

Dysentery is a condition in which the stool contains pus, mucus and blood. This results from colonic mucosal invasion by organisms such as enteroinvasive *E. coli*, *Shigella*, *C. jejuni* and rotavirus (8.122). Other invasive organisms may cause a predominantly septicaemic illness. The most important example is *Salmonella typhi*: intestinal symptoms occur relatively late in the evolution of typhoid fever (see p. 49). Pseudomembranous colitis is a serious infection with *Clostridium difficile* that may follow treatment with broad-spectrum antibiotics (8.123).

Most acute infective diarrhoea is self-limiting, but oral or intravenous fluid replacement is always important if diarrhoea is profuse, and antibiotic treatment is indicated for some invasive infections.

Transmission of infection is usually by the faecal-oral route, and prevention is based on hygiene in food and water preparation.

Protozoal infections are another important cause of gastrointestinal symptoms. Giardiasis is common. The organism infests the small intestine and may cause acute diarrhoea or chronic malabsorption. The cysts may be evident on stool microscopy, but small intestinal aspiration or biopsy is sometimes needed to confirm the diagnosis (8.21). Eradication is achieved with metronidazole.

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**COMMON CAUSES OF DIARRHOEA**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>Rotavirus, Norwalk agent/small round structured viruses (SRSVs), Adenoviruses</td>
</tr>
<tr>
<td>Bacterial toxin</td>
<td><em>Escherichia coli</em> (enterotoxigenic), <em>Vibrio cholerae</em>, <em>Staphylococcus aureus</em>, <em>Clostridium perfringens</em>, <em>Clostridium difficile</em>, <em>Clostridium botulinum</em>, <em>Bacillus cereus</em></td>
</tr>
<tr>
<td>Bacterial invasion</td>
<td><em>Escherichia coli</em> (enteroinvasive), <em>Shigella</em>, <em>Salmonella</em>, <em>Yersinia enterocolitica</em>, <em>Vibrio parahaemolyticus</em>, <em>Campylobacter jejuni</em></td>
</tr>
<tr>
<td>Parasites</td>
<td><em>Giardia lamblia</em>, <em>Cryptosporidium parvum</em>, <em>Entamoeba histolytica</em></td>
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<tr>
<td>After infection</td>
<td>Lactase deficiency, Bacterial overgrowth</td>
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<tr>
<td>Drugs</td>
<td>Laxatives, Antacids with magnesium</td>
</tr>
<tr>
<td>Food toxins</td>
<td>Ciguatoxin, scombroid, puffer-fish</td>
</tr>
<tr>
<td>Chronic gastrointestinal disorders</td>
<td>Inflammatory bowel disease, Ischaemic colitis, Malabsorption, Irritable bowel syndrome</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Hyperthyroidism, Adrenal insufficiency, Hyperparathyroidism, Diabetes mellitus</td>
</tr>
</tbody>
</table>

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8.121 Common causes of diarrhoea.

8.122 Infective colitis. This patient presented with bloody diarrhoea which ultimately proved to be the result of enteroinvasive *Escherichia coli* infection. Colonoscopy is not routinely performed in infective colitis, but was carried out here to exclude other pathology before the infective nature of the condition was confirmed. The haemorrhagic lesions are typical, and there are no structural changes in the colon.
Entamoeba histolytica invades the colonic mucosa (8.124) and the patient suffers from bloody diarrhoea. The possibility of amoebiasis must always be considered in a patient with this complaint who is in, or has returned from, a developing country. An erroneous diagnosis of inflammatory bowel disease followed by corticosteroid treatment may be fatal. The management of amoebiasis and its complications is covered on p. 62.

Cryptosporidium parvum has been widely recognized as a cause of diarrhoea in cattle, and is now known to produce a self-limiting diarrhoeal illness in man. In patients with AIDS, it may produce a catastrophic illness with extreme dehydration, shock and death.

8.123 Pseudomembranous colitis may develop during, or up to 6 weeks after, treatment with antibiotics such as lincomycin, ampicillin and cephalosporins. The major symptom is diarrhoea, which may be bloody. Sigmoidoscopy or colonoscopy usually shows multiple yellow plaques and inflammatory changes and the diagnosis can be confirmed histologically. Clostridium difficile and its toxin are found in the stools. Patients with pseudomembranous colitis should be barrier-nursed, because there is a risk of cross infection. If the diarrhoea is severe, they may need intravenous fluid replacement, and treatment with vancomycin will eliminate the Clostridium infection.

8.124 Amoebic colitis. This barium enema performed during the recovery phase of fulminating amoebic colitis shows extensive strictures and areas of mucosal damage in the colon. It is essential that these are not misdiagnosed as inflammatory bowel disease or tumours. Stool examination, colonoscopy and biopsy may all be helpful in diagnosis.

INTESTINAL WORM INFESTATIONS

ROUNDWORMS

Threadworm infestation with Enterobius vermicularis is very common worldwide. It often causes pruritus ani, especially in children, but may be asymptomatic.

Infestation with Ascaris lumbricoides may also be asymptomatic, but some patients develop a cough and fever during the migration of the larvae to the lung after they penetrate the intestinal mucosa. After development, the worms are coughed up, swallowed and become established in the intestinal tract. Heavy infestation can lead to distal small intestinal obstruction and, rarely, migration can cause obstruction of the bile duct (8.125). Piperazine and mebendazole are effective treatments (8.126).

The whipworm, Trichuris trichiura, has a simple life cycle, and it does not migrate from the gut. Heavy infestation may lead to abdominal symptoms such as tenesmus and rectal bleeding as a result of mucosal penetration or occasionally to intestinal obstruction. Worms are sometimes found in the appendix at appendicectomy.

Hookworm larvae penetrate the skin and also migrate via the lungs. The adult worms such as Ancylostoma duodenale and Necator americanus are an important cause of anaemia in many developing countries (see p. 429, 10.20).
ticular importance in immunosuppressed patients: in those with AIDS, for example, hyperinfection by this route may result in severe disease of the lungs, heart, liver, kidneys and nervous system. Patients starting treatment with corticosteroids or other immunosuppressive drugs are also at risk of these complications. Thiabendazole and mebendazole are the drugs of choice in treatment.

Other roundworm infestations are covered on pp. 68–72.

8.126 Massive *Ascaris* infection in a child has been successfully treated by anthelminthic treatment. This bolus of roundworms had caused obstructive symptoms.

**FLATWORMS**

Flatworm (*Trematode*) infestations include *schistosomiasis* (see p. 72) and *paragonimiasis* (see p. 73).

*Fasciolopsis buski* is the most important intestinal fluke. It occurs in the Far East, has an intermediate water snail host, and is transmitted via metacercariae on edible water plants such as water chestnuts. Severe infestation may result in abdominal pain, malabsorption, diarrhoea and even obstruction as a result of the attachment of flukes to the intestinal mucosa. Preventive measures involve eradication of the intermediate host and education of affected populations. Treatment with praziquantel or niclosamide is usually effective.

8.127 Adult *Opisthorchis sinensis*. The young worms migrate up the common bile duct to the liver. At maturity, they may reach 2 cm in length.

8.128 Chinese liver fluke infestation. This cholangiogram shows dilatation of the main bile ducts and disorganization of the biliary tree (secondary sclerosing cholangitis), resulting from the presence of multiple adult *Opisthorchis sinensis* (which cannot be seen on the film).

8.129 Adult *Taenia saginata* tapeworm. This is only part of a worm that was passed after treatment with niclosamide. *T. saginata* can grow to 10 m or more in length.

**TAPEWORMS**

Tapeworms include *Taenia saginata* from beef and *T. solium* from pork. Infestation occurs with the ingestion of infected and inadequately cooked meat containing viable cysts that develop in the human intestine. There may be no symptoms, but occasionally tapeworms may cause abdominal discomfort, diarrhoea or 'hunger pains'. The patient may notice proglottids in the faeces. Treatment with niclosamide or alternative drugs is effective (8.129).
**GASTROINTESTINAL**

*T. solium* is important because humans can be affected by the larval stage. The larvae may penetrate the intestinal wall, enter the circulation and migrate to the brain, lungs, eyes, muscle and connective tissue to cause cysticercosis. Serious neurological symptoms may result if the brain is affected, and these may worsen when the cysticerci die and calcify. Radiology, CT scanning (8.130, 8.131) and MRI are of value in locating cysts. Treatment with praziquantel may be helpful, but surgery may be needed and neurological or ophthalmological damage may be irreversible.

*Diphyllobothrium latum*, the fish tapeworm, is a rare cause of vitamin *B*_12 deficiency, and may provoke megaloblastic anaemia in individuals who are genetically predisposed to the condition.

Humans may act as an intermediate host for the dog tapeworm (*Echinococcus granulosus*) and develop cysts — hydatid disease (see p. 73). The intestinal tract is not affected in this ‘dead-end’ infestation.

Various other tapeworm species may occasionally infest humans, and the larval forms of some may also invade directly, producing sparganosis (see p. 74).

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**IRRITABLE BOWEL SYNDROME**

The irritable bowel syndrome (IBS) is probably the most common intestinal disease in clinical practice in the developed world, but it is one of the most poorly understood. It may affect up to 20% of otherwise healthy individuals, and is the underlying problem in up to 50% of referrals to specialist gastrointestinal clinics. It is a functional disease in which intestinal motility may be increased or decreased. The most common symptom is abdominal pain, and this is often accompanied by variable diarrhoea or constipation, or both. The symptoms may be exaggerated during times of stress. Patients may gain symptomatic relief from passing gas and from defaecation. Despite this, they often feel their bowels have not emptied completely and may pass small motions many times a day. The stool is often compressed and ribbon-like. Patients with constipation often abuse purgatives, and may present with diarrhoea for this reason. Recently agreed criteria for the diagnosis of IBS are summarized in 8.132. Examination reveals very little except some vague lower abdominal tenderness. Rectal examination is normal. Colonoscopy and barium enema are indicated when the patient has rectal bleeding, signs of organic disease, persistent diarrhoea or progressive symptoms, or the first presentation is above the age of 50 years. Otherwise these investigations are not required; when performed to exclude other pathology, they are normal (8.133). There is no specific treatment, but patients should be reassured and may benefit from a high-fibre diet, an antimotility drug, and psychological support.

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**CRITERIA FOR THE DIAGNOSIS OF IRRITABLE BOWEL SYNDROME (THE ‘ROME’ CRITERIA)**

At least 3 months of continuous or recurrent symptoms of

- abdominal pain, relieved by defaecation or associated with a change in frequency and/or consistency of stool.
- and/or disturbed defaecation — two or more of
  - (a) altered stool frequency (>3 movements/day or <3/week)
  - (b) altered stool form (hard, or loose and watery)
  - (c) altered stool passage (straining or urgency, feeling of incomplete evacuation)
  - (d) passage of mucus
- usually with bloating or feeling of abdominal distension.

---

8.130 Cysticercosis. Pelvic CT scan shows numerous fusiform calcific opacities in the gluteal muscles, typical of cysticercosis.

8.131 Cysticercosis of the brain revealed by CT scanning. This ‘cut’ shows multiple cysts (dark areas) and multiple calcifications (light areas). The calcifications represent dead cysticerci, whereas the cysts represent the earlier stages of cysticercosis.

8.132 Criteria for the diagnosis of irritable bowel syndrome (the ‘Rome’ criteria).
### SYMPTOMS AND SYNDROMES THAT MAY BE RELATED TO FOOD

<table>
<thead>
<tr>
<th>Gastrointestinal symptoms</th>
<th>Swelling of lips or mouth</th>
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<tbody>
<tr>
<td></td>
<td>Oral ulceration</td>
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<td></td>
<td>Vomiting</td>
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<td>Diarrhoea</td>
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<td>Abdominal pain</td>
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<td>Bloating</td>
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<td></td>
<td>Constipation</td>
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<td></td>
<td>Pruritus ani</td>
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<table>
<thead>
<tr>
<th>Secondary symptoms</th>
<th>Steatorrhoea and 'coeliac-like syndromes'</th>
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<tbody>
<tr>
<td></td>
<td>Protein-losing enteropathy</td>
</tr>
<tr>
<td></td>
<td>Blood loss and anaemia (rare)</td>
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<tr>
<td></td>
<td>Eosinophilic gastroenteritis</td>
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<table>
<thead>
<tr>
<th>Remote effects</th>
<th>Anaphylaxis</th>
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<tr>
<td></td>
<td>Rhinitis</td>
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<tr>
<td></td>
<td>Nasal polyps</td>
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<tr>
<td></td>
<td>Asthma</td>
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<tr>
<td></td>
<td>Eczema</td>
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<tr>
<td></td>
<td>Urticaria and angioedema</td>
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<tr>
<td></td>
<td>Dermatitis herpetiformis</td>
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<tr>
<td></td>
<td>Transitory joint pains</td>
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<td></td>
<td>Migraine</td>
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<tr>
<td></td>
<td>Hyperactivity in children (food association very rare)</td>
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<tr>
<td></td>
<td>Henoch-Schönlein purpura (rare)</td>
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<tr>
<td></td>
<td>Nephrotic syndrome (rare)</td>
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</tbody>
</table>

### CAUSES OF FOOD INTOLERANCE

**Pharmacological**
- Caffeine
- Tyramine - e.g. in cheese
- Histamine - e.g. in fish and canned foods
- Histamine liberators - e.g. egg white, strawberries
- Nitrates - e.g. in preserved meat

**Toxic**
- Irritants of the intestinal mucosa - e.g. peppers and spices
- Poisons - e.g. from tropical sea fish; acetanilide in rape-seed oil; aflatoxin in mouldy peanuts

**Idiosyncracy**
- Deficiency of enzymes, e.g. lactase (cow's milk intolerance) and possibly phenolsulphotransferase (some cases of dietary migraine)

**Indirect associations**
- Fat intolerance caused by gall bladder disease, cystic fibrosis or steatorrhoea
- Intolerance to fried or spiced foods in peptic ulceration
- Irritable bowel syndrome (possible effects of fermentation of unabsorbed food residues)

**Food allergic disease**
- IgE-mediated - usually associated with other allergies
- Other immunological abnormalities - e.g. coeliac disease, cow's milk and soya protein intolerance in infants

A number of symptoms and syndromes can be clearly related to food and food additives (8.134). Both gastrointestinal and remote disorders may result from food intolerance in a number of ways, most of which do not directly involve allergic or immunological reactions (8.135). Even if immunological abnormalities or allergic reactions have been demonstrated clearly – as, for example, in gluten-sensitive enteropathy – it is often not clear whether these are involved in the primary disease process, or whether they are simply a secondary consequence of other initiating factors. The patient will often suspect an association, but when the food is part of the everyday diet, the association may be less obvious. The possibility of food intolerance should be considered in all patients with:
- urticaria and angioedema
- atopic eczema
- migraine
- asthma
- rhinitis.

In rhinitis with nasal polyps, and in some patients with asthma, intolerance to aspirin may also be present.
The manifestations of food intolerance may be immediate or delayed. Symptoms such as angioedema (swelling of lips and tongue — 8.136), urticaria (see p. 93), vomiting, rhinorrhoea and asthma often develop within minutes as a result of an IgE-mediated reaction or a direct pharmacological effect. In these circumstances, the provoking food is often obvious — as, for example, in most patients with the increasingly common problem of allergy to peanuts. Late reactions may develop some hours or even days after ingestion of food, possibly as a result of a delayed immune response involving circulating immune complexes. Such late reactions pose a particularly difficult diagnostic problem, because:

- There are no reliable laboratory tests for food allergy or idiosyncracy.
- Skin-prick testing with a few food extracts such as egg, fish, nuts and yeast gives results that correlate well with clinical symptoms, but positive results tend to persist even when clinical sensitivity has been lost.
- Serum IgE may be raised in an allergic response, but this does not demonstrate that the responsible antigen entered via the gut.
- Radioallergosorbent tests (RASTs) for specific IgE antibodies may sometimes demonstrate raised circulating antibody levels to specific foods, but for most of the food extracts used the correlation with symptoms is poor.
- ‘Fringe’ techniques, such as sublingual or cytotoxic food sensitivity tests, hair analysis, etc., are widely advertised but valueless.

A diagnostic exclusion diet, followed by appropriate food challenge, is the mainstay of investigation, but the difficulty of adhering to and interpreting such a diet should be considered before embarking on this course. Appropriate exclusion diets are summarized in 8.137.

Treatment involves prevention by avoidance of ingestion of provoking foods whenever possible. Problems such as urticaria, eczema, migraine, asthma and rhinitis should also be treated with appropriate therapy. Food avoidance alone is only rarely curative. Patients who are known to be at risk of anaphylaxis (for example, many patients with allergy to peanuts) should be provided with appropriate training and a syringe of adrenaline for self-administration in an emergency.

**8.136 Angioedema resulting from sensitivity to tartrazine.**
This girl had recurrent, severe angioedema and urticaria, with episodes of life-threatening laryngeal oedema. An exclusion diet showed tartrazine (E102) to be the cause of her symptoms. This food colouring is widely used in many processed foods and drinks, so a rigorous maintenance exclusion diet is required to prevent symptoms. The mechanism of tartrazine sensitivity is unclear, and it may not have an allergic basis. Cross-sensitivity with other azo dyes, salicylates (including aspirin) and benzoates is common.

**8.137 Diagnostic exclusion diets appropriate for possibly food-related symptoms.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria or angioedema</td>
<td>Tartrazine, salicylate and benzoate free</td>
</tr>
<tr>
<td>Eczema</td>
<td>Cow's milk and egg free</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>Gluten free</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Gluten free</td>
</tr>
<tr>
<td>Cow's milk sensitive enteropathy</td>
<td>Cow's milk free</td>
</tr>
<tr>
<td>Asthma and rhinitis</td>
<td>Full exclusion</td>
</tr>
<tr>
<td>Migraine</td>
<td>Full exclusion</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>Full exclusion</td>
</tr>
</tbody>
</table>

* A full exclusion diet should be tried if a more specific diet is unsuccessful.
GASTROINTESTINAL HORMONE-PRODUCING TUMOURS

The gastrointestinal tract contains the largest mass of endocrine cells in the body. The hormones produced in the gut and pancreas include gastrin, cholecystokinin (CCK), vasoactive intestinal polypeptide (VIP), somatostatin, enteroglucagon, secretin, insulin, glucagon, gastric inhibitory peptide, motilin, substance P, neurotensin, pancreatic polypeptide, enkephalin and endorphins, bombesin and other peptides.

Pancreatic endocrine tumours are rare. The Zollinger-Ellison syndrome is caused by a gastrin-secreting tumour; 85% of these arise in the pancreas (see p. 372). Appropriately two-thirds are sporadic, whereas one-third form part of the multiple endocrine neoplasia (MEN) Type 1 syndrome (see p. 319). The major symptoms are caused by hyperacidity, which causes multiple duodenal and even jejunal peptic ulceration. High gastrin levels and hypertrophied gastric folds suggest the diagnosis. Treatment with H$_2$-blockers or the hydrogen–potassium ATPase inhibitors is effective, but the tumours should ideally be removed, as 60% are malignant.

Verner-Morrison syndrome and VIPomas present with chronic profuse watery diarrhoea leading to hypokalaemia, hypochlorhydria, dehydration and flushing. Treatment of the symptoms by corticosteroids, metoclopramide, indomethacin and opiates has limited effects, whereas somatostatin analogues appear to be useful, particularly if the tumour is inoperable.

The glucagonoma syndrome is usually caused by a malignant pancreatic tumour, and patients have a characteristic rash. The skin lesions (necrolytic migratory erythema) start as erythematous areas that become raised with superficial central blistering and rupture to leave crusts (8.138). They tend to heal from the centre leaving increased pigmentation. Diagnosis is based on clinical suspicion in patients with the rash, weight loss, glucose intolerance and often thromboembolic complications, combined with a plasma glucagon level above 300 pmol/litre. Treatment is by tumour removal and the rash may improve with oxytetracycline, steroids or zinc.

Somatostatinoma has been described in about 20 cases. Most were malignant pancreatic tumours occurring in patients with mild diabetes and gall bladder disease. Tumours secreting other gastrointestinal hormones have been described, particularly pancreatic polypeptide, but all are exceedingly rare, with the exception of insulinomas; patients with the latter present with hypoglycaemia.

8.138 Glucagonoma syndrome is usually associated with a characteristic rash, the cause of which is obscure. The rash evolves through stages of erythema, blistering and crusting, and may ultimately be much more severe than in this patient. Note the accompanying weight loss.
LIVER AND PANCREAS

HISTORY

Many patients have asymptomatic liver disease which is found incidentally as hepatosplenomegaly on routine examination, positive hepatitis serology after blood donation, abnormal liver biochemistry on routine screening or as abnormal haematology (high mean cell volume or low platelets) or positive autoantibodies in patients presenting with other problems. Acute liver disease may present dramatically, however, with acute anorexia, nausea and vomiting. There may be intolerance to the sight and smell of food, to alcohol and to cigarette smoke. An intense itch may develop in the skin and this may precede the development of jaundice, which may be noticed by the family before the patient. As jaundice appears, other symptoms may disappear. The patient may now notice dark urine and pale stools. There may now be right-sided abdominal discomfort caused by an enlarged or inflamed liver, or by an obstructed biliary tree.

Complications of liver disease include liver cell failure and portal hypertension. Hepatic encephalopathy tends to develop insidiously as liver cells fail, and a history of mood change, confusion and somnolence is often obtained from the family. Portal hypertension may be associated with a history of abdominal swelling and peripheral oedema, but the patient may become aware of this only when they have difficulty in putting on their shoes or trousers. Gastrointestinal blood loss may indicate the presence of oesophageal varices or reflect a coagulation defect caused by liver disease or associated thrombocytopenia. Key symptoms in liver disease are summarized in 9.1.

It is important in the history to ask about:
- previous jaundice – hepatitis or gallstones
- recent drug therapy – including self-administered drugs, drug misuse and herbal remedies
- alcohol intake
- close contact with a jaundiced person or someone in a high-risk group
- recent blood transfusion or injections
- sexual activity and proclivity
- occupation – health professional, farmer, sewer worker
- family history of liver disease
- foreign travel
- recent eating of shellfish, salads, etc. in risk areas of the world
- hobbies – canoeing, swimming, other watersports.

EXAMINATION

The diversity of signs in liver disease (9.1) reflects the key role that the liver plays in homeostasis.

Jaundice is a frequent sign, and it can be detected clinically when the serum bilirubin level rises above 50 μmol/litre.
- In haemolytic states the pigment circulates attached to albumin and does not appear in the urine – it usually imparts a pale yellow colour to the skin and sclerae (9.2).
- In hepatocellular and obstructive jaundice the conjugated bilirubin accumulates to very high levels and may give a much darker colour to the skin and sclerae, which may become orange or greenish in colour (9.3–9.5).

9.1 Common symptoms and signs in liver disease.
Other yellow pigmentation of skin, which may mimic jaundice, follows mepacrine ingestion or the excessive ingestion of carotenes (7.149), but these do not colour the sclerae. Pruritus may result from retained bile salts in cholestatic disorders, and it may appear before the onset of frank jaundice. Scratch marks may be present in accessible skin areas (9.6).

In obstructive jaundice, the stool is pale in colour, because of the lack of bile pigments and the presence of steatorrhoea. In haemolytic jaundice, the stool is dark. The urine is dark in obstructive and hepatocellular jaundice, as a result of conjugated bile pigments; whereas in haemolytic jaundice, no bile pigment is present but there is an excess of urobilinogen, which may darken on standing.

9.2 Haemolytic jaundice in a young man, who was subsequently found to have a lymphoma. The skin and sclerae have a pale lemon-yellow tinge, due to the elevation in unconjugated bilirubin.

9.3 Jaundiced sclerae in a patient with hepatitis A. Mild jaundice is often most evident in the sclerae, and may be unaccompanied by obvious jaundice in the skin.

9.4 Jaundiced skin in a youth with chronic active hepatitis. The jaundice results from an elevated level of conjugated bilirubin, which produces a deeper yellow colour than unconjugated bilirubin. Note the associated gynaecomastia.

9.5 Severe cholestatic jaundice in a patient with primary biliary cirrhosis (PBC). The high level of conjugated bilirubin, maintained over a long period, gives a characteristic dark brown–orange pigmentation to the skin and sclerae. Patients with PBC usually develop large xanthelasmata and corneal arcus as a consequence of disordered lipid metabolism.

9.6 Scratch marks associated with severe pruritus, and eruptive xanthomas, in a child with intrahepatic cholestasis resulting from biliary atresia.
A variety of signs may result from the failure of the liver to metabolize oestrogens.

- Spider naevi, which are usually found in the upper part of the body, above the nipple line, especially in areas exposed to sunlight (9.7–9.9); healthy people, especially women during pregnancy and patients on oestrogen therapy, may have one or two spider naevi, but a larger number is strongly suggestive of liver disease.

- Gynaecomastia is commonly seen in men with chronic liver disease (9.4, 9.10), though there are many other possible causes (9.11). It is important to differentiate gynaecomastia from obesity by feeling for breast tissue around the nipple.

- Palmar erythema is a red flushing on the thenar and hypothenar eminences (9.12). This is common but not specific to liver disease. Similar changes may also be found in the soles of the feet.

9.7 A typical spider naevus consists of a central spiral arteriole, which supplies a radiating group of small vessels. This spider naevus is of typical size, though larger and smaller examples may occur.

9.8 The spider naevus blanches if the central spiral arteriole is occluded by pressure, demonstrating that this is the single source of its blood supply.

9.9 Spider naevi. This barman had alcoholic cirrhosis, accompanied by multiple spider naevi on the head and neck. The occurrence of a large number of spider naevi points strongly to underlying liver disease, though occasional solitary spiders may be found in normal people.

9.10 Gynaecomastia in a male patient. This patient had cirrhosis, and a hepatocellular carcinoma.
• Loss of body hair, including pubic and axillary hair, and testicular atrophy are also common (9.13).
A range of other signs develops with long-standing liver dysfunction.
• Finger clubbing (2.104, 2.105) is a common feature of liver disease and may also involve the toes; it is nonspecific, being also found in respiratory, cardiac, alimentary and endocrine diseases.

**CAUSES OF GYNAECOMASTIA**

<table>
<thead>
<tr>
<th>Liver disease</th>
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<tbody>
<tr>
<td>Hyperthyroidism</td>
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<tr>
<td>Oestrogen-producing tumours (testis, adrenal)</td>
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<tr>
<td>Human chorionic gonadotrophin-producing tumours (testis, lung)</td>
</tr>
<tr>
<td>Starvation and refeeding</td>
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<tr>
<td>Carcinoma of breast</td>
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<tr>
<td>Drugs:</td>
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<tr>
<td>Oestrogenic</td>
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<tr>
<td>Oestrogens</td>
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<tr>
<td>Digitalis</td>
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<tr>
<td>Cannabis</td>
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<td>Diamorphine</td>
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<tr>
<td>Anti-androgens</td>
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<tr>
<td>Spironolactone</td>
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<tr>
<td>Cimetidine</td>
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<td>Cyproterone</td>
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<tr>
<td>Others</td>
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<tr>
<td>Gonadotrophins</td>
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<td>Cytotoxics</td>
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<tr>
<td>Physiological:</td>
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<td>Neonatal</td>
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<tr>
<td>Pubertal</td>
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<td>Old age</td>
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</table>

9.11 Causes of gynaecomastia.

• White nails (2.102): the cause is unknown but their whiteness mirrors the severity of the liver disease. White nails are also found in other conditions in which the serum albumin is low.
• Spontaneous bruising and excessive bleeding (9.14) are a reflection of the failure of the liver to synthesize coagulation factors II, VII, IX and X, often compounded by the failure to absorb vitamin K, as a result of retention of bile salts.
• Xanthelasmata (7.125, 9.5, 9.49) develop as a result of long-standing cholestasis and hyperlipidaemia, and are a common feature of primary biliary cirrhosis; they develop in the soft tissues of the upper and lower lids. Xanthomas may also appear in other skin areas (7.128, 7.129, 9.6) and in tendons (7.130, 7.131).
• Hepatomegaly (9.15) is frequently found in liver diseases, particularly if the liver is infiltrated with carcinoma or fat, in cirrhosis, in some chronic infections (e.g. 1.219) and in some metabolic disorders (e.g. 7.164). The liver may be abnormally

9.12 Palmar erythema is a common finding in chronic liver disease, but is also found in pregnancy, during oral contraceptive use, in rheumatoid arthritis and in thyrotoxicosis. It may also occur without apparent cause. It is usually particularly marked on the thenar and hypothenar eminences.

9.13 Severe ascites in a patient with hepatocellular carcinoma. The accumulation of fluid within the peritoneal cavity has led to gross abdominal distension with downward displacement and eversion of the umbilicus. Note the presence of distended veins in the abdominal wall. The flow in these veins was away from the umbilicus, and the underlying diagnosis was alcoholic cirrhosis. Note the absence of body hair in this patient - another sign of chronic liver disease.

9.14 Spontaneous bruising in a patient with cirrhosis. Disturbance of coagulation mechanisms is a common problem in chronic liver disease, and the risk of excessive bleeding should always be assessed by coagulation studies before liver biopsy or other operative procedures.
firm, and localized masses or nodules may be felt. The liver may also be tender, especially if the enlargement is caused by inflammation or venous congestion. It is important to be aware of the anatomical variants of the normal liver, especially of Riedel’s lobe. The upper border of the liver may be pushed down into the abdomen by an extreme degree of emphysema, giving a misleading impression of hepatomegaly.

- **Ascites** (8.9, 9.13) is the accumulation of free fluid in the peritoneal cavity. The most common cause of ascites is the onset of liver failure, with resulting hypoalbuminaemia and portal hypertension. The differential diagnosis includes malignancy (primary or secondary), nephrotic syndrome, malnutrition causing protein deficiency, right heart failure from any cause (especially constrictive pericarditis), chronic infec-

**INVESTIGATIONS**

Investigations are of value in defining the cause of liver disease, the extent of damage and the effects of treatment. They should be used selectively.

- **Urinalysis:** in obstructive jaundice the urine is dark orange in colour and, as obstruction deepens, it may develop a greenish tinge; it gives a positive test for bile and a negative test for urobilinogen; in haemolytic jaundice, the urine may be dark in colour because of the increased levels of stercobilin; a positive faecal occult blood test is of value in detecting carcinoma of the ampulla of Vater and also primary alimentary lesions that may have produced hepatic secondaries.

- **Full blood count** is of value in detecting anaemia — often iron deficient because of bleeding from oesophageal varices; macrocytosis is often found in liver disease with biliary obstruction and may not reflect vitamin B12 deficiency (B12 levels may be elevated if there is hepatic cell necrosis); folate levels are often low, caused by a combination of malabsorption and poor dietary intake; thrombocytopenia is often present, because of a combination of factors that may include the direct effects of alcohol on the bone marrow, secondary hypersplenism, disseminated intravascular coagulation and marrow aplasia in acute fulminant hepatitis, and folate deficiency.

- **Stools:** the pallor of the stools depends on the degree of biliary obstruction and is associated with a degree of steatorrhoea as the bile salts are not excreted; the stool in haemolysis is dark in colour because of the increased levels of stercobilin; a positive faecal occult blood test is of value in detecting carcinoma of the ampulla of Vater and also primary alimentary lesions that may have produced hepatic secondaries.

- **Splenomegaly** (9.15), often the result of a rise in portal venous pressure, may be associated with the primary liver pathology and may occur in haematological (10.60, 10.98), infective (1.192, 1.195, 1.219) or metabolic (7.164) disorders (10.71); the spleen must be differentiated from the left kidney by palpation and percussion.

- Superficial veins may often be seen on the abdominal wall surface; these may originate from the umbilicus, representing a communication from the portal to systemic circulations (caput medusae); the blood flow is from the umbilicus outwards (9.13). Large veins may also be found running from the inguinal region to the chest wall; the blood flow is usually upwards, implying blockage of the inferior vena cava (9.54).

- **Weight loss** is common in patients with liver dysfunction; limb size is often in stark contrast to the swollen abdomen.

- **Encephalopathy** is an acute or chronic neurological impairment that may result from liver cell failure associated with shunting of blood from the portal system; it is probably caused by to the failure of the liver to detoxify some as yet unidentified component in the portal blood. There is progressive impairment of higher cerebral function, with eventual coma and death. Early features suggesting encephalopathy include fetor hepaticus — a sweet apple-like smell on the breath — a coarse flapping tremor and an inability to draw or write accurately. A clinical test to monitor changes in status is the patient’s signature (with date) on the casesheet.

**9.15 Hepatomegaly and splenomegaly**

commonly coexist in chronic liver disease in the presence of portal hypertension; hepatomegaly may also occur alone in many liver disorders. This patient shows signs of weight loss, and has dilated abdominal veins. Her hepatomegaly has just been further investigated by CT-guided biopsy.
- Coagulation abnormalities are common and often complex, as the liver makes most coagulation factors and destroys others; correct investigation often requires expert haematological advice; tests should include the activated partial thromboplastin time (APTT), the prothrombin time (PT), the thrombin time (TT), whole blood platelet count and simple tests of fibrinolysis such as measurement of fibrinogen – fibrin degradation products (FDPs).
- Routine biochemistry is the keystone of diagnosis and assessment of progress; tests should include total bilirubin, with direct and indirect values as necessary, alkaline phosphatase, the aminotransferases (especially alanine aminotransferase, ALT), γ-glutamyl transpeptidase, total proteins, albumin and γ-globulins; none of these tests is specific or diagnostic, but all are of value in combination and in following the course of the disease; two broad patterns of liver function tests may emerge: cholestatic and hepatitic (9.16); measurement of serum iron, total iron binding capacity, per cent saturation and ferritin level are of value when looking for haemochromatosis; a low serum iron and ferritin may be found in chronic blood loss states, such as after bleeding from oesophageal varices or neoplasia; serum albumin measures the synthetic capacity of the liver generally.
- The α-fetoprotein level is elevated in most primary hepatocellular carcinomas and is of value as a diagnostic and prognostic test.
- Levels of viral markers are a pointer to infection, and sequential samples provide evidence of the course of the disease.
- Autoantibodies: some immunological disorders are associated with liver disease; primary biliary cirrhosis is associated with the presence of anti-mitochondrial antibodies; different forms of autoimmune chronic active hepatitis are associated with different autoantibodies (see p. 407); diseases such as systemic lupus erythematosus (p. 139), rheumatoid arthritis (p. 125), dermatomyositis (p. 142) and CRST syndrome (p. 141) have specific immune abnormalities. Imaging investigations are often useful in disorders of the liver, pancreas and biliary tract.

Plain X-rays of the right upper quadrant are of value when lesions are calcified or contain air. About 10% of gallstones are radio-opaque (9.17), cysts of liver and pancreas may calcify, there may be generalized pancreatic calcification (9.76, 9.77), and the soft-tissue shadow of the spleen, or air in the biliary tree or under the diaphragm (8.70), may be seen. X-ray of the chest may show an elevated diaphragm caused by subphrenic pus or a paralysed diaphragm, or there may be a ‘sympathetic’ pleural effusion or empyema.

**CHOLESTATIC VERSUS HEPATITIC LIVER FUNCTION TESTS**

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<tr>
<th>Cholestatic</th>
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<td>Extrahepatic</td>
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<tr>
<td>• gall stone(s) in common bile duct</td>
<td>• virus infection – hepatitis A, B, C, D, E, cytomegalovirus, Epstein-Barr virus</td>
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<td>• cholangiocarcinoma</td>
<td>• alcohol or drugs, or both</td>
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<td>• bile duct strictures</td>
<td>• metabolic – haemochromatosis, Wilson’s disease, α1-antitrypsin deficiency</td>
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<td>• extrinsic masses compressing ducts</td>
<td>• autoimmune – chronic active hepatitis</td>
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<td>• sclerosing cholangitis</td>
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• Cholecystogram, intravenous cholangiography and T-tube cholangiography involve the administration of a contrast medium to outline, respectively, the gall bladder, hepatic ducts, and the hepatic ducts after surgery.

• Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic technique in which the ampulla of Vater is cannulated and contrast medium is injected to outline the biliary tree and pancreatic ducts (8.96, 9.19, 9.51); it is of value in detecting and removing stones impacted in the lower biliary tree; pancreatitis and ascending cholangitis are potential complications.

• Percutaneous transhepatic cholangiography (PTC) involves passing a needle under anaesthesia towards the hilum of the liver in patients with obstructive jaundice under radiological control; contrast can then be injected to show the site of blockage (9.61). PTC has been largely superseded by ERCP but is still useful when the common bile duct cannot be cannulated or is completely obstructed.

• Ultrasound is a simple, cheap, easily repeatable noninvasive test, which is now widely used for imaging of the liver bile ducts and gall bladder; it is of proven worth in gall stone disease, malignant tumours, cysts, abscesses, haematomas and vascular malformations (9.20, 9.59, 9.64, 9.81); it is invaluable in controlling and directing liver biopsies. The technique is sensitive for lesions down to approximately 5 mm in diameter.

9.18 Duodenoscopy with a side-viewing endoscope is an essential preliminary to common bile duct cannulation and endoscopic retrograde cholangiopancreatography (ERCP). It may also reveal abnormalities in the duodenum or the ampulla of Vater. Here, a normal ampulla (centre of picture) is flanked by two duodenal diverticula. These abnormalities are found in 10–15% of patients endoscoped, and are usually of no clinical significance; but large duodenal diverticula may be associated with symptoms due to bacterial overgrowth (see page 375).

9.19 Endoscopic retrograde cholangiopancreatography (ERCP) is of great value in assessing and sometimes treating abnormalities in the biliary tree and pancreatic ducts. In this patient a cholangiocarcinoma is causing major obstruction of the common bile duct (black arrow). The biliary tree proximal to the obstruction is grossly dilated. The pancreatic duct is also filled with contrast medium (white arrow).

9.20 Ultrasound is the optimal initial investigation for gallstones. The scan shows a typical gall stone (A) in the gall bladder (B). The acoustic shadow (C) cast by the stone is typical.


- **CT** (9.21) and **MRI** are of major value in detecting intra-hepatic lesions, regional lymph nodes, associated tumours, abnormalities of the pancreas, and lesions in the porta hepatis; they can also be used to locate sites for biopsies.

- **Angiography and portal venography**: selective angiography of the hepatic artery may reveal vascular tumours; the portal venous system can be imaged by splenic venography (9.22) and by digital subtraction angiograms.

- **Isotope scans**: intravenous injection of \(^{99m}\text{Tc}\) sulphur colloid results in diffuse uptake of the isotope by the reticuloendothelial (RE) cells of the liver, spleen and bone marrow; the technique may show abnormalities in the position of the liver and filling defects caused by space-occupying lesions (9.58), but has been largely superseded by ultrasound and CT.

- **Laparoscopy** allows direct visualization of the liver, pancreas and gall bladder, and is of value in assessing the presence and the extent of disease (9.23); biopsy under direct vision is possible, and surgery may be undertaken without laparotomy (keyhole surgery).

- **Electroencephalography (EEG)** is of value in determining the presence and severity of encephalopathy.

- **Liver biopsy** will often give the tissue diagnosis of a lesion; it may be done blind when the disease is diffuse, as in cirrhosis, or it may be performed under ultrasound or CT guidance; it is usually done percutaneously with Menghini needle or a ‘Trucut’ needle (6.26), but may also be done at laparoscopy or laparotomy; in patients with a bleeding tendency, a transjugular catheter advanced through the hepatic vein allows multiple biopsies to be done without any external bleeding; special histological stains help to define the pathology.

Before undertaking liver biopsy, some safety precautions are necessary. These include:

- informed patient consent
- measurement of prothrombin time (PT not greater than 3 seconds over control)
- measurement of platelet count (platelet count should be above \(100 \times 10^9/\text{litre}\))
- there should be no evidence of dilated bile ducts or a major degree of ascites
- the patient should be able to hold their breath for at least 20 seconds
- the patient should be cross-matched, with 2–4 units of blood immediately available for transfusion if necessary.

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**9.21 CT** is of major value in the assessment of patients with many disorders of the liver and pancreas. This patient has multiple secondary tumour deposits of various sizes throughout the liver, which have contributed to marked hepatomegaly. The primary tumour was in the breast.

**9.22 Splenic venography** can be used to delineate the portal venous system in patients with portal hypertension. Contrast is injected via a needle inserted into the enlarged spleen (on the right of the picture). In this patient, with advanced cirrhosis, the technique demonstrates the extent of the collateral circulation. Note the dilated splenic and hepatic veins, which contrast with narrowed intrahepatic vessels (top left), affected by the cirrhotic process. A tortuous, grossly dilated vein leads towards the umbilicus. The patient had a typical dilatation of the superficial abdominal veins (9.13).

**9.23 Laparoscopy** is valuable in many disorders of the liver and biliary tract. This picture was taken immediately before laparoscopic cholecystectomy and shows an enlarged, turgid gall bladder. Above the gall bladder, the smooth lower border of a normal liver is clearly seen, and abnormalities in the liver can often be well visualised by this technique. Note also the loops of normal bowel to the right of the liver (left of picture) and the pylorus to its left.
CLINICAL PRESENTATIONS OF LIVER DISEASE

CIRRHOSIS

Cirrhosis is a descriptive term for a liver in which there is a combination of abnormal fibrosis and nodular regeneration of liver cells (9.24). The balance between the two processes varies in different patients and in the same patient over time. The normal liver architecture is distorted, and the processes interfere with portal circulation, raising its pressure, opening up communications between the portal and systemic circulations and sometimes causing splenomegaly. Cirrhosis is the end result of a variety of pathological processes (9.25), the most common causes being viral hepatitis, alcohol and immunological and metabolic diseases.

Portals hypertension may arise from obstruction in the portal vein before it reaches the liver (prehepatic), within the liver (intrahepatic) or between the liver and the inferior vena cava (posthepatic). A rise in pressure rapidly leads to the opening up of latent anastomoses between the systemic and portal venous systems, which are mainly to be found in the gastro-oesophageal region (9.22), in the rectum and at the umbilicus. Dilatation of these collaterals allows portal—systemic shunting and this may give rise to specific clinical problems. The spleen may be grossly enlarged.

Ascites may be gross (9.13). The first aim in its management is to create a net negative balance of sodium (dietary restrictions and diuretics). It is simple to monitor abdominal girth, weight, blood urea and electrolytes and 24-hour urinary sodium loss. Paracentesis is of value in excluding other diagnoses by biochemistry and cytology. It may also have a place in treatment in association with plasma expanders (e.g. albumin). Peritoneovenous shunts drain the ascitic fluid and return it into the venous system (9.26). Their long term complications include infection and shunt obstruction.

CAUSES OF CIRRHOSIS

| Alcohol |
| Chronic viral hepatitis |
| Chronic active hepatitis |
| Primary biliary cirrhosis |
| Primary and secondary sclerosing cholangitis |
| Cryptogenic (unknown) |
| Haemochromatosis |
| Hepatic vein obstruction |
| Wilson's disease |
| Drugs |
| α1-antitrypsin deficiency |
| Cystic fibrosis |
| Galactosaemia or fructose intolerance |
| Veno-occlusive disease |
| Cardiac failure |

The clinical features of cirrhosis are a result of portal hypertension and liver cell failure, and at different stages of the disorder may include any of the symptoms and signs shown in 9.1. Initially, the liver may be normal in size or even enlarged; as cirrhosis progresses it usually becomes contracted and shrunken. Primary liver cell cancer is a potential complication of cirrhosis.

CAUSES OF CIRRHOSIS

9.24 Cirrhosis. In this typical histopathological section, bands of fibrous tissue run between nodules of regenerated hepatocytes. Only some nodules contain a central vein, and the bile ducts and portal vessels run in the fibrous septa. These changes are associated with portal hypertension.

9.25 Causes of cirrhosis.

9.26 A peritoneovenous shunt in a patient with cirrhosis and severe ascites. The subcutaneous course of the valved shunt is clearly seen. Despite the presence of the shunt, which has helped to maintain his serum albumin level, this patient still has severe ascites.
Oesophageal varices lie in the submucosa of the lower oesophagus and are liable to rupture because of portal pressure and local trauma. Bleeding is also compounded by severe coagulation defects caused by liver cell failure. Haematemesis and melena or chronic iron deficiency are the main presentations. Diagnosis is made by barium swallow or at endoscopy (1.219, 9.27; 9.28), and varices may also occur in the fundus of the stomach (9.29). Some endoscopic appearances are associated with a particularly high risk of bleeding (9.28). The mortality is high; after a first bleed from varices about one-half of the patients die within 6 weeks and each subsequent bleed carries a 30% mortality.

Emergency treatment of bleeding varices may be carried out by balloon tamponade with a Sengstaken-Blakemore or Minnesota tube. Sclerotherapy, by direct injection (9.30), is of value in up to 90% of cases. There is a high complication rate (20–25%)—mainly due to oesophageal ulceration and infection (9.31). Ligation of the base of the varix by application of a rubber band is also claimed to have a 90% success rate with fewer complications.

Vasopressin reduces portal vein flow by provoking splanchnic vasoconstriction, but also affects other vessels. Risk to the coronary and cerebral circulation may be reduced by the simultaneous administration of glyceryl trinitrate. Somatostatin (or

9.27 Oesophageal varices. A barium swallow, showing the typical appearance of multiple lower oesophageal varices, evident as barium-coated filling defects. In addition, gastric varices can be seen, along the lesser curvature of the stomach. These thin-walled varices are easily damaged, and bleeding is a frequent complication.

9.28 Oesophageal varices seen through the endoscope. 'White' varices like these have been shown to have a relatively low risk of immediate bleeding, because they are covered with a thick layer of mucosa. The presence of red lines (red wale markings) or spots (cherry-red spots) is associated with a strong likelihood of bleeding.

9.29 Varices may also occur in the gastric fundus in portal hypertension. In this patient the gastric varices (to the right of the picture) are above the diaphragm in a hiatus hernia. Portal hypertension may also lead to other changes in the stomach, including congestive gastropathy and 'watermelon' stomach, in which areas of erythematous and pale mucosa are intermingled.

9.30 Injection sclerotherapy is commonly effective in the treatment of bleeding oesophageal varices. The needle is introduced through an endoscope, and retained within its protective sheath until it is applied to the surface of the varix. It is then used to inject sclerosant (usually ethanalamine or sodium tetradeyl sulphate) into the vein.
its synthetic analogue) has the same effects on portal vein flow but fewer side effects. Portocaval anastomosis or the insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS) may lead to a dramatic reduction in portal vein pressure and in ascites. A preliminary investigation is portal venography.

The most important problem is the potential for encephalopathy but this does not occur frequently. As a last resort the patient should be considered for liver transplantation.

Rectal anastomoses may become extremely large and bleed after bowel movements. Massive bleeding is extremely rare. Surgery is the treatment of choice.

Umbilical anastomoses are rarely clinically obvious. The anastomotic veins radiate from the umbilicus across the abdomen to join systemic veins, forming a 'caput medusae'. Lesser degrees of anastomosis are more common.

LIVER FAILURE

Liver failure can develop acutely in a previously normal liver (as in fulminant viral hepatitis or drug-induced hepatitis), or it may develop insidiously in a chronically damaged liver. Fluid retention is an early problem; patients present with ankle and leg oedema, ascites and small pleural effusions. Bruising is seen spontaneously and after trauma, sometimes even from the pressure induced by a blood pressure cuff. This results from defective coagulation factor synthesis and from thrombocytopenia associated with splenomegaly. A bleeding tendency may also be shown by excessive bleeding at venepuncture sites. Nausea, vomiting, anorexia, drowsiness, tremor and confusion may lead on to encephalopathy: deep coma with fits and decerebrate posture.

Other metabolic disturbances, including hypoglycaemia, pancreatitis and renal failure, are common.

9.31 Oesophageal varices after treatment by sclerotherapy. The injection of a sclerosant via the endoscope results in local variceal thrombosis, followed by fibrosis and, often, mucosal ulceration. Definitive treatment (transjugular intrahepatic portosystemic stent shunt or porto-systemic anastomosis) may subsequently be necessary.

9.32 Insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS). The hepatic vein is cannulated via the jugular vein and the superior and inferior vena cava. A track is then created between the hepatic vein and the right main portal vein branch using a special needle. The track is dilated using a balloon, and an expandable metal stent is inserted to create the shunt. This view shows the inflated balloon and the expanded stent.

9.33 Umbilical anastomoses in portal hypertension, demonstrated by infrared photography. The patient had ascites but the veins were not obvious clinically. An extensive network of veins radiating from the umbilicus is seen. Note the coexistence of gynaecomastia.

9.34 Liver failure in a patient with alcoholic cirrhosis, who presented with major haematemesis from known oesophageal varices. There is gross distension of the abdomen due to severe ascites, and visible superficial dilated veins, originating in the umbilical region. The blood flow was from the umbilicus outwards. There is also atrophy of the muscles of both upper and lower limbs. The patient was icteric, and she had fetor hepaticus. There is a large pressure sore over her left gluteal region. Close examination of her skin showed that she had purpura. Note that she is receiving a blood transfusion and that a urinary catheter is in place.
LIVER AND PANCREAS

Treatment requires cooperation between a variety of specialities. Bleeding requires the intravenous administration of vitamin K, and often fresh frozen plasma. Haemodialysis may be required for renal failure. Oesophageal varices must be identified and bleeding arrested. Blood and other proteins, which contribute to the encephalopathy, must be removed from the bowel.

Death is usually caused by cerebral oedema or gastrointestinal bleeding.

ACUTE HEPATITIS

Acute hepatitis may result from a variety of causes, the most common of which are viruses and drugs (9.35). The clinical features at onset are usually similar, but the course and ultimate prognosis are different. Hepatitis may be so mild that the patient does not become jaundiced but has malaise, anorexia and aversion to alcohol. In more severe cases, jaundice appears after 7–14 days (9.36), often accompanied by flitting arthralgia, lymphadenopathy, splenomegaly, a skin rash and hepatic discomfort. The urine is usually dark and the stools become pale. Usually the jaundice is mild and lasts only a few days with gradual recovery. In some patients, an intrahepatic cholestatic phase develops, with pruritus, deepening jaundice and increasing hepatomegaly. Occasionally the disease is progressive with deepening jaundice, peripheral oedema and ascites, bleeding, encephalopathy and death. Investigations should include:

• **Biochemistry:** the first changes are rises in the levels of ALT and alkaline phosphatase, followed by a rise in serum bilirubin; urine tests for urobilinogen are positive before jaundice occurs, and then bilirubin is found in the urine; persistence of enzyme disturbance suggests the persistence of hepatitis.

• **Haematology:** there is often leucopenia.

• **Viral markers** can be detected in the blood. Liver biopsy is not a routine investigation in acute hepatitis, but may be carried out when there is diagnostic difficulty or severe impairment of liver function. Typically, biopsy shows swelling and vacuolation of hepatocytes, with focal necrosis affecting the centrilobular areas (9.37).

Treatment of severe hepatitis should be carried out in a specialist unit that offers elective ventilation, prophylactic

<table>
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<th>CAUSES OF ACUTE HEPATITIS</th>
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<td><strong>Pregnancy</strong></td>
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9.35 Causes of acute hepatitis.

9.36 Acute viral hepatitis. This 19-year-old man presented with a 7-day history of malaise, nausea and vomiting and was found to be mildly jaundiced on examination. His hepatitis was found to be caused by Epstein-Barr virus (EBV), and he went on to develop the classic clinical features of infectious mononucleosis. This is a relatively uncommon presentation for EBV infection, but typical of the presentation of viral hepatitis of any cause.

9.37 Acute viral hepatitis. The most prominent feature is centrilobular necrosis, and many of the hepatocytes outside this zone are abnormally swollen. In uncomplicated hepatitis, full regeneration of normal liver architecture will ultimately occur.
antibiotics, antifungal and antiviral therapy, inotropic support, intracranial pressure monitoring, renal dialysis and extracorporeal liver assist treatment.

**VIRAL HEPATITIS**

**Hepatitis A** virus is a picornavirus, waterborne or foodborne, and occurs especially in countries with poor water and sewerage facilities (see 1.5). A Western traveller to most Third World countries has a 2 in 100 chance per month of contracting the infection. The incubation period is 3–6 weeks. Prodromal symptoms last 10–14 days, and the icteric phase is associated with a lessening of symptoms. Jaundice usually disappears in a week and most patients recover rapidly. In a very small number of patients, severe liver necrosis ensues, followed by coma and death. The diagnosis of hepatitis A infection is established by demonstrating a rise in specific IgM. Treatment is supportive. Immunoglobin may be given to those at risk, and protection lasts 3 months. Inactivated hepatitis A vaccine gives 95% immunity over the subsequent 10 years.

**Hepatitis B** virus is found in most body fluids and tissues. It is usually transmitted by sexual activity, by transfusion of blood and blood fractions, on needles (by nurses and doctors pricking fingers), tattooing (9.38), intravenous drug misusers (1.12), from mothers to babies and by aerosol during dental treatment. It may also be transmitted by medical and dental attendants who are carriers through open wounds. The mean incubation period is 10–16 weeks. The specific diagnosis is made by finding hepatitis B antigen and antibodies in serum. The symptomology and course are similar to those of the other viral hepatitides. A small percentage of people develop fulminant hepatitis and die, a small number develop chronic liver disease and a small number become carriers. Vaccination against hepatitis B is essential in health care workers, relatives of those with hepatitis B and other high-risk groups. Emergency immunoglobulin cover may be given after exposure such as needle-stick injury. There is no specific treatment for carriers.

**Hepatitis C** virus is transmitted by blood and blood products, and also sexually. Those who have a high incidence of infection include haemophiliacs, regular blood transfusion recipients ( aplastic anaemia, sickle-cell disease, thalassaemia), renal dialysis patients, those who have recently undergone cardiopulmonary bypass, intravenous drug misusers and dentists. This type of hepatitis tends to be more serious than A or B, with neurological manifestations and bone marrow suppression. There is a high incidence of progression of the hepatitis to chronic disease (50%). The diagnosis is by finding viral RNA in the serum using a PCR technique or finding anti-hepatitis C virus ( anti-HCV ) antibodies. In the Blood Transfusion Service careful screening of donated blood by anti-hepatitis C virus antibodies has significantly reduced the incidence of cases. In selected patients interferon α may be of therapeutic value.

**Hepatitis D** ( delta ) is caused by a virus that is transmitted in close association with the hepatitis B virus, and this form of hepatitis is most common in those with active hepatitis B or who are carrying hepatitis B. Hepatitis D may be clinically severe.

**Hepatitis E** is transmitted enterically and occurs in large epidemics. The disease is self-limiting and does not progress to chronic liver disease. There is as yet no serological test but hepatitis E viral RNA can be detected in the stool. Hepatitis E should be prevented by provision of a clean water supply and efficient sewage disposal.

Studies of the incubation period of acute hepatitis suggest that there are other strains of virus still to be described. Newly discovered hepatitis viruses include the GB-viruses ( GB-A, GB-B, GB-C ). Viral hepatitis may also be caused by Epstein-Barr virus ( p. 31 ), cytomegalovirus ( p. 30 ) and yellow fever virus ( p. 21 ), and it is a component of many viral haemorrhagic fevers ( p. 26 ).

**9.38 Tattooing is an important route of transmission for viral hepatitis.** This patient developed acute hepatitis B after being tattooed in the Far East, and he subsequently became a long-term carrier of the hepatitis B virus. The presence of tattoos always raises the possibility of transmissible infections, including viral hepatitis and HIV.
DRUG-INDUCED HEPATITIS AND CHOLESTASIS

Drugs and chemicals may cause a range of hepatic damage, from acute and chronic hepatitis to cirrhosis and liver tumours. An acute hepatitis-like picture may be produced by a number of drugs (9.35, 9.39). The most common of these in the UK is paracetamol, usually taken as an intentional overdose. Early features are nausea and vomiting. Most patients have few sequelae, but in some who have taken a larger dose, presented late or taken alcohol (which induces the hepatic microsomal enzymes), mild jaundice, liver tenderness and disturbance of liver biochemistry appear on the third or fourth day. Despite treatment at this stage, there is progressive deepening of jaundice, increasing liver cell failure and sometimes death. The prothrombin time is a good predictor of outcome. N-acetylcysteine prevents further paracetamol-induced damage and may partially reverse the hepatic necrosis.

Halothane hepatitis is rare and usually follows multiple exposures to the gas for general anaesthesia. The clinical picture is of acute hepatitis that may be fatal.

Other drugs may cause liver damage with a predominantly cholestatic picture. These include chlorpromazine, oral contraceptives and anabolic steroids, often used for body-building (9.40). Poisoning with other toxins is rare. Epidemics of liver failure caused by exposure to Amanita phallides occur when this fungus is mistaken for the edible mushroom.

CHRONIC LIVER DISEASE

CHRONIC PERSISTENT HEPATITIS

Hepatomegaly may persist after an attack of hepatitis. In chronic persistent hepatitis (CPH), liver biopsy shows continuing periportal inflammation, but there is normal liver architecture (9.41). Enzymes may remain persistently high but other biochemistry is normal. Although there are often no long-term sequelae, a proportion of patients with this histological diagnosis progress to chronic active hepatitis and cirrhosis.

CHRONIC ACTIVE HEPATITIS

Chronic active hepatitis (CAH) is also known as chronic aggressive hepatitis and is defined as chronic hepatic inflammation continuing progressively for up to 6 months without any evidence of improvement, confirmed by characteristic...
CHRONIC LIVER DISEASE

features on liver biopsy (9.42). It may occur as a sequel to hepatitis B, C, D (9.43), autoimmune disease, drug-induced hepatitis and Wilson’s disease. Many patients present with evidence of advanced liver damage. Biochemistry shows raised bilirubin, AST, ALT and alkaline phosphatase. Markers for hepatitis B, C and D may be present. Liver biopsy shows a plasma cell infiltrate with extensive parenchymal necrosis. Progression to cirrhosis is common, and this is associated with a high incidence of primary liver cell cancer. Treatment is unsatisfactory, but some patients respond to interferon.

AUTOIMMUNE CHRONIC ACTIVE HEPATITIS

Autoimmune chronic active hepatitis is a disease of unknown cause that is usually associated with hyperglobulinaemia, autoantibodies in the blood and the coexistence of other autoimmune disorders, for example rheumatoid arthritis, ulcerative colitis, Hashimoto’s thyroiditis, peripheral neuropathy, renal tubular acidosis or keratoconjunctivitis sicca (Sjögren’s syndrome). It is typically a disease of women aged 20-40 years but may occur in other patients. Four subtypes have been described, which are differentiated according to the specificity of the autoantibody produced and their clinical presentations.

• Type I patients used to be said to have ‘lupoid’ hepatitis; they often have a past history or family history of autoimmune disease. Chronic active hepatitis usually starts insidiously with fatigue, malaise and anorexia; there may be early stigmata of liver disease with vascular spiders (9.8, 9.9) and palmar erythema (9.12); occasionally, the onset may be more acute with rapid onset of jaundice, hepatomegaly, splenomegaly and ascites. Some patients also develop features of Cushing’s syndrome (before being administered steroids). Biochemical tests show elevation of aminotransferases, low serum albumin and prolongation of prothrombin time; there is hyperglobulinaemia. There are usually circulating anti-nuclear and smooth muscle antibodies; about 10–20% of patients have positive tests for LE cells (see p. 139).

• Type 2 patients have anti-liver and kidney microsomal autoantibodies. Type 2 chronic active hepatitis occurs mostly in younger children as an acute onset disease process that rapidly progresses to cirrhosis and hepatic decompensation.

• Type 3 and type 4 chronic active hepatitis are poorly defined and present a similar clinical picture to that of type 1. Type 3 chronic active hepatitis has antibodies directed against a soluble liver antigen, but no specific antibodies have yet been found in type 4.

The diagnosis of autoimmune chronic active hepatitis is dependent on the finding of autoantibodies that are not organ-specific in a patient with the liver biopsy findings of chronic active hepatitis (9.42). Treatment of all four types of autoimmune chronic active hepatitis is with corticosteroids or azathioprine, or both. Steroids, used long term, have very significantly reduced the long-term mortality (from 30% to 6%).

DRUG-INDUCED CHRONIC ACTIVE HEPATITIS

A wide range of drugs may cause chronic active hepatitis, even after being used without adverse effects for several years. Some common drugs are methyldopa, halothane, nitrofurantoin, isoniazid, aspirin and sulphonamides. Occasionally the presentation may be florid and fulminating. In addition to the expected biochemical changes of hepatitis, there is hyperglobulinaemia, and LE cells and anti-nuclear and smooth muscle antibodies may be found in the serum. Treatment is to withdraw the suspected drug and follow the liver function tests. Steroids and immunosuppression are of little or no value.

9.42 Chronic active hepatitis. Here the inflammatory infiltrate is not confined to the portal tracts, in contrast to chronic persistent hepatitis (see 9.41). Small inflammatory cells can be seen in bands through the liver parenchyma, and some of the parenchymal cells are swollen and vacuolated. This form of hepatitis is also known as chronic aggressive hepatitis, and it commonly leads to cirrhosis and liver failure.

9.43 Chronic active hepatitis. This patient developed chronic active hepatitis as a sequel to hepatitis B infection, and ultimately developed cirrhosis, portal hypertension and liver failure.
ALCOHOL-INDUCED LIVER DISEASE

Excessive alcohol intake over a prolonged period may cause damage to almost every organ in the body – especially to the liver. Three separate conditions are recognized:

- alcohol-induced fatty liver
- alcoholic hepatitis
- alcoholic cirrhosis.

Fatty liver is common in the heavy drinker, and its only clinical feature is a large, palpable liver. Liver function tests, especially the liver enzymes (ALT and \( \gamma \)-glutamyl transpeptidase), may be abnormal. With abstinence the liver can return to normal size and function.

Acute alcoholic hepatitis usually follows an acute bout of heavy drinking and may occur in the drinker with a fatty liver or in one who has already become cirrhotic. The usual presentation is with sudden onset jaundice that becomes rapidly deeper (9.44) and the liver usually enlarges. If there is pre-existing cirrhosis, there may be an exacerbation of the signs of liver failure and portal hypertension. There may be persistent leucocytosis and fever, with dark urine and pale stools.

In the chronic alcoholic, the features of cirrhosis and its consequences are usually identical to those resulting from cirrhosis of other causes, but some features are suggestive of an alcoholic origin:

- parotid enlargement (9.45)
- Dupuytren's contracture (9.46)
- red, sore, smooth tongue caused by associated vitamin deficiency (9.47)
- beri-beri (p. 347)
- neuropathy (p. 511)
- cardiomyopathy (p. 250)

9.44 Acute alcoholic hepatitis. The patient presented with sudden onset jaundice. At first sight, the condition might be confused with acute viral hepatitis, but the patient had a history of several previous admissions after alcoholic excess.

9.46 Dupuytren's contracture may be seen in association with alcoholic cirrhosis, though it may also occur as a completely independent abnormality. Contracture of the palmar fascial bands produces flexion contracture of the metacarpophalangeal and proximal interphalangeal joints, the flexor tendon apparatus and the skin itself. In this patient, the condition particularly affects the right middle finger and the left little finger. Surgical correction is usually possible.

9.45 Parotid enlargement in association with cirrhosis is most common when alcohol is the cause of the cirrhosis. In addition to painful parotid enlargement, this patient had multiple vascular spiders and early acne rosacea.

9.47 A red, sore, smooth tongue may be seen in patients with alcoholic cirrhosis as a result of associated vitamin deficiency. A similar appearance may occur in patients with nutritional deficiencies of other origins.
CHRONIC LIVER DISEASE

- acne rosacea (2.84, 9.45)
- associated chronic pancreatitis (p. 419)
- associated peptic ulceration (p. 371).

The diagnosis is made on the basis of the history and clinical features. The extent of liver damage can be monitored by blood tests and liver biopsy (9.48). The tests which predict a poor outcome are a rising prothrombin time, a rising bilirubin, a falling serum albumin and a falling haemoglobin.

Treatment is by abstinence from alcohol and correction of associated vitamin deficiencies. Hepatic failure and portal hypertension may require treatment in their own right.

9.48 Liver biopsy in alcoholic hepatitis. There is widespread fatty change (as shown by the clear macrovesicles, which contained fat before the processing of the section). Focal necrosis of hepatocytes is indicated by the surrounding foci of neutrophils. Mallory's hyaline, shown as eosinophilic globules, has accumulated in some of the hepatocytes; this is typical but not diagnostic of alcoholic hepatitis.

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis is a slowly progressive disease of unknown aetiology that affects women more commonly than men (9:1) and usually occurs between the ages of 40 and 60 years. It has a prevalence of 5–15 per 100,000 population, and an incidence of 10 per million per year. Many patients are diagnosed by chance observation of disturbed liver function tests measured for some unrelated problem. Clinical presentation is often with itching of the skin caused by retention of bile salts or with increased pigmentation of skin, part of which is due to a progressive rise in bilirubin levels. Cholestatic jaundice appears later (9.5, 9.49, 9.50). Autoimmune disorders, including Sjogren's syndrome, Raynaud's phenomenon, thyroid disorders, Addison's disease, rheumatoid arthritis, dermatomyositis and scleroderma, are sometimes an associated feature. During the course of the illness, the patient becomes more icteric and pigmented, usually with marked periocular xanthelasmata (9.5, 9.49) and hepatosplenomegaly. Patches of vitiligo may be present. The patient may complain of persistent steatorrhoea, weight loss and metabolic bone disease. The end result of the disease is liver failure, encephalopathy and bleeding from oesophageal varices. There is also an increased risk (x4) of extrahepatic malignancy, especially carcinoma of the breast.

Serum anti-mitochondrial antibodies are present in over 90% of patients. Serum immunoglobulins are elevated (IgG and especially IgM) and autoantibodies against thyroid and platelets may be found, as well as anti-nuclear and anti-centromere antibodies. Liver function tests are abnormal, with elevated bilirubin and alkaline phosphatase, and modest elevation of ALT, AST and y-glutamyl transpeptidase. Serum cholesterol is usually high. Coagulation may be abnormal, because of a combination of loss of functioning hepatocytes and malabsorption of vitamin K. Liver biopsy shows an inflammatory reaction in the portal tracts with the formation of fibrous septae and granulomas.

Ultrasound and, if necessary, ERCP should be carried out to exclude sclerosing cholangitis (8.96) and to ensure the patient does not have obstruction of the larger biliary ducts, as stone formation is a common association (9.51). These investigations may show splenomegaly and evidence of portal hypertension as the disease advances.

9.49 & 9.50 Primary biliary cirrhosis. This 55-year-old woman presented originally with severe pruritus, and jaundice developed slowly over the next 3 years. When these photographs were taken, she had deep jaundice, typical brown pigmentation, spider naevi, xanthelasmata around both eyes, enlargement of the liver and spleen, and ascites. The deepening jaundice and ascites are poor prognostic signs, and are usually followed by encephalopathy and death within weeks or months.
LIVER AND PANCREAS

There is no specific treatment for the disease, but the hyperlipidaemia and the malabsorption can be treated. Persistent pruritus may respond to the use of cholestyramine. Immunosuppression with steroids, azathioprine, methotrexate and cyclosporin may be of some value in limiting progression.

9.51 Endoscopic retrograde cholangiopancreatography (ERCP) in a patient with primary biliary cirrhosis. The intrahepatic and common bile ducts are normal, but gallstones are present in the gall bladder. Gallstones are a common association with primary biliary cirrhosis.

HAEMOCHROMATOSIS AND HAEMOSIDEROSIS

Haemochromatosis is an autosomal recessive inherited condition, with a gene frequency of 5–10% in which excess iron is absorbed and stored in the body tissues. It typically appears in middle-aged men (male:female ratio 10:1). In women it appears much later in life, because of iron loss at menstruation and in child-bearing. The prevalence of haemochromatosis is 2–5 per 1000 population.

There is a wide spectrum of clinical features at presentation. Asymptomatic patients showing biochemical abnormalities alone may be found by screening families of known patients, whereas others present with the later effects, including hepatic cirrhosis, pancreatic insufficiency with diabetes mellitus (which affects at least 70% of patients) and pigmentation of the skin (bronze diabetes). Skin pigmentation is usually slatey-grey in colour (9.52) and results from the deposition of a combination of melanin and iron. Many patients also develop a pyrophosphate arthropathy in which chondrocalcinosis involves the articular cartilages (see p. 139). This particularly involves the first and second metacarpophalangeal joints and the knees.

Excess iron deposition is also found in the pituitary, where it reduces hormone production, and in the testes. The end result is gonadal atrophy. Cardiac involvement is also common and arrhythmias and heart failure are the presenting features.

The main organ involved is the liver, which is often cirrhotic at the time of presentation, and the patient may have the additional features associated with hepatic failure and portal hypertension. Primary liver cell cancer is a common complication (one-third of patients) and is often associated with a significant decline in liver function. Osteoporosis resulting from gonadal atrophy is a long-term complication.

The diagnosis is made by finding a high serum iron with a very high saturation of iron-binding protein. Serum ferritin is also high and there may be disturbance of the profile of liver function tests. Excess iron is found in most tissues; on liver biopsy, iron stains show iron in the parenchyma and in the Kupffer cells (9.53). There is also a coarse macronodular cirrhosis.

9.53 Liver biopsy in haemochromatosis, stained for iron. Excessive iron is present in the hepatic reticuloendothelial (Kupffer) cells adjacent to the sinusoids, and in parts of the liver parenchyma.
CHRONIC LIVER DISEASE

Treatment usually involves long-term repeated venesection. Chelating agents are rarely used, because of their expense and difficulty of administration and the success of venesection. Diabetes mellitus, other endocrine failure and joint disease may all require specific treatment.

Haemosiderosis (secondary haemochromatosis) occurs if there is excess tissue iron but no subsequent damage. This is usually seen in patients with chronic haemolytic states who have been treated with repeated blood transfusions, for example sickle-cell anaemia and thalassaemia (see p. 435). The iron overload in these patients may give rise to a picture similar to primary haemochromatosis which may be treated by chelating agents (see p.436).

VASCULAR DISEASE OF LIVER

The Budd-Chiari syndrome is a rare disorder that results from a large number of pathologies which ultimately obstruct the flow of blood from the hepatic veins into the inferior vena cava. These include congenital webs in the vena cava, thrombosis in the hepatic veins or adjacent vena cava as a result of thrombophilic states or use of oral contraceptives, infiltration by tumours, Behçet’s disease, alcoholic hepatitis and trauma. The signs depend on how acutely the syndrome develops. Usually this is gradual and the patient presents with an enlarged, sometimes tender, liver. There may be associated jaundice, ascites, peripheral oedema and splenomegaly. A characteristic of the disease is the development of masses of dilated veins on the abdominal wall, the flow being upwards (9.54). The diagnosis may be surmised by the finding of centrilobular necrosis in the liver biopsy, and is established by CT scanning or by failure to catheterize the hepatic veins. Inferior venacavography may also be of value. The usual treatment is portocaval shunting, but liver transplantation has been used in severe cases in which the inferior vena cava is normal.

Veno-occlusive disease of the liver is a small-vessel variant of the Budd-Chiari syndrome that involves the hepatic venules. It develops in people who drink medicinal teas containing alkaloids from Senecio and Crotalaria plants, and rarely after bone marrow transplantation and the use of antimitotic therapy (e.g. thioguanine).

WILSON’S DISEASE (HEPATOLENTICULAR DEGENERATION)

Wilson’s disease is caused by a defective autosomal recessive gene on chromosome 13. There is an abnormality in the handling of copper, which accumulates in various tissues, especially the liver, basal ganglia, bones, renal tubules and cornea. The clinical presentation is usually with a combination of liver function impairment and enlargement and neurological features from loss of function of the basal ganglia (parkinsonian tremor, expressionless facies, athetoid movements and dysarthria). A Kayser-Fleischer ring may be found in the cornea – this is most easily seen in blue-eyed patients as a brown ring (9.55). In brown-eyed patients slit-lamp examination is usually necessary. The diagnosis is made on finding an increased 24-hour urinary copper excretion and liver biopsy evidence of cirrhosis with excess copper in the liver cells. A low serum ceruloplasmin level is found in 90% of patients. Treatment is with long-term penicillamine to chelate the excess copper.

9.54 The Budd-Chiari syndrome (hepatic venous obstruction). Note the grossly dilated veins in the abdominal wall, in which the flow of blood was upwards. The patient had continued to work as a builder’s labourer without symptoms, until he was admitted with coincidental appendicitis. The cause of his hepatic venous obstruction was unclear.

9.55 Wilson’s disease. The clinical features of impaired liver function and neurological disorder are usually accompanied by Kayser-Fleischer rings in the corneae. The rings show as a rim of brown pigment, and are more clearly seen in patients with blue eyes.
LIVER AND PANCREAS

OTHER CAUSES OF CIRRHOSIS

Metabolic causes of chronic liver disease that may lead to cirrhosis include α1-antitrypsin deficiency, glycogen storage disorders (9.56), galactosaemia, fructose intolerance and the Fanconi syndrome. All of these are rare disorders.

α1-antitrypsin deficiency is associated with neonatal hepatitis and cirrhosis in childhood. The aetiology is unknown, but liver biopsy shows the hepatocytes to contain granules of α1-antitrypsin. The diagnosis is made by finding a low serum α1-antitrypsin.

Cardiac cirrhosis is a rare complication of long-standing right heart failure, seen in patients with cor pulmonale, tricuspid incompetence, cardiomypathy and constrictive pericarditis. The clinical features are those described in right heart failure (p. 222). Ultrasound may show dilatation of the inferior vena cava and the hepatic veins.

Drugs are rarely implicated in the generation of cirrhosis. The most common is methotrexate if used for a prolonged period, for example in chronic psoriasis.

Hereditary haemorrhagic telangiectasia (10.7, 10.113) has been associated with cirrhosis. This may be caused by hepatitis viruses transmitted in blood transfusions used for the treatment of long-term anaemia.

Ulcerative colitis and Crohn’s disease are associated with a variety of liver pathologies. These include fatty infiltration of the liver, granulomas, cirrhosis, pericholangitis, primary sclerosing cholangitis (8.96) and carcinoma of bile ducts (see also p. 375).

FIBROPOLYCYSTIC DISEASES

There are a number of rare, congenital fibropolycystic hepatobiliary diseases, including adult polycystic liver, congenital hepatic fibrosis, congenital intrahepatic biliary dilatation and choledochal cysts. There is a high association with similar renal disorders and a risk of malignant change. Diagnosis is made on ultrasound or CT scan (9.57). Liver transplantation is a treatment option if there is serious liver decompensation or portal hypertension.

9.57 Polycystic liver disease, as seen on CT scanning. The patient has massive hepatomegaly, and a typical example of the many cysts in the liver is arrowed (1). She also had bilateral polycystic kidneys (2) (see also p. 299).

LIVER ABSCESS

Pyogenic infection may result from biliary tract obstruction (ascending cholangitis), from infection carried in the portal vein (portal pyaemia) or, more rarely, from the hepatic artery in the course of generalized septicaemia.

Liver abscess is now uncommon as a result of better surgical management of intra-abdominal sepsis, but intra-abdominal pus may still occur with ruptured appendix, a perforated viscus (duodenal ulcer, diverticulitis, etc.), cholecystitis and cholangitis, infiltrating carcinomas and perinephric abscesses. Often, the origin of intra-abdominal sepsis is unclear.

A wide range of bowel origin Gram-negative organisms may be involved. The commonly found organisms include Escherichia coli, Streptococci, Clostridia (mainly perfringens), Klebsiella and Bacteroides. Early administration of antibiotics often results in failure to culture the infecting organisms.

Patients with liver abscess are usually acutely unwell, and present with a high swinging fever, rigors, malaise, nausea, vomiting and, later, liver tenderness. There may be associated features of Gram-negative septicemua with hypotension, peripheral vasoconstriction and oliguria. There may be associated icterus, caused by related biliary pathology or by a forming abscess. In addition, there may be a right-sided pleural effusion, especially if there is pus in the subphrenic space.
Investigations usually show a leucocytosis, elevation of the ESR and disturbance of liver function tests (elevation of bilirubin, alkaline phosphatase and ALT). Blood cultures are positive in one-half to three-quarters of patients who have not been treated with antibiotics. Chest X-ray often shows elevation of the right hemidiaphragm and a reactive pleural effusion. Ultrasound (9.58), CT scan or isotope scanning will localize the site and size of the abscess and treatment is usually surgical evacuation under appropriate antibiotic cover. The pus collected should be sent for culture, and the antibiotic regimen finalized.

Amoebic liver abscess is a frequent complication of patients with enteric amoebic infection, but may occur in the absence of a clinical episode of dysentery (see p. 62). The organism is carried to the liver in the portal vein, usually forming multiple abscesses that coalesce and may rupture into the peritoneal cavity or into the pleural space. Amoebic abscesses may also be revealed by ultrasound or CT scan (1.182). Diagnostic aspiration (1.183, 1.184) produces reddish-brown pus (anchovy or chocolate sauce), which may contain motile amoebae. Small single abscesses may not require drainage and will respond to metronidazole alone. Larger, multiple abscesses, and abscesses in the left lobe of the liver may require drainage under ultrasound guidance.

OTHER INFECTIONS OF THE LIVER

Schistosomiasis is a common cause of liver infection in the developing world, and is the most common cause of portal hypertension worldwide. It is usually found in patients who also have disease in the colon or bladder. Migration of ova via the portal vein to the liver causes multiple granulomas and a generalized fibrotic reaction that results in portal hypertension and splenomegaly (see p. 72 and 1.219, 1.220).

Liver fluke infestation may lead to cholangitis, cirrhosis and cholangiocarcinoma (see p. 387).

Hydatid disease may result in multiple cysts in the liver and in many other organs (see p. 73). The cysts are often multiple and have daughter cysts. They act as space-occupying lesions and may produce pressure on the hepatic ducts. Eosinophilia is common. Many of the cysts calcify and may be seen on plain X-rays. Diagnosis is made by ultrasound or by CT scan (1.226).
PRIMARY TUMOURS

Primary hepatocellular carcinoma (primary liver cancer) is one of the most common cancers in West Africa and the Far East, but is relatively rare in the West. It is associated with chronic carriage of hepatitis B and C and related viruses, cirrhosis of any cause, haemochromatosis, use of some androgenic steroids, previous exposure to thorotrust, and aflatoxin from decayed food. The lesions are often multifocal and aggressively invasive. The patient often has pre-existing hepatomegaly and there is right upper quadrant pain with localized enlargement. There may also be weight loss, ascites and occasionally features of hypoglycaemia. Jaundice usually occurs only when the tumour is hilar in site. The diagnosis is confirmed by the finding of a raised circulating level of α-fetoprotein (AFP), mild distur-
bance of the liver function tests and single or multiple defects on ultrasound or CT scanning. Arteriography may be helpful. Histological diagnosis is made on guided ultrasound or laparoscopic biopsy. A solitary lesion may be treatable by surgical resection of a liver lobe, but the overall outlook is poor, with a median survival of 1 year.

Cholangiocarcinoma is the second most common primary malignant tumour of the liver and may be intrahepatic or extra-
hepatic. Intrahepatic tumours have a similar clinical presentation to hepatocellular carcinoma; extrahepatic tumours commonly present with obstructive jaundice. Chinese liver fluke infestation is an underlying factor in the Far East. Bile duct obstruction caused by extrahepatic cholangiocarcinoma can sometimes be palliatively relieved by the insertion of a stent via a side-viewing duodenoscope.

Haemangiosarcoma is a rare, highly malignant tumour of the liver that may result from occupational exposure to vinyl chloride monomers. Hepatic enlargement, local pain and blood-stained ascites often develop rapidly.

Benign tumours of the liver include:

- liver adenomas, which may be associated with prolonged use of high-oestrogen oral contraceptives; they are highly vascular and may cause intraperitoneal bleeding
- cystadenomas, derived from bile ducts or from parenchymal cells
- haemangiomas, which may be diagnosed by hearing a vascular hum over the liver or more commonly, as an incidental finding on ultrasound; they are usually symptomless.
**DISEASES OF THE GALL BLADDER**

**GALLSTONES**

Gallstones are extremely common and will affect one in three women and one in five men in the UK. Most stones are totally asymptomatic and are found by chance during other investigations or at autopsy. There are three types of gallstones.

- **Cholesterol stones** are often solitary; they form in bile in which cholesterol is in excess relative to bile salts, and are found in about 10% of patients with stones; they are common in women who have had many children or who have taken oral contraceptives.

- **Pigment stones** are usually multiple and green–black in colour; they account for about 10–15% of all stones and are the result of bilirubin precipitation, caused by overproduction in chronic haemolytic states; they are later associated with recurrent ascending cholangitis.

- **Mixed stones** are by far the most common, are usually multiple and are a mixture of cholesterol, pigment, calcium carbonate and phosphate; they are found in people who are obese, who have taken oestrogen or who have lived on a diet rich in unrefined carbohydrate and high in calories.

In most patients stones form and remain in the gall bladder without causing symptoms, but they may produce a range of symptoms, including intolerance to fatty foods, with nausea, vomiting, flatulence and epigastric pain. In a minority of patients, gallstones may be associated with significant complications (9.63).

- Migration of stones may lead to additional symptoms such as colicky right hypochondrial pain, obstructive jaundice and recurrent bouts of ascending cholangitis or acute pancreatitis, or both.
- Chronic cholecystitis may lead to adhesion of the gall bladder to surrounding organs, for example the small bowel, colon or stomach, with subsequent erosion of a stone, which may then pass along the bowel and even cause intestinal obstruction if very large. The presence of a fistula leads to recurrent ascending infections in the biliary tree. Chronic cholecystitis may lead to carcinoma of the gall bladder.
- The principal mode of therapy is surgery. Gallstones may be removed by a course of extracorporeal shock-wave lithotripsy in association with oral bile acid (ursodeoxycholic acid) dissolution therapy. This is a lengthy and tedious procedure which has a 30–80% success rate after 1 year.

**ACUTE CHOLECYSTITIS**

In acute cholecystitis, there is acute inflammation of the gall bladder, caused by migration of stone(s) and impaction either in the cystic duct or in Hartman’s pouch. This leads to painful distension of the gall bladder. The swelling and inflammation may resolve, leaving the gall bladder full of mucus (hydror or mucocele), with a risk of recurrence of pain and inflammation. Often by the time the patient seeks medical advice, little is to be found. Occasionally, the mucus becomes infected (usually with *Escherichia coli* or other gut flora) and the inflammatory process continues with local pain and peritonitis. The gall bladder may be palpable at this time as it is distended with pus (empyema of gall bladder). There is usually an associated fever with rigors. The pain radiates to the lower rib cage at the back and to the right shoulder tip. The patient may be jaundiced if a stone has migrated into the common bile duct. The key sign is Murphy’s sign, which is elicited by placing the hand under the rib cage and asking the patient to breathe deeply. As the inflamed gall bladder descends and contacts the palpating hand, pain is elicited and the breath is held. In acute cholecystitis, the patient has a fever and a polymorph leucocytosis. Liver function tests are often normal. Plain X-ray may show a stone(s) (9.17) and sometimes also a soft-tissue shadow of a distended gall bladder. The diagnosis is made on ultrasound which shows a distended gall bladder and cystic duct and single or multiple stones (9.20, 9.64). 99mTcHIDA scans may also be of value.

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**COMPLICATIONS OF GALL STONE DISEASE**

- acute cholestatics
- chronic cholecystitis
- fistula formation – gall stone ileus
- impaction of stone in common hepatic duct
- gangrene of gall bladder, perforation or empyema
- pancreatitis

9.63 Complications of gall stone disease.

9.64 Ultrasound scanning of the gall bladder is now the preferred first investigation for gallstones. This scan shows the gall bladder containing one large stone, which casts a typical acoustic shadow (see 9.20), together with many much smaller stones.
but oral cholecystograms (9.65) have been largely replaced by ultrasound unless oral dissolution therapy for gallstones is planned, in which case it is essential to confirm that the gall bladder is functioning.

Treatment consists of intravenous fluids, analgesics and a broad-spectrum antibiotic. Patients usually settle rapidly and cholecystectomy should be performed early, because recurrence of symptoms is common. Laparoscopic removal is often possible and minimizes the recovery time for the patient.

**CHRONIC CHOLECYSTITIS**

Multiple episodes of acute disease lead to chronic cholecystitis, in which the wall of the gall bladder becomes thickened and fibrous, and does not usually distend when obstructed. Repeated infections also lead to the formation of mixed stones, which are small and have a greater chance of migrating into the common bile ducts and obstructing further down the system.

**COMMON BILE DUCT STONES**

Bile duct obstruction may result from a number of disorders (9.66). A common cause is obstruction by multiple mixed stones, which may lodge at the ampulla of Vater or just above. Colicky pain in the right upper quadrant is usually associated with obstructive jaundice, fever, rigors, acute nausea and vomiting. Ascending cholangitis may occur and lead to sepsicaemia. The features of obstructive jaundice may progress over several days and the patient develops pale stools with progressive darkening of the urine. The gall bladder is not usually felt, as it cannot distend because of progressive fibrosis from previous attacks of acute cholecystitis; there may, however, be some degree of hepatomegaly.

The patient usually has a fever with a brisk polymorphonuclear leucocytosis. Liver function tests are grossly deranged with a high conjugated bilirubin and alkaline phosphatase; the ALT may also be raised if there is ascending cholangitis. Tests of coagulation become abnormal, especially the prothrombin time, which is very sensitive to vitamin K malabsorption. Plain X-ray may show a stone, but the diagnosis is usually made by ultrasound, which may show the stone and also shows the dilated bile ducts. Often the diagnosis requires an ERCP to define the position of the stone(s) more accurately (9.67) and also to remove them. Plain X-ray of the area may show gas in the biliary tree if infection is with a gas-producing organism (e.g. *Clostridium perfringens*), and ultrasound will usually identify and locate stones.
DISEASES OF GALL BLADDER

Reflux of bile into the pancreatic duct, as a result of the obstruction, may produce acute pancreatitis, as may the ERCP itself.

Treatment is with fluids, bed rest, control of nausea and vomiting and pain control. Elective surgery is necessary to remove the gall bladder, but ERCP is valuable to remove the impacted stones in the acute phase (9.68-9.71).

ACUTE CHOLANGITIS

Acute cholangitis is an ascending infection that results from any obstruction to the flow of bile, for example gallstones, carcinoma of the ducts and biliary stricture. The symptoms are similar to those described for stones in the common duct, but acute cholangitis is potentially fatal. Patients present with Charcot’s triad of jaundice, rigors and upper abdominal pain. The common infecting organisms are Escherichia coli, Klebsiella, enterococci and a range of anaerobes. The treatment is urgent decompression of the biliary system and involves endoscopic sphincterectomy with stone removal (9.68-9.71) or passing a drainage tube past the obstruction to relieve the blockage (8.84, 9.62). Supportive treatment and appropriate antibiotics are essential, and surgery may be necessary.

CARCINOMA OF THE GALL BLADDER

Carcinoma of the gall bladder is an uncommon primary tumour that may be associated with the long-standing presence of gallstones and chronic cholecystitis. The presenting feature is a mass in the right upper quadrant. Jaundice occurs only when the liver is invaded. Treatment is surgical, but the outlook is poor, with a survival rate at 1 year of 20%.

9.68, 9.69, 9.70 & 9.71 Endoscopic removal of gallstones from the common bile duct is successful in many cases. When endoscopy and endoscopic retrograde cholangiopancreatography (ERCP) confirms the presence of one or more stones, endoscopic sphincterotomy can be performed to relieve stenosis or to enlarge the ampulla of Vater to allow stones to pass through. A sphincterotomy knife, composed of a diathermy wire at the end of a teflon catheter, is passed into the common bile duct. The wire is then tightened (9.68) to cut into the ampullary wall while diathermy is applied to minimize bleeding. The view of the ampulla in 9.69 was obtained immediately after sphincterotomy.

Some bleeding has occurred, but a large gall stone can be seen protruding through the enlarged ampulla. Such stones would then often pass spontaneously, but they are usually removed by the endoscopist using a balloon catheter, passed beyond the stone, inflated and pulled back (9.70); or a wire basket, passed inside a catheter beyond the stone, then opened and pulled back (9.71), trapping the stone. Clearance of stones should be checked by cholangiography 4-6 weeks later. Mechanical or endoscopically directed shock-wave lithotripsy are other methods of removing impacted stones.
LIVER AND PANCREAS

PANCREATIC DISEASE

PRESENTATION AND INVESTIGATION

Clinical features of pancreatic disease may be extremely late in appearing, partly because of the deep position of the organ. Acute inflammation of the pancreas may present with epigastric pain, nausea and vomiting and occasionally hypotension. A pancreatic pseudocyst may present as a large abdominal mass. Chronic pancreatitis presents with epigastric pain, weight loss and steatorrhoea. Many patients have diabetes mellitus. There may be other features to suggest the role of alcohol in the disease process (see p. 408).

Investigations in pancreatic disease include:
- serum amylase (amylase is released from inflamed parenchymal cells)
- stimulation tests of exocrine function with measurement of bicarbonate and enzymes (trypsin and lipases)
- faecal fat estimation
- $^{14}$C breath tests
- ERCP
- plain X-ray of the abdomen to show calcification
- ultrasound or CT scans
- exfoliative cytology by ERCP.

ACUTE PANCREATITIS

Acute pancreatitis is defined as an acute inflammatory process of the pancreas with variable involvement of adjacent tissues or remote organ systems. The major causes of acute pancreatitis are shown in 9.72. These stimuli trigger the release of pancreatic enzymes that then autodigest the pancreas. There is a wide spectrum of severity of the disease with mild to major autolytic digestion of the pancreas — often with haemorrhage.

The clinical presentation is usually with recurrent attacks of continuous epigastric pain that often radiates to the back. There is usually fever, and nausea and vomiting that does not relieve the pain. Examination shows the patient to be shocked and hypoxic (65% of acute deaths are caused by respiratory failure). Spontaneous bruising may be present as a result of inactivation of the coagulation mechanism by absorbed activated pancreatic enzymes. Bleeding may also track in the tissue planes of the body via the falciform ligament to the umbilicus (the umbilical black eye or Cullen's sign) and to the flanks (Grey Turner's sign 9.73). The patient may be jaundiced. The abdomen is rigid, with guarding on palpation. After some days, an abdominal mass may be felt.

The diagnosis is usually confirmed by an elevated serum or urine amylase. There may also be hyperglycaemia, hypocalcaemia, hypoalbuminaemia, raised levels of liver enzymes and renal impairment. Methaemalbumin may also form, as a result

CAUSATIVE FACTORS IN ACUTE PANCREATITIS

- Gallstones and common bile duct obstruction
- Excessive alcohol intake
- Viral infections, e.g. mumps, coxsackie B, Epstein-Barr virus, hepatitis A and B
- Trauma — during ERCP and other instrumentation
  - major abdominal injury, blunt trauma
- Metabolic — hyperlipidaemia, hypercalcaemia, renal failure
- Drug-associated — corticosteroids, azathioprine, thiazide diuretics, valproate, oestrogens
- Anorexia and bulimia nervosa

9.72 Causative factors in acute pancreatitis.
of intravascular haemolysis. Elevation of bilirubin and of alkaline phosphatase may occur as the bile duct is obstructed during passage through the oedematous pancreas. Ultrasound and CT scanning of the pancreas may show extreme swelling of the gland, an obstructing gall stone, a pancreatic abscess or pseudocyst formation (9.74). An obstructing gall stone may be shown on ERCP (9.67).

Over 70% of cases recover fully within a few days of treatment with intravenous fluids, nasogastric suction and analgesia. The rest have more severe disease and require intensive therapy — especially to prevent or support the patient through renal and respiratory failure. Complications include hypovolaemic shock, adult respiratory distress syndrome, pseudocysts, abscess formation and pancreatic necrosis. Surgery is occasionally required for abscess or pseudocyst formation.

**CHRONIC PANCREATITIS**

In chronic pancreatitis, continuing inflammation of the pancreas leads to atrophy and loss of exocrine and endocrine function. Most cases of chronic pancreatitis are associated with alcoholism, a few have had prior episodes of acute pancreatitis, often associated with gallstones and alcohol, and in a few cases no cause is evident. Worldwide there is a great range of incidence. In the UK there are about 5–10 cases per 100,000 population whereas in some countries (e.g. southern France) there is a vastly greater increase. In the Third World, protein-energy malnutrition (PEM) is a common association. The most common presentation is with chronic abdominal pain, usually in the epigastrium or left upper quadrant, which radiates through the back. Weight loss is common, caused by a combination of anorexia and steatorrhoea (9.75). Continued alcohol consumption and smoking may exacerbate symptoms. Calcification of the pancreas is also common, and may be associated with diabetes mellitus. Measurement of faecal fat sometimes shows steatorrhoea. Plain X-ray may show diffuse pancreatic calcification (9.76), and the extent of the pancreatic disease is apparent on CT scan. Functional pancreatic tests are also of value and show a low bicarbonate and enzyme output. The serum amylase level is variable. If it remains high it is a reflection of continuing inflammation. The ESR, plasma viscosity and C-reactive protein also reflect this. Blood glucose should be measured, as should glycosylated haemoglobin and a coagulation screen.
All patients should have an ultrasound scan to exclude gallstones or a dilated biliary tree. The pancreatic structure is best seen on CT – with contrast. An ERCP involves direct cannulation of the pancreatic duct for radiology (9.77) and sampling for pancreatic duct cytology.

Treatment of chronic pancreatitis is difficult and total abstinence from alcohol is essential. Pain is the major symptom that needs control, but care must be taken to avoid addiction to analgesics. If the patient is extremely malnourished, admission to hospital for parenteral nutrition is of value (see p 345). This also facilitates stopping alcohol and smoking and better analgesic control. Surgical resection and drainage may sometimes be helpful. Cholecystectomy or sphincterotomy are sometimes indicated. Malabsorption is treated with pancreatic extract taken with food and supplemented with vitamins. Diabetes mellitus may require insulin, but care should be taken to prevent hypoglycaemia as the glucagon response is absent.

PANCREATIC PSEUDOCYSTS

Pseudocysts are a common complication of acute and chronic pancreatitis, as shown by repeated ultrasound examination. Most are small and asymptomatic and will resolve if the pancreatitis is treated. Occasionally, very large cysts appear and produce local pain and palpable swelling in the epigastrium (9.78). Their extent may be revealed on CT scan (9.74) or barium meal and they may need to be treated by repeated aspiration under ultrasound control or by marsupialization.

CARCINOMA OF PANCREAS

Carcinoma of the pancreas is increasing in frequency and is the sixth most common cause of death from cancer in the USA. The disease appears late because of the anatomical position of the pancreas, and only 5% of carcinomas are suitable for surgical resection. The incidence of cancer is twice as high in smokers as in nonsmokers and twice as great in diabetics as in nondiabetics. Over 70% occur in the head of the pancreas and patients often present with progressive obstructive jaundice caused by obstruction of the common bile duct (9.79). Pain may also be a feature, starting with epigastric discomfort and...
Thrombophlebitis in superficial or deep veins is relatively common in many forms of malignant disease, but it is particularly associated with carcinoma of the pancreas, and it is sometimes the presenting feature. In this patient, thrombosis in the veins of the upper arm is associated with an extensive collateral circulation in the superficial veins around the shoulder. Recurrent episodes of thrombophlebitis ('thrombophlebitis migrans') may precede the diagnosis of pancreatic carcinoma by many months, and their occurrence in an otherwise apparently fit patient should lead to a search for underlying malignancy — especially in the pancreas.

Pancreatic carcinoma. This ultrasound scan shows a mass in the head of the pancreas (arrows), containing several areas of decreased echogenicity, an appearance typical of carcinoma.

Pancreatic carcinoma. This ultrasound scan shows a mass in the head of the pancreas (arrows), containing several areas of decreased echogenicity, an appearance typical of carcinoma.
9.83 Pancreatic carcinoma, revealed by combined barium meal and percutaneous transhepatic cholangiography (PTC). The pancreatic tumour is compressing the stomach (1), obstructing the common bile duct as it passes through the head of the pancreas (2), leading to dilatation of the common bile duct and hepatic ducts (3), and leading to distension of the gallbladder (4), which was easily palpable.

9.84 Pancreatic carcinoma may be diagnosed first when a barium meal is performed for undiagnosed gastrointestinal symptoms. In this patient, a large carcinoma in the head of the pancreas has led to a characteristic widening of the duodenal loop with compression of the second and third parts of the duodenum (arrows). This compression may lead to symptoms of intestinal obstruction, which may require palliative bypass surgery.

OTHER PANCREATIC TUMOURS

A variety of other rare endocrine tumours are found in association with the pancreas. Each may occur with a specific set of symptoms and diagnosis is by measurement of tumour-specific peptides. Localization of these tumours may be very difficult even with selective arteriography.

Primary carcinoid (p. 376) can occur in the pancreas – the symptoms arise from hepatic metastases, and diagnosis rests on urinary excretion of 5-HIAA – a serotonin (5HT) metabolite. Treatment may be surgical, but recently a somatostatin analogue has been successfully used.

The other pancreatic tumours all arise from a single cell line – APUD cells (amine precursor uptake and decarboxylation). They are classified by the main peptide produced, but they often produce more than one and the predominant peptide secreted can alter. The major tumour types are summarized on p. 391.
Symptoms often develop late in the course of disorders of the blood and lymphoid system. In their early stages, anaemias, chronic leukaemias and other myeloproliferative disorders may be completely asymptomatic, or they may be associated with only vague symptoms, many of which are common in the general population, including fatigue, headaches, faintness, shortness of breath, palpitations, angina pectoris, intermittent claudication and recurrent minor infections.

Patients with acute leukaemia commonly present with a short history of more definite symptoms, which may include—in addition to the symptoms of anaemia—mouth ulceration, sore throat and other signs of infection, enlarged lymph nodes, bruising and bleeding, bone pain and symptoms caused by tissue infiltration. Those with thrombocytopenias present with characteristic skin changes; other major bleeding disorders also produce obvious symptoms, but more minor degrees of bleeding disorder may be subclinical and thus asymptomatic.

Thrombotic disorders usually have symptoms and signs related to arterial or venous thrombosis; however, disseminated intravascular coagulation (DIC) may cause haemostatic failure and is usually seen in severely ill patients, who are likely to have multiple symptomatology from the underlying cause of the condition.

Patients with lymphomas often present with lymphadenopathy, fever or symptoms resulting from tissue infiltration or compression by the lymphomatous process, with failure of the immune system, or with a haemorrhagic or haemolytic disorder; nevertheless, some patients remain asymptomatic and are diagnosed largely by chance.

Because of the absence of specific diagnostic symptoms in many disorders of the blood, clinical examination of the patient is of great importance. Clinical signs in haematology may result from abnormalities of red cells, white cells, platelets, plasma globulins or coagulation factors.

Excess or lack of red cells in the circulation is often obvious on examination. Polycythaemia is associated with plethora, especially of the face, which may show a bluish, cyanotic tinge because of the high levels of unsaturated haemoglobin. Comparison with a normal skin is helpful (4.5, 10.1).

Anaemia is often suggested by pallor of the face, lips, tongue (10.2, 10.3), conjunctivae (8.3), nailbeds and palms (10.4), but clinical examination is not always a good guide to the level of

10.1 Polycythaemia and anaemia in identical newborn twins. The cause of this unusual condition was an arteriovenous fistula in the placenta; the picture is included here because it clearly exemplifies the difference in the appearance of polycythaemia (the twin on the left) from anaemia (the twin on the right). For a comparison of a polycythaemic adult with her normal sister see 4.5.

10.2 Iron deficiency anaemia commonly leads to pallor of the face, lips and tongue, and—when chronic—to atrophic glossitis and angular stomatitis. All these are seen in this young woman whose iron deficiency anaemia resulted from excessive menstrual bleeding. She responded to oral iron supplementation.

10.3 Severe anaemia commonly leads to generalized pallor, which is particularly obvious in the face. This patient had iron deficiency anaemia. Her haemoglobin was 5.0 g/dl.
haemoglobin (10.5, 10.6). Examination of the mouth, lips and tongue may give a clue to the aetiology of the anaemia: for example, iron deficiency is associated with atrophy of mucosa, especially on the tongue and often with the presence of angular stomatitis (7.153, 10.2). Lack of vitamin B12 and other B vitamins produces a tongue that is red and 'beefy' (9.47, 10.35). The fingernails may show evidence of tissue iron deficiency with 'spooning' (koilonychia, 2.103, 10.6, 10.21).

Excessive breakdown of red cells results in changes in urine colour; if the red cell destruction has occurred in the intravascular compartment, the urine passed is black to brown in colour (black-water, 1.191); in extravascular haemolysis, it becomes dark and orange on standing because of the presence of excess urobilinogen, which is converted to urobilin.

Haemolysis leads to excessive production of indirect bilirubin which usually imparts a pale lemon-yellow colour to the skin and conjunctivae, such as is seen in pernicious anaemia (9.2, 10.33, 10.35), or a deeper yellow to orange colour in more active haemolytic anaemias (10.44).

General examination may also show the cause of anaemia, as in the perioral black-brown pigmentation in Peutz–Jeghers syndrome (2.88), the telangiectasia in hereditary haemorrhagic telangiectasia (10.7, 10.113), or the skin purpura or ecchymosis of a bleeding disorder (2.113, 7.28, 9.14). The associated neurological features of a vitamin B12 deficiency anaemia include combined deficiencies in the posterior and lateral column function of the cord.

If anaemia develops quickly, it can lead to rapid cardiac decompensation and patients present with acute left ventricular failure (see p. 222). However, if it develops insidiously, there are compensatory mechanisms with tachycardia, tachypnoea and gradual onset of heart failure.

Bone and soft-tissue changes may result from extreme erythroid hyperplasia in chronic anaemia such as thalassaemia.

Deficient production of mature normal white cells leads to neutropenia (below 1.5 x 10⁹/litre), which increases the chances of infection—patients often present with bacterial, viral, fungal or protozoal invasion of the skin, gums, throat or lungs. In conditions with malignant white cell production, the skin, liver, spleen, lymph nodes, tongue, testes and ovaries may be infiltrated and enlarge. High white and red cell turnover may be associated with elevation of the serum uric acid, and occasionally with acute and chronic gout (see p. 138).

Increased production of collagen in the marrow cavity in myelofibrosis or myelosclerosis leads to haemopoiesis elsewhere, especially in the liver and spleen, which become massively enlarged. Similar enlargement of the liver, spleen and lymph nodes (10.8, 10.9) may be found in lymphomas and chronic leukaemias.

Reduction of platelet number below about 40 x 10⁹/litre, or defects in platelet function, result in purpura and haemorrhages into the skin (10.10) and mucous membranes and may be associated with overt external or internal bleeding. Platelet number increases to over 1000 x 10⁹/litre result in a likelihood of thrombosis, usually in the periphery, with gangrene of the fingers or toes, but also occlusion in the cerebral or coronary arteries.
10.7 Hereditary haemorrhagic telangiectasia (HHT) is a condition in which occult blood loss in the gut may lead to severe iron deficiency anaemia. Patients commonly present with lesions on or close to mucous membranes (10.11), but the telangiectasia may occur anywhere on the body, as in this patient whose fingers were affected. The lesions are dilated capillaries, and they blanch if pressure is applied with a glass slide.

10.8 Gross enlargement of the cervical lymph nodes in a patient with Hodgkin’s disease. The cervical lymph nodes are a common presenting site for lymphomas of all types and for leukaemia — especially chronic lymphatic leukaemia. This patient was severely mentally retarded, but he lived in the community and presented late in the course of the disease. It is unusual to see such advanced disease on presentation.


10.10 Purpura — in this case thrombocytopenic purpura (TP). The patient was a 15-year-old boy whose antiepileptic treatment regimen had recently been modified to include sodium valproate. This is just one of a number of drugs that may induce TP (see p. 458 and 10.110), but the disorder is almost always reversible if the drug therapy is stopped.

INVESTIGATIONS

The full blood count (FBC) (10.11) is easily measured using automated blood cell counters and is a routine hospital investigation (10.12, 10.13). Preparation and staining of a blood film allows microscopic examination (10.14), particularly if the FBC shows an abnormality or if a haematological disorder is suspected for other reasons. This may reveal morphological changes characteristic of particular systemic diseases, for example eosinophilia in worm infestations and allergy (1.19), atypical lymphocytes in infectious mononucleosis (1.93), malaria parasites (1.194), trypanosomes (1.20) or other parasites (1.206), or of particular haematological disorders, for example the misshapen red cells of hereditary elliptocytosis (10.48), or leukaemic cells (10.80, 10.81, 10.83, 10.84, 10.86). More commonly, a general abnormality is suggested, for example anaemia or infection, and this may require more detailed investigation.

In the investigation of anaemia, the reticulocyte count (10.15) provides an assessment of effective red cell production. Reticulocytes are young red cells that still contain ribosomal RNA and a residual capacity to synthesize haemoglobin. The RNA is lost within about 1 day of their release from the bone marrow and, as the red cell life span is approximately 120 days, the ‘normal’ proportion of reticulocytes is about 1%. In anaemic patients, hypoxia stimulates increased production of erythropoietin by the kidneys, and the reticulocyte count should thus markedly increase. The absence of an appropriate increase suggests anaemia caused by disordered red cell production (either because of inadequate numbers of red cell precursors, i.e. hypoplasia, or as a result of their premature death within the marrow, i.e. ineffective erythropoiesis) rather than increased red cell destruction (haemolysis) or blood loss.
Red cell size and colour are important. Decreased production related to impaired haemoglobin synthesis, whether of haem (e.g. in iron deficiency) or globin (in thalassaemias), tends to give rise to hypochromic, poorly haemoglobinized, often small (microcytic) red cells. In contrast, the larger, well haemoglobinized (macrocytic) cells are associated with disordered nuclear maturation (e.g. in megaloblastic anaemias). In many anaemias secondary to systemic disorders, the red cells are of normal size and haemoglobin content (normocytic, normochromic). The red cell mean cell volume (MCV) and mean cell haemoglobin (MCH) can thus be helpful, with the reticulocyte count, in the initial classification of the cause of anaemia. Precise diagnosis in haemolytic anaemias may then require extensive further immunological, cell membrane, haemoglobin or red cell enzyme studies.

A bone marrow examination may be indicated if the cause

### Normal Values for the Full Blood Count (FBC)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>13.5–17.5</td>
<td>11.5–15.5</td>
<td>g/dl</td>
</tr>
<tr>
<td>Red cells</td>
<td>4.5–6.0</td>
<td>3.8–5.2</td>
<td>x 10¹²/litre</td>
</tr>
<tr>
<td>PCV (haematocrit)</td>
<td>0.4–0.52</td>
<td>0.37–0.47</td>
<td>%</td>
</tr>
<tr>
<td>MCV (mean cell volume)*</td>
<td>80–96</td>
<td>27–32</td>
<td>fl</td>
</tr>
<tr>
<td>MCH (mean cell haemoglobin)</td>
<td>31–36</td>
<td>25–85</td>
<td>pg</td>
</tr>
<tr>
<td>MCHC (mean cell haemoglobin concentration)</td>
<td>1.5–4.0</td>
<td>1.0–7.5</td>
<td>x 10⁹/litre</td>
</tr>
<tr>
<td>Reticulocytes **</td>
<td>25–85</td>
<td>0.04–0.4</td>
<td>x 10⁹/litre</td>
</tr>
<tr>
<td>WBC (white blood cells)*</td>
<td>0.2–0.8</td>
<td>&lt;0.1</td>
<td>x 10⁹/litre</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>4–11</td>
<td>1.5–4.0</td>
<td>x 10⁹/litre</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>2.0–7.5</td>
<td>0.2–0.8</td>
<td>x 10⁹/litre</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.04–0.4</td>
<td>0.04–0.4</td>
<td>x 10⁹/litre</td>
</tr>
<tr>
<td>Platelets</td>
<td>150–400</td>
<td>150–400</td>
<td>10⁹/litre</td>
</tr>
</tbody>
</table>

* In the neonate Hb and MCV are normally higher, and in children below 12 years of age lower, than these adult values. Children also have higher lymphocyte counts.

** Reticulocytes are often expressed as a percentage of total red cells (normal range 0.2–2.0% of red cells), but are best reported as absolute number since the red cell count may vary considerably.

10.11 Normal values for the full blood count (FBC).

10.12 Venous blood sampling is a routine procedure, but it is important that it is carried out correctly for haematological and biochemical investigations to be accurate. In particular, it is essential that blood is not drawn up rapidly through a narrow-gauge needle, as this may cause artefactual haemolysis. The minimum possible degree of venous occlusion should be used for sampling, as stasis can affect the results of both biochemical and haematological investigations. It is essential that the blood sample is immediately transferred into the appropriate container for the investigation required, and that the blood is processed rapidly.

10.13 Venous blood sampling using a vacuum tube. This method is now commonly used in many countries. It allows blood to be drawn into several containers on a single occasion without the risk of creation of a potentially infective aerosol, and without a significant risk of spillage.
of anaemia is obscure or if an abnormality of production of one or more of the blood cell lines is suspected, or if there is other evidence of a malignancy that commonly involves the bone marrow (e.g. lymphoma). Marrow smears from a needle aspirate of sternal or posterior ilium marrow cavities are taken for detailed morphological studies of haemopoietic cells (10.16). A marrow aspirate can also provide cells for cytogenetic studies, detailed immunological studies of cellular antigens (cell-marker studies) or molecular analysis of DNA, all of which may help in defining the precise cell type of abnormal cells (e.g. in leukaemia or lymphoma). Histology of a trephine biopsy may be needed if marrow is scanty. It provides less information about individual cells, but retains the marrow architectural relationships, gives a better guide to overall cellularity and may identify focal lesions (e.g. tumour infiltration) that are absent in the aspirate.

Biochemical studies are of value in further defining the causes of anaemia.

• Serum iron with total iron binding capacity (TIBC) gives information about iron transport and is complemented by the ferritin level, which more accurately reflects total body iron stores
• Serum levels of vitamin \( B_12 \) and folate, and the red cell folate level, give a clue to the presence or absence of essential components for red cell haemoglobin synthesis; low levels of vitamin \( B_12 \) necessitate a two-stage Schilling test, which may indicate whether malabsorption of \( B_12 \) is caused by lack of intrinsic factor or by intestinal disease
• Excessive breakdown of haemoglobin can be monitored by measurement of indirect bilirubin, urobilinogen in the urine and stercobilinogen; occasionally, in intravascular breakdown, haemoglobin will appear in the urine and there is depletion of haptoglobins and appearance of methaemalbumin.

The cause of haemolysis may become obvious from examination of the blood film (e.g. parasites), from the presence of antibodies coating the red cells, or from the presence of abnormal haemoglobins on electrophoresis or abnormal enzymes within the red cells.

10.14 A blood film can often aid the interpretation of the full blood count. This patient had an elevated white cell count, and the film showed that most of the cells were neutrophils. Some of the neutrophils contain small blue-staining areas in the cytoplasm. These are known as Dohle bodies. They are a nonspecific finding, but are common in patients with infections.

10.15 The reticulocyte count showed gross reticulocytosis in this patient. Up to 80% of the red cells in the peripheral blood film are reticulocytes, as shown by supravital staining for RNA. This patient had haemolytic anaemia caused by congenital pyruvate kinase (PK) deficiency.

10.16 Bone marrow aspiration is now most commonly carried out from the posterior iliac crest, though satisfactory samples may be obtained from the sternum. Local anaesthetic is injected in the skin and down to the level of the periosteum, and a needle is pushed through the outer layer of the ilium into the marrow cavity. Marrow can then be aspirated into the syringe. A relatively small amount of marrow is required for investigation, but an inadequate or dry tap may be an indication for trephine bone biopsy, which may also be performed through the Jamshidi needle shown here.
Abnormalities of blood coagulation and related systems require the expertise of highly specialized laboratories and physicians.

Initial bedside investigations are still sometimes helpful (10.17–10.19), but laboratory studies are usually needed.

The basic screening tests should include a platelet count, the activated partial thromboplastin time (APTT), the prothrombin time (PT), the thrombin time and a test for fibrin degradation products (the D Dimer test). These indicate which part of the coagulation cascade is likely to be defective.

Acquired haemostatic deficiencies (e.g. DIC, hepatic disease) may be the result of multiple deficiency in the coagulation and platelet system. Examination of the quality of the fibrin clot is worthwhile and it may also be incubated to see if there is active fibrinolysis present. These tests also may form the basis of control of anticoagulant therapy, but generally purpose-designed tests are more accurate. It is probable that the biggest group of patients with haemostatic defects are those on oral anticoagulant therapy or prophylaxis.

10.17 Blood clotting time can be measured simply by placing a sample of venous blood in a plain glass tube and measuring the time taken to form a clot at body temperature. A portable water bath can be taken to the bedside. The normal clotting time ranges from 4 to 8 minutes. A prolonged blood clotting time implies a deficiency in coagulation factors.

10.18 Bleeding time. This can be measured by pricking the ear, and removing the escaping blood every 15 seconds with the edge of a filter paper. The frequent blotting prevents the formation of a surface blood clot, and in these circumstances the arrest of bleeding depends largely on capillary contraction and platelet adhesion and aggregation. The normal bleeding time is 3–5 minutes; it is prolonged if capillary contractility is impaired, in thrombocytopenia or in platelet function defects.

10.19 A positive capillary resistance test (Hess test). A circle is drawn on the surface of the forearm, and any purpuric spots within it are counted. A sphygmomanometer cuff is applied to the upper arm and inflated to a pressure midway between systolic and diastolic blood pressure for 5 minutes. The cuff is then deflated, and the skin within the circle is re-examined. Normally not more than two or three tiny haemorrhagic spots are to be seen, but if there is abnormal capillary fragility – as in this patient – a large crop of small haemorrhagic spots is found. The level of the bottom of the cuff is obvious. A positive result may be found in thrombocytopenia, after aspirin ingestion and, occasionally, in normal people (especially young women) (see also 10.106).
ANAEMIAS

Anaemia is defined as a condition in which the blood has a deficient concentration of haemoglobin, which reduces its ability to transport oxygen. The most common form of anaemia worldwide, which affects over 500 million people, is that caused by iron deficiency. In hospital practice secondary ‘anaemia of chronic disorders’ predominates.

IRON-DEFICIENCY ANAEMIA

A normal diet containing green vegetables, red meat, eggs and milk should contain 15–20 mg of iron of which about 5–15% is absorbed in the duodenum and jejunum. Iron deficiency commonly arises from a combination of reduced dietary intake of iron (especially from vegetarian diets) with a physiological increase in iron requirement (e.g. in pregnancy, and in pre-menopausal women). Occult blood loss, usually into the gut, and more rarely malabsorption (e.g. in coeliac disease or after gastrectomy) can also give rise to negative iron balance. The most common form of blood loss worldwide is hookworm infection (10.20 and see p. 386).

It is important to take a detailed dietary history extending over the past year or so, and enquiry should be made about intake of meats, liver, green vegetables, eggs and milk. In Asians who eat chapattis, iron deficiency may result from iron binding by phytate in the gut. Strict vegetarians may eat iron in a nonabsorbable form. Babies who are breast fed for a prolonged time may become iron deficient.

A history of obvious blood loss should be sought, as in women who have had multiple pregnancies or in whom there has been excess loss at menstruation. It is important to ask directly about the frequency and heaviness of the periods (i.e. number of days between the periods, their duration, the presence of clots and the number of towels and tampons used). Obvious blood loss may also occur in patients with haemorrhoids and questions should be asked about blood on the stools or toilet tissue. If bleeding occurs higher up in the alimentary tract, the red colour of haemoglobin is converted to give the stool the black colour of acid haematin (melena). Occult alimentary bleeding may occur in patients taking aspirin or related nonsteroidal anti-inflammatory drugs (3.9, 8.53), with duodenal or gastric ulceration and from carcinomas and polyps in the bowel. Right-sided colonic carcinoma is particularly likely to manifest itself as unexplained anaemia. A history of previous alimentary surgery is important, especially if this has involved the removal of part of the acid-secreting portion of the stomach or the creation of a bypass. Evidence of malabsorption should also be sought (see p. 372).

The patient should be examined for the signs of anaemia (10.2–10.6), especially for those that point to iron deficiency, such as koilonychia (2.03, 10.6, 10.21) and angular stomatitis (10.22), and for pointers to possible underlying blood loss such as telangiectasia (10.7) and haemorrhoids (10.23).

10.20 Hookworm infection is the most common cause of iron-deficiency anaemia worldwide. The worms are seen attached by their buccal capsules to the villi of the small intestine, where they feed by sucking blood (up to 0.2 ml per day per worm). In gross hookworm infection, severe iron-deficiency anaemia may result.

10.21 Koilonychia or ‘spooning’ of the nails is a result of a nonhaemopoietic effect of iron deficiency. For views of koilonychia see 2.09, 10.6.

10.22 Angular stomatitis in a patient with iron-deficiency anaemia. Like other signs of anaemia this is nonspecific, but it is an indication for the performance of a full blood picture.

10.23 Haemorrhoids are a common cause of rectal bleeding. Interoexternal piles – as seen here – commonly bleed on defaecation, and over time this blood loss can lead to iron deficiency.
In iron deficiency, iron stores are mobilized first (reflected by a falling serum ferritin concentration) and only when these have been exhausted does the iron supply to the tissues, assessed by the serum iron and transferrin saturation, begin to decline, eventually giving rise to frank anaemia. Iron is essential for maturation and function of all cells and nonhaemopoietic effects of deficiency include koilonychia and oral changes. The underlying cause of the negative iron balance must always be sought, paying particular attention to possible gastrointestinal blood loss. Investigations should include:

- FBC and film. This shows a reduction in red cell numbers and haematocrit. The red cell size (MCV) is reduced (<75 fl) and may be as low as 60 fl. The cells have a reduced MCH that is below 25 pg. The film confirms that the cells are microcytic, hypochromic and have variations in size and shape (3.9, 10.24). There may be early forms present. The platelet count may be raised, and white cells are usually normal. If the cause of anaemia is hookworm infection, eosinophilia is often present (1.19).

- Faecal occult blood measurement is of value, but the results must be interpreted with caution because of the possibility of false-positive and false-negative results.
- Serum ferritin is low, reflecting reduction of tissue iron; a low serum iron and a high transferrin with a low percentage saturation is a reflection of deficient transport.
- Bone marrow aspiration shows a hyperplastic marrow dominated by active red cell series proliferation (10.25); staining with Prussian Blue shows reduced or absent iron staining (10.26).
- Endoscopy of the upper and lower alimentary tract may define bleeding lesions (8.41, 8.42, 8.52, 8.53, 8.59, 8.60, 8.69, 8.98, 8.99).
- Barium series of the upper and lower alimentary tract may show associated changes of iron deficiency, for example the Plummer–Vinson or Paterson–Brown Kelly syndrome (8.38) or a lesion that may have bled (8.103, 8.104).
- Occasionally, mesenteric arteriography or nuclear medicine studies may help to reveal obscure sources of blood loss in the gut.

Treatment is usually with simple oral iron salts (ferrous sulphate or fumarate), and any adverse effects (e.g., constipation) may be ameliorated by reducing the dose or by changing to a preparation that contains less available iron in each tablet (e.g., ferrous gluconate). Failure of response is most commonly caused by lack of compliance, but should lead to reassessment of the diagnosis as other causes of hypochromic anaemia include alpha- or beta-thalassaemia trait and sideroblastic anemias, which may be associated with excessive iron absorption and thus with a risk of damage from iron overload with prolonged oral iron therapy.
SIDEROBLASTIC ANAEMIA

Sideroblastic anaemias are a rare group of hypochromic anaemias in which the serum iron levels are high and the transferrin is saturated. A variety of acquired and inherited defects in porphyrin biosynthesis lead to diminished synthesis of haem. The key diagnostic feature is the presence of the ringed sideroblast in the marrow aspirate. This is a normoblast, containing iron granules in the mitochondria that have a perinuclear distribution (10.27, 10.28). The common acquired causes are alcoholism, drugs such as isoniazid, lead poisoning, myelodysplasia and myeloproliferative disease. Patients should abstain from alcohol and possibly causative drugs should be withdrawn. Lead poisoning may require treatment with chelating agents. Transfusion should be used as infrequently as possible in these patients, because of the dangers of iron overload. Some patients may respond to large doses of vitamin B<sub>6</sub> or rarely to androgens.

10.27 Bone marrow in sideroblastic anaemia. The marrow has been stained for free iron, thus revealing ringed sideroblasts. These are erythroblasts with free iron granules arranged as a nearly continuous ring around the nucleus. This iron is chiefly concentrated in mitochondria.

10.28 Bone marrow smear in sideroblastic anaemia. In this case, the bone marrow has been stained with Prussian Blue (the same method as used in 10.26) revealing increased (blue) iron stores. Normal subjects have stainable free iron amounts midway between the appearance seen here and that in 10.26.

ANAEMIA OF CHRONIC DISEASE

The main differential diagnosis for early iron-deficiency anaemia is the anaemia associated with many chronic disorders, for example chronic arthritis, chronic infections, renal and liver failure, neoplasia and endocrine disorders (10.29). This anaemia, at least initially, is normocytic and normochromic and is multifactorial in origin, with a slight reduction in red cell survival, inappropriately low production of erythropoietin, and a disturbance of iron delivery to the developing erythroblasts, which in time can give rise to a degree of hypochromia and microcytosis of the red cells (10.30). In contrast to uncomplicated iron deficiency, the iron stores in this form of anaemia tend to be normal or increased (high serum ferritin); increased storage by macrophages of the iron released from destroyed red cells results in impaired release of iron to circulating transferrin and thus reduced delivery of iron to the bone marrow (low serum iron and low transferrin).

10.29 Anaemia of chronic disease, manifest as severe pallor in a diabetic patient with severe uraemia. Her haemoglobin was 6.5 g/dl, but the blood film demonstrated that the anaemia remained normochromic and normocytic.

10.30 Anaemia of chronic disease. The anaemia is normocytic, but some hypochromia is obvious. In addition, there is prominent rouleaux formation — red cells are grouped together in piles or stacks. In a properly prepared smear, rouleaux formation suggests the same range of abnormalities that are revealed by a high erythrocyte sedimentation rate, so rouleaux formation may be found in any chronic inflammatory process or malignancy and, especially, in multiple myeloma and other monoclonal gammopathies.
铁缺乏性贫血和慢性疾病引起的贫血可能共存（例如，在患有类风湿关节炎的患者中，也可能有慢性炎症引起的贫血）。在这种情况下，骨髓检查将确定铁储存是否减少（见10.26, 10.28）。

首部为慢性疾病的贫血在不经过铁治疗或其他造血因子的情况下，只在治疗原发疾病时才能改善。在慢性肾功能衰竭的患者中，重组人促红素（rEPO）的使用已经显示出初步的疗效。

MACROCYTIC ANAEMIA

巨幼细胞性贫血

巨幼红细胞通常与肝病（在肝细胞膜中可能有过多的脂质沉积）、慢性酒精中毒和溶血有关。它们也可能在甲亢和红细胞增多症中出现。巨幼细胞性贫血是骨髓中血细胞前体成熟缺陷的常见原因，导致骨髓为巨幼细胞性。这通常由维生素B12或叶酸缺乏引起，尽管抗肿瘤化疗和某些其他骨髓疾病也可能出现类似的图片。叶酸是合成DNA的嘌呤和嘧啶的必要成分，而维生素B12则维持细胞内叶酸的活性形式。

10.31 Causes of vitamin B12 deficiency.

<table>
<thead>
<tr>
<th>Causes of vitamin B12 deficiency.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional deficiency</td>
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<tr>
<td>Vegan diet</td>
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<tr>
<td>Alcoholism</td>
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<tr>
<td>Severe protein-calorie malnutrition</td>
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<tr>
<td>Competition by gut microflora or fish tapeworm</td>
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<tr>
<td>Malabsorption</td>
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<tr>
<td>Intrinsic factor deficiency (Addisonian pernicious anaemia)</td>
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<tr>
<td>Diseased terminal ileum</td>
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<tr>
<td>Surgical removal of terminal ileum</td>
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<tr>
<td>Pancreatic failure</td>
</tr>
<tr>
<td>Drugs – biguanides, potassium supplements</td>
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</tbody>
</table>

10.31 Causes of vitamin B12 deficiency.

铁和叶酸缺乏可导致贫血，这种贫血通常进展缓慢，常在铁或叶酸缺乏时才出现。贫血的常见表现为乏力、疲倦和体重减轻。临床表现为贫血，皮肤黄疸与胚胎期红细胞的过早死亡相关，通常出现柠檬黄色皮肤（10.33）。过早的头发变白可能出现在巨幼细胞性贫血（9.47, 10.34）。舌炎可能出现（9.47, 10.35）。皮下出血和瘀斑可能提示同时存在血小板减少症，视网膜出血在任何严重贫血中也可能出现。可能有肝脾肿大和心力衰竭的征象。

10.32 Causes of folate deficiency.

<table>
<thead>
<tr>
<th>Causes of folate deficiency.</th>
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<tbody>
<tr>
<td>Decreased intake</td>
</tr>
<tr>
<td>Nutritional deficiency</td>
</tr>
<tr>
<td>Elderly</td>
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<tr>
<td>Alcoholism</td>
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<tr>
<td>Milk-fed premature infants</td>
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<tr>
<td>Malabsorption</td>
</tr>
<tr>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Tropical sprue</td>
</tr>
<tr>
<td>Post-gastrectomy</td>
</tr>
<tr>
<td>Crohn's disease</td>
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<tr>
<td>Drugs – phenytoin</td>
</tr>
<tr>
<td>Increased requirement</td>
</tr>
<tr>
<td>Physiological</td>
</tr>
<tr>
<td>Pregnancy</td>
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<tr>
<td>Lactation</td>
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<tr>
<td>Prematurity</td>
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<tr>
<td>Growth in childhood</td>
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<tr>
<td>Pathological</td>
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<tr>
<td>Haemolytic states</td>
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<tr>
<td>Myeloproliferative disorders</td>
</tr>
<tr>
<td>Severe inflammatory states</td>
</tr>
<tr>
<td>Dialysis</td>
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<tr>
<td>Impaired folate utilization</td>
</tr>
<tr>
<td>Cytotoxic drugs – methotrexate</td>
</tr>
<tr>
<td>Trimethoprim</td>
</tr>
<tr>
<td>Anticonvulsants – phenytoin, phenobarbitone</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
</tbody>
</table>

10.32 Causes of folate deficiency.
family history of other autoimmune disorders (e.g. thyroid disease, diabetes, Addison's disease, rheumatoid arthritis or vitiligo, 2.89) may suggest pernicious anaemia. Pernicious anaemia affects 1% of individuals over the age of 60 years. There is a strong association between pernicious anaemia and carcinoma of the stomach; this may be an indication for GI investigation in the presence of symptoms or a family history of gastric carcinoma.

Defective maturation of all proliferating cell lines means that a pancytopenia with reduction in neutrophils and platelets may be present. There may be nucleated megaloblasts in the circulation (10.37), but bone marrow examination is usually needed to confirm a megaloblastic basis for the macrocytosis of the circulating red cells (10.38). Serum $B_12$ and folate assays and red cell folate assay help to identify the underlying deficiency.

In vitamin $B_12$ deficiency, it is essential to demonstrate that impaired absorption of the vitamin is corrected by the addition of oral intrinsic factor, before making a diagnosis of classic

10.33 Pernicious anaemia often gives rise to characteristic pallor with a lemon-yellow tinge. The pallor relates directly to the haemoglobin level, whereas the mild jaundice is the result of the premature breakdown of erythroblasts (ineffective erythropoiesis). Typically, patients with pernicious anaemia have blue eyes and (often prematurely) grey hair.

10.34 Prematurely grey hair in a 45-year-old patient with pernicious anaemia. The patient developed grey hair at the age of 25 years and had two close relatives who died from gastric carcinoma.

10.35 Pernicious anaemia. This patient shows similar skin coloration to that seen in 10.33. In addition, she has a ‘raw beef’ tongue. The surface is smooth, with an absence of filiform papillae. Similar changes may be seen as a result of deficiency in other B-group vitamins.

10.36 Loss of vibration sense is often an early sign of subacute combined degeneration of the cord in pernicious anaemia. This is most significant in younger patients because it becomes progressively impaired as part of normal ageing. Higher cerebral function is also frequently affected. The response of these early manifestations of neurological involvement to $B_12$ therapy may be good; at later stages, arrest of progression may be the most that can be achieved.

10.37 Peripheral blood in macrocytic anaemia caused by $B_12$ deficiency. Note the presence of two late megaloblasts with nuclear rosette formation and basophil stippling. The red cells show macrocytosis, anisocytosis and poikilocytosis.
pernicious anaemia, as other gut pathology (e.g. Crohn's ileitis) may also impair vitamin B$_{12}$ absorption from the terminal ileum. This can be done using the Schilling test, in which urinary B$_{12}$ is measured after oral administration, or by whole-body counting of orally administered radiolabelled B$_{12}$.

There is often elevation of the indirect bilirubin and this is also reflected in the finding of excess urobilinogen in the urine. The serum iron is often elevated and the percentage saturation increased, except in the case of malabsorption (see p. 372), when the serum iron, B$_{12}$, and folate levels are all low and a dimorphic blood picture may be present.

In pernicious anaemia, virtually all patients have circulating gastric parietal cell antibodies; 50% also have antibodies to intrinsic factor (which are more specific for pernicious anaemia), and a small percentage have a range of other circulating autoantibodies.

Treatment is with oral replacement of folate and vitamin B$_{12}$ if the cause is dietary. In classic pernicious anaemia, after gastrectomy, and with other uncorrectable gut pathologies, regular injections of hydroxocobalamin are required. Treatment results in a rapid rise in the reticulocyte count, which can be monitored (10.39) and precedes the rise in haemoglobin levels. There may also be a fall in the serum iron and a need for supplemental iron therapy. Hydroxocobalamin therapy may reverse early neurological changes in pernicious anaemia; progression of later changes may also be arrested by this therapy. Folate treatment should not be given in megaloblastic anaemia until B$_{12}$ deficiency is ruled out, as folate administration may precipitate neurological changes in patients with B$_{12}$ deficiency.

**APLASTIC ANAEMIA**

Marrow aplasia is a rare condition in which there is a peripheral pancytopenia resulting from failure of the stem cells of the bone marrow to continue to produce all cell lines. The marrow architecture remains normal, but fat replaces the normal haemopoietic cells. The result is anaemia and a fall in the white cell and platelet counts. Rarely, only one cell line may be initially affected — as in agranulocytosis — but this usually progresses to total aplasia.

Aplasia is the end result of a variety of processes that include autoimmunity, drugs, toxins, viral infections and radiation. Rarely, there may be a genetic component, and in many cases a cause is not found. In clinical practice the most common causes are drugs (10.40), some of which may damage one cell line more than another. Often the drug therapy is being given as part of a treatment regimen for neoplasia or immuno-

**DRUGS THAT MAY CAUSE MARROW APLASIA**

<table>
<thead>
<tr>
<th>Antimitotics</th>
<th>Methotrexate, cytosine arabinoside, busulphan, cyclophosphamide, 6-mercaptopurine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Chloramphenicol, methicillin, penicillin, tetracyclines, sulphonamides</td>
</tr>
<tr>
<td>Anti-rheumatics</td>
<td>Gold salts, penicillamine, indomethacin, colchicine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Phenytoin, carbamazepine</td>
</tr>
<tr>
<td>Anti-diabetic</td>
<td>Chlorpropamide, tolbutamide</td>
</tr>
<tr>
<td>Anti-thyroid</td>
<td>Carbimazole, thiouracil, potassium perchlorate</td>
</tr>
<tr>
<td>Tranquillizers</td>
<td>Chlorpromazine, chlor Diazepoxide, meprobamate, promazine</td>
</tr>
</tbody>
</table>

10.40 Drugs that may cause marrow aplasia.
suppression. In these cases the aplasia is usually reversible. There is also an association of aplastic anaemia with the later development of acute lymphocytic leukaemia in childhood, and in adults exposed to benzene or radiation there is a significant incidence of acute myeloid leukaemia after many years.

Clinical symptoms and presentation in aplastic anaemia relate to the lack of functional cells in the peripheral blood. There is an insidious onset of the symptoms of anaemia, with recurrent infections as the white cell count falls, and bleeding from multiple sites as a result of thrombocytopenia. Clinical examination usually shows purpura and ecchymoses (10.41), and there may also be internal bleeding, especially from the gums and alimentary tract and into the eye. There may be infection in the mouth (10.42), or skin. There is rarely any splenic enlargement, and this helps to distinguish aplastic anaemia from pancytopenias associated with hypersplenism (see p. 446).

The diagnosis is made on finding pancytopenia in the peripheral blood. Bone marrow aspirate may yield little available marrow and a trephine bone biopsy may be required for histological section (10.43). Treatment should be initially directed at the cause. Androgens and corticosteroids are of value in some patients. Supportive treatment with red cell, platelet and white cell transfusions may be necessary. Bone marrow transplantation is successful in about 70% of patients with aplastic anaemia, but a matched donor is not always available. Anti-lymphocyte globulin (ALG) or other immunosuppressive therapy is sometimes helpful if marrow transplant is not possible. Recently, growth factors produced by recombinant DNA technology have been shown to be of value.

**HAEMOLYTIC ANAEMIAS**

Haemolysis is suggested by evidence of both increased red cell production (reticulocytosis) and increased red cell destruction. The destruction may be intravascular (giving rise acutely to haemoglobinuria, or chronically to haemosiderinuria) with a reduced concentration of serum haptoglobin (haemoglobin-binding protein), or extravascular (mediated by macrophages) and associated with increased unconjugated bilirubin in the blood. Clinically, the combination of pallor, jaundice (9.2, 10.44) and splenomegaly should suggest haemolysis, and, in chronic cases, there may be symptoms or signs of pigment gallstones, or signs of iron overload (10.45). A blood film may sometimes show red cell abnormalities that are diagnostic of particular causes of haemolysis, but it may show only a non-specific polychromasia associated with the reticulocytosis.
Haemolysis may result from intrinsic, nearly always inherited, defects of the red cell, or from acquired disorders, usually related to extracorporeal changes.

- Intrinsic disorders include those of the cell membrane (e.g., hereditary spherocytosis, hereditary elliptocytosis), of haemoglobin synthesis (e.g., sickle-cell disease) and of cell metabolism (e.g., pyruvate kinase or glucose-6-phosphate dehydrogenase deficiencies).
- Extrinsic causes of haemolysis include chronic renal failure and liver disease, but the shortening of red cell survival in these conditions is usually only modest; excepting these, the most common acquired haemolytic anaemias are immune in origin: isoimmune, as in haemolytic disease of the newborn or haemolytic blood transfusion reactions, autoimmune with antibodies directed against red cell antigens and giving rise to positive direct antiglobulin (Coombs') test, or drug-induced, in which the effect may result from autoantibodies or neoantigens involving the drug as a hapten; nonantibody-mediated haemolytic anaemia may also be acquired, as in paroxysmal nocturnal haemoglobinuria and in some drug-induced haemolyses.
- Fragmentation haemolysis may be seen in association with DIC (microangiopathic haemolysis, 10.132), in patients with artificial heart valves and in malaria.
- Hypersplenism with haemolysis may be a feature of a variety of disorders associated with splenomegaly.

### Red cell membrane defects

A variety of chemical and physical defects have been described in the red cell membrane. The most common and most important is hereditary spherocytosis, which is found in 1–2 per 10,000 of the population, and is usually transmitted as an autosomal dominant. The biochemical defect, which may be quantitative or qualitative, is in the production of the protein spectrin; the result is the production of spherical red cells that have an altered permeability and a significantly shortened half-life. Clinically there is a wide spectrum of severity, even within families, but the picture usually includes haemolytic anaemia, acholuric jaundice and splenomegaly (10.46). Most patients can lead a normal life, even when slightly anaemic. However, at times (e.g., in acute infections) an acute haemolytic crisis may occur, which requires blood transfusion. Aplastic crises may also occur during parvovirus and other infections in these patients, especially in young children (see p. 26). The erythroid hyperplasia leads to an increased need for folic acid, which should be given prophylactically. The chronic haemolytic state is associated with pigment gall stones in most adults and patients may present with a confusing mixed haemolytic and obstructive jaundice. Other cells require spectrin for normal function and associated abnormalities have been described in neurological and cardiac cell function.
The diagnosis is confirmed by finding evidence of chronic haemolysis and a typical blood film with microspherocytosis of red cells and reticulocytosis (10.47). The red cells are osmotically fragile and this provides a useful screening test. Assay of spectrin is possible in some laboratories. It is important to screen all available family members for the condition. The treatment of choice is splenectomy, which should be preceded by appropriate vaccination against the pneumococcus, meningococcus and *Haemophilus influenzae* and followed by long-term prophylactic penicillin therapy (see p. 446). It is important at surgery to ensure that there are no accessory splenunculae as these will hypertrophy if not removed and haemolysis will continue.

**10.47 Hereditary spherocytosis.** This low-power view of a peripheral blood film shows that approximately one-half of the red cells are small and very deeply stained. These cells have the characteristic appearance of spherocytes, though the other cells in the film are within the normal range. Often, only a proportion of the red cells are affected in spherocytosis. Supravital staining revealed a reticulocyte count of 60% in this patient.

**10.48 Hereditary elliptocytosis.** This inherited anomaly of red cells leads to their assuming an oval or cigar shape. As in hereditary spherocytosis, some normal red cells are also usually present – in this case, about 50%. Pseudo-elliptocytosis may occur as a result of bad technique when a blood smear is prepared; however, when this occurs, the ‘elliptocytes’ are usually found only at one end of the smear, and the long axes of the cells are roughly parallel.

Hereditary elliptocytosis is caused by a variety of molecular defects and is usually asymptomatic. The diagnosis is made on the typical appearances of the blood film (10.48), but only a few patients have significant anaemia or any evidence of haemolysis.

**Enzyme deficiencies in red cells**

Normal function of red cells depends on the integrity of two enzyme systems to provide energy from glucose as the substrate. These are the Embden–Myerhof pathway and the hexose-monophosphate shunt. Many enzyme defects have been described, but only two are common: glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency.

- **G6PD deficiency** results in inability of the red cell to resist oxidants that may result from infections or from drug administration. As a result, haemoglobin is oxidized to methaemoglobin, which is functionless in terms of oxygen carriage, is relatively insoluble and precipitates in the red cells as Heinz bodies (10.49). The red cells are then vulnerable to destruction in the spleen. A large number of variants of enzyme activity have now been identified, accounting for a wide spectrum of disease activity. The disorder usually presents with acute intravascular haemolysis – jaundice, haemoglobinuria, anaemia and methaemoglobinaemia. A large number of drugs and foods have been implicated in precipitating the acute episodes. Offending substances should be avoided or withdrawn. Blood transfusion may be life-saving during acute attacks.

- **Pyruvate kinase deficiency** is the most common of the many enzyme defects of the glycolytic pathway. The disease is inherited as an autosomal recessive, and it is only the homozygotes that haemolyse. The enzyme-deficient cells have a significantly shortened life span, and the haemolysis is chronic and not related to infections, drugs or foods. Splenomegaly is usually found. The definitive diagnosis is made by measurement of enzyme activity, and homozygous patients are usually clinically anaemic with a reticulocytosis.
Sickle-cell syndromes
A single amino acid substitution (valine for glutamic acid) at position 6 of the beta-chain of globin results in a haemoglobin with abnormal physical and chemical properties. Haemoglobin S (HbS) can be found in the homozygous state (Hb SS, sickle-cell disease), in the heterozygous state (Hb AS, sickle-cell trait), or in association with all the other globin chain variants including haemoglobin C, D and F or with beta-thalassaemia. The abnormal gene has a worldwide distribution, but is most common in those of African origin. It may confer a biological advantage against infection with falciparum malaria and have increased in this ethnic group by natural selection.

Disease results from polymerization of HbS molecules within the red cells. This causes chronic haemolytic states, chronic organ damage from vascular occlusion and acute crises with haemolysis, vascular occlusion and tissue death. Polymerization occurs only when HbS is in the deoxy form, and the subsequent crystallization results in cells that become rigid and sickle shaped and are unable to deform to pass through capillaries. This physical alteration is reversible when

10.50 Bossing of the skull caused by hyperplasia of the bone marrow in sickle-cell disease. Similar appearances are more commonly seen in thalassaemia and other severe congenital haemolytic anaemias.

10.51 A 'hair on end' appearance of the skull on X-ray is commonly associated with frontal bossing. As with bossing, this appearance is most common in thalassaemia and other severe congenital haemolytic anaemias.

10.52 A bone scan in a patient with sickle-cell disease. There is increased activity in both epiphyseal growth plates (1) and an area of abnormal isotope uptake in the lower right femur (2). This abnormality reflects recurrent episodes of avascular necrosis with repair, but this process also renders the bone especially susceptible to osteomyelitis caused by Salmonella or other organisms.

10.53 Sickle-cell retinopathy. Intermittent occlusion of small blood vessels by inflexible sickle-shaped cells commonly leads to characteristic 'salmon-patch' haemorrhages in the retina. These may evolve into pigmented retinal scars. The retinal vessels are also tortuous. At a later stage, proliferative retinopathy may also occur. Similar changes may be seen in other severe haemolytic anaemias, including thalassaemia.
the molecules are again oxygenated, unless the red cell membrane is severely damaged.

People heterozygous for HbS (sickle-cell trait) are usually asymptomatic unless exposed to lowered oxygen tensions (as in unpressurized aircraft, at high altitude, or sometimes during anaesthesia). Renal microinfarcts occur in heterozygotes, however, and patients may complain of haematuria and eventually develop renal impairment.

People who are homozygous for HbS (sickle-cell disease) suffer from chronic haemolysis, which is usually adequately compensated. Their haemoglobin level runs at 5-10 g/dl, with a reticulocyte count of 10-30%. There is usually mild jaundice resulting from elevation of the unconjugated bilirubin fraction. Acute haemolytic crises may be precipitated by infections, pregnancy, drugs, surgery and anaesthesia, which may also precipitate acute vascular occlusion in the microcirculation with tissue death. Sickle-cell crises are associated with fever, malaise and pain, which may be severe, and can occur in most parts of the body. Organs affected include bone (10.50-10.52), muscle, brain, eye (10.53), lung, spleen, liver, kidney and skin. Infection often occurs in the infarcted tissue, and chronic infection frequently complicates bone and joint ischaemia (3.155, 10.54). Pigment gall stones are common as a result of the chronic haemolysis. The disease carries a high mortality in young children, and death usually results from renal failure, overwhelming infection or vascular occlusion. Such patients should be managed in the same way as splenectomized patients with immunization and antibiotic prophylaxis (see p. 446).

The diagnosis is confirmed by a positive sickling test (10.55, 10.56) and by haemoglobin electrophoresis (10.57). Prenatal and cord-blood screening programmes should aid early diagnosis, and subsequent medical supervision may prevent long-term sequelae.

Management should be aimed at the prevention of infections and other situations that cause acute haemolytic and vascular crises. Acute crises require adequate oxygenation, rehydration, antibiotics and adequate pain control. Anaemia may be treated by blood transfusion but, in the long term, this may result in haemosiderosis or secondary haemochromatosis.

10.54 Severe dactylitis (inflammation of the fingers) is a common presentation of sickle-cell disease in children, and similar changes may occur in the feet. The painful swelling of the fingers commonly results from destructive changes in the small bones resulting from multiple infarctions, and sometimes complicated by osteomyelitis.

10.55 A fresh blood smear from a patient with sickle-cell disease shows few elongated or sickled cells, but anisocytosis, poikilocytosis and target cells are all seen.

10.56 Sickle cells can be formed by exposing red cells from a patient with sickle-cell disease to the reducing action of sodium metabisulphite under a sealed coverslip. As the reduced HbS crystallizes within the cells, they all come to assume the distorted, elongated sickle shape.

10.57 Haemoglobin electrophoresis.
Haemoglobins containing variant globin chains may have different electrophoretic mobility. Cellulose acetate electro-phoresis at alkaline pH is commonly used as an initial screen. Lane 1, normal adult (predominantly HbA, α2 42); lane 2, neonatal cord blood (predominantly Hbf, alpha2 gamma2), lane 3, heterozygous HbE (containing both HbA and HbE, α2 βE2); lane 4, HbS heterozygote (sickle-cell trait containing both HbA and HbS, α βS2).
Thalassaemia

Thalassaemia is the name given to a group of haemoglobinopathies that result from genetic mutations affecting synthesis of normal globins. The two major types are alpha- and beta-thalassaemia, which are caused by defective synthesis of the α- and beta- globin polypeptides. This results in failure of normal haemoglobin synthesis and the production of abnormal red cells that are hypochromic and microcytic.

Thalassaemia trait

The most common abnormality is thalassaemia trait (or thalassaemia minor), which is the heterozygous form of α- or beta- thalassaemia. This is usually associated with very mild defects in the red cells with microcytosis (MCV 55–75) and hypochromia (MCH 20–22) and sometimes with a chronic very mild anaemia with a haematocrit of about 0.30 and a slightly raised red cell count (10.58). The condition is common in certain parts of the world and affects up to 20% of people from parts of Africa, Asia and the Mediterranean. There are many variants of thalassaemia minor associated with a range of other minor abnormal haemoglobins. Thalassaemia trait probably confers protection against falciparum malaria and this selective advantage accounts for the high gene frequency in areas where malaria is evident.

No treatment is required for thalassaemia minor, but it is important to exclude iron deficiency that may compound the anaemia; routine measurement of ferritin and serum iron is necessary. Detection of the condition before reproductive age allows appropriate genetic counselling.

Severe β-thalassaemia (Cooley’s anaemia)

People homozygous for β-thalassaemia (in whom both genes are defective) have a marked defect in β-globin synthesis, whereas α-globin synthesis continues normally. This results in the accumulation in red cells of excessive α-globin chains, which are relatively insoluble when uncombined with β-globin chains and thus form large intracellular inclusions. The red cells have a high incidence of failure of maturation within the marrow (ineffective haemopoiesis), and those that are released have a short life span because of splenic trapping. The resultant severe anaemia stimulates production of excess erythropoietin which in turn stimulates further erythroblast proliferation, extension of marrow production to most bones and increased absorption of iron. The process is so active that osteoporosis and pathological fractures may occur, and some bones may become extremely hyperplastic (10.50, 10.51, 10.59). Compression of the cord may result from vertebral growth, and alteration of the facies may result from overgrowth of the bones of the face ('chipmunk facies'). Retinal changes may occur, as in sickle-cell disease (10.53). In severe anaemia (thalassaemia major), there is an absolute need for repeated blood transfusion (which results in iron overload) to maintain oxygenation. In less severe forms (thalassaemia intermedia), the patient is able to maintain a reasonable haemoglobin level (6–8 g/dl) without recourse to blood transfusion, and these patients survive into adult life.

In thalassaemia major, the clinical picture emerges in the first year of life with severe anaemia, failure to thrive and retardation of growth. Examination shows evidence of both

10.59 Thalassaemia major is usually associated with widespread bone changes resulting from marrow hyperplasia. The distal femur in this patient is expanded, giving a ‘flask shaped’ appearance. The bones are generally osteopenic (A), with a sparse, coarse, dense trabecular pattern. This appearance is not in itself diagnostic of thalassaemia: similar appearances may occur in other haemolytic anaemias, especially sickle-cell disease.
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spleen and liver enlargement (10.60). Laboratory tests show typical red cell appearances (10.61), and examination of the parents' blood shows the presence of thalassaemia trait. The diagnosis is confirmed by haemoglobin electrophoresis (10.57) and demonstration of defective β-globin synthesis by the reticulocytes.

There is a high morbidity and mortality unless the infants are regularly transfused with blood to suppress their own haemopoiesis. This can reduce the disease manifestations and allow normal growth and bone development. Repeated transfusion produces problems of iron overload with secondary haemochromatosis, and also a risk of viral infections (especially with hepatitis viruses and HIV). Cardiac disease is also common, with heart failure, myocarditis and pericarditis.

Iron overload can be treated with desferrioxamine infusions and there is evidence that this will prolong life, but it must be given by subcutaneous infusion, is difficult to administer to large numbers of patients and is expensive. Vitamin C may also be given to enhance iron chelation. Splenectomy should be considered, in an attempt to increase the life span of red cells. If neutropenia and thrombocytopenia are present, this is good evidence that there is hypersplenism. It is important to immunize the child against infection before splenectomy and to administer long-term prophylaxis with penicillin (see p. 446). Bone marrow transplantation should be considered in selected cases.

Thalassaemia intermedia

Some patients with thalassaemia are able to maintain their haemoglobin levels adequately without recourse to blood transfusion. However, iron accumulation occurs because of increased intestinal absorption and eventually causes secondary haemochromatosis with all the effects already described. Osteoporosis, bone overgrowth and arthritis are frequent and produce disfiguring skeletal abnormalities.

α-Thalassaemia

Various gene mutations or deletions may lead to defects in the synthesis of α-globin chains, and a spectrum of red cell abnormalities in which the red cells are hypochromic, microcytic and easily fragmented. The defective α-chains may be accompanied by the production of abnormal β-chain polymers, which are unstable and lead to rapid haemolysis.

From one to four genes may be involved, resulting in:
- No detectable disease (one- or two-gene defect)
- Moderately severe haemolysis (three-gene defect — haemoglobin H disease)
- Fetal death — hydrops fetalis (10.62) (four-gene defect).

In haemoglobin H disease, splenomegaly is frequent, and the spleen may require removal if there is evidence of hypersplenism. Folic acid and occasional blood transfusion may be required.

10.60 β-Thalassaemia major.
Hepatosplenomegaly is usual, as in this young patient.

10.61 Severe β-thalassaemia. The blood film shows much more severe changes than those seen in 10.58, with hypochromia, target cells, macrocytes, spherocytes, schistocytes — including helmet cells — and small cell fragments.

10.62 Hydrops fetalis in severe α-thalassaemia. The most severe form of the disease is incompatible with life, and the fetus usually dies in utero.
Acquired haemolytic anaemias

The most common type of acquired haemolytic anaemia results from the presence of autoantibodies, which attach to the red cells and reduce their survival by enhancing their phagocytosis by reticuloendothelial cells. This condition is diagnosed by finding a positive Coombs’ test. The antibodies may be ‘warm antibodies’, most active at 37°C (usually IgG), or ‘cold antibodies’, most active at lower temperatures (usually IgM). Both types of anaemia may be idiopathic, but underlying causes may be found.

- **Warm autoimmune haemolysis** may be associated with lymphoma, chronic lymphatic leukaemia (10.44), systemic lupus erythematosus, AIDS or hypogammaglobulinaemia. It gives rise to red cell spherocytosis, which can be morphologically indistinguishable from that of congenital spherocytosis (10.47); treatment with prednisolone may produce a remission, but splenectomy needs to be considered if this is ineffective or requires an unacceptably high steroid dose.

- **Cold autoimmune haemolysis** (10.63, 10.64) may be transient in association with infectious mononucleosis (see p. 31) or mycoplasm pneumonia (see p. 57, 192), may be seen in malaria (see p. 64), and may occur with a monoclonal IgM paraprotein in idiopathic cold haemagglutinin disease (CHAD) and with lymphoma; avoidance of the cold is the main line of treatment to avoid precipitating intravascular haemolysis or exacerbating the Raynaud’s phenomenon that is common in this disorder (see p. 264). Cold antibodies often do not cause haemolysis; they may then be suspected from the presence of a strikingly raised ESR.

Drug-induced immune haemolysis

Drugs may induce haemolysis in three ways
- Acute intravascular haemolysis may occur when a drug stimulates antibody formation and the resulting immune complex is absorbed on to the red cell where it fixes complement; haemolysis occurs on a second exposure; drugs such as chlorpropamide and quinine are involved.
- Slow-onset haemolysis may occur when a drug becomes attached to the red cell membrane and acts as a hapten; IgG antibody against the drug attaches to the cell and leads to extravascular destruction of the coated cell; this type of reaction is seen with penicillins and cephalosporins.
- Autoimmune haemolysis may be seen after some months of therapy with methyldopa, L-dopa, mefenamic acid and flufenamic acid; the mechanism is not well understood. In up to 20% of patients on methyldopa, there is IgG coating of red cells, but only a small percentage of these patients (5–10%) show evidence of haemolysis.

Stopping the drug usually leads to rapid resolution, but a short course of prednisolone may be necessary in the autoimmune haemolysis caused by methyldopa.

Haemolytic disease of the newborn

In haemolytic disease of the newborn, maternal IgG antibodies to fetal red cell antigens cross the placenta and affect the fetal red cells, leading to isoimmune haemolysis. Antibodies are usually against the rhesus-group antigens, usually Rh(D), and they develop if the mother is Rh(D) negative, but they may also be against ABO and other rarer blood groups. Sensitization in a Rh(D)-negative mother occurs after a first pregnancy with a Rh(D)-positive fetus, usually as a result of leakage of fetal red cells into the maternal circulation at parturition; it may also result from a previous blood transfusion. Subsequent pregnancies may be affected with increasing severity, depending on the antibody levels that result. Severe haemolytic anaemia may appear in the fetus at the end of the first trimester or in the second trimester, and may result in fetal death (hydrops fetalis, 10.62). In less severe cases, icterus may be apparent at birth and may lead to kernicterus, the deposition of indirect bilirubin in the basal ganglia of the neonate brain (10.65).

All mothers should have their blood tested for anti-Rh(D) antibodies at the initial booking visit to the antenatal clinic. A rising titre of antibody is an indication for fetal blood transfusion and careful fetal monitoring. Early delivery may be required, in which case prematurity with its complications must be weighed against the risks of anaemia.

10.63, 10.64 Cold autoimmune haemolysis. A blood film from the patient viewed at 37°C (10.63) shows slight clumping of the red cells. By contrast, in a film made at room temperature (10.64), extreme agglutination of the cells has occurred.
If the presentation is at birth, the cord blood sample will show anaemia with a positive Coombs’ test, an elevated indirect bilirubin and normoblasts and a high reticulocyte count on the blood film. Exchange transfusion is urgently indicated.

The incidence of this disease has fallen dramatically as a result of the administration within 72 hours of delivery of human anti-D IgG to all Rh(D)-negative mothers who have their first Rh(D)-positive child and who are not already sensitized. This attaches to fetal red cells in the maternal circulation and neutralizes their sensitizing effect. Fetal cells can be detected in the maternal circulation using the Kleihauer technique (10.66); if they are still present after treatment, further anti-D may be needed. Occasional cases of haemolytic disease of the newborn still occur because of ABO blood group antibodies or because of Rh(D) sensitization at earlier stages in pregnancy.

Polycythaemia

Paroxysmal nocturnal haemoglobinuria (PNH) is a clonal change in red cells in which the red cell lacks a factor that destroys the complement that normally accumulates on red cells. This results in an intermittent type of acute intravascular haemolysis. PNH may complicate aplastic anaemia. Acute attacks of intravascular haemolysis are precipitated by infection, surgery and anaesthesia and the patient passes dark red-brown urine, often first thing in the morning. There is an association with acute thrombotic episodes caused by platelet and white cell activation and there may be a sequel of acute myeloid leukaemia or aplastic anaemia.

Often, the diagnosis is reached by chance, with the finding of an elevated haemoglobin on a routine blood sample, or the chance finding of splenomegaly on clinical examination; it may be recognized only after an acute thrombotic event. The major clinical clues are facial plethora (10.68), conjunctival suffusion and splenomegaly, present in 70% of patients. Other associated features are acne rosacea (see p. 103), urticaria, leg ulcers, retinal changes (10.69) and loss of vision because of retinal haemorrhage. The liver is enlarged in up to 50% of patients, and hypertension is present in about 20%. Evidence should be sought of previous stroke, peripheral vascular disease or deep vein thrombosis. Itch is found in about 15% of patients, and there may be signs of chronic excoriation. The condition is also associated with peptic ulcer and acute gout (see p. 138).

The diagnosis is suspected from the FBC and confirmed by the measurement of red cell mass. There may be associated elevation of the white cell count and platelets. The bone marrow shows gross erythroid hyperplasia with normoblastic erythropoiesis. There may be associated iron deficiency, seen
on staining the marrow with Prussian Blue. The leucocyte alkaline phosphatase score is high, which is the opposite of that found in chronic myeloid leukaemia. The uric acid levels are characteristically elevated. About 60% of untreated patients die of thrombotic events, about 20% progress to myelofibrosis and a small number (<10%) progress to acute myeloid leukaemia. Treatment is required to lower the haemoglobin and this is done with repeated venesection or with \(^{32}\text{P}\). Because radio-phosphorus is associated with a tenfold increase in the risk of leukaemia, its use is best reserved for elderly patients. Allopurinol should be routinely administered to patients with hyperuricaemia to prevent gout.

Secondary polycythaemia (4.5) is not associated with such a large risk of thrombotic events. Treatment should be directed at the cause, but often this is not amenable to change. A reduction in haematocrit may be achieved by continuous oxygen therapy. Patients must stop smoking.

### POLYCYTHAEMIAS

<table>
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<tbody>
<tr>
<td>Primary proliferative polycythaemia</td>
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<td>(a) Hypoxic</td>
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<td>Altitude</td>
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<td>Chronic lung disease</td>
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<td>Cyanotic congenital heart disease</td>
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<td>Smoking</td>
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<td>Polycystic kidneys</td>
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<td>Renal cysts</td>
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<td>Hepatocellular carcinoma</td>
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<td>Ovarian carcinoma</td>
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<td>Bronchial carcinoma</td>
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<tr>
<td>(b) Excess erythropoietin</td>
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<td>(c) Overtransfusion</td>
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<td>Apparent</td>
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<tr>
<td>Acute fluid loss</td>
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<td>‘Gaisbock’s syndrome’</td>
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10.67 Polycythaemias.

10.68 Primary proliferative polycythaemia (polycythaemia rubra vera). The patient has a generalized plethoric appearance, most obvious on, but not confined to, the face. Note that he also has a prominent temporal artery, which raises the possibility of temporal arteritis (see p. 146). His ESR could not be used as a guide to the diagnosis of temporal arteritis, as it should be very low in polycythaemia. Plasma viscosity or C-reactive protein would be a better guide.

10.69 The fundus in polycythaemia of any cause usually shows engorged and tortuous vessels. Other causes of blood hyperviscosity, including multiple myeloma, may lead to a similar retinal appearance (see p. 466). Thrombosis in the retinal vessels and retinal haemorrhages may occur in patients with hyperviscosity of any cause.

### MYELOFIBROSIS

In myelofibrosis increased fibrous tissue is formed within the marrow cavity, normal haemopoiesis is disturbed and there is extramedullary haemopoiesis in spleen and liver. It is in the same group of myeloproliferative disorders as polycythaemia, chronic myeloid leukaemia and essential thrombocythaemia and it may be a consequence of these disorders, the fibrous tissue being reactive to the other events in the bone marrow.

In many patients the disease is asymptomatic and the diagnosis is made by finding hepatosplenomegaly on routine clinical examination for some other reason. Alternatively, blood examination for some other purpose may show a leucocytopenic- thrombocytopenic state. Some patients present with anaemia or with progressive abdominal swelling (caused by the hepatosplenomegaly) and some with splenic infarction as the enlarging spleen outgrows its blood supply. Portal hypertension may also develop in some patients, with ascites and even bleeding from oesophageal varices compounding the anaemia. Purpura and bleeding may result from thrombocytopenia caused by hypersplenism, and also from coagulation abnormalities caused by liver disease. Gout may occur, as a result of the hyperuricaemia.
In a typical patient there is usually evidence of weight loss, with thin spindly legs and arms that contrast with the obvious abdominal distension. The spleen is usually grossly, and the liver moderately, enlarged (as in other conditions, see 1.192, 1.195). There may be some ascites. Lymph nodes may also be large but nontender. Bruises and purpura may be present.

Characteristic changes in routine blood tests include a low haemoglobin, which may partly result from blood loss with iron deficiency, folate deficiency and dilution from an increased plasma volume. Normoblasts may be present in great numbers in peripheral blood (this may interfere with automated white cell counters) showing a leucoerythroblastic state (10.70). The platelet count and white cell count may be low. The leucocyte alkaline phosphatase is high, as in primary proliferative polycythaemia, and this allows differentiation from chronic myeloid leukaemia. Attempts to aspirate bone marrow often result in a ‘dry tap’ because of the amount of fibrous tissue. Trephine biopsy shows a hypercellular marrow with an increase in fibrous tissue, a decrease in fat and haemopoietic tissue, but often an excess of megakaryocytes. It is important to remember other causes of marrow fibrosis, including carcinomatous infiltration (especially from breast and prostate), previous radiation exposure, infections such as tuberculosis and osteomyelitis, and Paget’s disease. Using cyclotron-produced iron-52 it is possible to identify the sites of active erythropoiesis, which will include the liver, spleen and lymph nodes (extramedullary haemopoiesis). X-ray of bones will show an increase in bone density, particularly in the vertebrae.

Treatment is supportive and symptomatic. Iron and folate deficiency should be corrected and gout treated with allopurinol. Blood transfusion may be necessary for severe anaemia. In some situations splenectomy should be considered to reduce haemolysis, remove an infarcted spleen, or when there is severe abdominal discomfort or swelling. Unfortunately, this may often lead to rapid enlargement of the liver. Splenic size may also be controlled with radiotherapy.

Death usually occurs from progressive marrow failure, with bleeding from thrombocytopenia, leucopenia and overwhelming infection, and persistent anaemia. Transformation to acute myeloid leukaemia sometimes occurs.

**ESSENTIAL THROMBOCYTHAEMIA**

Essential thrombocythaemia is part of the myeloproliferative spectrum in which there is proliferation of the megakaryocyte series with the production of excessive numbers of platelets, which may be functionally impaired. Patients present with some of the features of the associated disorders (polycythaemia, chronic myeloid leukaemia and myelofibrosis), including spontaneous bruising, epistaxis and gastrointestinal, vaginal or respiratory tract bleeding. Thrombotic occlusion of arteries, leading to myocardial infarction, stroke, gangrene or intestinal infarction, is common.

Clinical examination may show evidence of bleeding or of thrombosis. The spleen and liver are often felt, although in the later stages splenic atrophy is common.

The diagnosis is made on the finding of platelet counts of 1000–2000 x 10^9/litre. The red cell and white cell counts may also be high. The bleeding time may be prolonged and platelet function studies are often abnormal. Megakaryocytes are increased in the marrow. Straight X-ray of the abdomen may show an atrophic calcified spleen.

Treatment is aimed at reduction of the platelet count either by platelet phaeresis or by use of ^32^P or a cytotoxic agent such as busulphan or cyclophosphamide.

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10.70 Leucoerythroblastic peripheral blood film in myelofibrosis. A leucoerythroblastic state is characterized by the presence of abnormally immature white cells and nucleated red cells, and the appearance commonly reflects severe marrow dysfunction. The appearance is not in itself diagnostic of myelofibrosis: it may be seen in chronic infection, malignancy, metabolic disorders that affect bone and in acute severe haemolytic anaemia. This blood picture is usually an indication for marrow aspiration and trephine biopsy.
**HYPERSPLENISM**

Any pathological condition that causes splenomegaly (10.71) may result in peripheral blood cytopenia caused by

- Pooling of cells within the spleen and their subsequent destruction
- Increased plasma volume with dilution of cell numbers.

The diagnosis is usually obvious from the findings of peripheral cytopenia, a hypercellular marrow and splenomegaly. The diagnosis may be confirmed by $^{51}$Cr-red cell labelling with surface counting over the spleen.

Splenectomy results in a rapid reversal of these abnormalities. Acutely, there is a transient thrombocytosis and neutrophil leukocytosis. In the long term in the red cells there may be nuclear remnants (Howell–Jolly bodies; 10.72), siderocytes, target cells and occasional normoblasts.

**IMMUNITY AND THE ASPLENIC PATIENT**

The normal spleen has the role of removing opsonized encapsulated bacteria and red cells parasitized by malaria parasites from the blood. Individuals who have had their spleens removed surgically (usually for trauma) or who have splenic hypofunction caused by disease (e.g. coeliac disease, lymphoma, systemic lupus erythematosus, sickle-cell disease or thalassemia) have a 12-fold greater risk of severe infection. This risk persists throughout life although it is greatest in the early years after splenectomy.

The most common infections are with *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and *Neisseria meningitidis*. Malaria also presents a significant risk for the traveller.

Patients should be made aware of the risk of infection and of the early symptoms of bacteraemia, such as malaise and fever, which may be interpreted as no more than mild influenza. Infections are usually fulminant, with pneumonia, meningitis, multiple organ failure and death.

It is essential that patients at risk are given pneumococcal vaccine before splenectomy (if elective) and this should be repeated every 5 years to maintain lifelong immunity. In young children (<4 years) consideration should be given to *H. influenzae* type b (Hib) vaccination if this has not already been given. Meningococcal vaccine should be given at the same time as pneumococcal vaccine.

Antibiotic prophylaxis with penicillin or ampicillin (or erythromycin) is also indicated for at least 2 years after splenectomy, and this should be continued until at least the age of 16 years in children.

In the long term patients should be supplied with a course of antibiotics for self-administration if 'flu-like' symptoms appear.

**CAUSES OF SPLENOMEGALY**

<table>
<thead>
<tr>
<th>Infections</th>
<th>Viral: Infectious mononucleosis</th>
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<tr>
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<td>Helminths:</td>
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<td>Hepatic or portal vein thrombosis</td>
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<td>Lymphoproliferative disorders</td>
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**10.72 Peripheral blood film in an asplenic patient** whose spleen was removed after trauma in a road traffic accident. Howell–Jolly bodies and punctate basophilia are seen in the red cells, which also show anisocytosis, poikilocytosis and abnormal burr forms. There is also thrombocytosis.
LEUKAEMIAS

The leukaemias result from the clonal proliferation of cells derived from a single early haemopoietic progenitor cell that has undergone somatic mutation. In the acute leukaemias, this results in the accumulation of early myeloid or lymphoid precursors ('blast' cells) in the bone marrow, blood and other tissues; marrow failure rapidly follows as normal blood cell production ceases. In the chronic leukaemias, either the malignant clone allows differentiation to functional end cells (as in chronic myeloid leukaemia), or the malignant proliferation progresses more slowly (as in chronic lymphocytic leukaemia).

ACUTE LEUKAEMIA

Acute leukaemias have an incidence of between 5–10 cases per 100 000 of the population, and this is increasing. Acute lymphoblastic leukaemia (ALL) is found mainly in young children (peak incidence 3–5 years). In adults, acute myeloblastic leukaemia (AML) is more common. The aetiology of acute leukaemia is unknown, but may include viruses, chemicals and radiation; it is sometimes a sequel to the administration of chemotherapy or radiotherapy for previous cancers. Acute leukaemia presents with infection, bleeding or anaemia — all the result of bone marrow failure — and occasionally with bone pain. There may also be organ infiltration with lymphadenopathy, splenomegaly or CNS involvement. The peripheral blood may contain blast cells, or occasionally the leukaemic infiltration is discovered on bone marrow examination carried out to determine the cause of a pancytopenia. No clinical features absolutely distinguish between AML and ALL.

The clinical presentation is often with pallor and tiredness resulting from anaemia. Other signs of anaemia include dyspnoea, tachycardia and occasionally pulmonary oedema. The cause of the anaemia is usually infiltration of the marrow.

Fever is also usually present and is often related to infection, especially when the white cell count falls below $1 \times 10^9$/litre (10.73, 10.74, 10.75). Bleeding is usually due to thrombocytopenia and skin purpura is a frequent finding, especially when the platelet count falls below $20 \times 10^9$/litre. There may also be a qualitative platelet defect and occasionally DIC. The skin and gums are common sites of bleeding, but bleeding may occur from any site.
Leukaemic infiltration is common in the terminal stages of the disease, and multiple small purple popular lesions can often be found in the skin (10.76, 10.77). There may also be gingival infiltration (10.75), often with involvement of the tongue and tonsils. The eye may also be affected and infiltrates may be visible in the retina and choroid (10.78). The testicles may be involved, usually causing painless swelling. Involvement of the testicles or ovaries and of the meninges (found on CSF examination) may be an important source of cells that cause relapse and this requires special consideration in treatment planning. Liver, spleen and bone marrow involvements are common. Bone and joint involvements are rare at presentation, but become more common as the disease advances (10.79). Bone pain is often present at the sites of major marrow production, especially over the sternum. Periosteal elevation may be seen on X-ray, and bone infarction may occur.

10.76 Leukaemic skin deposits in a patient with acute myeloblastic leukaemia. Similar small deposits may occur in patients with lymphomas or carcinomas; if the deposits are an isolated finding, biopsy is essential for diagnosis.

10.77 Extensive leukaemic infiltration of the skin may sometimes occur - most commonly, as here, in patients with acute myeloblastic leukaemia.

10.78 Leukaemic retinal infiltrates are often seen in acute leukaemia, as in this patient with acute lymphoblastic leukaemia. Retinal haemorrhage is often also seen but is probably a consequence of the thrombocytopenia that accompanies the leukaemia, rather than a manifestation of the leukaemic process itself. Similar haemorrhages are seen in patients with thrombocytopenic purpura.

10.79 Acute, painful swelling of the hand was the presenting feature of acute lymphoblastic leukaemia in this 10-year-old child. Radiological examination confirmed leukaemic infiltration at the bases of the metacarpals and extensive periostitis.
The distinction of the types of leukaemia depends upon the morphology of the blasts and on detailed cytochemical and monoclonal antibody cell marker studies (10.80, 10.81).

Management should be carried out in specialized units. Chemotherapy may include combinations of steroids, vincristine, asparaginase, daunorubicin and cytosine arabinoside, and other combinations are currently under trial. Treatment with intensive cytotoxic chemotherapy exacerbates immunosuppression in the short term and isolation nursing and supportive therapy with broad-spectrum antibiotics sometimes including antifungal agents, and blood products, particularly red cells and platelets, are almost invariably required. In addition fluids are often needed to correct dehydration, and allopurinol to correct hyperuricaemia. In childhood ALL, around two-thirds of patients will enter long-term remission, and the inclusion of prophylactic treatment to the CNS largely prevents meningeal relapse. Similarly, testicular and ovarian radiotherapy may be of value. In adults with either AML or ALL, the outlook is much less good with chemotherapy alone; if the patient is less than approximately 40 years old and has an HLA-compatible sibling, allogeneic bone marrow transplantation would now be recommended after achieving a first remission.

**CHRONIC LEUKAEMIAS**

In chronic leukaemias, there is an accumulation of abnormal white cells in the marrow with resultant disruption of normal marrow function and progressive infiltration into other tissues. Chronic leukaemias differ from the acute forms in that the time course is longer and the onset is more insidious, the cells are more mature and the treatments required are less intense. The classification depends on the cell type involved.

**Chronic lymphocytic leukaemia (CLL)**

CLL is the most common leukaemia in Europe and the USA and accounts for 30% of leukaemic deaths. It is a disease predominantly of the elderly, with a mean age at diagnosis of 60 years. In CLL, there is neoplastic proliferation of moderately mature lymphocytes, primarily in the marrow and blood, but also in the lymph nodes, spleen and liver. It is the result of a monoclonal transformation, usually of B lymphocytes (only 5% show a T-cell phenotype). The monoclonal nature of the disorder is confirmed by the finding of surface and cytoplasmic (and sometimes serum) immunoglobulins restricted to one light or heavy chain class.

CLL may present with lymphadenopathy, or increased numbers of small lymphocytes may be found coincidentally when a blood count is carried out for another reason (in about 25% of cases). Weight loss, night sweats, anorexia and lymph node enlargement in the superficial lymph nodes (10.44, 10.82), mediastinum and mesenteric nodes are common. On examination of the patient, there is usually moderate splenomegaly and sometimes hepatomegaly. Jaundice may develop as a result of lymphocytic infiltration of the liver or haemolysis (10.44). Later in the disease there may be extreme weight loss, pressure effects caused by lymph node involvement and skin infiltration that may be compounded by local infections with bacteria, viruses or fungi. Shingles is common (p. 28). Generalized infections are also common, as immunosuppression is related to a
combination of hypogammaglobulinaemia, lymphocyte dys-
function and, in more advanced disease, neutropenia. Related
disorders with a different phenotype and prognosis have been
recognized, including hairy-cell leukaemia and prolymphocytic
leukaemia, both typically associated with more pronounced
splenomegaly and less lymphadenopathy than CLL.

The diagnosis depends on finding a persistent lymphocyto-
sis of >15 x 10^9/litre lymphocytes, with a total white cell count
that can range up to 200 x 10^9/litre (85-95% of the white cells
are lymphocytes; neutrophil count reduced). Peripheral blood
films show typical CLL lymphocytes (10.83, 10.84) with
characteristic staining. Anaemia becomes more marked as the
disease advances and is usually normochromic and normocytic.
There is often a haemolytic component because of the presence
of warm antibodies (10.44 and see p. 442). Marrow aspirate or
trephine biopsy shows a reduction in normal marrow elements
with a lymphocytic infiltrate (10.85). Serum immunoglobulin
measurement and electrophoresis reveals hypogammaglobu-
linaemia and a monoclonal paraprotein spike. Lymph node
histology shows a similar picture to that in well-differentiated
lymphocytic lymphoma (see p. 453). X-ray of the chest may
show marked mediastinal enlargement caused by bilateral
lymphadenopathy.

Combinations of these clinical and laboratory criteria form
the basis of a variety of staging techniques that may be used to
plan treatment or as prognostic indicators. Poor prognostic
factors include
• Lymphocyte counts >50 x 10^9/litre
• Lymphocyte doubling time of <1 year
• Prolymphocyte count >15 x 10^9/litre
• Extensive lymph node involvement
• Splenomegaly >10 cm
• Diffuse pattern of bone marrow infiltrate
• Poor response to treatment.

Complete remission is defined as the disappearance of the
abnormal lymphocytes from blood and marrow, and the nor-
malization of blood counts, immunoglobulins and light chains.
A partial response is defined as a 50% reduction in lymphocy-
tosis and a 50% reduction in adenopathy and splenomegaly,
with haemoglobin >11 g/dl and platelets >100 x 10^9/litre.

Asymptomatic CLL usually requires no treatment, but more
advanced cases with bone marrow failure, tissue infiltration or
severe lymphadenopathy are treated with single alkylating
agents (e.g. chlorambucil or cyclophosphamide) or local radio-
therapy. Chemotherapy with a single agent can induce partial
remission in 50-60% of cases and complete remission in
10-15%. Addition of corticosteroids increases the number of
partial remissions to 70-80%, but also increases the chances of
infectious complications. Resistant or advanced cases may
require the use of vincristine, melphalan and doxorubicin. All
these agents may be associated with side effects such as
nausea, vomiting, anorexia and weight loss. Myelosuppression

10.83 Chronic lymphocytic leukaemia. The intact
white cells on the peripheral blood film are nearly all
lymphocytes. A few precursor cells can be seen, and
there are numerous smeared disrupted cells – a typical
finding in this disease.

10.84 Hairy-cell leukaemia. The peripheral blood
film shows cells containing a typical eccentric nucleus
and fine surface projections or hairs. The distinction
between chronic lymphocytic leukaemia and hairy-cell
leukaemia has therapeutic importance.

10.85 Chronic lymphocytic leukaemia. This high-
power view of a trephine biopsy of bone marrow
shows overwhelming, diffuse, uniform infiltration by
lymphocytes – a picture found typically at advanced
stages of the disease and commonly associated with
marked anaemia and thrombocytopenia.
is inevitable, but improves when therapy is stopped or the dosage reduced. There is a significant incidence of acute myeloid leukaemia (10%) after 5–10 years of treatment. In the case of the prolymphocytic leukaemic variant, the very high white cell number may rarely require reduction by leucopheresis for chemotherapy to be effective. In hairy-cell leukaemia α-interferon is of value.

All patients require general supportive measures, often including the supportive treatment of anaemia with blood or red cell transfusions, treatment of thrombocytopenia with platelet concentrates and treatment of infections with antibiotics and gammaglobulin. Prevention of hyperuricaemia with allopurinol may be required, and the patient must be adequately hydrated throughout treatment. About 50% of patients with CLL die from unrelated causes, mainly cardiovascular disease and other malignancy.

**Chronic myeloid leukaemia (CML)**

CML accounts for 15% of leukaemias and is a disorder predominantly of middle life (median age at diagnosis is 45 years). The malignant clone of haemopoietic cells that spill into the peripheral blood is marked by the presence of the Philadelphia chromosome in about 95% of cases. In the minority of cases in which this is absent, there may be differences in the course of the disease and in the response to treatment. The common cell type involved is the granulocyte series, but rare cases of eosinophilic, basophilic and neutrophilic leukaemia occur.

The clinical course of chronic myeloid leukaemia is insidious with overgrowth of cells, predominantly those of the myeloid series but also those of the erythroid and megakaryocytic series. This often results in a leucoerythroblastic picture (10.70) that may terminate after several years in an acute leukaemia relatively resistant to therapy, or in myelofibrosis.

Clinical features on presentation include those caused by anaemia, weight loss, abdominal distension from massive splenomegaly and bone tenderness from periosteal infiltration. Purpura and bleeding from other sites as a result of thrombocytopenia may occur. Hyperviscosity syndromes may result in retinal haemorrhages, priapism and neurological deficit. Gouty arthropathy is rare despite the presence of hyperuricaemia.

The diagnosis is suspected when a white cell count in excess of $50 \times 10^9$ litre is found that is composed of myelocytes, metamyelocytes and blast cells in the peripheral blood film (10.86). There is also usually a normochromic normocytic anaemia, with a haemoglobin in the region of 9 g/dl. There may also be thrombocytosis with giant platelets and other fragments of megakaryocytes.

Bone marrow aspirate (10.87) or trephine biopsy shows a generalized increase in cellularity, with loss of fat spaces caused by the myeloid hyperplasia. The leucocyte alkaline phosphatase is greatly reduced in CML, and this allows its differentiation from the neutrophils resulting from infection and from other myeloproliferative disorders. The Philadelphia chromosome is of diagnostic and prognostic importance (10.88).

Treatment is by control of the hyperproliferation using

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**10.86 Chronic myeloid leukaemia.** This low-power view of peripheral blood shows granulocytes at all stages of maturation. A peripheral blood smear with as many leucocytes of different stages of maturity as shown here is virtually diagnostic of chronic myeloid leukaemia.

**10.87 Bone marrow smear in chronic myeloid leukaemia (low-power view).** There is a preponderance of neutrophil granulocytes, with all stages of development represented. Some erythroblasts and a pro-erythroblast can also be seen.

**10.88 Philadelphia chromosome in chronic myeloid leukaemia.** The Philadelphia chromosome is number 22 from which the long arms are deleted (22q−) and is found in nearly all patients with chronic myeloid leukaemia. It is part of a reciprocal translocation usually involving chromosome 9 (9q−). In this karyotype, the arrows indicate the truncated Philadelphia chromosome 22 and the extended chromosome 9 in a Giemsa-banded metaphase from bone marrow cells of a patient with chronic myeloid leukaemia: the inset (lower right) shows the affected chromosomes and their normal partners in more detail. The reciprocal translocation results in the formation of a chimaeric gene, formed from part of the chromosome 22 and the c-abl gene from chromosome 9; this transcribes a novel mRNA to produce a protein with enhanced tyrosine kinase activity thought to be the metabolic basis of this leukaemia.
busulphan or hydroxyurea, but after a median of 2–3 years the disease becomes more difficult to control, with increasing marrow fibrosis or a sudden transformation to acute leukaemia, or both.

In patients with a hyperviscosity syndrome caused by the presence of excess white cells, leucapheresis is of value. During initial treatment, a high fluid intake and allopurinol are important in the control of hyperuricaemia. Splenic irradiation or splenectomy have little place in modern management.

Allogeneic bone marrow transplantation is of value in the chronic phase for younger patients who have a compatible donor, and this represents the best chance for cure.

**MYELODYSPLASTIC SYNDROMES**

The myelodysplastic syndromes are a heterogeneous group of disorders, characterized by the liability to develop acute myeloid leukaemia, which present with multiple cytopenias in the presence of a hypercellular marrow. The range of abnormalities includes refractory anaemia – which may be associated with excessive marrow iron or with ringed sideroblasts in the marrow – and chronic myelomonocytic leukaemia (10.89). These disorders occur particularly in the elderly, and clinical presentation is often caused by failure of the marrow, with signs of bleeding (10.90) or with infection. Up to 20% of patients have splenomegaly.

Laboratory investigation usually shows that all three cell lines are involved. The red cells often show macrocytosis, ovalocytes and poikilocytosis with 'tear-drop' forms. Circulating normoblasts may be seen. Anaemia is usually present. The white cells are often functionally defective, with defects in their granules and loss of peroxidase activity, are poorly lobulated and show nuclear and cytoplasmic anomalies. Platelet function is often abnormal, with qualitative and quantitative abnormalities and prolongation of the bleeding time. The bone marrow is often hypercellular with granulopoiesis shifted to the left. Erythropoiesis is often megaloblastic with abnormal sideroblasts. Giant megakaryocytes are present and these show fragmented nuclei.

The prognosis is generally poor because of the patient's age, increasing anaemia, infection resulting from granulocytopenia and bleeding from thrombocytopenia. The median survival is of the order of 30 months.

Treatment consists of supportive care, with correction of anaemia with blood transfusion, and appropriate treatment of infections and bleeding.

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**MYELODYSPLASTIC SYNDROMES**

This classification, devised by a French, American and British (FAB) co-operative group, is based on findings in the peripheral blood and the bone marrow.

<table>
<thead>
<tr>
<th>Classification</th>
<th>% Marrow blasts</th>
<th>% Peripheral blood blasts</th>
<th>Ringed sideroblasts</th>
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</thead>
<tbody>
<tr>
<td>Refractory anaemia (RA)</td>
<td>&lt;5</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Refractory anaemia with ringed sideroblasts (RAB)</td>
<td>&lt;5</td>
<td>&lt;1</td>
<td>+</td>
</tr>
<tr>
<td>Refractory anaemia with excess blasts (RAEB)</td>
<td>5–20</td>
<td>&lt;5</td>
<td>+/-</td>
</tr>
<tr>
<td>RAEB in transition (RAEB-t)</td>
<td>20–30</td>
<td>&gt;5</td>
<td>+/-</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukaemia</td>
<td>&lt;20</td>
<td>&lt;5</td>
<td>+/-</td>
</tr>
</tbody>
</table>

10.89 Myelodysplastic syndromes.

10.90 Excessive bruising after trauma in a patient with a myelodysplastic syndrome. This lady was beaten in a domestic assault but her bruising was excessive for the described severity of the attack. She proved to be seriously anaemic (Hb 5.7 g/dl), and marrow findings showed that she had refractory anaemia, RAB type (see 10.89).
LYMPHOMA

The lymphomas are a group of malignant disorders originating in one of the lymph nodes or other lymphatic tissues of the body and disrupting the normal lymphoid architecture. The disorders are divided into Hodgkin’s disease (in which the origin of the abnormal Reed–Sternberg cell is still a matter of debate), and the non-Hodgkin’s lymphomas (which can be shown to be of clonal B- or T-cell origin).

HODGKIN’S DISEASE

Hodgkin’s disease is the most common of the lymphomas. It occurs more frequently in men than in women and has bimodal peaks of increased incidence in early adult life and after 45 years of age. The tumour is unusual in that the putative malignant cell (the Reed–Sternberg cell) forms a tiny proportion of the cells in the tumour, the remaining tissue being thought to be ‘reactive’. In 70% of cases patients present with isolated painless swelling of a lymph node in the neck, axilla or groin, which spreads to adjacent groups of lymph nodes (10.8, 10.91).

In advanced cases there may be hepatosplenomegaly. Skin lesions may develop at a late stage (10.92).

Investigations show a variety of nonspecific features, usually including a normochromic normocytic anaemia and elevation of the ESR (especially in the presence of ‘B’ grading). Lymphopenia is present in about one-third of cases, and there may also be neutrophilia, eosinophilia and monocytosis. There may rarely be autoimmune thrombocytopenia or haemolytic anaemia. The diagnosis is made on lymph node or tissue biopsy, which should be conventionally fixed and stained (10.93) and also examined immunohistochemically.

The extent of the disease (10.94) and its prognosis is determined by staging procedures (10.95).

10.91 Gross, painless, rubbery lymph node enlargement is the common presenting feature of Hodgkin’s disease. This patient had generalized lymphadenopathy, but his left axillary nodes were particularly prominent.

10.92 Skin deposits of tumour may occur in advanced Hodgkin’s disease. This patient had multiple skin nodules, and their nature was confirmed by biopsy. Palliative radiotherapy is about to be started.

10.93 The histopathological appearance of Hodgkin’s disease varies, but the presence of Reed-Sternberg cells is usually essential for the diagnosis. Here, a typical ‘owl-eye’ Reed–Sternberg cell is seen in a tumour of mixed cellularity (H&E staining). The histological subtype of Hodgkin’s disease is an important factor in prognosis and, in general, lymphocyte-depleted Hodgkin’s lymphomas have the worst prognosis.
**ANN ARBOR STAGING IN HODGKIN'S DISEASE.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of lymph nodes in a single region (I) or infiltration of a single extralymphatic site (IE)</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of lymph nodes in two distinct regions on the same side of the diaphragm (II) which may also include spleen (IIs), localized extralymphatic involvement (IIIE) or both (IIsE)</td>
</tr>
<tr>
<td>Stage III</td>
<td>Involvement of lymph nodes on both sides of the diaphragm (III) which may include the spleen (IIIs), localized extralymphatic involvement (IIIE) or both (IIIsE)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Diffuse or disseminated involvement of extralymphatic sites (e.g. bone marrow, liver and lung)</td>
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</table>

In addition, the suffix letters A and B are used to denote the absence (A) or presence (B) of any of the additional systemic features of fever, night sweats and loss of 10% of body weight in the previous 6 months.

10.94 Ann Arbor staging in Hodgkin's disease.

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**RECOMMENDED STAGING PROCEDURES IN HODGKIN'S DISEASE.**

**Required evaluation procedures**
- Adequate surgical biopsy (10.93)
- Detailed history with emphasis on the presence or absence of B symptoms
- Complete physical examination with special attention directed to the evaluation of lymphadenopathy, liver and spleen size, and the detection of bony tenderness
- Laboratory studies: FBC and platelet count, liver and kidney function, serum alkaline phosphatase
- Chest X-ray PA and lateral (10.96)
- Bilateral lower extremity lymphangiogram (10.97)
- Abdominal CT scan (10.98)
- Bone marrow aspirate and biopsy

**Required evaluation procedures under certain conditions**
- Chest tomography of chest CT scan (10.99)
- Bone scan
- Staging laparotomy including splenectomy

**Useful ancillary procedures**
- Skeletal radiographs
- Gallium scan

10.95 Recommended staging procedures in Hodgkin's disease.

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10.96 Chest X-ray in a patient with Hodgkin's disease, showing bilaterally enlarged mediastinal lymph nodes.

10.97 A lymphangiogram in Hodgkin's disease, performed by cannulating lymphatics in the feet. Grossly abnormal and enlarged inguinal, iliac and para-aortic lymph nodes can be seen.
Systemic symptoms (B-stage), including fever with sweats, especially at night (Pel–Ebstein pattern), and weight loss are characteristic of more advanced disease.

Hodgkin's disease is associated with impaired cell-mediated immunity and an increased risk of infections, including herpes zoster (see p. 28, 10.100).

Prognostic factors in stages I and II Hodgkin's disease are shown in 10.101. Treatment of localized disease is by radiotherapy, especially where the disease is above the diaphragm, when the cervical, axillary, mediastinal and para-aortic nodes can be irradiated ('the mantle'). The prospects for cure are of the order of 80–90% over 5 years.

For more advanced disease (stage IIIB and IV) treatment is with a combination of chemotherapeutic agents that include mustine, vincristine (Oncovin), procarbazine and prednisolone (MOPP), and sometimes also chlorambucil, vinblastine, adriamycin and bleomycin. Such combinations must be given in specialized units and can give an 80% remission rate. Cure can be expected in 30–40% of patients. If relapse occurs, different drugs are required and may be given in combination with radiotherapy.

Cytotoxic therapy compounds the existing defect in cell-mediated immunity and makes infective complications likely, for example disseminated tuberculosis, herpes zoster, and other bacterial, viral, fungal and protozoal infections.
NON-HODGKIN'S LYMPHOMAS

Non-Hodgkin's lymphomas are a heterogeneous group of neoplasms of the immune system that differ in cell type, natural history and outcome from Hodgkin's disease. Their incidence is approximately 14/100 000 population (in the UK) and is rising. The median age at diagnosis is 64 years, but they may occur in younger patients, especially in association with advanced HIV infection.

Non-Hodgkin's lymphoma may present in exactly the same way as Hodgkin's disease, with the diagnosis being made at lymph node biopsy (1.50, 10.9, 10.102). However, the range of presentations and course of disease is highly variable, and extranodal tissue involvement, including the bone marrow and organs as varied as the tongue and the testis (10.103), is much more common.

Histological classification of the non-Hodgkin's lymphomas has been difficult but has been improved by immunophenotyping (10.104). In general, tumours showing a diffuse (rather than follicular) pattern and larger 'blastic' cells (rather than small lymphoid cells) have a more aggressive course and are regarded as 'high-grade' rather than 'low-grade' lymphomas. Paradoxically, 'high-grade' lymphomas, which include B-lymphoblastic (Burkitt's) lymphoma (p. 32), are curable in a proportion of cases with intensive cytotoxic chemotherapy combined with radiotherapy to 'bulky' areas of disease, whereas the 'low-grade' lymphomas, although compatible with long survival, are not currently curable, though they may be controlled by intermittent 'gentle' chemotherapy with alkylating agents, or with local radiotherapy. The cytotoxic drug of choice is chlorambucil, with or without steroids. Combination chemotherapy may be required in the presence of marrow impairment. Splenectomy may be required if there is hypersplenism.

Important prognostic features in non-Hodgkin's lymphomas include
- Age at onset
- Advanced stage
- Level of peripheral blood white cell count
- Presence of systemic ('B') symptoms.

The majority of non-Hodgkin's lymphomas are B-cell in origin and present with some of the features of CLL. Tumours of small lymphocytes or lymphoplasmacytoid cells may be associated with the production of paraproteins, and an IgM paraprotein may give rise to hyperviscosity problems (Waldenström's macroglobulinaemia, see p. 468).

The rarer T-cell lymphomas tend to be more aggressive. They include mycosis fungoides, a chronic skin lymphoma that progresses from psoriasiform lesions and skin plaques (2.123), sometimes associated with generalized erythroderma, to more generalized lymph node involvement and the appearance of typical convoluted lymphocytes (Sézary cells) in the blood. When the disease is localized to the skin it may run a benign course and be amenable to local therapy with ultraviolet light or radiotherapy or to local or generalized nitrogen mustard. Once it has spread to local lymph nodes the prognosis is bleak, with a median survival time of only 2 years despite intensive combination therapy.
PLATELET DEFECTS

Defects in either the number or the function of platelets may produce easy bruising, epistaxis and intestinal bleeding. Purpura is usually seen only when there is a fall in circulating platelets to around 10–20 x 10⁹/litre from the normal of 200–300 x 10⁹/litre. Bleeding may occur at a level of up to 50 x 10⁹/litre if there has been major surgery or extensive trauma. The causes of thrombocytopenia are numerous and are summarized in 10.105.

There is usually a history of spontaneous bruising and bleeding, especially recurrent bilateral nose bleeds, mucous membrane bleeding in the mouth, persistent menorrhagia and intestinal bleeds. It is important to ask about recent drug therapy. Careful examination is required to identify a basic disease process such as infection, malignancy, liver disease or a connective tissue disorder. The age of the purpuric lesions may give a clue to the duration of the disease. Evidence of splenic enlargement should be sought. Investigations include FBC, platelet count, coagulation screen, bone marrow aspirate and bleeding time.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

ITP is an autoimmune disorder characterized by the accelerated removal of platelets coated with antibody by cells of the reticulo-endothelial system. These antibodies may be found in lymphoproliferative disorders or after infections; rarely, they may be associated with drug therapy. The likelihood of haemorrhage is related to the degree of thrombocytopenia or interference with normal function. Clinically, ITP can be classified as acute or chronic.

In acute ITP, purpura (10.10, 10.106, 10.107), bruises and bleeding appear abruptly, usually in children or young adults. There is often a history of an upper respiratory tract infection in the preceding 2 weeks. Occasionally, there may have been an obvious viral disease such as measles, mumps or infectious mononucleosis. The blood film is usually normal, but may show some atypical lymphocytes. The platelet count is significantly reduced and some platelets may be larger than normal. Bone

<table>
<thead>
<tr>
<th>CAUSES OF THROMBOCYTOPENIA</th>
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<tbody>
<tr>
<td>Infections</td>
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<tr>
<td>Immune</td>
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<tr>
<td>Marrow disorders</td>
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<td></td>
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<tr>
<td>Haemolytic anaemias</td>
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<td>Hypersplenism</td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td>Excess consumption</td>
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10.105 Causes of thrombocytopenia.

10.106 Acute idiopathic thrombocytopenic purpura (ITP) commonly manifests itself with purpuric lesions of this kind, though they may often be more widespread by the time the patient seeks medical attention. It is important to remember that purpura of identical appearance may result from many other causes.

10.107 Diffuse purpuric rash with areas of sheet haemorrhage (ecchymosis) in a patient with thrombocytopenia of unknown cause.
BLOOD

marrow examination shows an increase in megakaryocytes (10.108). Most children have a spontaneous remission in a week or so and few have any serious haemorrhage. If frank bleeding occurs, steroids should be given in a short course. Failure to remit spontaneously or with steroids should lead to re-evaluation for an alternative cause or to consideration of splenectomy, or both.

Chronic ITP is a disease of adults that affects women more often than men. The usual presentation is with progressive purpura, ecchymoses and mucocutaneous bleeding. There may be a history of multiple episodes over many years, or of a concomitant systemic illness, especially an autoimmune disease or lymphoproliferation. Examination shows purpura and ecchymoses, and lesions may also be found in the mouth (10.109) and eye (10.78). The spleen is palpable in only 5% of patients.

The peripheral blood is usually normal unless blood loss has produced anaemia. The platelet count may vary over the years from normal to very low; the level correlates well with episodes of bleeding. Bone marrow aspirate shows normal erythroid and myeloid cell lines with a normal or increased number of megakaryocytes. There may be evidence of increased platelet-associated immunoglobulin with reduced platelet survival. Other diseases should be excluded by appropriate investigations.

Treatment is with steroids, or sometimes cytotoxic immunosuppressive drugs. Splenectomy may be necessary. Temporary remissions to allow surgery can sometimes be gained using high doses of human IgG.

In pregnancy the chief danger is to the fetus, which may be thrombocytopenic as a result of transplacental passage of anti-platelet IgG and thus at risk of cerebral haemorrhage at delivery.

Drug-induced immune thrombocytopenia

Many drugs may be associated with antibody-mediated thrombocytopenia (10.10). There are probably two principal mechanisms

- The drug may bind to the platelet to produce a neoantigen that stimulates an autoantibody
- The drug binds to a plasma protein that is antigenic and the resultant antibody produces an immune complex that binds to the normal platelet Fc receptor.

Drugs that have been implicated in immune-mediated thrombocytopenia are listed in 10.110. Bleeding may range from mild to life-threatening. Stopping the drug usually results in the cessation of signs. Steroids may aid the return of the platelet count to normal.

When this condition is associated with the use of heparin, the bleeding may be extremely severe because of the existing state of anticoagulation of the patient. Protamine sulphate should be given to reverse the action of the heparin, along with steroids to raise the platelet count.

10.108 The bone marrow in idiopathic thrombocytopenic purpura shows numerous megakaryocytes, but few or no platelets are seen on the peripheral blood film.

10.109 Petechiae on the soft palate may be a sign of thrombocytopenic purpura, as in this patient (but it is important to remember that similar transient appearances may occur harmlessly during the course of the common cold or other viral throat infections).

<table>
<thead>
<tr>
<th>DRUGS THAT MAY CAUSE IMMUNE-MEDIATED THROMBOCYTOPENIA</th>
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<tbody>
<tr>
<td>Thiazide diuretics</td>
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<tr>
<td>Gold salts</td>
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<tr>
<td>Heparin</td>
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<tr>
<td>Carbamazepine</td>
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<td>Phenothiazines</td>
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<tr>
<td>Quinine</td>
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<tr>
<td>Rifampicin</td>
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<td>Valproate</td>
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<tr>
<td>Sulphonamides</td>
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<td>Penicillins</td>
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10.110 Drugs that may cause immune-mediated thrombocytopenia.
VASCULAR AND NONTHROMBOCYTOPENIC PURPURA

Integrity of the endothelium is essential to maintain blood within the vascular tree. Abnormalities of the endothelium may be primary or secondary (10.111) and, depending on their nature, extent and site, can give rise to a variety of clinical syndromes.

It is important to elicit any history of easy bruising or bleeding in the family, of epistaxis in childhood or of excessive bleeding after dental extraction, after surgery or during menstruation. Careful examination of the skin is necessary for petechiae, purpura or bruises. Tests of vascular function may be required and biopsy of lesions may give a diagnosis. Often the cause of the defect is not apparent.

CAUSES OF VASCULAR AND NON-THROMBOCYTOPENIC PURPURA.

Primary
- Senile purpura
- Hereditary haemorrhagic telangiectasia
- Giant cavernous haemangioma (10.129)
- Connective tissue disorders, e.g.
  - Ehlers-Danlos syndrome (see p. 150)
  - Marfan's syndrome (see p 150)

Secondary
- Henoch-Schönlein purpura
- Metabolic: scurvy
  - Cushing's syndrome and steroid use (see 7.28)
  - uraemia
  - liver disease
- Dysproteinaemia
- Purpura fulminans
- Embolic purpura
- Mechanical purpura

10.111 Causes of vascular and non-thrombocytopenic purpura.

Senile purpura

Senile purpura is a benign disease of the elderly, in which the characteristic lesions develop on the extensor surfaces of the hands (10.112), forearms and face and neck. The defect is loss of collagen support of dermal capillaries, associated with thinning of the skin. The purple spots tend to stay the same colour over many months before they fade to a brownish colour. They are often called 'age spots'. They are of no significance and are of only cosmetic importance. No treatment is available.

Hereditary haemorrhagic telangiectasia

Hereditary haemorrhagic telangiectasia (also known as HHT or the Rendu-Osler-Weber syndrome) is transmitted as an autosomal dominant trait so both sexes are equally affected. The lesions consist of dilated arterioles and capillaries that are superficial, easily traumatized and likely to ooze (10.113). They blanch on pressure with a glass slide. The most common site is the nasal mucosa, and epistaxis in childhood may be a presenting feature, although the disorder does not usually present until middle age. In the adult, lesions are to be found on the lips, mouth, tongue, face, hands (10.7), oesophagus, stomach and rectum, and more rarely in the eyes, bronchi, and gynaecological and urinary tracts. Bleeding may occur from any of these sites; a common presentation is with recurrent iron-deficient anaemia associated with occult intestinal bleeding. There is an association of this disease with pulmonary arteriovenous fistulae, cirrhosis of the liver, hepatomas and splenomegaly.

10.112 Senile purpura is a common and benign condition that results from impaired collagen production and capillary fragility in the elderly. In the absence of other signs of disease, no investigation is necessary.

10.113 Hereditary haemorrhagic telangiectasia (HHT) is a condition in which occult blood loss in the gut may lead to severe iron deficiency anaemia. The diagnosis is usually clear from a careful clinical examination, although the telangiectases are not always as obvious as in this patient with multiple lesions on the face, lips and tongue. This patient had received multiple blood transfusions over many years because of HHT-associated gastrointestinal blood loss, and he had developed cirrhosis associated with hepatitis B antigen positivity—probably as a result of transmission of hepatitis B virus in transfused blood.
There may also be abnormalities of coagulation factors and platelet function that compound the bleeding tendency. Treatment is difficult because of the diffuse nature of the lesions. If individual lesions can be identified as the source of bleeding, they may be cauterized. Oestrogens may help to prevent epistaxis.

SECONDARY ABNORMALITIES

Henoch–Schönlein purpura
Henoch–Schönlein purpura is an immunological disease in which the vascular endothelium is damaged by the deposition of immune complexes. It may result from reactions to drugs, food, insect bites or bacterial or viral infections. Bleeding may occur into the joints or into the bowel and there is often a generalized skin rash of a diffuse macular type which then becomes purpuric (2.133). Lesions may also be found in the brain and renal tract. The disorder is most common in children, and it usually resolves without complications, but about one-third of patients have an associated glomerulonephritis (see p. 290) and there may be an associated pleurisy, pericarditis or pneumonia.

Scurvy
Scurvy results from deficiency of vitamin C (ascorbic acid) in the diet – from a lack of fresh fruit or vegetables or from their prolonged cooking. It is rarely seen in the Western world except in groups with special problems, such as the isolated elderly, the demented, the alcoholic and food faddists. Deficiency results in failure to synthesize a normal quantity and quality of collagen fibres. Bleeding occurs from the resulting capillary wall weakness.

In babies, subperiosteal bleeding is a common presentation and is usually associated with anaemia. In adults, there may be gingival bleeding (8.22), purpura and perifollicular haemorrhages. Severe deficiency in the adult may result in gastrointestinal and brain haemorrhages. The diagnosis is essentially clinical, and confirmation is obtained by observing the response to added ascorbic acid. Measurement of ascorbate levels in platelets and white cells is possible in specialized laboratories.

Cushing’s syndrome and steroid use (see also p. 313)
Excessive corticosteroids produce thin, friable, easily bruised skin that also contains purpuric spots and ecchymoses (7.27, 7.28). This is a result of the loss of collagen that supports the dermal capillaries. Treatment of Cushing’s syndrome or cessation of steroid therapy results in healing of the lesions.

Mechanical and factitious purpura
Sudden increase in venous pressure from coughing, vomiting, asphyxia or during an epileptic fit may cause leakage of blood even from normal capillaries (1.151, 10.114, 10.115). A similar situation may occur as the result of skin suction, social or professional, or as an attempt deliberately to deceive the doctor by a disturbed patient.

10.114 Traumatic asphyxia may produce severe petechiae and frank haemorrhage. This woman was crushed in a crowd: and on admission was unconscious as a result of cerebral petechiae and oedema. She was treated with steroids and oxygen, but retained widespread skin petechiae and a right subconjunctival haemorrhage when this photograph was taken.

10.115 Petechiae of the sclera and cyanosis of the eyelids developed in another patient with traumatic asphyxia. Similar appearances may develop in children with whooping cough (see 1.151).
DISORDERS OF BLOOD COAGULATION

Blood coagulates by a complex series of reactions (a 'cascade') that involves the sequential activation of otherwise inert factors (proenzymes) in the plasma. A platelet thrombus forms first and is the main component of primary haemostasis; this is stabilized by the fibrin clot that results from the coagulation cascade.

COAGULATION FACTOR DEFECTS

Inborn defects (quantitative or qualitative) have been described in all known coagulation factors, but the clinical presentations tend to be very similar. The most common defects result in haemophilia and Christmas disease (factor VIII and factor IX deficiency, respectively). Both are transmitted as X-linked recessive characteristics and, using gene probes, the unaffected female carriers may be identified and counselled. There is a wide range of clinical severity.

Surprisingly, there is little bleeding at birth, though excessive cord bleeding may be noted, and the signs of excess bruising and internal bleeding usually start to manifest themselves at 6–9 months when the toddler starts to move around and fall. Bleeding may occur in every tissue of the body but the most common bleeding site is into the joints. Acute haemarthrosis causes a sudden onset of acute pain and swelling, associated with signs that are similar to those of

10.116 A typical family tree in haemophilia, showing the X-linked transmission of the abnormal gene. All the daughters of a haemophiliac man are carriers but none of his sons. When the carrier female has children, half of the male offspring have the defective gene and are affected, and half of the daughters are carriers. The clinical severity of the defect tends to run true in individual families. In the rare event of a carrier female marrying an affected haemophiliac the possibility arises of a female with two abnormal X chromosomes. These rare homozygous females bleed. Up to 25% of cases of haemophilia have no previous family history.

10.117 Massive haematoma in a patient with haemophilia. In the absence of major trauma, haematomas of this size always indicate a severe coagulation abnormality. Possible causes include haemophilia, Christmas disease, von Willebrand’s disease and uncontrolled anticoagulant therapy. Internal bleeding is a common accompaniment, and patients require urgent investigation and treatment.

10.118 Massive haematoma of the arm in a patient with haemophilia. A major bleed resulted from very minor trauma. Again, other disorders of blood coagulation can produce a similar appearance.

10.119 Severe haemorrhage after dental extraction is often the first clue to more minor degrees of coagulation disorder and is a common presentation in haemophilia, Christmas disease and von Willebrand’s disease.
acute inflammation — hotness, redness, swelling and pain (10.120). The joint is usually held in a rigid semiflexed position and movement (and examination) is resisted by the patient. Recurrent episodes of bleeding lead to chronic degenerative joint disease which may cause chronic pain in the affected joint, with severe deformity and limitation of movement (10.121–10.123). There is usually atrophy of the surrounding muscle cuff. Compression neuropathy is also common if bleeding occurs around a nerve, for example femoral nerve compression commonly follows bleeding into the ilio-psoas muscle. The most common cause of death from bleeding is cerebral haemorrhage, which produces a range of neurological deficits.

Intrarenal bleeding often produces renal pelvic or ureteric obstruction, which causes colicky abdominal pain associated with haematuria. Bleeding into the bowel wall may produce intestinal obstruction.

Investigation shows a prolongation of the APPT; this finding should be followed up by measurement of the individual factor levels.

Treatment and management of these bleeding defects is best carried out in specialized haemophilia units. The deficient plasma factors are infused intravenously until bleeding stops. Surgery or trauma necessitate the use of appropriate plasma factor cover.

10.120 Acute haemarthrosis of the knee is a common complication of haemophilia. It may be confused with acute infection unless the patient's coagulation disorder is known, because the knee is hot, red, swollen and painful.

10.121 Severe chronic arthritis may occur in patients with haemophilia and Christmas disease as a result of recurrent episodes of haemorrhage into joints. The knee is the most commonly affected joint. Both knees are severely deranged in this patient. Note that he is unable to stand with both feet flat on the floor.

10.122 Genu recurvatum is a severe deformity of the knee that results from destruction of the joint by recurrent haemarthrosis. Note also the presence of acute skin haemorrhage in this haemophiliac patient.

10.123 X-ray of the knees in a patient with haemophilia. The left knee joint has been severely damaged by recurrent haemarthrosis. Note the narrowing of the joint space, the presence of irregular erosions, and the evidence of cyst formation in the tibial head.
As a result of contamination of the source plasma, many patients with these disorders have been infected with HIV and many have developed AIDS. This resembles AIDS in other groups, but Kaposi's sarcoma is a rarity in the profile of HIV disorders in haemophilia. In addition, many patients have chronic active hepatitis as a result of transmitted viral hepatitis.

Von Willebrand's disease is a group of similar types of bleeding disorders to haemophilia but is wholly transmitted by an autosomal recessive route and thus affects both men and women. There is a greater range of severity from symptomless to severe. The main defect is in the synthesis of von Willebrand factor, and this produces abnormalities of platelet function and of low levels of factor VIII coagulant activity. Clinical presentation is mainly with bleeding, usually from mucosal sites, especially from the genital, renal and alimentary tracts. Severely affected patients can also bleed internally into the joints and brain, but bleeding into joints is unusual. Diagnosis is made by finding prolongation of the skin bleeding time, a platelet functional defect and a low level of factor VIII.

Minor degrees of bleeding may be controllable with tranexamic acid or vasopressin preparations, but more serious bleeding requires treatment with cryoprecipitate or plasma.

**DEFICIENCY OF VITAMIN K**

Lack of vitamin K in the diet, its malabsorption or the presence of anticoagulant drugs of the coumarin group leads to deficient hepatic synthesis of the plasma clotting factors, prothrombin, and factors VII, IX and X. Vitamin K is the cofactor necessary for the carboxylation and thus biological activation of glutamic acid. Deficiency from any of these causes can result in a bleeding tendency which may be seen in:

- Haemorrhagic disease of the newborn
- Intestinal malabsorption, for example Crohn's disease, coeliac disease
- Hepatobiliary disease, for example hepatic failure, obstructive jaundice
- Dietary deficiency
- Oral anticoagulant usage.

**Haemorrhagic disease of the newborn**

In the premature or immature infant there is defective synthesis of the vitamin K-dependent factors, which are significantly lower than those in adult life. Bleeding results on the third or fourth day of life, usually into the skin or internal organs. It is usual to give vitamin K parenterally at birth to prevent bleeding, but this policy is currently under review.

**Malabsorption and dietary deficiency**

These are extremely common and result from a range of disorders of the gut (see p. 372) and pancreas, and from obstructive biliary tract disease. They are usually part of a mixed clinical picture and other features often dominate. The problem is often picked up on routine screening, for example before liver biopsy, or by excessive bleeding after a minor surgical procedure. Very occasionally, severe bleeding may occur from the skin, mucous membranes and the gastrointestinal tract, and in this situation it is common to find coincidental deficiency of vitamin C. Vitamin K by injection will reverse the biochemical lesion in malabsorption, but if there is serious liver cell necrosis it may not be effective.

**Use of oral anticoagulants**

Oral anticoagulant drugs (coumarins) such as warfarin, inhibit the action of vitamin K and result in the production of defective molecules of factors II, VII, IX and X which lack clotting activity. For normal therapeutic purposes, this depression of coagulation is maintained by testing the patient's plasma using a modification of the prothrombin time (the International Normalized Ratio; INR). It is usual to extend this to 2-3 times that of a normal control. Only when this value is exceeded is bleeding likely to occur, and this may be from or into any tissue of the body. Patients who have been stabilized on a particular dose of warfarin often bleed because other drugs have been taken that interfere with the coagulation mechanism (e.g. aspirin interferes with platelets), displace warfarin from its binding site on the albumin molecule (e.g. mefenamic acid), or decrease its metabolism (e.g. cimetidine). Bleeding often occurs early in the skin (10.117, 10.118, 10.124), bowel or urinary tract and patients must be instructed to maintain careful observation and seek advice if signs of bleeding appear. Always consider the possibility of undeclared anticoagulant therapy in a bleeding patient. All patients receiving oral anticoagulant therapy must be supervised in a specialized anticoagulant clinic.

10.124 Spontaneous black eye in a patient on poorly controlled anticoagulant therapy. He reported no trauma to his eye, and his INR was grossly elevated. More massive bleeding may also result from uncontrolled anticoagulant therapy (see 10.117, 10.118).
Parenchymal liver disease
Necrosis of liver cells as a result of hepatitis or alcohol or other toxins results in failure of coagulation factor synthesis, and severe bruising or bleeding may result (9.14). The defect is usually complex and may be associated with thrombocytopenia (see p. 457) and DIC (see below). Defects of the vitamin K-dependent factors may not respond to the injection of vitamin K in this situation.

THROMBOPHILIA
Proteins C and S are vitamin K-dependent proteins that are synthesized in the liver, and are critical regulators of activation of blood coagulation. A range of hereditary deficiencies in the production or activity of these proteins has been described, and these are associated with the likelihood of venous thromboembolism.

In its activated form protein C(a) destroys both factor V and VIIIc. Activation of protein C is via thrombin generation in the presence of endothelial-bound thrombomodulin. Functional activity of protein C should be measured routinely in patients with deep vein thrombosis, especially if other family members have also been affected.

Protein S serves as a cofactor for activated protein C and is an important regulator of coagulation in its own right. Protein S is found in plasma in both a free form and attached to C1b complement.

Acute skin necrosis may result when patients with protein C deficiency are given warfarin (10.125). This can begin dramatically with rapid onset of gangrene and extensive sloughing due to small vessel thrombosis resulting from the warfarin-induced reduction of protective protein C. Treatment is to stop warfarin and start heparin. Skin grafting is often necessary as the slough separates.

Antithrombin III (AT III) is the most important antithrombin in the plasma and also has a major protective role against coagulation activation products at all stages in the coagulation cascade. Its activity is enhanced many hundred-fold by binding with heparin. Deficiency of AT III is found in 1 in 4000 of the population and is associated with an enhanced tendency to recurrent venous thrombosis and pulmonary embolism. It may also run in families, so an accurate family history is essential. Symptoms of venous thrombosis usually occur in the late teens and affect the deep veins of the legs.

The diagnosis is easily made in the laboratory by measurement of AT III levels and treatment is with lifelong oral anticoagulants. A determined effort should be made to measure AT III levels in other family members.

DISSEMINATED INTRAVASCULAR COAGULATION
DIC (also known as consumption coagulopathy) occurs when the coagulation cascade is activated by a stimulus that results in the widespread deposition of fibrin–platelet thrombi in the arterial and venous tree. This in turn stimulates secondary fibrinolysis and, as the two processes continue in parallel, the end result is depletion of platelets, consumption of clotting factors, loss of haemostasis and excessive bleeding. A large number of conditions may be the stimulus to production of acute or chronic DIC (10.126–10.129 and see 10.130).
Patients suffering from acute DIC present with a dramatic illness with haemorrhagic manifestations. They are usually severely ill, with fever, acidosis, and hypoxia and hypotension caused by severe blood loss. There may be extensive petechiae or frank bleeding into the skin (1.62, 1.111, 10.126), especially at sites of trauma, for example wounds, venepuncture sites or under a blood-pressure cuff. There may also be bleeding in the eyes (1.111, 1.190) and the alimentary, respiratory, genital or renal tracts. On occasions, thrombosis may dominate the initial picture, and there may be gangrene of skin and digits (10.131), with signs of ischaemia of heart, brain, kidneys and lungs.

**CAUSES OF DIC**

| Infections/infectious diseases: | Haemorrhagic fevers (see pp. 22, 26), meningococcal septicaemia (see p. 26), other septicaemia, malaria (see p. 64), etc. |
| Obstetric causes: | Amniotic fluid embolism, pre-eclampsia, abruptio placenta, dead fetus syndrome |
| Malignant disease: | Especially lung, pancreas, ovary, prostate, acute leukaemias |
| Shock: | Traumatic, cardiac arrest, blood loss, extensive burns |
| Intravascular haemolysis/massive blood transfusion | Envenomation Vasculitis: e.g. haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) |
| Extracorporeal circulation: | E.g. cardiopulmonary bypass, artificial heart, dialysis |

**10.127 DIC resulting from staphylococcal septicaemia in a 56-year-old man.** Note the characteristic skin haemorrhage ranging from small purpuric lesions to larger ecchymoses. The patient had non-insulin-dependent diabetes, and the septicaemia developed from an untreated large boil on his thigh.

**10.128 Snakebites and other venomous bites and stings are a potent cause of DIC.** Adder bites in Europe rarely cause more than the severe local swelling experienced by this man, but envenomation by many other snakes and animals commonly causes DIC, and this may lead to death. Snakebite remains an important cause of death worldwide, especially in developing countries.

**10.129 Cavernous haemangiomas may be associated with DIC (the Kasabach-Merritt syndrome).** The damaged subendothelial surface of the neoplasm leads to excessive consumption of circulating platelets and clotting factors, which may result in the full clinical picture of DIC. Occasional diagnostic difficulty results from the presence of a visceral haemangioma with similar properties. Surgical excision, injection of multiple therapeutic emboli under angiographic control or radiotherapy may be successful in eliminating the lesion and the consumptive coagulopathy.

**10.130 Causes of DIC.**
A specialist haematology laboratory should look for evidence of coagulation consumption, fibrinolysis and platelet activation. A routine blood film may show fragmentation of red cells (a microangiopathic haemolytic blood picture, 10.132) that results from cell damage by strands of fibrin thrombus. Simple screening tests for DIC include the platelet count (which is reduced), the APPT (which is prolonged) and the presence of fibrinogen–fibrin degradation products that have resulted from fibrin digestion. The cause of the process (10.130), should be identified and treated whenever possible. The other keystones of treatment are

- General intensive support of the patient
- Restoration and maintenance of the peripheral circulation
- Replacement therapy with plasma or plasma products.

Control of the thrombotic component with heparin is rarely useful, and is complicated by the effects of some heparins on platelets.

Chronic DIC occurs in some patients with chronic inflammatory or malignant disorders, and is characterized by a combination of features relating to thrombosis as well as bleeding. On investigation, fibrinogen, cryofibrinogen and fibrinogen-fibrin degradation products (FDP) levels are all high.

10.131 Peripheral gangrene can be a feature of DIC, as the balance between thrombosis and haemorrhage will vary from one part of the body to another and from time to time. This patient has meningococcal septicaemia, and despite his gangrenous toes he had haemorrhagic manifestations elsewhere in his body (see 1.111, 1.112, 10.126).

10.132 The peripheral blood film in DIC usually shows a microangiopathic haemolytic picture. Abnormal red cells, including burr cells, acanthocytes with multiple sharp projections and schistocytes of irregular fragmented shape, result from physical damage to the cells caused by their passage between strands of fibrin. The platelet count is reduced. This patient presented with acute renal failure and hypertension.

MULTIPLE MYELOMA AND RELATED PARAPROTEINEMIAS

The paraproteinaemias are a group of disorders in which there is proliferation of B cells leading to excessive production of immunoglobulins. Of these conditions, multiple myeloma is the most common and results from the neoplastic proliferation of mature and immature plasma cells. It is usually a disease of the middle-aged and elderly. The clinical features result from the uncontrolled growth of plasma cells in the marrow and the production of an abnormal paraprotein – usually an IgG, but sometimes IgA or light chains and rarely IgD, IgM or other group – to give

- Lytic bone lesions resulting from local infiltration of bone, associated with hypercalcaemia (see p. 155) and painful pathological bone fractures
- Bone marrow failure from infiltration, leading to anaemia, leucopenia and thrombocytopenia
- Suppression of normal immunoglobulin synthesis, with resultant susceptibility to infections
- Hyperviscosity syndromes caused by the physical properties of the paraprotein (M-protein); these are most common with IgG paraprotein and result in tissue ischaemia with overt arterial and venous thrombosis predominantly in the eye (10.69), heart, brain and kidneys
- Renal impairment, which is common and is a critical factor in life-expectancy (p. 297); the kidney is damaged by hypercalcaemia, infection, deposition of amyloid, the deposition of light-chain fractions in the proximal tubules and hyperuricaemia
- Neurological involvement, which results from ischaemia associated with hyperviscosity and from amyloid deposition.

Patients present with infections (70%), bleeding defects (10%) or renal failure (50%). Bone pain develops in all patients as the disease progresses.

Suggestive features of myeloma include a very high ESR (usually over 100 mm in the first hour), a normochromic normocytic anaemia with rouleaux formation (10.30), and often neutropenia and thrombocytopenia. The serum
calcium levels are often elevated.

The diagnosis can be made by finding evidence of two factors out of the following three: paraproteinaemia, bone marrow plasmacytosis and lytic lesions of bones.

- Paraprotein may be found in serum or urine (Bence-Jones-protein, 10.133)
- Bone marrow aspiration or trephine shows sheets of plasma cells (10.134)
- Plain X-rays of the skeleton show 'punched out' areas, especially in skull (10.135), ribs, pelvis and long bones (10.136); there may also be pathological fractures.

A range of other investigations aid prognosis.

10.133 Serum and urine electrophoresis in multiple myeloma provide evidence of the presence of a paraprotein in serum and urine. In this case, the patient had IgA myeloma; the paraprotein band shows clearly in the urine (arrows) and a corresponding band is present in the serum.

10.134 Bone marrow film in myeloma. This view is taken from the outer edge of the marrow smear to show individual cells. The marrow is generally hypercellular and contains an excess of diverse plasma cells (myeloma cells). Some are large, with immature-looking chromatin; others are small with clumping of chromatin. The cytoplasm is often pale, and Russell bodies are present in the cytoplasm, representing accumulations of IgG.

10.135 Myeloma lesions in bones show up as characteristic 'punched out' lesions without surrounding sclerosis. Secondary deposits from other tumours may occasionally give a similar appearance, but this appearance on skull X-ray is strongly suggestive of multiple myeloma.

10.136 Myeloma in the humerus, scapula, clavicle and ribs. The lesions have the same 'punched out' appearance as those seen in the skull. Myeloma lesions are also commonly seen in other long bones, in the ribs and the pelvis. Pathological fractures may occur, and hypercalcaemia is common.
Treatment of patients with multiple myeloma is supportive, with antibiotics for infection, analgesics for bone pain, a high fluid intake and effective management of hypercalcaemia. Hyperviscosity and cryoglobulinaemia may be managed by plasma exchange until the tumour mass can be controlled with either melphalan or cyclophosphamide or with radiotherapy for local lesions.

The overall median survival remains about 2 years despite widespread use of chemotherapy. Poor prognostic features include increasing age, a very high ESR and elevated serum creatinine at the time of diagnosis.

SOLITARY PLASMACYTOMAS

In a small number of cases of paraproteinaemia (7%) there is a localized plasma cell proliferation and the marrow elsewhere is normal. Such local plasmacytomas may arise in bone or in soft tissues and may grow to a large size before being diagnosed. Diagnosis is made by finding a solitary lytic lesion of bone, with an abnormal M-protein on electrophoresis, histological evidence of plasma cell tumour on biopsy and normal marrow at a distant site. Surgical removal or radiotherapy may produce a cure with a rapid disappearance of the M-proteins.

WALDENSTRÖM’S MACROGLOBULINAEMIA

Waldenström's macroglobulinaemia is a condition characterized by the presence of monoclonal IgM in association with excessive numbers of tissue lymphocytes and plasma cells (lymphocytic lymphoma with plasmacytoid differentiation). This is a disease of the elderly with a male preponderance of 2:1. The common presentation is with fever, anaemia, weight loss, weakness and fatigue. Bleeding may occur as a result of qualitative platelet defects and usually manifests as epistaxis, skin petechiae and gastrointestinal haemorrhage. Hyperviscosity features may dominate the picture and result in strokes, myocardial infarction, loss of vision, Raynaud’s phenomenon and pyoderma gangrenosum (2,135).

Bence–Jones protein may be found in the urine and amyloid may develop. The lymphocytic infiltrate may cause hepatomegaly and splenomegaly, but can occur in any other body tissue. Osteolytic lesions are rare.

Investigations show a normochromic normocytic anaemia with rouleaux formation on the blood film (10.30). There may be leucopenia but more usually there is an atypical lymphocytosis. The ESR is characteristically elevated to above 100 mm in the first hour. Bone marrow shows a generalized diffuse lympho-plasmacytoid infiltrate with excess eosinophils. Such appearances may also be found in the peripheral lymph nodes. Examination of the serum shows an abnormal M-protein, cryoglobulin, and cold-reacting antibodies.

Treatment should be aimed at the hyperviscosity that dominates the clinical picture. This may be altered by haemodilution or plasmaphaeresis. Chemotherapy with chlorambucil, cyclophosphamide or melphalan may be helpful. Supportive management is required for haemorrhage, anaemia, infections and cold-precipitation syndromes.

BENIGN MONOCLONAL GAMMOPATHY

A monoclonal paraprotein sometimes appears in the absence of a detectable B-cell tumour. Some patients develop this paraprotein transiently in response to an infection such as viral hepatitis or leptospirosis, in an autoimmune disease such as rheumatoid arthritis, and occasionally in non-B-cell tumours. In other patients there is a stable benign paraproteinaemia that remains unchanged for many years, except in a small number who develop an overtly malignant plasma-cell myeloma.

Investigations should be directed at the underlying cause: non-B-cell malignancy, infection or autoimmune disease. Bence–Jones proteins and M-band proteins are present. A level of paraprotein below 10 g/litre usually indicates a benign cause. There is no marrow infiltration or immunosuppression, and no lytic bone lesions. Patients should be followed-up carefully over many years, as 10% develop overt myeloma. No specific treatment is necessary initially. Because the outcome is now realized not to be always 'benign', the term monoclonal gammopathy of undetermined significance (MGUS) is now being used.

CRYOGLOBULINAEMIA

Malignant paraproteinaemias may be associated with the presence of circulating cryoglobulins (i.e. globulins which precipitate out when blood is cooled). They may also be found in rheumatoid arthritis, systemic lupus erythematosus, infectious mononucleosis, lymphoma and primary biliary cirrhosis. This most commonly causes problems in the limbs and the resultant

10.137 Skin infarction in cryoglobulinaemia. There is a reticulated pattern to the skin due to leakage of red cells from damaged skin capillaries. Necrosis and ulceration has occurred in peripheral sites due to vessel blockage. This patient eventually required plastic surgery.
deposition on the walls of small vessels produces a generalized vasculitis, which presents with a reticular pattern of microthrombosis, and usually larger areas of gangrene, which eventually slough and require skin grafts (10.137). In more severe cases infarction of internal organs, especially the kidneys, may occur. There is also a high incidence of venous thrombosis, pulmonary embolism and other arterial occlusion.

Treatment is with plasmapheresis to reduce the levels of circulating cryoglobulins and also to reduce the blood viscosity due to IgG and IgM. This may allow time for appropriate chemotherapy to control the underlying pathology.

**BLOOD TRANSFUSION**

The availability of blood components for transfusion underpins the management of major elective surgery, many medical emergencies and the supportive therapy necessary in marrow failure.

Red cell grouping and crossmatching before transfusion is essential. Selection of red cells of the correct ABO group is the prime concern, as an ABO-mismatched transfusion can result in a catastrophic immediate transfusion reaction with intravascular haemolysis, consumptive coagulopathy (DIC) and renal failure. Delayed haemolytic transfusion reactions, with extravascular haemolysis, are more common with antibodies to other red cell antigens, including Rh antigens, and give rise to jaundice and anaemia over several days.

Febrile transfusion reactions are common especially after multiple transfusions. They are often related to the development of antibodies to HLA antigens present on white cells and platelets, and can be largely avoided by removing white cells, for example by using in-line white cell filters at the time of transfusion (10.138).

Routine screening of donors now means that the risk of transmission of known viruses such as HIV and hepatitis B has been greatly reduced. However, hepatitis C is still a hazard, and blood products should be used only with good reason; red cell transfusions for chronic anaemia that can be treated, albeit more slowly, with haematinics, should be avoided unless the patient is clinically compromised.

**COMPLICATIONS OF BLOOD TRANSFUSION**

Despite the acknowledged value of blood transfusion in a wide range of life-saving procedures, it is not generally realized how common and severe the side effects may be. The need for blood transfusion should always be questioned. Side effects may include:
- Circulatory overload
- Febrile nonhaemolytic reactions
- Urticaria
- Anaphylaxis
- Mismatch of cells, with haemolysis and renal failure
- Transmission of bacteria
  - *Escherichia coli*
  - *Staphylococcus aureus*
  - *Yersinia enterocolitica*
  - *Pseudomonas sp.*
  - *Treponema pallidum*
- Transmission of viruses
  - HIV
  - Hepatitis viruses
  - Cytomegalovirus
  - HTLV - 1
- Transmission of protozoa
  - Malaria
  - *Leishmania*
- Transfusion haemosiderosis
- Graft versus host disease.

10.138 Blood transfusion. This patient receives regular monthly blood transfusions for refractory sideroblastic anaemia. Multiple transfusions may lead to sensitization to the white cell (HLA) antigens, with resulting febrile transfusion reactions. These can be greatly ameliorated by passing the blood through a white cell filter such as the Sepacell filter shown 'in line' here. This patient was also receiving regular overnight subcutaneous infusions of desferrioxamine to deal with the iron overload inevitable with a chronic blood transfusion regimen.
Common neurological disorders, as seen in a nonspecialist setting.

<table>
<thead>
<tr>
<th>Principal presentation</th>
<th>Relative frequency in family practice (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache or migraine</td>
<td>37</td>
</tr>
<tr>
<td>Vertigo</td>
<td>25</td>
</tr>
<tr>
<td>Stroke or transient ischaemic attack</td>
<td>20</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>10</td>
</tr>
<tr>
<td>Tremor or rigidity (parkinsonism)</td>
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</tr>
<tr>
<td>Features suggesting multiple sclerosis</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
</tr>
</tbody>
</table>

NERVOUS SYSTEM

HISTORY

Consultations for neurological disorders are relatively common in general or family practice. Headache is the most common presentation, but other disorders are also seen quite frequently (11.1).

Important facets of the history in a patient with neurological symptoms include:

- higher cerebral dysfunction — dementia, confusional states and coma are common features and are the end results of a large number of acute and chronic neurological diseases
- fits: a wide range of epileptic phenomena may result from neurological diseases, including generalized or partial seizures, and are often best described by family or friends rather than the patient
- headache, the causes of which include tension, stress, migraine and cranial arteritis; space-occupying lesions cause headache that is often worse on waking and on coughing or bending; there may be associated vomiting; it is particularly important to define site of pain, exacerbating factors, radiation of pain and duration
- loss of power results from abnormalities of the upper or lower motor neuron in the brain or cord as well as disorders of the neuromuscular junction and muscle; loss of power may be of acute or gradual onset; lower motor neuron lesions result in localized muscle atrophy; upper motor neuron lesions result in spasticity that produces a typical gait
- vertigo is the feeling that the surroundings are moving; it reflects disease of the labyrinth or vestibular connections; dizziness is a common symptom — the patient usually implies unsteadiness or lightheadedness
- abnormal movements: a variety of tremors may suggest a diagnosis, for example the typical ‘pill rolling’ tremor of Parkinson’s disease, or the coarse flapping tremor associated with liver, respiratory or renal failure; in contrast are the coarse movements of chorea, athetosis and hemiballismus; these are the result of extrapyramidal lesions
- cerebellar ataxia may produce a loss of fine control of movement that results in dysmetria, dyssynergia and a broad-based gait, with a tendency to fall to the side of the lesion if it is unilateral; there are usually other symptoms and signs of the cerebellar lesion, including diplopia, dysarthria and hypotonia; sensory ataxia results from lesions of the sensory pathways in the peripheral nerves or spinal cord and produces a stamping gait; there is compensation from visual stimuli and when the eyes are closed the problem is exacerbated
- recent head injury may lead to transient or progressive neurological disorder; subdural haematomas may lead to symptoms many weeks after the original injury, which may only be recalled on close questioning
- general medical, occupational, social and family history — all of which may point to underlying causes for neurological symptoms.
EXAMINATION

Knowledge of the anatomy and physiology of the brain, spinal cord and peripheral and autonomic nervous system is essential before embarking on CNS examination.

Appropriate tests must be planned and carried out with care, in an attempt to localize any focal lesions and assess possible causes.

GENERAL ASSESSMENT

It is important to observe the patients and their movements. Their posture and gait may reveal abnormalities (11.2–11.4); they may show signs of personal neglect or psychiatric disorder; there may be signs of systemic disease, or of local abnormalities.

HIGHER CEREBRAL FUNCTION

Aspects of higher cerebral function often become obvious from the history, but the examination should include observations on conscious level, orientation in time and space, general level of intelligence, mental state, general attitude, speech and memory. Most of these functions can be quantified when necessary, using rating scales. Apraxia (11.5) and agnosia may be revealed by appropriate tests. Cognitive function can be rapidly screened using the mini-mental state examination and other rating scales, before a more detailed assessment.

SYSTEMATIC EXAMINATION

The upper and lower limbs and trunk must be examined systematically to assess motor power, sensation, the extrapyramidal system and the cerebellum. In each muscle group, assess
• muscle bulk, and look carefully for trophic changes and involuntary movements
• tone — spastic (clasp knife) or plastic (lead pipe)
• power
• reflexes: superficial and tendon
• coordination.
In any abnormality it must be decided whether the upper or lower motor neuron is involved. Upper motor neuron lesions produce weakness of arm extensors and leg flexors (a ‘pyramidal’ pattern). Lower motor neuron lesions produce a deficit in a root or nerve distribution. Patients with polyneuropathies usually present with distal weakness. Abnormal movements suggest probable extrapyramidal involvement.

Lesions of the cerebellum result in loss of tone, incoordination, altered posture, speech defects and nystagmus.

If patients have sensory symptoms, the following sensory modalities must be tested carefully. The functions to be tested include
• tactile sensation and discrimination
• pain and deep pain
• temperature
• vibration (10.36)
• proprioception
• two-point discrimination, stereognosis, and graphaesthesia if cortical lesions are suspected.

11.2-11.4 Posture and gait can provide important clues to neurological diagnosis. Both these patients have Parkinson’s disease. The patient in 11.2 and 11.3 demonstrated rigidity and poverty of movement. Note his stooped posture and the typical position of his arms, which are held slightly flexed at the sides. The patient in 11.4 has a typical parkinsonian gait. He finds it difficult to initiate movement and walks with small shuffling steps. To stop himself falling forward he flexes his knees, and the forward movement on the forepart of the foot gives rise to a characteristic ‘festinant’ gait.

11.5 Apraxia is the inability to perform a familiar action that cannot be attributed to physical disability, incomprehension or agnosia. This patient has dressing apraxia, associated with thromboembolic stroke that followed myocardial infarction. Apraxia results from higher cerebral dysfunction. Note the recent insertion of a cardiac pacemaker – treatment for a conduction defect that followed the myocardial infarction.
CRANIAL NERVES

I. Olfactory nerve
Chemoreceptors are present in the mucosa on the roof of the nose and pass through the cribriform plate in the ethmoid to synapse in the olfactory bulb. Secondary fibres then pass via the olfactory tract to the olfactory cortex on the anteromedial temporal lobe. Loss of smell (anosmia) may result from lesions of the
- mucosa, for example the common cold
- cribriform plate, for example fracture
- olfactory tract, for example space-occupying lesions
- rarely, temporal lobe, for example space-occupying lesions, haematoma, or trauma.
The nerve is tested by asking the patient to smell a scent. Lesions may be unilateral or bilateral. Parosmia is a distorted sense of smell.

II. Optic nerve
From an inverted image on the light-sensitive cells of the retina, the impulses pass via the optic nerves to the optic chiasma; at the decussation, fibres from the nasal side of the retina cross to the contralateral optic tract, whereas the temporal retinal fibres remain uncrossed. The optic tracts then pass to the lateral geniculate body where they synapse. The optic radiation fibres sweep posteriorly through the temporal and parietal lobes to the occipital cortex. The left half of the field of vision is represented in the cortex of the right hemisphere and vice versa. Some fibres from the optic tract do not synapse at the lateral geniculate body but pass directly to the midbrain as the afferent limb of the pupillary light reflex.

Full examination of the second nerves should include examination of the eyes (11.6), including the retina, and an assessment of
- visual acuity — using Jaeger or Faculty of Ophthalmologists' charts for near vision or Snellen test type for distance vision
- Fields of vision by confrontation and perimetry (11.7)
- Colour vision by Ishihara plates is required for individuals in many occupations
- Pupillary reflexes — to light and accommodation.
The Argyll Robertson pupil (11.8) is the hallmark of neurosyphilis and is now very rare. The pupil is small, irregular and reacts to accommodation but not to light directly or consensually. The abnormality is present bilaterally.

11.6 Unilateral proptosis resulted from a meningioma on the sheath of the optic nerve in this patient. A similar appearance may develop in Graves' disease (see p. 323), but exophthalmos is usually bilateral in that condition.

11.7 Visual field testing, using the Humphrey computer-based printout. The patient had advanced acromegaly, with bitemporal hemianopia as a result of compression of the optic chiasma by an enlarging pituitary tumour. In the earlier stages of tumour enlargement, asymmetric bitemporal upper quadrantic defects are typical.

11.8 Argyll Robertson pupils are a feature of tertiary neurosyphilis. They are usually bilateral, but the abnormality was more marked in this patient's left eye. Argyll Robertson pupils are small, irregular and unresponsive to light, but they react normally on accommodation if the patient's visual acuity is adequate. They may also be found in patients with diabetes mellitus.
The Holmes–Adie pupil (11.9) is characterized by a delayed or absent response to light and to accommodation. Once constricted it dilates only very slowly. The lesion may be unilateral and it may be associated with bilateral absent or diminished tendon reflexes.

Horner's syndrome (4.173, 11.10) results from paralysis of the cervical sympathetic nerve. Sympathetic supply to the pupil leaves the CNS in the lower cervical and upper thoracic portions of the cord, emerges in the first thoracic nerve root and runs via the sympathetic chain and along the internal carotid artery to the cavernous plexus and then via the ophthalmic division of the trigeminal nerve to the eye.

Any disorder that interferes with the integrity of the pathway causes Horner's syndrome, which comprises ptosis, pupillary constriction (miosis), enophthalmos and loss of sweating on one-half of the face and neck (anhidrosis). The common causes of Horner's syndrome are shown in 11.11.

III, IV and VI. Oculomotor, trochlear and abducens

The oculomotor, trochlear and abducens nerves together control the muscles of ocular movement.

Lower motor neuron lesions may lead to defective movements, squint, diplopia and pupillary abnormalities.

• Oculomotor lesions: ptosis is present, the eyeball is rotated downwards and outwards, and the pupil is dilated and fixed (3.79, 11.12, 11.13); unilateral pupillary dilatation may be the sole manifestation of an early lesion.

• Trochlear lesions cause impaired downward movement – diplopia occurs on looking down (11.14).

• Abducens lesions cause convergent squint with inability to move the eye outwards and diplopia on trying to look outwards (7.9, 7.94, 11.15).

The differential diagnosis of ptosis includes

• third nerve palsy
• posterior communicating artery aneurysms (see p. 500)

11.9 Holmes–Adie pupil in the right eye of a young woman. The affected pupil is 'tonic', that is it responds slowly to light and accommodation, but on rapid testing will appear unresponsive. The site of the lesion is usually obscure, but the condition is benign. There may be associated areflexia.

11.10 Horner's syndrome. Note the characteristic ptosis of the left eye, associated with constriction of the pupil (miosis). This patient had syringomyelia, but Horner's syndrome has many possible causes (11.11).

11.11 Disorders causing Horner's syndrome.

11.12 & 11.13 Third nerve palsy. Note the complete right ptosis. In the resting position, the right eye was rotated laterally and downwards, but in 11.13 the patient is looking to the left, and the right eye has rotated to the mid position, demonstrating that the trochlear (fourth) nerve is intact. This patient's third nerve palsy was the result of compression by an aneurysm of the posterior communicating artery.
- myasthenia gravis (see p. 517)
- Horner's syndrome (see p. 474).

V. Trigeminal nerve
Lesions of the trigeminal nerve lead to loss of sensation in the skin of the face and crown of the head (11.16), the conjunctivae and the nasopharynx. The angle of the jaw is spared as this is supplied by the second cervical nerve. There is also diminished secretion by the lacrimal and salivary glands, which results in dry eyes and mouth, and trophic ulceration may be found in the cornea, nose and mouth. The corneal reflex is lost. The distribution of the first division of the fifth nerve is graphically demonstrated in ophthalmic herpes (1.86).

If the motor branch is involved, there is weakness and wasting of the muscles of mastication and, if this is unilateral, the jaw deviates to the affected side on opening the mouth.

VII. Facial nerve
The facial nerve is almost entirely motor in function, supplying all the muscles of the face and scalp except for the levator palpebrae superioris. Paralysis leads to loss of facial expression and movement.

In supranuclear paralysis only the lower part of the face is involved because of the bilateral upper motor neurone innervation of the forehead. In infranuclear (lower motor neurone) paralysis both the upper and lower parts of the face are involved equally (11.17, 11.18).

Bell's palsy is the most common cause of infranuclear palsy of the facial nerve. The nerve is often involved around the stylomastoid foramen, but symptoms and signs depend on the site of nerve involvement. The onset is usually acute. There is a rapid onset of unilateral paralysis of the muscles of facial expression and occasionally some pain behind the ear. Taste
sensation from the ipsilateral anterior two-thirds of the tongue may be lost, and there may be undue sensitivity to sounds (hyperacusis).

On the affected side, there is drooping of the corner of the mouth, with loss of skin creases and folds, particularly the nasolabial fold, and of the furrows on the forehead; the eye will often not close and attempts to close it result in it rolling upwards (Bell's phenomenon). Tears tend to run down the cheek as the lower lid sags and because of paralysis of the lip muscles, saliva dribbles from the corner of the mouth and food collects between the cheeks and gums.

The cause is possibly viral but unknown. Diagnosis is made on clinical grounds, and electromyography may be of some value in detecting interruption in the continuity of nerve fibres.

The disease is usually self-limiting and most patients recover in a few weeks. There is no specific treatment but local measures to prevent exposure keratitis are of value, and local massage and splinting may be of use. Steroids are often prescribed.

Other lesions of the facial nerve may produce similar symptoms and signs, for example mononeuritis (7.94), trauma and compression by tumours such as acoustic neuromas.

The Ramsay Hunt syndrome (1.88, 11.19) results when herpes zoster affects the geniculate ganglion of the seventh nerve. Patients present with severe pain in the ear and a facial palsy on the same side. There may be a herpetic rash in the external auditory meatus and in the pharynx.

VIII. Vestibulocochlear nerve
Two sets of fibres run in the vestibulocochlear nerve which serves the cochlea (for hearing) and the labyrinth and semicircular canals (for balance). Patients with lesions of the nerve may present with tinnitus, hyperacusis, deafness and dizziness.

Acoustic neurofibromas (neuromas) may develop at the cerebellopontine angle and present with insidious onset of unilateral deafness, headache, tinnitus, vertigo, ataxia, loss of sensation on the face resulting from trigeminal compression and facial weakness caused by compression of the facial nerve. Signs of a unilateral cerebellar lesion, including nystagmus, soon appear; there may be raised intracranial pressure with papilloedema. In advanced cases hydrocephalus, long tract signs and coma may develop.

Skull X-ray with special views shows widening of the internal auditory meatus but diagnosis is best made by CT scan or MRI (11.20, 11.21, 11.60, 11.131), which clearly show the site and extent of the lesion.

IX, X and XI. Glossopharyngeal, vagus and accessory
The glossopharyngeal, vagus and accessory nerves can be considered together. The glossopharyngeal nerve (IX) is predominantly sensory and supplies the posterior third of the tongue, palate, pharynx and fauces. The motor supply to this area is the vagus (X), which also supplies the oesophagus. The accessory nerve (XI) is purely motor, supplying the larynx and pharynx as well as fibres for the sternomastoid and trapezius.
Disorders of these nerves result in paralysis of the soft palate with regurgitation of fluids through the nose, difficulty in swallowing (11.16), change in the voice – which may become deeper and hoarse – and a diminution of coughing. Palsy of the accessory nerve leads to difficulty in flexion or extension of the neck and in shrugging the shoulders (11.22).

The left recurrent laryngeal nerve branch of the vagus is particularly liable to damage as it loops round the aorta and runs a long course back up to supply sensation and motor fibres to the larynx below the level of the vocal cords. Lesions of this branch result in dysphonia (4.174) and a 'bovine' cough.

XII. Hypoglossal
The hypoglossal nerve is wholly motor, supplying the tongue and the depressors of the hyoid bone. Lesions of the nerve result in unilateral paralysis, wasting and fasciculation of the tongue, which is pushed over to the paralysed side when put out (11.23).

INVESTIGATIONS
As in other systems, investigation of abnormalities in the CNS starts with simple investigations that lead to more specific tests to define the site and nature of the lesion and its consequences. These tests are usually more expensive, more invasive or both, and they must be selected with care.

HAEMATOLOGY
A simple Coulter printout of the profile of absolute values may show evidence of polycythaemia (in a stroke patient), anaemia and macrocytosis (in a patient with subacute combined degeneration), macrocytosis and thrombocytopenia (in alcoholism). A high ESR or plasma viscosity may suggest the possibility of vasculitis, infection or neoplasia.

BIOCHEMISTRY
Liver function abnormalities may suggest the presence of alcoholism in patients with peripheral neuropathy or coma, or of metastases or liver failure with an associated neurological syndrome. Direct measurement of levels of alcohol or narcotic drugs is of value in patients admitted in coma. Disturbances in serum potassium levels may explain episodes of paralysis; and abnormal thyroid hormone or parathyroid hormone and calcium levels are associated with peripheral and central neuron dysfunction. Calcium and glucose levels are of value in patients presenting with epileptic fits. Measurement of levels of creatine kinase is of value in patients suspected of muscular dystrophy. The concentration is usually over 100 iu/litre, but it must be remembered that mild exertion or an intramuscular injection can raise the level to 300–400 iu/litre.

Measurement of myoglobin in the urine gives an indication of muscle necrosis, and high levels may be associated with precipitation in the renal tubules and subsequent renal failure. Under these circumstances exceptionally high levels of creatine kinase may be observed.

Optimal control of epilepsy demands monitoring of the serum levels of anticonvulsants to maintain safe and effective therapeutic levels.

SEROLOGY
Evidence of infection may be found by the presence of various antibodies, for example HIV infection, herpes simplex, neurosyphilis, neuroborreliasis.

Measurement of IgG antibodies to cholinergic receptors in skeletal muscle is of value in confirming the diagnosis of myasthenia gravis.
NERVE CONDUCTION STUDIES

Motor and sensory conduction rates can be readily measured in large axons. There are differences in rates of conduction in different nerves and most laboratories apply their own standards. Demyelination greatly reduces conduction, as in the Guillain–Barré syndrome, nerve entrapment or diabetes mellitus, whereas in axonal degeneration, as found in drug-induced neuropathy, conduction velocity is only slightly reduced.

ELECTROMYOGRAPHY

Muscle or nerve action potentials can be recorded with needle or surface electrodes and are used in the differentiation of myopathic or neuropathic processes and in monitoring healing after nerve injury. In myopathies, damage to the motor units produces typical polyphasic responses. The specific cause of a myopathy cannot usually be diagnosed by this technique.

EDROPHONIUM (TENSILON) TEST

This diagnostic test is used in patients with suspected myasthenia gravis (see p. 517).

ELECTROENCEPHALOGRAPH

The EEG is a record of the spontaneous electrical signals generated within the brain. It is usually recorded from surface electrodes placed on the scalp, but in selected patients additional valuable diagnostic information may be obtained by neurosurgical implantation of sphenoidal, foramen ovale or cortical electrodes. A profile of waves is obtained from the electrodes and these wave patterns reflect the summation of electrical rhythms and are termed alpha, beta, theta and delta. The basic waveforms alter with eye closure, during sleep and with voluntary movements.

The EEG is valuable in detecting general abnormalities in physiological function such as occur in epilepsy (11.47, 11.48), encephalitis or encephalopathies (11.24). It can be of value in localizing a structural abnormality, but has largely been replaced by CT and MRI. Distinct patterns form the basis of classification of epilepsy. Videotelemetry is sometimes of value in diagnosing patients with ‘funny turns’ of unknown origin and is particularly important when localizing seizure foci before surgery.

EVOKE RESPONSES

Sensitive scalp electrodes allow the measurement on EEG of cortical responses to controlled stimuli, which may be visual, auditory or somatosensory. Delayed or abnormal waveforms may provide evidence of physiological dysfunction. Visual-evoked responses are used in the diagnosis of multiple sclerosis, but the test is not specific and abnormalities in any part of the pathway from the eye to the occipital cortex will prolong the response time. If the patient’s vision is normal, however, it is likely that the delayed response is caused by demyelination (11.25).

11.24 The EEG in late-stage Creutzfeldt–Jakob disease. The typical repetitive discharges are confirmatory of the diagnosis, but are only seen in advanced disease.

11.25 Visual-evoked response in optic neuritis of the right eye. Visual stimulation with a chequered pattern produces a predictable response on the EEG, and this response is delayed and deformed in this patient (bottom right trace). Optic neuritis is the most common cause of this abnormality and, as damage caused by subclinical or forgotten episodes can be detected, the test is of value; however, it is not specific (see text).
LUMBAR PUNCTURE

Samples of CSF are usually obtained by lumbar puncture at L3—L4 level (11.26). The important clinical indications are:
- probable infections of the CNS, including meningitis, encephalitis and neurosyphilis
- possible subarachnoid bleeding
- possible myelopathies or multiple sclerosis
- pressure measurement, for example in benign intracranial hypertension.

Definite contraindications to lumbar puncture are raised intracranial pressure caused by space-occupying lesions, cord compression, local skin sepsis and any bleeding tendency (including anticoagulant therapy). Access to the subarachnoid space allows the pressure of CSF to be measured; it normally ranges from 80 to 180 mm of CSF and moves with respiration.

Pressure on the jugular vein (Queckenstedt's test) results in a rise of up to 40 mm in CSF pressure. If the pressure does not rise, a block in the spinal canal is possible. This is usually associated with a dense yellow coloration of CSF caused by its protein content (Froin's syndrome).

CSF is collected for cell count, biochemistry and serology. If blood staining is present initially, the CSF should be collected in three tubes to determine if the later tubes clear. Samples should be examined for pus (1.23) and blood, and centrifuged to see if the supernatant is xanthochromic (11.27). (See 11.65 for changes in infection and 11.28 for changes in other conditions.)

If CT or MRI is readily available, lumbar puncture is sometimes unnecessary (e.g. subarachnoid haemorrhage can often be diagnosed on CT scan). In all patients with altered consciousness or focal neurological signs, CT scanning is advisable before carrying out lumbar puncture.

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**NERVOUS SYSTEM**

**BIOPSIES**

Biopsy of peripheral nerves may give valuable information that can be both diagnostic and prognostic and may suggest therapy. The biopsy is best done at the wrist (superficial radial nerve) or at the ankle (distal sural nerve) and should involve partial thickness biopsy to reduce the sensory loss.

Muscle biopsy may be done by needle or open biopsy under local anesthesia. Enough material should be taken for histology, including electron microscopy, and histochemistry for muscle enzymes. Diagnostic changes are found in muscular dystrophies and inflammatory myopathies. In addition, vessel changes may indicate polyarteritis nodosa.

Brain biopsy is carried out in highly selected patients when there is a possibility that a course of therapy might be indicated, for example in suspected brain tumours or in possible herpes simplex encephalitis. It is not justified in dementia as there are currently no therapeutic possibilities, but meningeal biopsy may identify potentially treatable angiitides.

**IMAGING TECHNIQUES**

Straight X-rays of the skull are usually of limited value in neurological disease, unless there is a history of head injury that may be seen as a fracture (11.29) or a foreign body, or a disorder associated with ectopic calcification. Special views of the pituitary fossa, orbit, internal auditory canal, sinuses and spine give valuable additional information.

CT is extremely valuable in outlining the anatomy of the brain and skull, especially in defining cerebral haemorrhage and infarction, space-occupying lesions (11.30), subdural haematomas, the presence of hydrocephalus and cerebral atrophy. Structures above the tentorium are better seen than those in the posterior fossa. The spinal canal, disc spaces and cord are also well visualized. Modern techniques allow discrimination down to 5mm. Intravenous contrast media may be given to enhance imaging.

MRI is another useful noninvasive technique. Differences between white and grey matter are better demonstrated than with CT and the contents of the posterior fossa and the cranio cerebellar region of the spinal canal are well visualized. Brain and spinal cord tumours, vascular abnormalities, anatomical abnormalities (syringomyelia) and demyelinating disorders are particularly well shown (3.80, 11.31-11.34). As with CT, contrast medium injected intravenously may add to the yield of MRI. Dynamic MRI may provide information about blood flow.

Radionuclide scans have been largely replaced by MRI and CT scans for anatomical localization, but are still of value in assessing blood flow and in the detection of large ischaemic infarcts, arteriovenous malformations and subdural haematomas. A development of this technique is single photon emission computed tomography (SPECT scanning) (11.35). Technetium is given attached to a carrier molecule.
(hexamethylene propyleneaniline oxime, HMPAO) that enters the cerebral cells, and its presence is a reflection of blood flow and cell metabolism. It has a value in the investigation of patients with epilepsy because it may allow localization of foci. Another radionuclide test involves the use of isotopes of oxygen and glucose, which localize in cerebral cells and provide information on local cerebral perfusion and function – positron emission tomography (PET) scans.

Ultrasound and the Doppler flow technique are now widely used to define the waveform, measure blood flow and define anatomical abnormalities in the carotid arteries (11.80). The techniques are noninvasive, cheap and readily repeatable and they have transformed the investigation of transient ischaemic attacks and permitted the screening of patients before selection for arteriography.

11.31 MRI picture of a right frontal meningioma. MRI shows the fissures of the brain more clearly than CT, it shows the tumour well, and parts of its vascular supply appear as hyperdense images (arrows).

11.32 MRI sagittal view of the patient seen in 11.31. This view demonstrates the relationship of the meningioma to the dura and skull very clearly, and shows the vascular capsule posteriorly (arrow).

11.33 MRI sagittal view, showing a large cerebellar cyst. MRI is of particular value in demonstrating lesions in the posterior fossa.

11.34 MRI sagittal view, showing leptomeningeal sarcoidosis. This gadolinium-enhanced MRI scan shows a mass around the optic chiasma, with extensive meningeal thickening along the adjacent brain surfaces.

11.35 Single photon emission computed tomography (SPECT scan), demonstrating a right parieto-frontal cerebral tumour, which proved to be a meningioma.
Cerebral angiography may be carried out by direct injection of contrast into the carotid or vertebral arteries, usually via a catheter inserted into the femoral artery. There is a small morbidity and mortality associated with the procedure. A series of films is taken in two planes to detect arterial and venous obstruction, aneurysms, arteriovenous malformations, tumour circulations (11.36, 11.37) and arteritides. An alternative technique is digital subtraction angiography (DSA), in which the injection of contrast may be made intravenously and images of the artery are obtained by computer subtraction of images (11.38).

**HEADACHE**

Headache is an extremely common symptom and affects most people many times in their lives. It rarely is a symptom of serious neurological disease and usually responds rapidly to analgesics. However, more significance should be given to headache if it has any of the following features.

- Dramatic onset — may suggest a subarachnoid haemorrhage (see p. 499).
- Accompanied by confusion, coma or impairment of higher function.
- Scalp tenderness in middle or old age — suggesting temporal arteritis (see p. 146).
- Pyrexia and petechial rash may suggest meningococcal meningitis (see p. 38).
- Neck stiffness suggests meningism or meningitis (see p. 492).
- Headache on rising in morning suggests intracranial space-occupying lesion (see p. 490).
- Headache after recent head trauma suggests subdural haematoma (p. 500).

The most common headaches are tension headaches and migraine. These can usually be distinguished from other causes on the clinical history alone.

**TENSION HEADACHE**

Tension headache is usually a dull, nagging pain in the frontal, occipital or temporal regions, around the head 'like a band', or pressing on the vertex. There may be tender spots in the scalp and also a throbbing sensation behind the eyes. The headaches may persist for hours, days or weeks, and are often worse at the end of the day. Many, but not all, sufferers recognize a relationship to stress. Tension-type headaches are rarely caused by visual refractive errors or hypertension, but these possibilities should be excluded. Tension headaches are benign in nature and respond to reassurance, avoidance of stress and simple analgesics; beta blockers may also help if there is a vascular component and some patients respond to antidepressant therapy.

**MIGRAINE**

Migraine affects 8–12% of the population, and 75% of sufferers are female. It is an episodic, severe headache that lasts for several hours and occurs in association with visual and gastrointestinal symptoms. There may be a prodromal phase in which there are flashing spots (teichopsia) or zigzag lines (fortification spectra), and vision may be blurred. Additional neurological features may include photophobia, hemianesthesia, hemiparesis, dysphasia and cranial nerve lesions. There is usually associated nausea and vomiting. Migraine is usually familial. There is evidence for vascular mechanisms (altered serotonin mechanisms in platelets and blood vessels) and for
other abnormal brain mechanisms. Trigger factors often include cheese, shellfish, chocolate, red wine, coffee, smoking, menstruation, menopause, pregnancy, oral contraceptives and minor head trauma. Stress and, paradoxically, relief from stress may also trigger attacks. Some patients describe change in mood, appetite and fluid retention for hours or a day or two before and after the headache. Migraine by definition should have two of the following characteristics.

- Pulsating pain
- Unilateral
- Severe intensity
- Worse on activity
- Nausea or vomiting
- Photophobia or phonophobia.

The main classification is as follows.

- **Common migraine**: usually unilateral but sometimes bilateral throbbing headache, accompanied by nausea, vomiting and photophobia; sleep may relieve symptoms
- **Classic migraine**: there is a prodromal visual disturbance such as flashing lights, zigzag lines, colours, and scotomas; these evolve over 10–30 minutes and are followed by headaches as above; some variants involve sensory or hemisensory loss, hemiplegia, more complex perceptual changes, or dysphasia; variants include vertebrobasilar system migraine, associated with brainstem dysfunction, the symptoms of which are acute vertigo, diplopia, bilateral weakness, drowsiness or coma; ophthalmoplegic migraine, in which an ocular palsy persists for hours or days; and hemiplegic migraine, which mimics a stroke, but from which rapid recovery is usual
- **Complicated migraine**: a very small proportion of migraines are complicated by a stroke.

The first approach to management is to identify and prevent migraine by eliminating trigger factors. Acute headaches may be treated with bed rest in a darkened room, with ergotamine, aspirin or paracetamol, often with metoclopramide, or with sumatriptan. Prophylactic drugs such as pizotifen, propranolol and amitriptyline may be useful for patients with frequent migraines.

### OTHER FORMS OF HEADACHE

**Migrainous neuralgia (cluster headache)**

Migrainous neuralgia occurs mainly in men as an intense, throbbing, unilateral pain, usually retro-orbital but often spreading to the upper face. It occurs in bouts or ‘clusters’, with one or more episodes daily, often at regular times, including wakening from sleep. Bouts last for days or weeks before clearing for weeks, months or years. There may be associated lacrimation, rhinorrhea, and a transient Horner's syndrome, but nausea is not a feature. Acute attacks may be prevented with ergotamine; prophylactic treatment with pizotifen, propranolol or lithium carbonate is sometimes successful.

**Temporal arteritis**

Temporal or cranial arteritis usually occurs in older patients with throbbing or persistent headache and tenderness in the temporal region (11.39), or more rarely in the occipital regions or the jaw on chewing. Urgent diagnosis and treatment are essential (see p. 146).

**Atypical facial pain**

The syndrome of ‘atypical facial pain’ is a nagging, protracted pain in the maxillary region, usually occurring in middle-aged depressed women. The pattern of pain does not usually conform to an anatomical distribution. It may respond to amitriptyline.

**Headache of increased intracranial pressure**

Increased intracranial pressure (see p. 489) is suggested by early morning headache, usually in the occipital region, with exacerbation on coughing or bending. Nausea, vomiting and brief visual disturbance, often on bending, may occur. There are often additional neurological features such as papilloedema, confusion and localizing neurological signs. Sixth cranial palsy may occur as a false localizing sign.

**Meningeal pain**

Subarachnoid haemorrhage produces sudden severe headache and neck stiffness, usually with focal signs or coma, or both (see p. 499). Meningitis also produces headache and neck stiffness together with nausea, vomiting and photophobia (see p. 492).

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11.39 Temporal arteritis, with typical thickening and dilatation of the right temporal artery. This patient presented with temporal pain and sudden visual impairment in the right eye, but responded to prompt treatment with systemic steroid (see also p. 146).
Cervical spondylosis
Cervical spondylosis may cause headaches referred to the occipital region or anteriorly, which are often worse with head movement (see p. 149).

Trigeminal neuralgia
Trigeminal neuralgia (tic douloureux) is a disease of unknown origin that manifests itself more commonly in women than men (usual age 50–80 years) with excruciating paroxysms of stabbing pain over the distribution of the trigeminal nerve. Paroxysms of pain are often provoked by minor touch, such as shaving, brushing teeth or chewing. The syndrome may be associated with an aberrant vascular loop and in younger patients may occasionally be an early feature of multiple sclerosis, but usually no cause is found. Severe pain usually occurs in the distribution of the maxillary or mandibular branches of the trigeminal nerve. The ophthalmic division is rarely affected. The brief, agonizing bouts are triggered by touch, chewing or cold. Carbamazepine is the drug treatment of choice but, if this fails selective thermocoagulation of trigeminal branches is of value and decompression of the trigeminal nerve may be attempted.

Miscellaneous other headaches
Headaches may occur with cough (cough headache), and in the masticatory syndrome (Costen syndrome), in which there is pain in the maxillary regions and exacerbation with chewing. In patients with severe headache, orbital pain and visual failure, the possibility of acute glaucoma must also be considered.

Chronically Fatigue Syndromes
Chronic fatigue syndromes form an ill defined group of problems that risks becoming a 'catch-all' diagnosis for many undefined disorders. Fatigue after a whole range of illnesses is well recognized and is usually self-limiting and not recurrent. However, after some virus illnesses it may be prolonged and recurrent.

Myalgic encephalomyelitis (ME) is now generally accepted as a true 'disease', but no patient should be given such a diagnosis until the most strenuous efforts have been made to exclude other recognized and treatable diseases. ME affects all ages and all social classes and often affects people who have been extremely conscientious and highly motivated. There is usually both a physical and psychosocial element to the illness. The presenting symptoms are all nonspecific, for example mental and physical fatigue, great variation in symptoms day by day, fatigue that is worse after stress or exercise and emotional lability. There may occasionally be physical signs such as low grade fever, lymphadenopathy (cervical), recurrent tonsillitis, muscle tenderness and generalized weakness.

Extensive investigations may be required to exclude other diseases and these should include a search for evidence of recent viral infection. No diagnostic tests for ME are available.

There is no recognized treatment. Patients often require continuing psychosocial counselling. Complementary medical techniques are often advocated, but there is no scientific evidence of benefit.

Dementia
Dementia is a persistent or progressive impairment of multiple cognitive capacities such as intellect, behaviour and personality. The diagnosis requires careful assessment of short-term and long-term memory, language, calculation, behaviour, mood, and personality. A relative's history of the patient's decline may be useful in the diagnosis. Dementia differs from acute confusional states that have toxic, metabolic or infectious causes. Causes of dementia include vascular, traumatic, degenerative, infectious, demyelinating, inflammatory, neuroplastic, metabolic and toxic disorders.

Alzheimer's disease is the most common cause of slowly progressive dementia over several years. The mental symptoms and signs precede the physical signs by several months to years. Nearly all patients are over 60 years of age, and it is estimated that 5–10% of people over 65 are affected. Pathologically, there are characteristic senile plaques, neurofibrillary tangles and amyloid angiopathy. In addition to ageing, other risk factors include a family history of the disease, head injury, low educational achievement and Down's syndrome.

The most common presentation is with a loss of recent memory, often associated with a personality change, apathy and antisocial behaviour followed by focal signs such as dysphasia, dyslexia, dyspraxia, agnosia and later loss of sphincter control. Sleep disturbance is common. Disturbance of gait reduces mobility, but patients are inclined to wander, especially at night, and may injure themselves by falling. The end result is that patients become bed-bound and incontinent.

In addition to Alzheimer's disease, a wide range of other conditions may cause dementia (11.40). Some are treatable, so investigation is important in younger patients with dementia. Tests should include CT scanning (11.41), MRI or SPECT scanning (11.42), and may also involve full blood count (including serum B12 and folate), renal, liver and thyroid function tests, blood sugar, calcium, serology for syphilis and HIV, chest and skull X-rays, EEG, CSF examination and heavy metal screening.

Multi-infarct dementia can be difficult to distinguish clinically from Alzheimer's disease. The cause is occlusion of vessels supplying the cerebral cortex and subcortex. The clinical presentation is with features of cortical dysfunction. Sudden deteriorations in neurological status are common in this form of disorder in which there are multiple small infarcts in the brain, best shown on a CT scan (11.43). Clinical examination usually demonstrates physical signs that correspond to the lesions.

Subdural haematoma may produce gradually increasing mental impairment over several weeks or months (see p. 500). The initiating head injury may have been slight and unrecognized. It is treated by surgical decompression.
In normal-pressure hydrocephalus there is dementia with gait and bladder disorder caused by marked ventricular dilatation. Meningitis, cerebral haemorrhage and trauma are predisposing factors, but it may occur without this history. The surgical creation of a shunt from ventricle to peritoneum may arrest the process.

Alcoholism is a common cause of behavioural change and dementia, and is often complicated by B-group vitamin deficiencies, especially of thiamine (see p. 347). Vitamin B₁₂ deficiency can produce severe mental impairment, and hypothyroidism can also cause a marked slowing of mental function.

### Causes of Dementia

<table>
<thead>
<tr>
<th>Unknown</th>
<th>Alzheimer’s disease</th>
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<tbody>
<tr>
<td></td>
<td>Multiple sclerosis</td>
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<tr>
<td></td>
<td>Parkinson’s disease</td>
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<tr>
<td>Vascular</td>
<td>Multiple cerebral infarcts</td>
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<td></td>
<td>Diffuse small vessel disease</td>
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<tr>
<td>Metabolic</td>
<td>Uraemia</td>
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<td>Liver failure</td>
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<td>Hypothyroidism</td>
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<td>Vitamin B₁₂ deficiency</td>
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<td></td>
<td>Other vitamin B deficiency</td>
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<td></td>
<td>Hypoparathyroidism</td>
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<td></td>
<td>Hypoglycaemia</td>
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<tr>
<td>Physical</td>
<td>Space-occupying lesions (tumour, haematoma)</td>
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<tr>
<td></td>
<td>Post-head-injury, especially in subdural haematoma</td>
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<tr>
<td>Genetic</td>
<td>Huntington’s chorea</td>
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<tr>
<td></td>
<td>Down’s syndrome</td>
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<tr>
<td>Infections</td>
<td>HIV infection</td>
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<td></td>
<td>Tuberculosis</td>
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<td></td>
<td>Toxoplasmosis</td>
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<tr>
<td></td>
<td>Syphilis</td>
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<tr>
<td></td>
<td>Creutzfeldt-Jakob disease</td>
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<tr>
<td>Toxic</td>
<td>Poisoning with mercury, manganese, carbon monoxide, alcohol, copper</td>
</tr>
</tbody>
</table>

11.40 Causes of dementia.

11.442 Single photon emission computed tomography (SPECT scan) in Alzheimer’s disease. There is a marked symmetrical reduction in perfusion to both post-temporoparietal areas.

11.41 CT scan in Alzheimer’s disease at ventricular body level. Note the marked dilatation of the sulci and fissures, especially frontally, the poor visual distinction between grey matter and white matter, the ventricular enlargement – greater on the patient’s left (right of picture) – and the general reduction in brain size. The picture is not diagnostic of Alzheimer’s disease: similar abnormalities occur in Huntington’s disease and Niemann–Pick’s disease.

11.43 CT scan in multi-infarct dementia (cut at same level as that seen in 11.41). The ventricles are normal in size, but there are patchy radiolucencies throughout the white matter. These indicate the presence of demyelinated patches, which result from multiple small infarcts in the brain.
Dementia as a part of AIDS is now increasingly common (see p. 11); whereas general paralysis of the insane from neurosyphilis (see p. 78) is very rare. Creutzfeld–Jakob disease (CJD) is a rare but rapidly progressive dementia now shown to be transmissible from infected human nervous tissue and thought to be caused by a prion (see pp. 75 and 11.24).

In severe brain damage from encephalitis, abscess, tumour, cerebral infarction (11.44), head injury, severe ischaemia or hypoglycaemia, the cause is usually clear.

Huntington's chorea is a dominantly transmitted condition that is associated with progressive dementia and chorea. The onset of symptoms is usually gradual in the middle years of life. There is usually a family history and, because of knowledge of the outcome, there is a high incidence of depression. The course is progressively downhill over a few years with increasing chorea and dementia. The diagnosis is made on clinical grounds and on the family history. Genetic counselling is mandatory in all adolescents and the availability of a DNA probe aids this process in certain families.

Management of dementia involves:
- Treating the disorder that is causing the cognitive problem (if possible)
- Controlling the symptom or behaviour pattern
- Controlling the resultant disability
- Providing help for the carers at a social, nursing and medical level; this includes especially home care, day care and long-term residential care.

Lithium has a place in the management of depression in dementia, but it may cause damage to thyroid, kidneys, nervous system and gastrointestinal tract, so lithium therapy must be carefully monitored.

**EPILEPSY**

Epileptic seizures are manifestations of abnormal synchronous activity of populations of neurons in the brain. Even a normal brain can generate such activity given a sufficient stimulus (e.g. electric shock, drug withdrawal). People with epilepsy have a lower 'threshold' for seizure activity, and have epileptic seizures that are unprovoked or reflexly induced (e.g. by flashing lights). Different types of seizures reflect varieties and distributions of synchronous neuronal activity, and are classified according to their clinical and EEG manifestations as partial or generalized seizures.

A large number of potential underlying mechanisms contribute to epilepsy, some genetically determined and some acquired. Epileptic syndromes can be broadly divided into those thought to be associated with focal brain pathology, and those associated with a diffuse increase in brain excitability.

- Partial seizures arise focally within the brain and have variable spread
- Generalized (tonic/clonic) seizures are associated with widespread bilateral activity in the EEG from their onset.

In many individuals with epilepsy, however, it is likely that there is a combination of underlying mechanisms, explaining, for instance, why one person develops epilepsy after a head injury, whereas another with an apparently identical injury does not.

A first epileptic seizure can occur at any age. About 1 person in 30 has an epileptic seizure during his or her lifetime, and the prevalence of active epilepsy is 1 in 200. Patients may be seriously injured during attacks (11.45) and must be managed carefully during any period of unconsciousness or drowsiness that follows them.

**11.45** Serious injury may occur during generalized seizures in epilepsy. This patient has a large full-thickness burn, sustained when he fell in a fire during a fit.
An accurate diagnosis of epilepsy is crucial in view of the potential social implications and possible initiation of long-term treatment. Typical attacks are easy to diagnose but the interpretation of odd 'falls and faints' is extremely difficult. The main differential diagnoses are shown in 11.46. A witnessed account of the attacks is of great importance. It is a common misconception that the EEG (11.47, 11.48) is diagnostic, but it is only rarely so, and the diagnosis is essentially based on an adequate history that may include observed convulsions, unconsciousness, biting the tongue (11.49), incontinence and a slow recovery. In adult life, symptomatic partial epilepsy is most common and few clinical signs are found. Investigations usually include CT scanning, which is essential if there are focal signs.

A decision to recommend antiepileptic drug treatment (AEDs) is easy in subjects with recent recurrent seizures, but is controversial in those who have had a single unprovoked seizure or a small number of very infrequent seizures. After a single seizure the risk of a further attack is initially high (about 70%), but it subsequently falls rapidly (to about 30% at 2 months). The choice of AED depends on the seizure type(s). Up to 80% will have their seizures controlled, usually by a single AED, once appropriate dose adjustments have been made. Drug-level monitoring is essential with phenytoin, because of saturation kinetics, and can be useful with other drugs to assess compliance and adverse effects.

All AEDs have potential side effects, and all present risks if taken during pregnancy. A particularly well-recognized side effect is gingival hyperplasia in patients on phenytoin therapy (8.23). A small proportion of patients with epilepsy not controlled by AEDs can be offered neurosurgery (most commonly temporal lobectomy), with a good chance of complete seizure relief.

Discussion of the diagnosis of epilepsy with the patient needs to be clear and detailed. Misconceptions and prejudices remain common (e.g. equating it with mental illness or insanity). The provision of written material is essential, and discussion

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**DIFFERENTIAL DIAGNOSES OF EPILEPSY.**

- Syncope (including convulsive syncope)
- Pseudoseizures
- Hypoglycaemia
- Parasomnias (sleep walking, sleep talking)
- Cataplexy
- Transient ischaemic attacks
- Migraine

**11.46 Differential diagnoses of epilepsy.**

**11.47 EEG in a patient with generalized seizures.** This shows the typical spike and wave discharge of epilepsy. If the EEG is taken during an attack, this appearance may be diagnostic of epilepsy, but gives no indication of the cause; if spike and wave activity is observed between attacks, the appearance does not prove that an episode was epileptic, but the findings support the diagnosis. Ambulatory monitoring of the EEG provides a much more valuable assessment of the relationship of EEG abnormalities to symptoms.

**11.48 EEG in a patient with partial seizures.** Characteristic 3Hz spike and wave activity is always present during an attack and is frequently seen in the interictal intervals. Here an attack was induced by hyperventilation.

**11.49 The bitten tongue as a sign of epilepsy.** Damage to the tongue is a common complication of generalized seizures. During epileptic attacks the patient should be protected from harm if possible; but forcible attempts to open the mouth or restrain the patient often do more harm than good.
with other family members is usually important. Areas to be covered include implications for driving, employment, social activities and other interests, what to do when seizures occur, safety precautions, drug interactions and genetic implications. Advice on pregnancy is essential as there is a higher than normal risk of fetal malformation, which is worsened by some AEDs.

In many patients who become seizure-free on AED treatment, it is subsequently possible to withdraw their medication. This should be considered after at least 2 years of freedom from seizures, when the statistical risk of further seizures, with or without continued treatment, is approximately one-third.

**COMA**

Coma is defined as a state of unrousable unresponsiveness (11.173, 11.189, 11.200, 11.50), and for practical clinical purposes this may be refined into a spectrum of symptoms and signs by use of a coma scale such as the 'Glasgow' Coma Scale (11.51).

Coma has many possible causes (11.52), and the management of patients in coma always involves the investigation of underlying cause together with appropriate supportive and specific treatment. Immediate maintenance of airway patency is essential (11.50) and further treatment is dependent on the underlying cause and duration of the coma.

**CAUSES OF COMA RANKED IN APPROXIMATE ORDER OF INCIDENCE**

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Head injury</td>
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<tr>
<td>Drug overdose</td>
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<tr>
<td>Meningitis</td>
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<tr>
<td>Encephalitis</td>
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<tr>
<td>Cerebral malaria</td>
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<tr>
<td>African trypanosomiasis</td>
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<tr>
<td>Other</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypoglycaemia (common)</td>
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<tr>
<td>Hyperglycaemia (rare)</td>
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<tr>
<td>Stroke or transient ischaemic attack</td>
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<tr>
<td>Epileptic seizure</td>
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<tr>
<td>Infection</td>
</tr>
<tr>
<td>Metabolic</td>
</tr>
<tr>
<td>Renal, hepatic or respiratory failure, myxoedema, chemical toxins, non-diabetic hypoglycaemia</td>
</tr>
<tr>
<td>Cardiorespiratory arrest</td>
</tr>
<tr>
<td>Psychiatric causes</td>
</tr>
</tbody>
</table>

**11.50 The correct position for the unconscious patient.** The patient should be placed in the semiprone position, and a simple airway should be placed in the mouth. Exactly the same management should be applied to any unconscious patient who does not require cardiac or respiratory support.

**11.52 Causes of coma ranked in approximate order of incidence.**
RAISED INTRACRANIAL PRESSURE

A rise in the pressure of CSF above 250 mm is usually a reflection of serious neurological disease, caused by a space-occupying lesion, obstruction to the outflow of CSF or obstruction of the venous return.

It is usual to measure CSF pressure by lumbar puncture, but this may not accurately reflect pressure in the brain, for example if there is obstruction by spinal tumours or herniation of brain through the foramen magnum. The main causes include tumours, abscesses, hydrocephalus, haematomas and benign intracranial hypertension.

A rise in intracranial pressure is usually associated with headache, especially in the morning, nausea, vomiting and loss of vision and balance. There may be false localizing signs, for example sixth nerve palsies. The most reliable sign is the appearance of papilloedema (7.10, 11.53), but this is not always seen even when the pressure is high.

Urgent action to reduce pressure is needed in patients with impending herniation of brain through the foramen magnum. This should usually include high doses of dexamethasone and intravenous mannitol. The airway must be maintained and hyperventilation to reduce the Pa CO\textsubscript{2} may be of transient value. After stabilization, imaging procedures should be used to establish the underlying diagnosis, which should be treated appropriately.

Benign intracranial hypertension (pseudotumour cerebri) is an unexplained disorder, occurring mainly in pregnant, obese young and middle-aged women, producing headache and papilloedema (11.53); there is increased intracranial pressure as measured on lumbar puncture, without local structural cause. Long-term consequences include blindness from optic nerve atrophy (7.11). Diagnosis is made on lumbar puncture and the CT scan is used to exclude other pathology. Treatment includes weight reduction, diuretics, occasionally a shunt and optic nerve decompression.

HYDROCEPHALUS

Hydrocephalus is the enlargement of the cerebral ventricles that is associated with the accumulation of CSF. This may result from a variety of causes including:

**Communicating hydrocephalus:**
- excess production of CSF – choroid plexus papilloma
- impaired CSF absorption – in meningitis
- cerebral dysgenesis or atrophy

**Noncommunicating hydrocephalus**
- obstruction to the flow of CSF – intracerebral tumours, aqueduct or foramen stenosis, by blood in subarachnoid haemorrhage.

The clinical features depend on whether the disease process is acute or chronic and whether the process produces complete or partial obstruction. The acute presentation is usually accompanied by severe headache, nausea and vomiting. There are usually no localizing symptoms or signs, but there is papilloedema (7.10, 11.53) and there may be a sixth nerve lesion. Neurological signs usually suggest a bilateral upper motor neuron disorder (i.e. bilateral extensor plantar signs and brisk reflexes). There is progressive impairment of higher cerebral functions with loss of memory, impairment of mobility and loss of sphincter control.

CT imaging and MRI show the abnormality of the ventricles (11.54) and may suggest the site of the block (11.133). Lumbar puncture may be of little value as the pressure is often normal.

If the primary lesion is not amenable to treatment, a drainage procedure of the affected ventricles is of value. This involves the surgical creation of a shunt with a valve that allows the one-way drainage of CSF from the ventricles to the peritoneal cavity.

11.54 Hydrocephalus in a 69-year-old man. This axial MRI at the level of the ventricular bodies shows severe ventricular enlargement, but the sulci of the brain are normal.

11.53 Chronic papilloedema in the right eye of a middle-aged woman with benign intracranial hypertension. The disc margins are completely blurred, and there are widespread haemorrhages and ischaemic areas in the retina. The appearance of chronic papilloedema should be compared with the less-marked changes seen in early papilloedema (7.10).
INFANTILE HYDROCEPHALUS

A variety of congenital abnormalities may lead to hydrocephalus which may be present before birth (and hence produce difficulties at birth) or develop during childhood or adult life.

Progressive enlargement of the head is usually obvious, with failure of closure of the fontanelles (11.55). Milestones of development are delayed and the end result may be mental retardation complicated by epilepsy and motor impairment. CT scan (11.56) or MRI may show the abnormality and sometimes the cause, and the early implantation of a shunt may arrest the physical and mental deterioration that would otherwise occur.

CEREBRAL TUMOURS

Cerebral tumours represent about 1 in 10 of all tumours. The most common are gliomas, which account for 40–50% of all intracerebral tumours, metastases from tumours of other sites (20–30%), meningiomas (10%), pituitary adenomas (10%) and other tumour types (each about 1–2%).

The usual clinical presentations include:
- headache, vomiting and papilloedema (7.10, 11.53), that is symptoms and signs of raised intracranial pressure
- epileptiform seizures
- pressure effects on adjacent structures, which produce focal neurological defects
- endocrine changes in some pituitary lesions.

These symptoms are also found with other space-occupying lesions, such as intracerebral haematomas, abscesses and subdural haematomas.

GLIOMA

Gliomas account for 40–50% of all intracerebral tumours and arise from neuroglial cells – usually in the cerebral hemispheres and rarely in the cerebellum. The most common type is the astrocytoma, which originates in astrocytes and has a range of degrees of malignancy: grade I has a long survival (up to 25 years) and grade IV has a survival of only several months (this rapidly invasive tumour is also known as glioblastoma multiforme). Such tumours rarely metastasize beyond the brain, tending to invade locally in one hemisphere or, less commonly, across the corpus callosum (‘butterfly glioma’). In children, the most common sites are the hypothalamus, optic nerve and cerebellum (where they may be cystic and benign). Diagnosis of the space-occupying lesion is by CT scan (11.57) or MRI (11.58), followed by stereotactic biopsy. Solitary low-grade malignant lesions may be amenable to surgery and the more malignant lesions may respond to radiotherapy.

Oligodendrogliomas arise from oligodendroglia and grow extremely slowly. They may sometimes be recognized on a straight skull X-ray by the presence of calcium.

Ependymomas arise from the lining cells of the lateral and fourth ventricles. They tend to occur in the young and are asso-
CEREBRAL TUMOURS

MENINGIOMA

Meningiomas are slowly growing benign tumours that arise from the arachnoid and produce symptoms by compression of adjacent structures. They may arise at any site, even in the spinal canal, but most commonly over the hemispheres. Women over 40 years of age are most commonly affected, and because the tumours are slow growing they may reach a large size before patients present with partial seizures, features of raised intracranial pressure or localized neurological deficits. The tumours have a rich blood supply, may erode bone locally and may calcify. The diagnosis is usually suggested by CT scan (11.30, 11.59), MRI (11.31, 11.32, 11.131) or SPECT scanning (11.35) and occasionally localized calcification is seen on the plain X-ray of the skull. Surgery may be curative with early lesions, but local erosion of other structures may make resection extremely difficult, for example sphenoidal ridge tumours may envelop the carotid artery and other parapituitary structures. If incompletely removed, meningiomas tend to regrow. Malignant change is rare. If situated in the spinal canal, they are most likely to occur in the thoracic region where they manifest themselves with the gradual onset of paraparesis; surgery carries a good prognosis because of the earlier presentation.

PITUITARY TUMOURS

Pituitary tumours may produce endocrine and neurological symptoms (see also p. 308). A common presentation is with headache caused by expansion of the tumour, which may erode the clinoid processes and the floor of the pituitary fossa and eventually press on the optic chiasma (7.4–7.7, 7.26). Bitemporal hemianopia results (11.7). Extension laterally into the cavernous sinus affects the oculomotor nerve and the trigeminal nerve. A similar picture may be produced by pressure from aneurysms and meningiomas.

NEUROMA

Neuromas are benign tumours that arise from the Schwann cells of the cranial nerves and spinal roots. The most common intracranial site is on the acoustic nerve at the cerebellopontine angle. The presentation is with progressive deafness and tinnitus (eighth nerve), loss of sensation on the face (fifth nerve), facial weakness (seventh nerve) and ipsilateral cerebellar signs. Further enlargement produces erosion of the petrous part of the temporal bone and pressure effects on the brainstem, with long tract symptoms and signs in the arm and leg, followed by hydrocephalus. Diagnosis may be made on a plain X-ray of the skull with tomography, by CT scan or MRI (11.20, 11.21,

11.58 Cystic glioblastoma of the brainstem (arrowed), clearly demonstrated by MRI. The sagittal section shows that the tumour involves the posterior part of the brainstem and extends into the cerebellum.

11.59 Meningioma in the occipital lobe, as revealed on contrast-enhanced CT scan. The patient presented with a contralateral homonymous hemianopia.
11.60, 11.131). Partial surgical removal may be all that is possible but early resection may allow conservation of seventh and eighth nerve function.

METASTASES

Metastases account for about one-quarter of all cerebral tumours and most frequently arise from lung, breast, kidney, colon, skin and reticulosis. Metastatic lesions may develop in any part of the brain, including the cerebellum. Many lesions are found by chance at autopsy and they tend to be multiple. The diagnosis may be suggested by the development of neurological deficits in patients who have a known malignancy. The clinical course is variable: many patients present with slowly progressive symptoms, whereas in others an acute presentation may result from haemorrhage within the mass. Diagnosis is most easily made by CT (4.177, 11.61) or MRI. Solitary lesions may be amenable to surgical removal with occasional good long-term results. Corticosteroids are of interim value in reducing oedema and temporarily improving clinical status to allow chemotherapy or radiotherapy to be of value.

INFECTIONS OF THE NERVOUS SYSTEM

Many infections involve the CNS. Meningitis, encephalitis and cerebral abscess are considered here, and many other infections that may involve the CNS are reviewed in Chapter 1. CNS infections are a major problem in immunocompromised patients, including those with AIDS. The Guillain–Barré syndrome (see p. 511) is probably of infective origin, and infection may prove to have a causative role in some patients with dementia and other degenerative diseases of the nervous system.

MENINGITIS

Meningitis is defined as inflammation of the pia and arachnoid mater and is usually caused by bacteria or viruses (11.62); it may also be caused by fungi, malignant infiltration, blood (subarachnoid haemorrhage) or chemicals (drugs or contrast medium).

Viruses are the most common cause of meningitis. They produce a lymphocytic reaction in the CSF and there may be...
associated encephalitis. Bacteria are the second most common cause of acute meningitis and they usually provoke a polymorphonuclear leucocytosis in the CSF. A chronic reaction is found in tuberculosis. Fungal infection is uncommon, except in immunocompromised patients, and it may run a chronic or subacute course.

The clinical presentation may be with acute or gradual onset of fever, vomiting, headache, lethargy, impaired consciousness or seizures; signs include a stiff neck, focal signs such as cranial nerve abnormalities (third, fourth, sixth and seventh), hemiparesis, dysphasia, visual field defects and papilloedema. The consequences of infection may also be apparent elsewhere (1.112, 1.111). Two important clinical signs of meningitis are dependent on traction of spinal nerves causing pain in the inflamed meninges. These are

- Kernig's sign (11.63)
- Brudzinski's sign (11.64).

A search must also be made for associated diseases, for example mastoiditis, pulmonary tuberculosis or malignancy. Laboratory diagnosis depends on lumbar puncture, which may show a rise in CSF pressure and perhaps a turbid fluid (1.23) that should be sent for microbiology, microscopy and biochemistry. These results (11.65) will define the infection. If a space-occupying lesion (e.g. abscess) is suspected, then CT is essential before undertaking lumbar puncture.

In bacterial meningitis, antibiotic treatment is dictated by the organism found, though treatment will usually be started before culture results are available. Intrathecal antibiotic injection is now rarely used.

Viral meningitis is usually a benign, self-limiting condition.

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<tr>
<th>CEREBROSPINAL FLUID (CSF) FINDINGS IN MENINGITIS</th>
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<tr>
<td>Cells</td>
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<td>-------</td>
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<tr>
<td>Number (per mm³)</td>
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<tr>
<td>Normal</td>
</tr>
<tr>
<td>Viral infection</td>
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<tr>
<td>Acute bacterial infection</td>
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<td>Tuberculosis</td>
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</table>

11.65 Cerebrospinal fluid (CSF) findings in meningitis.
**ENCEPHALITIS**

Encephalitis is a generalized nonsuppurative inflammation of the brain that is usually caused by infection by a virus but is also found in a variety of bacterial infections. Such infections may also involve the spinal cord, cranial nerves and nerve roots. In the UK, encephalitis may follow infection with measles, rubella, chickenpox, influenza virus, herpes simplex and HIV. In the Far East and other parts of the world, epidemic viral encephalitis carries a high morbidity and mortality (see p. 222).

The usual clinical features include fever, nausea and vomiting, headache, impairment of the conscious level (1.63), the development of focal neurological signs, meningism and features of raised intracranial pressure. The disease is often followed by complete recovery after a period of weeks.

The EEG may show diffuse or focal abnormalities. CT scan or MRI often show abnormalities (11.66). Serology may show a changing level of viral antibody. Lumbar puncture may show a rise in CSF pressure with lymphocytosis, elevated protein content and a normal glucose level.

Treatment consists of nursing and supportive care. Acyclovir should be given in all cases of suspected encephalitis because the consequences of untreated herpes simplex encephalopathy in the minority are considerable. In patients who are immunocompromised cytomegalovirus should also be considered and this responds to ganciclovir.

Patients with acute demyelinating encephalomyelitis present in a similar manner to those with encephalitis; the former is an allergic demyelination disease. It follows some types of vaccination and may follow measles or chickenpox infection after several weeks. A proportion of patients will later develop multiple sclerosis.

**BRAIN ABSCESS**

Brain abscess is a localized collection of pus in the brain. The infection may be bloodborne from a distant site, be introduced by a penetrating head injury or extend from local infections in the head (mastoiditis or sinusitis). Anaerobic bacteria are particularly commonly found in brain abscesses.

The clinical symptoms are those of infection and of the development of a space-occupying lesion in the brain. There is usually fever, headache, nausea, vomiting, clouding of the conscious level, focal signs and fits. There may be signs of a focus of infection, of an increase in intracranial pressure and of papilloedema. Additional focal signs may occur depending on the anatomical site of the abscess.

The white cell count is elevated and the blood film usually shows a polymorphonuclear leucocytosis. The ESR is elevated. The lesion can be identified on CT scanning (1.42, 11.67, 11.68) as a ring-enhancing lesion and, if there is any doubt about the diagnosis, stereotactic biopsy is safer than lumbar puncture.

Treatment is with appropriate antibiotic combinations, corticosteroids to reduce swelling and, in selected patients, neurosurgery. If a predisposing cause has been identified, this also requires treatment.

Infections may also localize in the subdural or extradural spaces of both brain and spinal cord. Patients with spinal epidural abscesses present with severe back pain and paraparesis.
CEREBROVASCULAR DISEASE

STROKE

Completed stroke is defined as a focal loss of neurological function of presumed vascular origin, which causes death or lasts for over 24 hours. This timescale differentiates it from a transient ischaemic attack (see below). In addition, some clinicians describe a reversible ischaemic neurological deficit (RIND) in which the neurological deficit lasts more than 24 hours and reverses within 3 weeks. Stroke-in-evolution is a condition in which the symptoms and signs suggest a focal lesion within the distribution of a major artery and this gradually extends over a period of days or weeks to involve an adjacent motor or sensory site.

Over 90% of strokes result from thrombosis or embolism in a major cerebral artery, and under 10% result from haemorrhage.

Stroke remains one of the most common causes of death (10–15%) and disability in the Western world with an incidence of 2–5 per 1000. It is especially important because of the high mortality (40–50% in the first month) and the high dependency (60%) of the survivors. Most countries also have an ageing population and it is predicted that the incidence of strokes will rise by up to 40% in the next 10 years.

The clinical presentations of strokes caused by cerebral thrombosis, embolism and haemorrhage are similar. They involve a combination of features that may include hemiparesis (11.69), hemianaesthesia, loss of speech if the dominant hemisphere is involved and loss of vision. Lesions affecting the nondominant hemisphere are more likely to be associated with neglect. The clinical onset is often rapid and reaches a maximum within a few hours. The limbs are flaccid and reflexes are initially absent. The patient may have an impaired conscious level because of cerebral oedema, and there may also be papilloedema. Over the next 24-hour period tone increases, some power may return, the tendon reflexes are exaggerated and the plantar response is extensor.

Lacunar infarcts are small lesions around the basal ganglia, thalamus and pons that result in localized motor or sensory deficits. Brainstem infarcts produce complex neurological syndromes, as they involve the long tracts, the cranial nerve nuclei and cerebellar connections.

The signs of acute stroke are usually obvious, but careful examination is necessary to localize the site of damage and the artery involved. CT examination can be used to determine
whether the lesion is thrombosis, embolus or haemorrhage (11.70–11.72) and its anatomical site. This is important if any form of antithrombotic therapy is contemplated. Haemorrhage is evident immediately on CT examination, whereas infarction may not be evident until 6–8 hours or more after onset. MRI is rarely used for cerebral vascular lesions, but may be useful for lesions in the brainstem (11.73), as CT is unhelpful at this level.

Immediate examination and investigation should focus on the possibility of a treatable cause of stroke, such as temporal arteritis (see p. 146), embolism from the heart (5.84, 5.93) or embolism in a patient after cardiac surgery, demonstrated by unenhanced CT scan. The open arrowhead points to a high-density embolus within the distal right internal carotid artery; the filled arrowhead points to a similar embolus in the right middle cerebral artery. There is extensive hypodensity in the right middle cerebral artery distribution, reflecting an extensive area of infarction.
CEREBROVASCULAR DISEASE

the large arteries, or, occasionally, a surgically treatable haemorrhage. No specific treatment is available for most patients with stroke, so their immediate management is supportive. Skilled nursing care prevents the development of pressure sores (11.74) and allows adequate nutrition and hydration.

Permanent disability is a common consequence of stroke (11.75–11.77). Long-term rehabilitation, with intensive physiotherapy (11.78), speech therapy and occupational therapy, should be carefully planned and allows about 25% of stroke patients to return to work or normal retirement. Mortality dur-

11.74 Severe sacral pressure sore – one of the serious but preventable complications of immobility following stroke. Note also the presence of a urinary catheter, commonly associated with recurrent urinary infections.

11.76 Permanent flexion contracture of the right hand has occurred in this patient several months after the onset of a dense hemiplegia. This type of disability can be prevented by early and continuing physiotherapy.

11.77 Disuse oedema is a common long-term complication of stroke. In this patient, the left hand remains swollen months after the onset of a dense hemiplegia.

11.75 Loss of postural stability is common after stroke. When the nondominant hemisphere is involved, walking apraxia and loss of postural control are usually apparent. The patient is unable to sit upright and tends to fall sideways. Appropriate support with pillows or cushions should be provided.

11.78 Skilled assistance can greatly aid rehabilitation from stroke. This patient with hemiplegia is being taught to walk without the use of mechanical aids; however, a walking frame can be an important aid in the early stages of rehabilitation.
ing the first month is about 40–50% because of extension of the cerebral damage, aspiration pneumonia and deep vein thrombosis with pulmonary embolism.

Secondary prevention by control of cardiovascular risk factors (see p.228) is as important after stroke as in coronary heart disease. Hypertension must be controlled, and long-term antiplatelet therapy is usually indicated unless the stroke was haemorrhagic. Patients with atrial fibrillation should have cardiac ultrasound to determine whether thrombus is present in the fibrillating atrium. All patients with atrial fibrillation should be considered for oral anticoagulation or, if there is a major contraindication, should receive antiplatelet agents.

Primary prevention of stroke should be directed towards
• control of blood pressure
• diagnosis and surgical treatment of carotid atheroma
• lowering lipid levels
• antithrombotic treatment in atrial fibrillation
• stopping smoking
• control of diabetes mellitus
• reducing haemoglobin in primary proliferative polycythaemia.

TRANSIENT ISCHAEMIC ATTACKS

A transient ischaemic attack (TIA) is defined as sudden focal loss of neurological function, presumed to be caused by a vascular lesion, which lasts less than 24 hours and leaves no residual signs. TIAs become more frequent with advancing years and there is an annual incidence of 0.5 cases per 1000 of the population. Two distinct clinical varieties are described — those in which the damage occurs in the territory supplied by the carotid artery and those in which the territory of the vertebral arteries is affected. The diagnosis of the attack is made on clinical grounds, but often the actual cause is unknown. Most are assumed to be embolic in origin and the source of these emboli is most commonly a plaque of atheroma, which ulcerates and allows formation of small amounts of platelet–fibrin thrombus that, in turn, break off and produce multiple small emboli. Emboli may be seen in the retina (11.79). Sites of thrombus formation include the internal and common carotid artery, the mitral and aortic valves, the left ventricular wall after acute infarction (see p.234), a dilated fibrillating left atrium, especially when there is mitral stenosis (see p.237), and rarely an atrial myxoma (see p.252). In addition to emboli, a search must be made for cardiac arrhythmias, hypertension, bacterial endocarditis, polycythaemia or myeloma — all of which may predispose to TIA.

Patients with carotid territory TIAs (anterior circulation TIAs) present with transient monocular blindness (amaurosis fugax), loss of power or sensation, or loss of speech. Those with vertebrobasilar TIAs (posterior circulation TIAs) present with loss of balance, staggering, and sensory impairment.

Investigation may include 24-hour monitoring for abnormalities of heart rhythm, echocardiography for thrombus on the left ventricular wall or in the left atrium, for mitral valve lesions or for vegetations, and routine chest X-ray. A full blood count, ESR, blood sugar and serology for syphilis are also necessary. Colour flow Doppler (11.80) has revolutionized the imaging of carotid arteries. This technique is of great value for screening as it is noninvasive, easily repeatable and relatively cheap. It is now of such specificity that surgeons may use it to define the extent of proposed surgery without resorting to angiography (11.38), which carries a 1–2% risk of producing acute stroke. Treatment of patients with TIA is required to reduce the risk of completed stroke, which occurs at a rate of 5% per year. TIA is also a marker for subsequent myocardial
infarction, which is a frequent cause of later death. Antiplatelet agents such as aspirin and dipyridamole are helpful, as are conventional anticoagulants. Carotid artery surgery is useful for severe carotid artery atheroma; it is most likely to be beneficial if the arterial lumen is narrowed by 70% or more.

VERTEBROBASILAR INSUFFICIENCY

Vertebrobasilar insufficiency is a clinical syndrome that usually presents in the elderly with a clear history of dizziness associated with head movement, especially on looking upwards or laterally to the extremes. In severe cases, patients may fall down and injure themselves. Various other causes of dizziness must be considered, including benign positional vertigo, postural hypotension, Stokes–Adams attacks, epilepsy and TIA. There is a close relationship to cervical spondylitis (see p. 149) and compression of the vertebral arteries by osteophytes may result in reduction of flow to the cerebellum and occipital regions.

In most instances, the diagnosis is made clinically. X-ray of the neck is of little value as changes in the cervical vertebrae and disc spaces are just as common in those with clinical features as those without. Doppler ultrasound scans may be of value in assessing vascular patency of the vertebral and carotid arteries, but the vertebral arteries may only be revealed by angiography (11.81).

SUBARACHNOID HAEMORRHAGE

Subarachnoid haemorrhage usually results from rupture of an arterial berry aneurysm (70–80%), or leakage from an arteriovenous malformation (5–10%); in 10–20% of cases, no source for the bleeding is found. Berry aneurysms develop at the bifurcations of the intracerebral arteries, probably as a result of an inherited weakness in the vessel wall. They are multiple in about 20% of patients. The common sites are on the anterior cerebral artery or anterior communicating artery (30%), the internal carotid and posterior communicating artery (25%), the middle cerebral bifurcation (13%), at branches from the internal carotid artery (15%) and on the vertebrobasilar system (5%). Most aneurysms are in the subarachnoid space, so their rupture produces subarachnoid haemorrhage. Aneurysms of the internal carotid artery, when this runs in the cavernous sinus, produce pressure on the adjacent cranial nerves.

The clinical presentation is often dramatic with sudden onset of severe headache, often associated with nausea, vomiting and neck pain. The patient may become unconscious. Focal signs are usually absent. Rarely, an aneurysm may present before rupture, with signs of direct pressure on an adjacent nerve (11.12, 11.13). Examination demonstrates neck stiffness and a positive straight-leg raising test. Fundal examination may show papilloedema and occasionally a subhyaloid haemorrhage.

The investigation of choice is CT scanning, which shows...
blood in the subarachnoid space in 95% of cases (11.82) and CT or MRI may show the aneurysm (11.83) or the presence of an intracranial haematoma. If CT scanning is not available, lumbar puncture can be carried out provided there is no evidence of raised intracranial pressure. Within 24 hours of the onset of symptoms there will be uniform blood staining of the CSF; later, xanthochromia develops as a result of haemoglobin degradation (11.27). CT scanning and MRI have largely replaced the routine use of lumbar puncture because patients may have an undetected intracerebral haematoma that could cause brain herniation, and because it may be difficult to distinguish true blood in the CSF from the results of a traumatic tap (11.27). If the patient is fit, four-vessel cerebral angiography should be carried out to identify the site of the bleeding (11.84) with a view to clipping the aneurysm, ideally within 10 days of the incident, because of the highly significant incidence of rebleeding. About 5% of patients rebleed within 24 hours of the initial rupture, and an additional 20% within 2 weeks of the initial event. If untreated, about one-half of the surviving cases will rebleed within 6 months. In up to 10% of cases the aneurysms are multiple.

The goal of surgical treatment of the aneurysm is complete exclusion of the lesion from the circulation by placing a metallic clip on the neck of the aneurysm. Early surgery (within 96 hours) is the best option and should be carried out in a specialist neurosurgical centre.

The only other treatment of proven value once a diagnosis has been made is the use of calcium blockers, which relieve the spasm in adjacent arteries and hence reduce ischaemia in the surrounding brain.

Bleeding from an arteriovenous malformation (11.85) tends to be less severe and such patients present less acutely. There is also a significant incidence of previous epilepsy (see p. 486). Arteriovenous malformations may also be found in the spinal cord and may be difficult to remove safely. Some are amenable to interventional radiology (embolization procedures) and stereotactic radiotherapy, but both methods may damage the function of adjacent brain.

As this is a disease of young and otherwise fit people and the mortality is so high (60% if untreated; 35% if treated), consideration should be given to the question of organ donation in those who die.

**SUBDURAL AND EXTRADURAL HAEATOMAS**

Subdural haematoma is the accumulation of blood in the potential subdural space (i.e. the dura–arachnoid interspace). It often results from a deceleration head injury, as in a fall (11.86) or a road traffic accident, but may also occur spontaneously, especially in the elderly. About 40% of patients also have a skull fracture. The diagnosis is often missed because of
the slow development of symptoms. These include headache, intermittent fluctuation of conscious level, confusion and coma. There are often no immediate focal signs, but pupillary size may be asymmetrical. CT (11.87) or MRI (11.88) confirm the diagnosis. Later, hemiparesis and hemisensory loss may occur.

A chronic subdural haematoma is one that has been present for over 3 weeks. These occur particularly in the aged, often after a trivial injury, so insignificant that it is not remembered. About 20% are bilateral. In only a few cases (about 5%) is there X-ray evidence of a fractured skull. In the long term, if untreated, these chronic subdural haematomas may calcify (11.89). CT and MRI appearances reflect the location, extent and age of the haemorrhage.

Extradural haematoma is often caused by rupture of the middle meningeal artery, associated with skull fracture resulting from direct injury. A haematoma forms and expands between the dura mater and the calvarium. The patient may have a 'lucid interval' after awakening from the unconscious state after trauma. The rapidly accumulating haematoma compresses the hemisphere and produces coma and death.

11.86 Subdural haematoma often follows a fall in an elderly patient, as in this woman who developed suggestive symptoms within a few days of a fall, despite the absence of skull fracture. The diagnosis is often missed because of the slow development of symptoms.

11.88 Right subdural haemorrhage revealed by MRI. The high intensity (white) haemorrhage has dissected under the temporal lobe, and the midline has been displaced to the left.
An abnormal pupillary response may be the only focal sign early in the disease. The diagnosis is confirmed by CT scan (11.90) and the haematoma is removed surgically.

**NERVOUS SYSTEM**

**CEREBRAL VENOUS SINUS THROMBOSIS**

Thrombosis in the large dural venous sinuses is almost always associated with spread of infection from an adjacent focus, with obstruction caused by focal malignancy or with a thrombotic tendency. The lateral sinus, cavernous sinus and superior sagittal sinus may be involved. The common sites of initial infection are the middle ear, the maxillary sinus, the nose and the peri orbital region. Infection of the sagittal venous sinus may result from extension of thrombophlebitis from other dural veins or venous sinuses.

The presenting features are often acute, with abrupt onset of fever, rigors, headache, coma or paresis. Cavernous sinus thrombosis may cause severe eye manifestations (11.91) and there may be papilloedema with visual loss. Occasionally the adjacent cranial nerves may be involved (fifth, sixth).

The diagnosis may be made by a digital subtraction angiogram that defines the thrombus, or by MRI (11.92) or CT scan.

Treatment is with antibiotics. Anticoagulants may be added if there is an evolving neurological deficit.

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**11.90 Extradural haematoma.** A well defined biconvex collection of blood (arrows) compresses the left cerebral hemisphere. There is inward displacement of the grey–white junction (arrowheads) and slight rightward displacement of the left lateral ventricle.

**11.91 Cavernous sinus thrombosis** occurred as a complication of sinusitis in this patient who presented with fever, rigors, headache and painful swelling around the left eye. The eye was difficult to examine, but she had papilloedema. The underlying infection was with *Staphylococcus aureus*, and she responded to appropriate antimicrobial therapy, making a full recovery.

**11.92 Acute right sigmoid sinus thrombosis** (arrows) demonstrated by MRI.
CEREBRAL PALSY

Cerebral palsy is the end result of brain damage caused by a range of disorders which may have been present in the growing fetus, at birth or in early infancy. The most common factors are hypoxia, intracerebral bleeding, trauma, kernicterus, hypoglycaemia and cerebral infection.

The result is a degree of mental retardation, motor and sensory impairment and epileptic fits, all of which produce social and behavioural problems as the child grows. The most common defects are motor: spastic hemiplegias and paraplegia are often compounded by choreo-athetosis and dystonia (11.93, 11.94). There is a wide range of other neurological defects. Such children need careful assessment so that they may be given the opportunity to develop their residual mental and physical skills. Special schooling is often required. These children are now encouraged to lead independent and productive lives, and control of fits and surgical correction of muscle and joint abnormalities are important.

11.93 Spastic quadriplegia in cerebral palsy. Note the asymmetrical spasticity, with flexion contractures of the right arm and both knees, and internal rotation of the left lower limb. The spasticity was complicated by uncontrollable choreo-athetoid movements.

11.94 The spastic hand in cerebral palsy. This common deformity includes pronation of the forearm, flexion of the wrist, the 'thumb in palm' position and flexion of the metacarpophalangeal joints.

EXTRAPYRAMIDAL DISORDERS

PARKINSON'S DISEASE

Parkinson's disease is a progressive degenerative disease of the extrapyramidal system that results from loss of the functional dopaminergic neurons that radiate from the substantia nigra to the caudate nucleus and putamen. This loss results in bradykinesia or akinesia, a resting tremor, restricted mobility resulting from muscular rigidity (cogwheel rigidity) and postural instability. The cumulative lifetime risk of developing parkinsonism is about 1 in 40. Symptoms usually first appear over the age of 50 years. A slow tremor of the hands, often unilateral, is the most common initial sign (11.95). This is typically 'pill rolling' in form and it diminishes on voluntary movement. It usually becomes bilateral, and may involve the upper and lower limbs and the jaw. Slowness of movements is often noticed first by the family rather than the patient. Rigidity compounds this
11.97 Parkinson’s disease is characteristically associated with a mask-like face, devoid of emotion despite changes in circumstance. The patient often dribbles saliva, and commonly has monotonous speech.

Identified causes of Parkinsonism

Secondary causes:
- Drugs: phenothiazines, reserpine, methyldopa
- Infections: post-encephalitic
- Toxins: carbon monoxide, manganese and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) – a synthetic opiate by-product
- Hypoparathyroidism
- Vascular: cerebrovascular disease
- Trauma: e.g. in boxers (pugilist’s encephalopathy)
- Space-occupying lesions

Parkinsonism in combination with:
- Progressive supranuclear palsy (Steele–Richardson)
- Alzheimer’s disease
- Shy–Drager syndrome (primary autonomic failure)
- Normal pressure hydrocephalus
- Huntington’s chorea
- Hepato-lenticular degeneration (Wilson’s disease)
- Athetoid cerebral palsy

Involuntary disorders of movement

A number of involuntary disorders of movement may occur.

Physiological tremor at about 10Hz is normal, but increases to a noticeable level in anxiety and thyrotoxicosis.

Postural tremor, usually at about 6–7Hz, may occur spontaneously as an essential tremor or in families as a familial tremor. This is seen in the outstretched hands and during movement. Stress increases it and alcohol inhibits it. Beta blockade with propranolol is the treatment of choice.

Chorea is a rapid, semipurposeful movement seen in levodopa toxicity (dysexasia), and also in Huntington’s disease (see p. 486), and other disorders such as Sydenham’s chorea (see p. 236), pregnancy chorea, systemic lupus erythematosus and drug-induced chorea (11.99).

Hemiballismus is a unilateral disorder with dramatic, wild flailing of the limbs. It is attributed to a lesion, usually vascular, in the subthalamic nucleus.

Dystonias are a group of disorders in which spasm may be restricted to one area, for example in the neck (spasmodic torticollis, 11.100), in the facial muscles around the eyes (blepharospasm) or in the hand (writer’s cramp). Dystonias may rarely be widespread as a grossly disabling disorder that includes the trunk (torsion dystonia, 11.101). Muscle spasm is amenable to local treatment with injected botulinum toxin type A, which causes irreversible neuromuscular blockade over a period of 3
11.99 Chorea. A light tracing, obtained by following movements of lights held in both extended hands in a dark room for 30 seconds. Note the great extent of purposeless movement in this condition.

11.100 Spasmodic torticollis. In this condition, the head turns spasmodically as a result of asymmetrical contraction of the neck muscles. The condition is not usually associated with any other pathology.

11.101 Torsion dystonia. This congenital condition is associated with severe fixed posturing of the hands, arms, neck and trunk. It is difficult or impossible to treat.

11.102 Clinical features of multiple sclerosis.

**MULTIPLE SCLEROSIS**

Multiple sclerosis is the most common disorder of myelin affecting the CNS, but there are many other acquired and inherited leucodystrophies.

It is a disease of unknown cause in which there is patchy demyelination in brain and spinal cord. The acute lesions are infiltrated by lymphocyte and plasma cells and may have an immunological basis. The end result of recurrent acute lesions is a chronic disease with relapses and remissions, but with the development of progressive neurological deficit. The disease has a definite geographical predilection, being rare in equatorial countries and increasing in incidence further away from the equator. In the UK, there is a higher incidence in the northern Isles of Orkney and Shetland compared with the south of England. It affects mainly young adults and is the most common neurological disorder of early adult life. The clinical features take many forms (11.102).

<table>
<thead>
<tr>
<th>Site</th>
<th>Features</th>
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</thead>
<tbody>
<tr>
<td>Optic neuritis (retrobulbar neuritis)</td>
<td>Pain on ocular movement, loss of central vision, sometimes papillitis, Diplopia</td>
</tr>
<tr>
<td>Brainstem lesions, III, IV, VI nerves</td>
<td></td>
</tr>
<tr>
<td>Cerebellum and its brainstem connections</td>
<td>Ataxia, dysarthria, oscillopsia</td>
</tr>
<tr>
<td>Subcortex, brainstem, spinal cord</td>
<td>Paraesthesiae, numbness, impaired position sense, trigeminal or other acute pain syndromes</td>
</tr>
<tr>
<td>Pyramidal tract</td>
<td>Limb or bulbar weakness, spasticity, clonus, brisk tendon reflexes, extensor plantar responses, urgency, frequency, urinary retention</td>
</tr>
<tr>
<td>Subcortical demyelination</td>
<td>Dementia, euphoria, depression</td>
</tr>
</tbody>
</table>

months and may produce dramatic improvements in selected patients.

Tardive dyskinesias are involuntary movements of the face and tongue (orofacial dyskinesias), and of the limbs, caused by treatment with phenothiazines and butyrophenones. They are common in treated patients with chronic schizophrenia.
Optic neuritis is one of the most common early presentations of multiple sclerosis, but is not always followed by further features of progressive disease. It is usually unilateral, and is associated with loss of visual acuity, loss of colour vision and, sometimes, pain in the eye. These symptoms may come on suddenly and progress rapidly to a central scotoma. Examination shows the extent of visual loss and the presence and size of a scotoma. There is a defective pupillary response (afferent pupillary defect). The retina may show papilloedema (or papillitis; 11.103) in the early stages. Most patients show rapid resolution of the acute symptoms but residual signs often remain, such as visual impairment, optic pallor (11.104) or even optic atrophy (7.11).

Sensory impairment is also common at onset with numbness and paraesthesiae. Involvement of the pyramidal tracts usually occurs later. It is usually bilateral, and the patient presents with motor, sensory, and bladder function abnormalities. Brisk reflexes are usual with an extensor plantar response.

Brainstem involvement may present as sixth nerve palsy (11.15), as internuclear ophthalmoplegia (11.105) or with nystagmus. Involvement of the cerebellum results in ataxia and dysarthria. Subcortical involvement results in dementia and euphoria. Depression is also a common feature at all stages of the disorder.

There is no definitive diagnostic test, and sometimes the diagnosis only becomes clear clinically over the course of years because of the relapsing nature of the neurological findings. Evoked responses — visual (11.25), auditory or somatosensory — may be of value; they depend on the demonstration of delayed nerve conduction. Lumbar puncture shows a raised CSF total protein, with a selective rise in IgG and oligoclonal bands on electrophoresis. The most sensitive methods of demonstrating the areas of demyelination are CT (11.106) and MRI (11.107).

There is no specific treatment but high-dose intravenous steroids have a place in the acute episode. Dietary manipulation and hyperbaric oxygen have been used, but there is little evidence of their efficacy. Physiotherapy, psychotherapy and family counselling and support are mandatory. Depression should be actively treated and spasticity may respond to baclofen. Pain and troublesome paraesthesiae may respond to carbamazepine. Urinary retention and incontinence are treated symptomatically and care must be taken to avoid pressure sores (11.74) as the patient becomes immobile.

11.103, 11.104 Retrobulbar neuritis is a common initial presentation of multiple sclerosis. In the early stages the disc may appear normal, or may develop papillitis with blurred margins and occasional haemorrhages (11.103). Later, the patient may develop the complete pallor of optic atrophy (11.104); alternatively the disc may return to a normal appearance.

11.105 Internuclear ophthalmoplegia may be a presenting feature of brainstem involvement in multiple sclerosis. On lateral gaze to the right, adduction of the left eye is incomplete. On convergence, eye movement was normal. The lesion is in the left medial longitudinal bundle — between the nucleus in the pons and the third nerve nucleus on the opposite side.

11.106 Multiple sclerosis. This contrast-enhanced CT scan shows multiple areas of abnormal enhancement, each of which represents an area of demyelination.

11.107 Multiple sclerosis. This MRI picture shows multiple 'high signal' lesions in the white matter of both hemispheres. Again, these represent multiple areas of demyelination.
MOTOR NEURONE DISEASE

Motor neurone disease is found in 1 in 12,000 of the population (in the UK), with a male: female ratio of 3:2 and a peak incidence at the age of 70 years. It is a rare, progressive degenerative disease of the upper and lower motor neurons that causes severe disability; patients have a 5-year survival of about 40%. There is no impairment of intellect, sensation, sexual or bowel or bladder function or balance. Frontal lobe dementia may occur. No cause has been found, although there is, on occasion, a family history. Clinical presentation may be in one of three patterns.

• progressive muscular atrophy (PMA) patients present with wasting of the small muscles in one hand (11.108), which is rapidly followed by wasting in the other and proximal spread to involve the arms; the feet may be similarly involved; symptoms usually include weakness, easy fatigability, muscle cramps and lack of muscle strength; the main signs are muscle wasting with loss of power and fasciculation; tendon reflexes may be absent

• amyotrophic lateral sclerosis (ALS) patients present with features of degeneration of the upper motor neuron and the lateral corticospinal tracts; there is usually an associated progressive muscular atrophy, so that the clinical picture is of combined upper and lower motor neuron degeneration

• progressive bulbar palsy mainly affects women; patients have involvement of the cranial nerves with upper and lower motor neuron lesions; the dominant and distressing features are dysarthria and dysphonia, difficulties in chewing and swallowing, and regurgitation of food and fluids via the nose because of palatal palsy; the tongue may be wasted (11.109) and fasciculation is obvious; paralysis of the respiratory muscles is also apparent; aspiration pneumonia is a common complication and, with hypoventilation, causes death.

The diagnosis may be made on clinical grounds alone but electromyography may provide evidence of denervation. The CSF is normal. Cervical and lumbar spondylosis and motor neuropathies must be excluded, as they also cause amyotrophy (7.95). There is no specific treatment, but patients and their families need physical and psychosocial support.

DISORDERS OF THE SPINAL CORD

SYRINGOMYELIA

Syringomyelia results from the formation of a ‘syrinx’ in the spinal cord. This is a cavity filled with CSF that probably arises during development, when it may be associated with an Arnold–Chiari malformation. Less commonly it occurs after trauma. The syrinx may extend all the way down the central canal of the cord, but is usually most prominent in the upper cervical cord and in the brainstem (syringobulbia). As the cavity enlarges there is progressive neurological impairment, starting with the decussating fibres of the spinothalamic tract, which carry pain and temperature, and resulting in dissociation sensory impairment of the trunk and upper limbs. This impairment results in the development of painless ulcers of the hands from unrecognized trauma and burns (11.110) and later to Charcot’s joints in
the upper limb (11.111). Later, the anterior horn cells are affected, leading to wasting of the small muscles of the hand (11.110) and arms with absent reflexes. Extension to the corticospinal tracts produces a spastic paraplegia. A syrinx in the brainstem (syringobulbia) results in loss of cranial nerve motor function with dysphagia and dysarthria, impairment of hearing and loss of fifth nerve sensation or a Homer's syndrome (11.10).

The diagnosis is made by showing the presence of a cervical expansion of the cord on myelography, or — most commonly now — by demonstrating the presence of the cavity on CT scanning or MRI (11.112).

FRIEDREICH'S ATAXIA

Friedreich's ataxia is an autosomally transmitted (both dominant and recessive) form of spinocerebellar degeneration. Patients with the disease usually present between the ages of 5 and 10 years, with clumsiness in walking. This progresses inexorably and is associated with loss of proprioception and vibration sense, which produces lower limb atrophy and loss of tone. Tendon reflexes are lost and the plantar responses are extensor. The degenerative process moves upwards with time, to affect speech and eye movements.

In addition to the neurological defect, there are skeletal abnormalities, notably pes cavus (11.113), scoliosis, and a high-arched palate. There may also be conduction defects in the heart, cardiomegaly and heart failure.

Rare associated nerve defects include retinal degeneration, deafness, mental retardation and lower motor nerve degeneration.

Diagnosis is made on clinical finding and family history. Genetic counselling is important. Treatment is purely supportive.

SPINA BIFIDA

Spina bifida results from defective fusion of the vertebral arches. The most common site is in the lumbar region. Spina bifida occulta may be found in asymptomatic people who are X-rayed for some other reason (11.114). In some patients, there may be...
11.114 Occult spina bifida, discovered by chance on X-ray. The fifth lumbar and first sacral vertebrae have failed to fuse posteriorly in the midline, but the patient had no symptoms.

Disorders of the Spinal Cord

11.115 Occult spina bifida may be suggested by the presence of a tuft of hair over the base of the spine. This is usually a harmless anomaly, but may be associated with diastematomyelia.

11.116 Meningomyelocele and hydrocephalus in a neonate. This combination is likely to result in severe neurological disability despite any possible surgical treatment.

Paraplegia

Paraplegia is paralysis of both lower limbs and may be acute or chronic. The limbs are flaccid in the acute phase and become spastic later. There is loss of bladder control. A large number of diseases may produce similar clinical features (11.117).

<table>
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<th>Causes of Paraplegia.</th>
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<td>Falls, road traffic accidents</td>
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<tr>
<td><strong>Metabolic</strong></td>
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<td>Vitamin B12 deficiency</td>
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11.117 Causes of paraplegia.
Investigations should include a full blood count, sedimentation rate, plain X-rays, myelography and CT or MRI scan (11.118). A neurosurgical or orthopaedic opinion is urgently required in paraplegia of acute onset.

NEOPLASMS OF THE SPINAL CORD

Primary neoplasia causing nerve root or cord compression may arise from any of the tissues in the area, and metastases from distant organs may also involve the spinal cord, nerve plexi or surrounding structures. The lesions may therefore be paravertebral, extradural, intradural or intramedullary. Symptoms may be produced by direct invasion, by compression or, more rarely, by ischaemia resulting from invasion of the nutrient arteries. The process is usually insidious, with local pain that may radiate along a dermatome and may produce motor signs such as muscle wasting (4.172), sensory signs and occasionally autonomic changes (anhidrosis, hyperhidrosis or Horner's syndrome, 4.173, 11.10). Cord compression may result in lower motor neuron features at the level of the lesion, coupled with sensory loss and progressive features of upper motor signs below this level. Pain may be local or referred. Dysfunction of the bowel and bladder may be prominent early features. Occasionally, patients may present acutely with paraplegia.

Myelography will demonstrate most tumours and CSF examination usually reveals xanthochromia, a yellow CSF rich in protein. Queckenstedt’s test may be positive and malignant cells may rarely be found. The diagnosis may also be made on straight X-ray or by CT scan or MRI (11.119).

Treatment is dependent on the diagnosis. If the patient has suffered from previous malignancy, especially of lung or breast or a lymphoma, treatment may be possible with radiotherapy or appropriate chemotherapy, or both. Biopsy may be necessary to establish a diagnosis and surgical resection to relieve cord or nerve root compression.
DISORDERS OF PERIPHERAL NERVES (NEUROPATHIES)

Many disease processes produce peripheral neuropathy (11.120). Most patients present with features of lower motor neuron involvement and sensory changes, but sometimes also or predominantly with motor changes. The cranial nerves may be affected by the same processes (see p. 475). The condition may be symmetrical or localized to one side. There are great variations in the degree of defects and their distribution. Motor involvement is associated with wasting and loss of power (7.102, 11.121, 11.122). Sensory features include numbness, paraesthesiae or hyperaesthesiae, pain and impaired temperature sensation. There may be associated skin ulceration and loss of skin hair. The tendon reflexes are absent.

Patients with autonomic neuropathy typically present with orthostatism and may have associated dysphagia, gastric atony with vomiting, diarrhoea and gustatory sweating (7.103). There is usually retention of urine with overflow incontinence and failure of erection. Hypotension may occur on standing (postural hypotension).

IMMUNE POLYNEUROPATHY

Guillain–Barré syndrome (acute infectious polyneuropathy, AIP) is thought to be an immune polyneuropathy as it appears 2–3 weeks after a virus infection of the upper respiratory or gastrointestinal tract. It may affect all ages, but is most commonly found in the middle years of life. There may be a range of prodromal symptoms, including pyrexia, headache, nausea and vomiting; these are followed by back and limb pain, with a gradual onset of ascending motor neuropathy starting in the limbs, then involving the truncal muscles, cranial nerves and muscles of respiration. Sensory changes may be present early in the disease and dysaesthesia may be severe. Autonomic involvement may also be present and associated with postural hypotension and arrhythmias. Death may occur from respiratory impairment or arrhythmias.

The diagnosis is made on the clinical picture, and it may be substantiated by finding a normal cell count in the CSF, with normal pressure but a high protein level, which may give a deep yellow colour to the CSF. There may be evidence of delayed nerve conduction velocities.

11.120 Causes of peripheral polyneuropathies.

11.121 & 11.122 Wasting of the hand as a consequence of ulnar neuropathy. Note the marked wasting of the interosseous muscles, especially the first dorsal interosseous. This patient also had early finger clubbing, and he proved to have a bronchial carcinoma.
The natural history of the disease is of a progressive neuropathy over several days, a period of stable neuropathy and then gradual recovery of normal function in the majority of cases. Intensive respiratory support may be required at any stage if the respiratory muscles are involved. In the early stages of the disease, plasmapheresis has been used with benefit. Steroids may be of value in chronic inflammatory demyelinating polyneuropathy.

DIRECT INJURY AND COMPRESSION NEUROPATHY

Acute
Acute damage to peripheral nerves can result from direct penetrating or nonpenetrating trauma and may involve any nerve or plexus. The result is loss of motor and sensory function, and atrophy of muscle and skin in the areas supplied. The most common types of injury include acute stretching resulting from difficult delivery (11.123) or from trauma in later life (especially road traffic accidents), and compression from coma resulting from alcohol, drugs, during general anaesthesia or simply from lying or sitting in a cramped position for a prolonged period. Penetrating injuries include bullet or knife wounds and ill-placed intramuscular injections. The most common such lesion is that involving the radial nerve, which is usually injured as it winds round the back of the humerus (Saturday night palsy — as a result of alcoholic coma - 11.124). Other examples are the peroneal nerve which may be compressed as it passes over the head of the fibula and the ulnar nerve at the elbow (producing signs similar to those in 7.102).

Chronic
Carpal tunnel syndrome is more common in women (3 per 1000 patients per year) than in men (1 per 1000 patients per year) and is most common in middle-aged women. It results from compression of the median nerve as it passes through the carpal tunnel deep to the flexor retinaculum. The cause is often unclear, but sometimes a predisposing disorder is present (11.125). The main complaints are of pain, numbness and paraesthesiae in the fingers supplied by the median nerve. The symptoms are often worse on awakening. Pain may radiate up the arm to the elbow, and it may be relieved by elevation of the hand or by gentle shaking of the hand in the air (Flick test). Use of the hand leads to loss of the symptoms. Examination shows sensory loss over the distribution of the median nerve — usually the thumb, index and middle fingers and one of half the ring finger (11.126, 11.127). There may be power loss in the thumb, both in abduction and adduction (i.e. abductor pollicis brevis, flexor pollicis brevis and opponens) and there may be wasting of the thenar eminence (11.128).

Additional tests include
- Tinel’s sign which is elicited by tapping with a finger over the carpal tunnel — this produces paraesthesiae in the hand and travelling up the arm
- Phalen’s test is similar to the above, but the stimulus is flexion of the wrist for 60 seconds; a positive test is the production of paraesthesiae
- Tourniquet test is the testing of sensation deficit resulting from application of an upper arm tourniquet

Nerve conduction studies are also of value in early diagnosis.

Management depends on the cause. If this is temporary (e.g. pregnancy), then simple measures such as splints or diuretics may buy enough time for spontaneous resolution to occur after delivery. Steroid injection into the carpal tunnel gives symptomatic relief and is sometimes curative. Otherwise, surgical decompression is required; this leads to return of motor function and usually to some sensory recovery.

In the thoracic outlet syndrome there is compression of the lower trunks of the brachial plexus as they pass over an abnormal cervical rib (5.189) or fibrous band, or over the normal first rib and muscle. Damage is usually confined to the C8, T1 fibres. Patients present with paraesthesiae, weakness, numb-
ness of the ulnar fingers and wasting of the small muscles of the hand, especially the thenar muscles. There may be coincidental obstruction of the arterial supply of the limb (see p. 266). Symptoms are usually more apparent when the arm is abducted. Treatment is by removal of the fibrous band or rib.

Ulnar nerve damage (entrapment) is usually caused by recurrent trauma to the nerve in its shallow groove at the back of the medial condyle of the humerus. It can also occur after fracture of the condyle and subsequent healing. There is usually weakness and atrophy of the interossei with clawing of the fingers and difficulty with fine movements. Sensory loss may be detected in the small finger and the adjacent half of the ring finger and it may be possible to elicit sensory complaints by compressing the nerve at the elbow.

Compression of the lateral cutaneous nerve of the thigh may occur as it passes under the inguinal ligament, especially in grossly obese individuals wearing a tight belt or corset. Paraesthesiae occur in the nerve distribution, that is the lateral surface of the thigh as far down as the knee. Symptoms may be brought on by change in posture, especially by sitting. Resolution of symptoms can be produced by advice about clothing and by weight control and some patients require surgical decompression.

**NEUROCUTANEOUS SYNDROMES**

**STURGE–WEBER SYNDROME**

Sturge–Weber syndrome, a congenital condition with a diffuse capillary haemangioma of the face, forehead and anterior crown, in the distribution of the ophthalmic division of the trigeminal nerve (11.129), is associated with similar ipsilateral angiomata of the pia mater and underlying cortex, typically in the parieto-occipital region. This combination is associated...
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11.126 & 11.127

**Carpal tunnel syndrome.** The
common areas of sensory
impairment are marked in this
patient. Note that they usually
extend round the fingertips on to
the nail area in the affected
fingers and even further over the
extensor surface on the thumb.
Wasting of the thenar eminence
is also seen.

11.128 Carpal tunnel syndrome in the right
wrist, with wasting of the thenar eminence,
demonstrated by opposing the thumb. The abductor
pollicis brevis muscle is weak and wasted. Compare
the appearance with the normal left hand. The
patient has already undergone surgical decompression
on the right.

11.129 Sturge–Weber syndrome. This patient has a classic
diffuse capillary haemangiomata in the distribution of the
ophthalmic, nasociliary and maxillary branches of the trigeminal
nerve. The lesion extends backwards over the anterior two-thirds
of the crown of the head.
NERVOUS SYSTEM

11.130 Sturge-Weber syndrome. This enhanced CT scan shows increased density throughout the atrophic left cerebral hemisphere, probably representing a combination of calcification and enhancement of the pial angiomas. There is enhancement of an enlarged left ventricular choroid plexus, which is again angiomatous. The right frontal lobe also shows some atrophy, and this patient may have bilateral involvement.

11.131 Neurofibromatosis (Type II). This patient has multiple cerebral tumours, as demonstrated by gadolinium-enhanced MRI. This scan shows bilateral eighth nerve tumours, a meningioma along the left petrous bone and bilateral parasellar meningiomas.

with the development of epilepsy — usually generalized seizures — with associated mental retardation or hemiparesis, or both. Straight X-ray of the skull or CT scan (11.130) show calcification in the deep layers of the cortex.

Treatment is by drug control of epilepsy and cosmetic covering of the facial lesions.

NEUROFIBROMATOSIS

Neurofibromatosis (von Recklinghausen’s disease) is a rare disease with an autosomal dominant transmission, in which multiple neurofibromas develop in peripheral and cranial nerves, and in which CNS tumours also appear (gliomas and meningiomas). There is also a rare association with the development of phaeochromocytomas (see p. 318). Two distinct types are now recognized.

- **Type I** (abnormality on chromosome 17) is generally associated with peripheral lesions — papillomas of skin, multiple cutaneous neurofibromas (2.86), café-au-lait spots, pigmented hamartomas of iris (Lisch nodules), axillary freckling, spinal and autonomic neurofibromas, phaeochromocytomas and optic gliomas
- **Type II** (abnormality on chromosome 22) is generally associated with central lesions — bilateral acoustic neurofibromas,

11.132 Adenoma sebaceum of the face – a marker of tuberous sclerosis (epiloia). The lesions are angiofibromas and in tuberous sclerosis they are associated with mental retardation, epilepsy and other skin changes.

11.133 Tuberous sclerosis. This CT scan shows calcified periventricular lesions. These are hamartomatous tubers, containing both neurons and astrocytes. The patient also shows bilateral ventricular enlargement (hydrocephalus) that probably results from the presence of tubers near the foramen of Munro, causing CSF obstruction.
multiple intracranial meningiomas (11.131), schwannomas of cranial nerves and a few cutaneous lesions.
Diagnosis is readily confirmed by biopsy. Excision of peripheral lesions that rapidly change in size is important, because sarcomatous change may occur. Gene markers are of value in antenatal diagnosis and subsequent counselling is required.

TUBEROUS SCLEROSIS (EPILIOIA)

Tuberous sclerosis (epiloia) is inherited as an autosomal dominant trait and those affected present in childhood with mental retardation (50%), epilepsy (75%) and typical facial lesions (adenoma sebaceum, 11.132). These lesions are angiofibromas. They are rarely seen before the age of 2 years, and may not appear until middle age, but are present in 85% of all cases. The diagnosis is usually clinically obvious. There may also be nodules in the retina (phakomas). Skin changes in addition to those on the face include white oval patches on the thorax (ash leaf patches — found in 80% of all cases), fibromas under the nails and naevi at the base of the spine (shagreen patches). There is a rare association with intracranial gliomas and hamartomas of the kidney. X-ray of the skull or CT scan may show calcification in the walls of the lateral ventricles (11.133). There may also be cardiac rhabdomyomas.
Treatment involves control of epilepsy. Genetic counselling is important.

DISORDERS OF MUSCLE

MUSCULAR DYSTROPHIES

Muscular dystrophies are a large group of poorly understood genetic disorders in which there is progressive degeneration of selected muscle groups. Those affected usually present with progressive muscle weakness in the early years of life.
One of the most common is Duchenne muscular dystrophy (DMD), which is transmitted as an X-linked recessive disorder and affects males. DMD affects 1 in 3500 live male births and about one-third of cases arise in previously unaffected families. The syndrome is caused by deletion of the dystrophin gene on the X chromosome. This results in failure to produce dystrophin, which is located on the muscle fibre surface membrane and is necessary for optimum muscle function. Symptoms and signs become obvious at the age of about 2 years, with weakness of the pelvic and shoulder girdle muscles, and the first signs are commonly difficulty in walking, abnormal gait, frequent falling and difficulty in climbing steps and in getting off the floor (11.134, 11.135). Some muscle groups — especially in the calf — become hypertrophied. The course is inexorably downhill and by adolescence the boy is often deformed and invariably in a wheelchair (11.136, 11.137). The most common cause of death is hypostatic pneumonia associated with failure
of the muscles of respiration and associated cardiac failure.

The diagnosis is usually obvious clinically and from the family history. There is usually massive elevation of the serum creatine kinase. Muscle biopsy shows necrosis of short segments of muscle fibres in focal groups with some attempts at fibre regeneration. Eventually, the fibres become progressively distorted, replaced by dense collagenous bands infiltrated with fatty tissue.

No treatment will alter the course of the disease. Genetic counselling for the family and psychosocial support are important.

A number of less common dystrophies include
- Becker muscular dystrophy, a milder X-linked disease than DMD, in which the patients live well into adult life
- Limb-girdle dystrophy is an autosomal recessive disorder that affects the pelvic and shoulder girdle of boys and girls and is progressive in symptomatology (11.138)
- Facioscapulohumeral dystrophy is an autosomal dominant disease that affects the muscles of the face, neck and shoulders; these atrophy to give characteristic winging of the scapulae and atrophy of the deltoids and pectoralis major (11.139). Scoliosis occurs because of loss of support from weak truncal muscles. The pelvic girdle muscles may be similarly affected. The history is of progressive muscle weakness and atrophy.

**MYOTONIC DYSTROPHY**

Myotonia is increased spasm of muscle fibres that results from abnormalities of the muscle membrane producing a delay in relaxation. Myotonic dystrophy (dystrophia myotonica) is an uncommon disorder (prevalence 5–50 per 100 000 of the population). It is transmitted as an autosomal dominant disorder and presents in the age range 20–30 years with weakness of the limb muscles associated with myotonia. This becomes apparent as failure to relax a grip. There is also cranial muscle involvement, often with ptosis, difficulty in whistling and dysarthria. There is associated wasting of the temporalis, masseter and sternomastoid muscles. A variety of other signs may occur, including the development of cataracts, frontal baldness (in men) and testicular or ovarian atrophy. The facies is very typical (11.140). There may be associated cardiomyopathy with arrhythmias, especially atrial flutter; and there may occasionally be mental retardation.

The diagnosis is made on clinical grounds. Treatment is generally unsatisfactory and is directed at the myotonia (e.g. procainamide). Genetic counselling is important. Myotonia congenita (Thomsen's disease) is a rare myotonic disorder, which may be dominant or recessive and is characterized by muscle hypertrophy and a milder degree of myotonia that is provoked by cold weather and improves with exercise.

**MYOPATHIES**

Myopathy occurs in a number of systemic disorders, including dermatomyositis, polymyalgia rheumatica and a number of endocrine disorders such as Cushing's syndrome, Addison's disease, thyrotoxicosis and hypothyroidism; it may occur as a remote effect of malignant tumours. A number of other rare forms of myopathy also occur.
PERIODIC PARALYSIS

Disorders in this group are often familial, being transmitted as an autosomal dominant trait. Repeated attacks of generalized muscle weakness are associated with either a high or low serum potassium concentration. The symptomatology usually starts in adolescence and is often provoked by hard physical exercise. The limb muscles are usually affected and weakness may last for many hours before spontaneously improving. In the hypokalaemic variant, attacks may also be precipitated by a carbohydrate meal. Examination of the patient often shows very little except in the acute phase in which there may be myotonia and a positive Chvostek's sign.

The diagnosis may be confirmed by finding a low potassium (2.5–3.5 mEq/litre) or a high potassium (6–7 mEq/litre) concentration. It is important to exclude thyrotoxicosis and diuretic therapy as causes. Occasionally, the potassium levels are normal.

Remission of the condition may occur spontaneously after the age of 30 years. In the acute hypokalaemic attack, an infusion of potassium chloride will terminate the symptoms; in the hyperkalaemic variant, intravenous calcium gluconate is effective.

MYASTHENIA GRAVIS

Myasthenia gravis is a disease in which a reduction in the available functional nicotinic receptors at the neuromuscular junction is associated with increased fatigability and weakness of striated muscles. It may appear at any time of life and affects women more commonly than men.

The cause is not known, but it is an autoimmune condition with evidence of IgG antibodies to acetylcholine receptor protein in 90% of patients. There is an increased incidence of other autoimmune disorders, such as rheumatoid arthritis, pernicious anaemia and systemic lupus erythematosus in patients with myasthenia gravis. Some patients have a thymoma.

The common presentation is with muscle weakness and fatigability. This commonly involves the ocular muscles but any group may be affected. Ptosis and diplopia are common manifestations and get worse during the course of the day. Similarly affected are the muscles of mastication, swallowing and speech. Muscle bulk is usually maintained until late in the disease.

The diagnostic test is the edrophonium (Tensilon) test (11.141, 11.142). Electromyography shows a declining response to repeated stimuli. The presence of circulating antibodies to

11.141 & 11.142 Myasthenia gravis. The edrophonium (Tensilon) test can be used to confirm the diagnosis. Facial weakness is provoked by repeated facial movements (11.141). Edrophonium chloride, a short-acting anticholinesterase, is then injected intravenously – initially 2 mg as a test dose, followed after 1 minute by a further 8 mg if there are no adverse effects. In myasthenia gravis the facial weakness is rapidly relieved by this test (11.142). Objective testing of muscular power elsewhere in the body will reveal similar responses.
acetylcholine receptors is diagnostic but antibody-negative forms are recognized. A search for a thymoma should be made by X-ray (11.143) or thoracic CT scanning.

Drug treatment is with a long-acting anticholinesterase, which is usually symptomatically effective. Thymectomy may also result in long-term improvement, and immunosuppression with prednisolone and azathioprine may be beneficial, as is plasma exchange in severe cases.

The course of the disease is variable but progressive, and death may result from aspiration pneumonia.

**EATON-LAMBERT SYNDROME**

Eaton–Lambert syndrome (myasthenic syndrome) is a rare disorder of neuromuscular transmission that is found in patients with small cell (oat cell) carcinoma of the lung. It is associated with antibodies to presynaptic calcium channels, and patients present with proximal muscle weakness of the limbs, which worsens with exertion. There may also be sensory features, particularly paraesthesiae. Tendon reflexes are usually absent and cranial nerves are rarely affected.

The diagnosis is made by EMG which shows an increasing response on repetitive stimulation. As the neurological symptoms usually precede the overt appearance of the lung lesion an intensive search should be made of the lungs (see p. 210). Plasmapheresis may be of some value in treating the Eaton–Lambert myasthenic syndrome and some patients respond to guanidine.

11.143 Thymoma (arrow) in a patient with myasthenia gravis. A lateral film confirmed that this mass was in the anterior mediastinum. The differential diagnosis of this appearance includes lymphadenopathy, retrosternal thyroid tissue or a dermoid tumour; however, in the presence of myasthenia gravis, thymoma is the most likely diagnosis. Thymectomy may result in cure or great improvement in the myasthenia.