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546 • RESPIRATORY MEDICINE Insets (idiopathic kyphoscoliosis) Courtesy of Dr I. Smith, Papworth Hospital, Cambridge; (serous, mucopurulent and purulent sputum) Courtesy of Dr J. Foweraker, Papworth Hospital, Cambridge. Hands Digital clubbing Tar staining Peripheral cyanosis Signs of occupation CO_2 retention flap Radial pulse Rate Rhythm Jugular venous pulse Elevated Pulsatile Face, mouth and eyes Pursed lips Central cyanosis Anaemia Horner's syndrome (Ch. 25) Thorax (see opposite) – Palpation From the front: Trachea central Cricosternal distance Cardiac apex displaced Expansion From behind: Cervical lymphadenopathy Expansion Leg oedema Salt and water retention Cor pulmonale Venous thrombosis • Respiratory rate • Cachexia, fever, rash • Sputum (see below) • Fetor Observation Finger clubbing Blood pressure Arterial paradox Auscultation Breath sounds: normal, bronchial, louder or softer Added sounds: wheezes, crackles, rubs Spoken voice (vocal resonance): absent (effusion), increased (consolidation) Whispered voice: whispering pectoriloquy Percussion Resonant or dull 'Stony dull' (effusion) Idiopathic kyphoscoliosis • Locale: Oxygen delivery (mask, cannulae) Nebulisers Inhalers Serous/frothy/pink Pulmonary oedema Mucopurulent Bronchial or pneumonic infection Purulent Bronchial or pneumonic infection

Blood-stained Cancer, tuberculosis, bronchiectasis, pulmonary embolism Sputum

Inspection Deformity (e.g. pectus excavatum) Scars Intercostal indrawing Symmetry of expansion Hyperinflation Paradoxical rib movement (low flat diaphragm)

Insets (upper lobe collapse) From http://3.bp.blogspot.com; (pneumothorax) http://chestatlas.com; (pleural effusion) www.ispub.com. Chronic obstructive pulmonary disease Use of accessory muscles Hyperinflated 'barrel' chest Auscultation Reduced breath sounds – wheeze Pursed lip breathing Central cyanosis Prolonged expiration Reduced cricosternal distance Intercostal indrawing during inspiration Cardiac apex not palpable Loss of cardiac dullness on percussion Inward movement of lower ribs on inspiration (low flat diaphragm) Also: raised jugular venous pressure (JVP), peripheral oedema from salt and water retention and/or cor pulmonale Heart sounds loudest in epigastrium Pulmonary fibrosis Small lungs Reduced expansion Dull percussion at bases (high diaphragm) Central cyanosis Tachypnoea Auscultation Fine inspiratory crackles at bases See also Fig. 17.56 Also: finger clubbing common in idiopathic pulmonary fibrosis; raised JVP and peripheral oedema if cor pulmonale Right middle lobe pneumonia Right upper lobe collapse Right pneumothorax Large right pleural effusion Inspection Tachypnoea Central cyanosis (if severe) Palpation ↓Expansion on R Percussion Dull R mid-zone and axilla Auscultation Bronchial breath sounds and ↑vocal resonance over consolidation and whispering pectoriloquy Pleural rub if pleurisy Inspection ↓Volume R upper zone Palpation Trachea deviated to R ↓Expansion R upper zone Percussion Dull R upper zone Auscultation ↓Breath sounds with central obstruction Inspection Tachypnoea (pain, deflation reflex) Palpation ↓Expansion R side Percussion Resonant or hyper-resonant on R Auscultation Absent breath sounds on R Tension pneumothorax also causes

Deviation of trachea to

opposite side Tachycardia and

hypotension Inspection Tachypnoea Palpation ↓Expansion on R Trachea and apex may be moved to L Percussion Stony dull R mid- and lower zones Auscultation Absent breath sounds and vocal resonance R base Bronchial breathing or crackles above effusion Obscures R heart border on X-ray X-ray Deviated trachea (to R) Elevated horizontal fissure ↓Volume R hemithorax Central (hilar) mass may be seen

 outward movement of the ribs on the costovertebral joints, caused by contraction of the external intercostal muscles (innervated by intercostal nerves originating from the thoracic spinal cord). Expiration is largely passive, driven by elastic recoil of the lungs. The conducting airways from the nose to the alveoli connect the external environment with the extensive, thin and vulnerable alveolar surface. As air is inhaled through the upper airways, it is filtered in the nose, heated to body temperature and fully saturated with water vapour; partial recovery of this heat and moisture occurs on expiration. Total airway cross-section is smallest in the glottis and trachea, making the central airway particularly vulnerable to obstruction by foreign bodies and tumours. Normal breath sounds originate mainly from the rapid turbulent airflow in the larynx, trachea and main bronchi. The multitude of small airways within the lung parenchyma has a very large combined cross-sectional area (over 300 cm2 in the third-generation respiratory bronchioles), resulting in very slow flow rates. Airflow is virtually silent here and gas transport occurs largely by diffusion in the final generations. Major bronchial and pulmonary divisions are shown in Figure 17.1. The acinus (Fig. 17.2) is the gas exchange unit of the lung and comprises branching respiratory bronchioles and clusters of alveoli. Here the air makes close contact with the blood in the pulmonary capillaries (gas-to-blood distance < 0.4 μm), and oxygen uptake and CO_2 excretion occur. The alveoli are lined with flattened epithelial cells (type I pneumocytes) and a few, more cuboidal, type II pneumocytes. The latter produce surfactant, which is a mixture of phospholipids that reduces surface tension and counteracts the tendency of alveoli to collapse under surface Respiratory disease is responsible for a major burden of morbidity and untimely death, with conditions such as tuberculosis, pandemic influenza and pneumonia the most important in world health terms. The increasing prevalence of allergy, asthma and chronic obstructive pulmonary disease (COPD) contributes to the overall burden of chronic disease in the community. By 2025, the number of cigarette smokers worldwide is anticipated to increase to 1.5 billion, ensuring a growing burden of tobacco-related respiratory conditions. Respiratory disease covers a breadth of pathologies, including infectious, inflammatory, neoplastic and degenerative processes. The practice of respiratory medicine thus requires collaboration with a range of disciplines. Recent advances have improved the lives of many patients with obstructive lung disease, cystic fibrosis, obstructive sleep apnoea and pulmonary hypertension, but the outlook remains poor for lung and other respiratory cancers and for some of the fibrosing lung conditions. Functional anatomy and physiology The lungs occupy the upper two-thirds of the bony thorax, bounded medially by the spine, the heart and the mediastinum and inferiorly by the diaphragm. During breathing, free movement of the lung surface relative to the chest wall is facilitated by sliding contact between the parietal and visceral pleura, which cover the inner surface of the chest wall and the lung, respectively, and are normally in close apposition. Inspiration involves downward contraction of the dome-shaped diaphragm (innervated by the phrenic nerves originating from C3, 4 and 5) and upward, Fig. 17.1 The major bronchial divisions and the fissures, lobes and segments of the lungs. The angle of the oblique fissure means that the left upper lobe is largely anterior to the lower lobe. On the right, the transverse fissure separates the upper from the anteriorly placed middle lobe, which is matched by the lingular segment on the left side. The site of a lobe determines whether physical signs are mainly anterior or posterior. Each lobe is composed of two or more bronchopulmonary segments that are supplied by the main branches of each lobar bronchus. Bronchopulmonary segments: Right Upper lobe: (1) Anterior, (2) Posterior, (3) Apical. Middle lobe: (1) Lateral, (2) Medial. Lower lobe: (1) Apical, (2) Posterior basal, (3) Lateral basal, (4) Anterior basal, (5) Medial basal. Left Upper lobe: (1) Anterior, (2) Apical, (3) Posterior, (4) Lingular. Lower lobe: (1) Apical, (2) Posterior basal, (3) Lateral basal, (4) Anterior basal. Upper lobe Middle lobe

Lower lobe Upper lobe Lower lobe Middle lobe

T r a ns ver se fi ssure RIGHT LEFT Upper lobe Lower lobe

O bli que fissure Upper lobe

Lower lobe

Anterior

Lateral aspects of lungs Spine Spine Major bronchial subdivisions

the small airways unsupported, and their collapse on expiration causes air trapping and limits expiration at a high end-expiratory volume (p. 575). Control of breathing The respiratory motor neurons in the posterior medulla oblongata are the origin of the respiratory cycle. Their activity is modulated by multiple external inputs in health and in disease (see Fig. 17.9): • Central chemoreceptors in the ventrolateral medulla sense the pH of the cerebrospinal fluid (CSF) and are indirectly stimulated by a rise in arterial PCO_2. • The carotid bodies sense hypoxaemia but are mainly activated by arterial PO_2 values below 8 kPa (60 mmHg). They are also sensitised to hypoxia by raised arterial PCO_2. • Muscle spindles in the respiratory muscles sense changes in mechanical load. • Vagal sensory fibres in the lung may be stimulated by stretch, by inhaled toxins or by disease processes in the interstitium. • Cortical (volitional) and limbic (emotional) influences can override the automatic control of breathing. Ventilation/perfusion matching and the pulmonary circulation To achieve optimal gas exchange within the lungs, the regional distribution of ventilation and perfusion must be matched. At tension. Type II pneumocytes can divide to reconstitute type I pneumocytes after lung injury. Lung mechanics Healthy alveolar walls contain a fine network of elastin and collagen fibres (Fig. 17.2). The volume of the lungs at the end of a tidal (‘normal’) breath out is called the functional residual capacity (FRC). At this volume, the inward elastic recoil of the lungs (resulting from elastin fibres and surface tension in the alveolar lining fluid) is balanced by the resistance of the chest wall to inward distortion from its resting shape, causing negative pressure in the pleural space. Elastin fibres allow the lung to be easily distended at physiological lung volumes, but collagen fibres cause increasing stiffness as full inflation is approached, so that, in health, the maximum inspiratory volume is limited by the lung (rather than the chest wall). Within the lung, the weight of tissue compresses the dependent regions and distends the uppermost parts, so a greater portion of an inhaled breath passes to the basal regions, which also receive the greatest blood flow as a result of gravity. Elastin fibres in alveolar walls maintain small airway patency by radial traction on the airway walls. Even in health, however, these small airways narrow during expiration because they are surrounded by alveoli at higher pressure, but are prevented from collapsing by radial elastic traction. The volume that can be exhaled is thus limited purely by the capacity of the expiratory muscles to distort the chest wall inwards. In emphysema, loss of alveolar walls leaves Fig. 17.2 Functional anatomy of the lung. A The tapering, branching bronchus is armoured against compression by plates of cartilage. The more distal bronchioles are collapsible, but held patent by surrounding elastic tissue. B The unit of lung supplied by a terminal bronchiole is called an acinus. The bronchiolar wall contains smooth muscle and elastin fibres. The latter also run through the alveolar walls. Gas exchange occurs in the alveoli, which are connected to each other by the pores of Kohn. C Vascular anatomy of an acinus. Both the pulmonary artery (carrying desaturated blood) and the bronchial artery (systemic supply to airway tissue) run along the bronchus. The venous drainage to the left atrium follows the interlobular septa. From www.Netter.com: Illustrations 155 (bronchus, acinus) and 191 (circulation), Elsevier. Cartilage plates Smooth muscle Terminal bronchiole Bronchial artery Pulmonary artery Pulmonary vein Interlobular septum Alveolar capillaries Respiratory bronchiole Alveoli Pores of Kohn Elastin fibres Bronchus Bronchiole Terminal bronchiole Respiratory bronchiole

Alveoli A B C

550 • RESPIRATORY MEDICINE as a sphincter, closing to protect the airway during swallowing and vomiting. Lower airway defences The sterility, structure and function of the lower airways are maintained by close cooperation between the innate and adaptive immune responses (pp. 62 and 67). The innate response in the lungs is characterised by a number of non-specific defence mechanisms. Inhaled particulate matter is trapped in airway mucus and cleared by the mucociliary escalator. Cigarette smoke increases mucus secretion but reduces mucociliary clearance and predisposes towards lower respiratory tract infections, including pneumonia. Defective mucociliary transport is also a feature of several rare diseases, including Kartagener's syndrome, Young's syndrome and ciliary dysmotility syndrome, which are characterised by repeated sino-pulmonary infections and bronchiectasis. Airway secretions contain an array of antimicrobial peptides (such as defensins, immunoglobulin A (IgA) and lysozyme), antiproteinases and antioxidants. Many assist with the opsonisation and killing of bacteria and the regulation of the powerful proteolytic enzymes secreted by inflammatory cells. In particular, α1-antitrypsin regulates neutrophil elastase, and deficiency of this may be associated with premature emphysema. Macrophages engulf microbes, organic dusts and other particulate matter. They are unable to digest inorganic agents, such as asbestos or silica, which cause their death and lead to the release of powerful proteolytic enzymes that damage the lung. Neutrophil numbers in the airway are low but the pulmonary circulation contains a marginated pool that may be recruited rapidly in response to bacterial infection. This may explain the prominence of lung injury in sepsis syndromes and trauma. Adaptive immunity is characterised by the specificity of the response and the development of memory. Lung dendritic cells facilitate antigen presentation to T and B lymphocytes. Investigation of respiratory disease A detailed history, thorough examination and basic haematological and biochemical tests usually indicate the likely diagnosis and Fig. 17.3 The mucociliary escalator. Scanning electron micrograph of the respiratory epithelium showing large numbers of cilia (C) overlaid by the mucus 'raft' (M). M C 17.1 Respiratory function in old age • Reserve capacity: a significant reduction in function can occur with ageing with only minimal effect on normal breathing, but the ability to combat acute disease is reduced. • Decline in FEV1: the FEV1/FVC (forced expiratory volume/forced vital capacity, p. 55) ratio falls by around 0.2% per year from 70% at the age of 40–45 years, due to a decline in elastic recoil in the small airways with age. Smoking accelerates this decline threefold on average. Symptoms usually occur only when FEV1 drops below 50% of predicted. • Increasing ventilation–perfusion mismatch: the reduction in elastic recoil causes a tendency for the small airways to collapse during expiration, particularly in dependent areas of the lungs, thus reducing ventilation. • Reduced ventilatory responses to hypoxia and hypercapnia: older people may be less tachypnoeic for any given fall in PaO_2 or rise in $PaCO_2$. • Impaired defences against infection: due to reduced numbers of glandular epithelial cells, which lead to a reduction in protective mucus. • Decline in maximum oxygen uptake: due to a combination of impairments in muscle, and the respiratory and cardiovascular systems. This leads to a reduction in cardiorespiratory reserve and exercise capacity. • Loss of chest wall compliance: due to reduced intervertebral disc spaces and ossification of the costal cartilages; respiratory muscle strength and endurance also decline. These changes become important only in the presence of other respiratory disease. segmental and subsegmental level, hypoxia constricts pulmonary arterioles and airway CO_2 dilates bronchi, helping to maintain good regional matching of ventilation and perfusion. Lung disease may create regions of relative under-ventilation or under-perfusion, which disturb this regional matching, causing respiratory failure (p. 565). In addition to causing ventilation–perfusion mismatch, diseases

that destroy capillaries or thicken the alveolar capillary membrane (e.g. emphysema or fibrosis) can impair gas diffusion directly. The pulmonary circulation in health operates at low pressure (approximately 24/9 mmHg) and can accommodate large increases in flow with minimal rise in pressure, e.g. during exercise. Pulmonary hypertension occurs when vessels are destroyed by emphysema, obstructed by thrombus, involved in interstitial inflammation or thickened by pulmonary vascular disease. The right ventricle responds by hypertrophy, with right axis deviation and P pulmonale (tall, peaked p waves) on the electrocardiogram (ECG), and clinical features of right heart failure; the term 'cor pulmonale' is often used for these findings. Lung defences Upper airway defences Large airborne particles are trapped by nasal hairs, and smaller particles settling on the mucosa are cleared towards the oropharynx by the columnar ciliated epithelium that covers the turbinates and septum (Fig. 17.3). During cough, expiratory muscle effort against a closed glottis results in high intrathoracic pressure, which is then released explosively. The flexible posterior tracheal wall is pushed inwards by the high surrounding pressure, which reduces tracheal cross-section and thus maximises the airspeed to achieve effective expectoration. The larynx also acts

Fig. 17.4 The normal chest X-ray. The lung markings consist of branching and tapering lines radiating out from the hila. Where airways and vessels turn towards the film, they can appear as open or filled circles (see upper pole of right hilum). The scapulae may overlie the lung fields; trace the edge of bony structures to avoid mistaking them for pleural or pulmonary shadows. To check for hyperinflation, count the ribs; if more than 10 are visible posteriorly above the diaphragm, the lungs are hyperinflated. From Innes JA. Davidson's Essentials of medicine. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2009. Lung apex Right hilum Right atrial border Right costophrenic angle Right hemidiaphragm Right cardiophrenic angle Gastric air bubble Left hemidiaphragm (normally lower than right) Medial border of scapula Aortic arch Left hilum Left ventricular border Cardiac apex Trachea Clavicular heads symmetrical either side of spine – no rotation 17.2 How to interpret a chest X-ray Name, date, orientation Films are posteroanterior (PA) unless marked AP to denote that they are anteroposterior Lung fields Equal translucency? Check horizontal fissure from right hilum to sixth rib at the anterior axillary line Masses? Consolidation? Cavitation? Lung apices Check behind the clavicles. Masses? Consolidation? Cavitation? Trachea Central (midway between the clavicular heads)? Paratracheal mass? Goitre? Heart Normal shape? Cardiothoracic ratio (should be < half the intrathoracic diameter) Retrocardiac mass? Hila Left should be higher than right Shape (should be concave laterally; if convex, consider mass or lymphadenopathy)? Density? Diaphragm Right should be higher than left Hyperinflation (no more than 10 ribs should be visible posteriorly above the diaphragm)? Costophrenic angles Acute and well defined (pleural fluid or thickening, if not)? Soft tissues Breast shadows in females Chest wall for masses or subcutaneous emphysema Bones Ribs, vertebrae, scapulae and clavicles Any fracture visible at bone margins or lucencies? differential. A number of other investigations are normally required to confirm the diagnosis and/or monitor disease activity. Imaging The 'plain' chest X-ray This is performed on the majority of patients suspected of having chest disease. A posteroanterior (PA) film provides information on the lung fields, heart, mediastinum, vascular structures and thoracic cage (Fig. 17.4). Additional information may be obtained from a lateral film, particularly if pathology is suspected behind the heart shadow or deep in the diaphragmatic sulci. An approach to interpreting the chest X-ray is given in Box 17.2 and common abnormalities are listed in Box 17.3. Increased shadowing may represent accumulation of fluid, lobar collapse or consolidation. Uncomplicated consolidation should not change the position of the mediastinum and the presence of an air bronchogram means that proximal bronchi are patent. Collapse (implying obstruction of the lobar bronchus) is accompanied by loss of volume and displacement of the mediastinum towards the affected side (Fig. 17.5). The presence of ring shadows (thickened bronchi seen end-on), tramline shadows (thickened bronchi side-on) or tubular shadows (bronchi filled with secretions) suggests bronchiectasis, but computed tomography is a much more sensitive test than plain X-ray in bronchiectasis. The presence of pleural fluid is suggested by a dense basal shadow, which, in the erect patient, ascends towards the axilla (p. 547). In large pulmonary embolism, relative oligaemia may cause a lung field to appear abnormally dark.

 Computed tomography Computed tomography (CT) provides detailed images of the pulmonary parenchyma, mediastinum, pleura and bony structures. The displayed range of densities can be adjusted to highlight different structures, such as the lung parenchyma, the mediastinal vascular structures or bone. Cross-sectional formatting allows recognition of the axial distribution of the disease, while coronal reformation displays the craniocaudal distribution. In cases of suspected lung cancer, CT is central to both diagnosis and staging, and facilitates percutaneous needle biopsy. CT identifies the extent and appearance of pleural thickening (see Fig. 17.65) and reliably differentiates pleural and pericardial fat from other pathologies. High-resolution thin-section scanning provides detailed images of the pulmonary parenchyma and is particularly useful in assessing diffuse parenchymal lung disease (see Fig. 17.56), identifying airway thickening, bronchiectasis (see Fig. 17.29) and emphysema (see Fig. 17.27). The relative contribution of competing pathologies to a breathless patient may be assessed. Prone imaging may be used to differentiate the gravity-induced posterobasal attenuation seen in supine scans. CT pulmonary angiography (CTPA) has become the investigation of choice in the diagnosis of pulmonary thromboembolism (see Fig. 17.68), when it may either confirm the suspected embolism or highlight an alternative diagnosis. It has largely replaced the radioisotope-based ventilation–perfusion scan, although the latter continues to provide useful information in the pre-operative assessment of patients being considered for lung resection and in the assessment of pulmonary hypertension. CT may assist in identifying the cavitation of tuberculosis, fungal infection (p. 300) and other signs of infection (halo – air crescent). Finally, CT may be used to assess disease progression, thereby predicting prognosis, and in screening to detect the earliest signs of disease. Fig. 17.5 Radiological features of lobar collapse caused by bronchial obstruction. The dotted line in the drawings represents the normal position of the diaphragm. The dark pink area represents the extent of shadowing seen on the X-ray. 3LM[\WWLY SVIL 3PUN\SH 3LM[SV^LY SVIL 9PNO[\WWLY SVIL 9PNO[TPKKSL SVIL 9PNO[SV^LY SVIL 17.3 Common chest X-ray abnormalities Pulmonary and pleural shadowing • Consolidation: infection, infarction, inflammation and, rarely, bronchoalveolar cell carcinoma • Lobar collapse: mucus plugging, tumour, compression by lymph nodes • Solitary nodule: see page 560 • Multiple nodules: miliary tuberculosis (TB), dust inhalation, metastatic malignancy, healed varicella pneumonia, rheumatoid disease • Ring shadows, tramlines and tubular shadows: bronchiectasis • Cavitating lesions: tumour, abscess, infarct, pneumonia (Staphylococcus/Klebsiella), granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) • Reticular, nodular and reticulonodular shadows: diffuse parenchymal lung disease, infection • Pleural abnormalities: fluid, plaques, tumour Increased translucency • Bullae • Pneumothorax • Oligaemia Hilar abnormalities • Unilateral hilar enlargement: TB, lung cancer, lymphoma • Bilateral hilar enlargement: sarcoid, lymphoma, TB, silicosis Other abnormalities •

when paradoxical movement of the vocal cords may mimic asthma. Left-sided lung tumours may involve the left recurrent laryngeal nerve, paralysing the left vocal cord and leading to a hoarse voice and a ‘bovine’ cough. Continuous laryngoscopy during exercise tests allows the identification of exercise-induced laryngeal obstruction. Bronchoscopy The trachea and the first 3–4 generations of bronchi may be inspected using a flexible bronchoscope. Flexible bronchoscopy is usually performed under local anaesthesia with sedation, on an outpatient basis. Abnormal tissue in the bronchial lumen or wall can be biopsied, and bronchial brushings, washings or aspirates can be taken for cytological or bacteriological examination. Small biopsy specimens of lung tissue, taken by forceps passed through the bronchial wall (transbronchial biopsies), may be helpful in the diagnosis of bronchocentric disorders such as sarcoidosis and diffuse malignancy but are generally too small to be of diagnostic value in other diffuse parenchymal pulmonary disease (p. 605). Rigid bronchoscopy requires general anaesthesia and is reserved for specific situations, such as massive haemoptysis or removal of a foreign body (see Fig. 10.2, p. 179), and can facilitate endobronchial laser therapy and stenting. Endobronchial ultrasound Endobronchial ultrasound (EBUS) allows directed needle aspiration from peribronchial nodes and is used increasingly to stage lung cancer. It may also be useful in non-malignant conditions, such as tuberculosis of the mediastinal lymph nodes or sarcoid. Lymph nodes down to the main carina can also be sampled using a mediastinoscope passed through a small incision at the suprasternal notch under general anaesthetic. Lymph nodes in the lower mediastinum may be biopsied via the oesophagus using endoscopic ultrasound (EUS), an oesophageal endoscope equipped with an ultrasound transducer and biopsy needle. Thoracoscopy Thoracoscopy, which involves the insertion of an endoscope through the chest wall, facilitates biopsy under direct vision and is performed by surgeons and an increasing number of physicians. This modality is the gold standard for the evaluation of the pleural interface, characterisation of complex pleural effusion, and identification of exudate and haemorrhage, as well as the analysis of superior sulcus tumours, as it enables more accurate staging. Positron emission tomography Positron emission tomography (PET) scanners employ the radiotracer 18F-fluorodeoxyglucose (FDG) to quantify the rate of glucose metabolism by cells. The 18FDG is rapidly taken up by metabolically active tissue, where it is phosphorylated and ‘trapped’ in the cell. The assessment of 18FDG uptake may be qualitative (visual analysis) or semi-quantitative, using the standardised uptake value (SUV) (Fig. 17.6). PET is useful in the staging of mediastinal lymph nodes and distal metastatic disease in patients with lung cancer and in the investigation of pulmonary nodules. Co-registration of PET and CT (PET-CT) enhances localisation and characterisation of metabolically active deposits (Fig. 17.6). PET may also differentiate benign from malignant pleural disease and can be used to assess the extent of extrapulmonary disease in sarcoidosis. However, 18FDG uptake by a lesion is affected by a large number of parameters, including equipment used, the physics, and biological factors such as amount of body fat and brown fat uptake and the level of fasting blood glucose. Magnetic resonance imaging Conventional magnetic resonance imaging (MRI) of the lung parenchyma is seldom useful, although the technique is increasingly finding a role in the differentiation of benign from malignant pleural disease, and in delineating invasion of the chest wall or diaphragm by tumour. Ultrasound Transthoracic ultrasound has evolved into a point-of-care investigation to assess the pleural space (see Fig. 17.15). In the hands of an experienced operator it can distinguish pleural fluid from pleural thickening, identify a pneumothorax and, by directly visualising the diaphragm and solid organs such as the liver, spleen and kidneys, may be used to guide pleural aspiration, biopsy and intercostal chest drain insertion safely. It is also used to guide needle biopsy of superficial lymph node or chest wall masses and provides useful information on the shape and movement of the diaphragm. Endoscopic examination Laryngoscopy The larynx may be inspected directly with a fibreoptic laryngoscope and this is useful in cases of suspected vocal cord dysfunction, Fig. 17.6 Computed tomography and positron emission tomography combined to reveal intrathoracic metastases. A In a patient with lung cancer, CT shows some posterior pleural thickening. B PET scanning reveals FDG uptake in two pleural lesions (arrows). C The lesions are highlighted in yellow in the combined PET/CT image. A–C, From http://radiology.rsnajnls.org. A B C

 bronchoscopy. Molecular tests are increasingly being used to provide rapid and accurate identification of many infective organisms. Nucleic acid amplification tests (NAATs) identify common respiratory viruses, such as influenza, adenovirus and respiratory syncytial virus, and have largely replaced paired serology for Mycoplasma, Legionella and other organisms. NAATs are increasingly adopted as the first-line investigation for identification of tuberculosis and rapid identification of drug resistance. Cytology and histopathology Cytological examination of exfoliated cells in pleural fluid or bronchial brushings and washings, or of fine needle aspirates from lymph nodes or pulmonary lesions, can support a diagnosis of malignancy but a larger tissue biopsy is often necessary, particularly as this allows immunohistochemistry using a panel of antibodies to characterise the tumour. Histopathology may also allow identification of infective agents such as Mycobacterium tuberculosis, Pneumocystis jirovecii or fungi. Differential cell counts in bronchial lavage fluid may help to distinguish pulmonary changes due to sarcoidosis (p. 608) from those caused by idiopathic pulmonary fibrosis (p. 605) or hypersensitivity pneumonitis (p. 616). Respiratory function testing Respiratory function tests are used to aid diagnosis, quantify functional impairment, and monitor treatment or progression of disease. Airway narrowing, lung volume and gas exchange capacity are quantified and compared with normal values Immunological and serological tests The diagnosis of asthma may be supported by demonstrating an elevated level of immunoglobulin E (IgE), and the measurement of IgE directed against specific antigens can be useful in assessing the contribution of specific allergens to the presentation. Many autoimmune diseases present with pulmonary involvement and autoantibodies may be identified in the serum. Serum precipitins are antibodies that form visible lines of precipitated glycoprotein when they encounter their specific antigen in an agarose gel or on an acetate cellulose sheet. They may identify a reaction to fungi such as Aspergillus (p. 596) or to antigens involved in hypersensitivity pneumonitis, such as farmer’s lung (p. 616). IgG enzyme immunoassay may be used interchangeably. The presence of pneumococcal antigen in sputum, blood or urine may be of diagnostic importance in pneumonia. Respiratory viruses can be detected in nose/throat swabs by immunofluorescence and Legionella infection may diagnosed by detection of the urinary antigen. The detection of galactomannan, a component of the cell wall of Aspergillus, may assist in the diagnosis of invasive aspergillosis, and interferon-gamma release assays are useful in the detection of latent tuberculosis. Microbiological investigations Sputum, pleural fluid, throat swabs, blood, and bronchial washings and aspirates can be examined for bacteria, fungi and viruses. The use of hypertonic saline to induce expectoration of sputum may obviate the need for more invasive procedures, such as Fig. 17.7 Respiratory function tests in health and disease. A Volume/time traces from forced expiration in health, chronic obstructive pulmonary disease (COPD) and fibrosis. COPD causes slow, prolonged and limited exhalation. In fibrosis, forced expiration results in rapid expulsion of a reduced forced vital capacity (FVC). Forced expiratory volume (FEV1) is reduced in both diseases but disproportionately so, compared to FVC, in COPD. B The same data plotted as flow/volume loops. In COPD, collapse of intrathoracic airways limits flow, particularly during mid- and late expiration. The blue trace illustrates large airway obstruction, which particularly limits peak flow rates. C Lung volume measurement. Volume/time graphs during quiet breathing with a single maximal breath in and out. COPD causes hyperinflation with increased residual volume. Fibrosis causes a proportional reduction in all lung volumes. A B C Volume Inspiratory capacity Functional residual capacity Residual volume Time Total lung capacity Volume Time 1 sec Expiration Inspiration Volume

Normal COPD Fibrosis Tracheal obstruction Flow FEV1 Vital capacity

FVC

Arterial blood gases and oximetry The measurement of hydrogen ion concentration, PaO_2 and $PaCO_2$, and derived bicarbonate concentration in an arterial blood sample is essential for assessing the degree and type of respiratory failure and for measuring acid–base status. This is discussed in detail on pages 363 and 565. Interpretation of results is made easier by blood gas diagrams (Fig. 17.8), which indicate whether any acidosis or alkalosis is due to acute or chronic respiratory derangements of $PaCO_2$ or to metabolic causes. Pulse oximeters with finger or ear probes measure the difference in absorbance of light by oxygenated and deoxygenated blood and calculate the percentage of haemoglobin that is oxygenated (the oxygen saturation). This allows non-invasive continuous adjusted for age, gender, height and ethnic origin. In diseases characterised by airway narrowing (e.g. asthma, bronchitis and emphysema), maximum expiratory flow is limited by dynamic compression of small intrathoracic airways, some of which may close completely during expiration, limiting the volume that can be expired (‘obstructive’ defect). Hyperinflation of the chest results and can become extreme if elastic recoil is also lost due to parenchymal destruction, as in emphysema. In contrast, diseases that cause interstitial inflammation and/or fibrosis lead to progressive loss of lung volume (‘restrictive’ defect) with normal expiratory flow rates. Typical laboratory traces are illustrated in Figure 17.7. Measurement of airway obstruction Airway narrowing is assessed by asking patients to breathe in fully, then blow out as hard and fast as they can into a peak flow meter or a spirometer. Peak flow meters are cheap and convenient for home monitoring of peak expiratory flow (PEF) in the detection and monitoring of asthma but results are effort-dependent. More accurate and reproducible measures are obtained by maximum forced expiration into a spirometer. The forced expired volume in 1 second (FEV1) is the volume exhaled in the first second, and the forced vital capacity (FVC) is the total volume exhaled. FEV1 is disproportionately reduced in airflow obstruction, resulting in FEV1/FVC ratios of less than 70%. In this situation, spirometry should be repeated following inhaled short-acting β_2-adrenoceptor agonists (e.g. salbutamol); an increase of > 12% and > 200 mL in FEV1 or FVC indicates significant reversibility. A large improvement in FEV1 (> 400 mL) and variability in peak flow over time are features of asthma (p. 567). To distinguish large airway narrowing (e.g. tracheal stenosis or compression; see Fig. 18.12, p. 648) from small airway narrowing, spirometry data are plotted as flow/volume loops. These display flow in relation to lung volume (rather than time) during maximum expiration and inspiration, and the pattern of flow reveals the site of airflow obstruction

(Fig. 17.7B). Lung volumes Spirometry can measure only the volume of gas that can be exhaled; it cannot measure the gas remaining in the lungs after a maximal expiration. All the gas in the lungs can be measured by rebreathing an inert non-absorbed gas (usually helium) and recording how much the test gas is diluted by lung gas at equilibrium. This measures the volume of intrathoracic gas that mixes freely with tidal breaths. Alternatively, lung volume may be measured by body plethysmography (p. 175), which determines the pressure/volume relationship of the thorax. This method measures total intrathoracic gas volume, including poorly ventilated areas such as bullae. The terms used to describe lung volume are shown in Figure 17.7C. Transfer factor To measure the capacity of the lungs to exchange gas, patients inhale a test mixture of 0.3% carbon monoxide, which is taken up avidly by haemoglobin in pulmonary capillaries. After a short breath-hold, the rate of disappearance of CO into the circulation is calculated from a sample of expirate, and expressed as the TLCO or carbon monoxide transfer factor. Helium is also included in the test breath to allow calculation of the volume of lung examined by the test breath. Transfer factor expressed per unit lung volume is termed KCO. Common respiratory function abnormalities are summarised in Box 17.4. 17.4 How to interpret respiratory function abnormalities Asthma Chronic bronchitis Emphysema Pulmonary fibrosis FEV1 ↓↓ ↓↓ ↓↓ ↓ FVC ↓ ↓ ↓ ↓↓ FEV1/FVC ↓ ↓ ↓ →/↑ TLCO → → ↓↓ ↓↓ KCO →/↑ → ↓ →/↓ TLC →/↑ ↑ ↑↑ ↓ RV →/↑ ↑ ↑↑ ↓ (RV = residual volume; TLC = total lung capacity; see text for other abbreviations) Fig. 17.8 Changes in blood [H+], PaCO2 and plasma [HCO3 −] in acid–base disorders. The rectangle indicates normal limits for [H+] and PaCO2. The bands represent 95% confidence limits of single disturbances in human blood. To determine the likely cause of an acid–base disorder, plot the values of [H+] and PaCO2 from an arterial blood gas measurement.. The diagram indicates whether any acidosis or alkalosis results primarily from a respiratory disorder of PaCO2 or from a metabolic derangement. Reprinted with permission from Elsevier (Flenley D. Lancet 1971; 1:1921). Arterial PaCO2 Reference range 95% Confidence limits Acute respiratory acidosis

Resp. alkalosis pH [HCO3 –] mmol/L

7.0 7.1 7.2 7.3 7.4

7.5 7.6 [H+] nmol/L kPa mmHg Metabolic acidosis Chronic respiratory acidosis Metabolic alkalosis

 an inspiratory noise (stridor) indicates partial obstruction of a major airway (e.g. laryngeal oedema, tracheal tumour, scarring, compression or inhaled foreign body) and requires urgent investigation and treatment. Sputum production is common in patients with acute or chronic cough, and its nature and appearance can provide clues to the aetiology (p. 546). Aetiology Acute transient cough is most commonly caused by viral lower respiratory tract infection, post-nasal drip resulting from rhinitis or sinusitis, aspiration of a foreign body, or throat-clearing secondary to laryngitis or pharyngitis. When cough occurs in the context of more serious diseases, such as pneumonia, aspiration, congestive heart failure or pulmonary embolism, it is usually easy to diagnose from other clinical features. Patients with chronic cough present more of a challenge, especially when physical examination, chest X-ray and lung function studies are normal. In this context, it is most often explained by cough-variant asthma (where cough may be the principal or exclusive clinical manifestation), post-nasal drip secondary to nasal or sinus disease, or gastro-oesophageal reflux disease (GORD) with aspiration. Diagnosis of the latter may require oesophageal pH monitoring or a prolonged trial of anti-reflux therapy (p. 793). Between 10% and

15% of patients (particularly women) taking angiotensin-converting enzyme (ACE) inhibitors develop a drug-induced chronic cough. Bordetella pertussis infection in adults (p. 582) can result in cough lasting up to 3 months. While most patients with lung cancer have an abnormal chest X-ray on presentation, fibreoptic bronchoscopy or thoracic CT is advisable in most adults (especially smokers) with otherwise unexplained cough of recent onset, as this may reveal a small endobronchial tumour or unexpected foreign body (see Fig. 10.2, p. 179). In a small percentage of patients, dry cough may be the presenting feature of interstitial lung disease. Adapted from Munro JF, Campbell IW. Macleod's Clinical examination, 10th edn. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2000. 17.5 Cough Origin Common causes Clinical features Pharynx Post-nasal drip History of chronic rhinitis Larynx Laryngitis, tumour, whooping cough, croup Voice or swallowing altered, harsh or painful cough Paroxysms of cough, often associated with stridor Trachea Tracheitis Raw retrosternal pain with cough Bronchi Bronchitis (acute) and chronic obstructive pulmonary disease (COPD) Dry or productive, worse in mornings Asthma Usually dry, worse at night Eosinophilic bronchitis Features similar to asthma but airway hyper-reactivity absent Lung cancer Persistent (often with haemoptysis) Lung parenchyma Tuberculosis Productive (often with haemoptysis) Pneumonia Dry initially, productive later Bronchiectasis Productive, changes in posture induce sputum production Pulmonary oedema Often at night (may be productive of pink, frothy sputum) Interstitial fibrosis Dry and distressing Drug side-effect Angiotensin-converting enzyme (ACE) inhibitors Dry cough Aspiration Gastro-oesophageal reflux disease (GORD) History of acid reflux, heartburn, hiatus hernia Obesity assessment of oxygen saturation in patients and its response to oxygen therapy. Exercise tests Resting measurements may be unhelpful in early disease or in patients complaining only of exercise-induced symptoms. Exercise testing with spirometry before and after can help to reveal exercise-induced asthma. Walk tests include the self-paced 6-minute walk and the externally paced incremental 'shuttle' test, where patients walk at increasing pace between two cones 10 m apart. These provide simple, repeatable assessments of disability and response to treatment. Cardiopulmonary bicycle exercise testing, with measurement of metabolic gas exchange, ventilation and ECG changes, is useful for quantifying exercise limitation and detecting occult cardiovascular or respiratory limitation in a breathless patient. Presenting problems in respiratory disease Cough Cough is the most frequent symptom of respiratory disease and is caused by stimulation of sensory nerves in the mucosa of the pharynx, larynx, trachea and bronchi. Acute sensitisation of the normal cough reflex occurs in a number of conditions and it is typically induced by changes in air temperature or exposure to irritants, such as cigarette smoke or perfumes. Distinguishing characteristics of various causes of cough are detailed in Box 17.5. The explosive quality of a normal cough is lost in patients with respiratory muscle paralysis or vocal cord palsy. Paralysis of a single vocal cord gives rise to a prolonged, low-pitched, inefficient 'bovine' cough accompanied by hoarseness. Coexistence of

Individual patients differ greatly in the intensity of breathlessness reported for a given set of circumstances, but breathlessness scores during exercise within individuals are reproducible and can be used to monitor the effects of therapy. Differential diagnosis Patients with breathlessness present either with chronic exertional symptoms or as an emergency with acute breathlessness, when symptoms are prominent even at rest. The causes can be classified accordingly (Box 17.6). Chronic exertional breathlessness The cause of breathlessness is often apparent from a careful clinical history. Key questions are detailed below. How is your breathing at rest and overnight? In

COPD, there is a fixed, structural limit to maximum ventilation, and a tendency for progressive hyperinflation during exercise. Breathlessness is apparent mainly when walking and patients usually report minimal symptoms at rest and overnight. In contrast, patients with significant asthma are often woken from their sleep by breathlessness with chest tightness and wheeze. Orthopnoea is common in COPD, as well as in heart disease, because airflow obstruction is made worse by cranial displacement of the diaphragm by the abdominal contents when recumbent, so many patients choose to sleep propped up. Thus it is not a useful differentiating symptom unless there is a clear history of previous angina or infarction to suggest cardiac disease. Breathlessness Breathlessness or dyspnoea can be defined as the feeling of an uncomfortable need to breathe. It is unusual among sensations, as it has no defined receptors, no localised representation in the brain, and multiple causes both in health (e.g. exercise) and in diseases of the lungs, heart or muscles. Pathophysiology Stimuli to breathing resulting from disease processes are shown in Figure 17.9. Respiratory diseases can stimulate breathing and dyspnoea by: • stimulating intrapulmonary sensory nerves (e.g. pneumothorax, interstitial inflammation and pulmonary embolus) • increasing the mechanical load on the respiratory muscles (e.g. airflow obstruction or pulmonary fibrosis) • causing hypoxia, hypercapnia or acidosis, which stimulate chemoreceptors. In cardiac failure, pulmonary congestion reduces lung compliance and can also obstruct the small airways. Reduced cardiac output also limits oxygen supply to the skeletal muscles during exercise, causing early lactic acidaemia and further stimulating breathing via the central chemoreceptors. Breathlessness and the effects of treatment can be quantified using a symptom scale. Patients tend to report breathlessness in proportion to the sum of the above stimuli to breathing. Fig. 17.9 Respiratory stimuli contributing to breathlessness. Mechanisms by which disease can stimulate the respiratory motor neurons in the medulla. Breathlessness is usually felt in proportion to the sum of these stimuli. Further explanation is given on page 179. (CSF = cerebrospinal fluid; $\dot{V}/\dot{Q}$ = ventilation/perfusion match) Breathlessness Limbic drives (emotion) Cortical drive Carotid body (↓PaO_2, ↑$PaCO_2$) IX Central chemoreceptors (↓CSF pH) Spinal afferents Vagal lung afferents Type II respiratory failure, ↑$PaCO_2$ + acidosis Airway obstruction • Asthma • Emphysema Pulmonary fibrosis Increased mechanical load Altered V/Q Hypoxaemia Pulmonary embolus Interstitial disease • Inflammation • Infection • Fibrosis Deflation • Pneumothorax • Collapse • Effusion

 questionnaire can be used to score some of the typical symptoms of hyperventilation (Box 17.7). Arterial blood gases show normal PO_2, low PCO_2 and alkalosis. Pleuritic chest pain in a patient with chronic breathlessness, particularly if it occurs in more than one site over time, should raise suspicion of thromboembolic disease. Thromboembolism may occasionally present as chronic breathlessness with no other specific features and should always be considered before a diagnosis of psychogenic hyperventilation is made. Morning headache is an important symptom in patients with breathlessness, as it may signal the onset of carbon dioxide retention and respiratory failure. This is particularly significant in patients with musculoskeletal disease impairing respiratory function (e.g. kyphoscoliosis or muscular dystrophy). Acute severe breathlessness This is one of the most common and dramatic medical emergencies. Although respiratory causes are common, it can result from cardiac disease, metabolic disease or poisoning causing acidosis, or from psychogenic causes. The approach to patients with acute severe breathlessness is covered on page 179. Chest pain Chest pain can result from cardiac, respiratory, oesophageal or musculoskeletal disorders. The approach to this common symptom is covered on page 176. How much can you do on a good day? Noting ‘breathless on exertion’ is not enough; the approximate distance the patient can walk on the level should be documented, along with capacity to climb inclines or stairs. Variability within and between days is a hallmark of asthma; in mild asthma, the patient may be free of symptoms and signs when well. Gradual, progressive loss of exercise capacity over months and years, with consistent disability over days, is typical of COPD. When asthma is suspected, the degree of variability is best documented by home peak flow monitoring. Relentless, progressive breathlessness that is also present at rest, often accompanied by a dry cough, suggests interstitial fibrosis. Impaired left ventricular function can also cause chronic exertional breathlessness, cough and wheeze. A history of angina, hypertension or myocardial infarction raises the possibility of a cardiac cause. This may be confirmed by a displaced apex beat, a raised JVP and cardiac murmurs (although these signs can occur in severe hypoxic lung disease with fluid retention). The chest X-ray may show cardiomegaly and an ECG and echocardiogram may provide evidence of left ventricular disease. Measurement of arterial blood gases may help, as, in the absence of an intracardiac shunt or pulmonary oedema, the PaO_2 in cardiac disease is normal and the $PaCO_2$ is low or normal. Did you have breathing problems in childhood or at school? When present, a history of childhood wheeze increases the likelihood of asthma, although this history may be absent in late-onset asthma. A history of atopic allergy also increases the likelihood of asthma. Do you have other symptoms along with your breathlessness? Digital or perioral paraesthesiae and a feeling that ‘I cannot get a deep enough breath in’ are typical features of psychogenic hyperventilation but this cannot be diagnosed until investigations have excluded other potential causes. Additional symptoms include lightheadedness, central chest discomfort or even carpopedal spasm due to acute respiratory alkalosis. These alarming symptoms may provoke further anxiety and exacerbate hyperventilation. Psychogenic breathlessness rarely disturbs sleep, frequently occurs at rest, may be provoked by stressful situations and may even be relieved by exercise. The Nijmegen 17.7 Factors suggesting psychogenic hyperventilation • ‘Inability to take a deep breath’ • Frequent sighing/erratic ventilation at rest • Short breath-holding time in the absence of severe respiratory disease • Difficulty in performing and/or inconsistent spirometry measures • High score (over 26) on Nijmegen questionnaire • Induction of symptoms during submaximal hyperventilation • Resting end-tidal CO_2 < 4.5% • Associated digital and/or perioral paraesthesiae 17.6 Causes of breathlessness System Acute dyspnoea Chronic exertional dyspnoea Cardiovascular *Acute pulmonary oedema (p. 463) Chronic heart failure (p. 463) Myocardial ischaemia (angina equivalent) (p. 180) Respiratory *Acute severe asthma *Acute exacerbation of COPD *Pneumothorax *Pneumonia *Pulmonary embolus ARDS Inhaled foreign body (especially in children) Lobar collapse Laryngeal oedema (e.g. anaphylaxis) *COPD *Chronic asthma Lung cancer Interstitial lung disease (sarcoidosis, fibrosing alveolitis, extrinsic allergic alveolitis, pneumoconiosis) Chronic pulmonary thromboembolism Lymphangitis carcinomatosis (may cause intolerable breathlessness) Large pleural effusion(s) Others Metabolic acidosis (e.g. diabetic ketoacidosis, lactic acidosis, uraemia, overdose of salicylates, ethylene glycol poisoning) Psychogenic hyperventilation (anxiety- or panic-related) Severe anaemia Obesity Deconditioning *Denotes a common cause. (ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease)

vascular condition, e.g. arteriovenous shunts for dialysis. It is sometimes congenital but in over 90% of patients it indicates a serious underlying disorder. The most common underlying causes are suppurative or malignant lung disease but a variety of other conditions can cause clubbing (Box 17.8). Clubbing may recede if the underlying condition resolves, e.g. following lung transplantation for cystic fibrosis. Haemoptysis Coughing up blood, irrespective of the amount, is an alarming symptom and patients nearly always seek medical advice. Care should be taken to establish that it is true haemoptysis and not haematemesis, or gum or nose bleeding. Haemoptysis must always be assumed to have a serious cause until this is excluded (Box 17.9). Many episodes of haemoptysis remain unexplained, even after full investigation, and are likely to be due to simple bronchial infection. A history of repeated small haemoptysis, or bloodstreaking of sputum, is highly suggestive of lung cancer. Fever, night sweats and weight loss suggest tuberculosis. Pneumococcal pneumonia often causes ‘rusty’-coloured sputum but can cause frank haemoptysis, as can all suppurative pneumonic infections, including lung abscess (p. 586). Bronchiectasis (p. 578) and intracavitary mycetoma (p. 597) can cause catastrophic bronchial haemorrhage, and in these patients there may be a history of previous tuberculosis or pneumonia in early life. Finally, pulmonary thromboembolism is a common cause of haemoptysis and should always be considered. Physical examination may reveal additional clues. Finger clubbing suggests lung cancer or bronchiectasis; other signs of malignancy, such as cachexia, hepatomegaly and lymphadenopathy, should also be sought. Fever, pleural rub and signs of consolidation occur in pneumonia or pulmonary infarction; a minority of patients with pulmonary infarction also have unilateral leg swelling or pain suggestive of deep venous Finger clubbing Finger clubbing describes painless swelling of the soft tissues of the terminal phalanges, causing increased longitudinal and lateral convexity of the nail (Fig. 17.10). Upward displacement of the proximal nail margin causes the anteroposterior diameter of the finger at that point to exceed that at the distal interphalangeal joint. It also removes the normal hyponychial angle between the proximal part of the nail and the adjoining skin. Clubbing usually affects the fingers symmetrically and commonly also involves the toes, but can be unilateral if caused by a proximal Fig. 17.10 Finger clubbing. A Anterior view. B Lateral view. From Douglas G, Nicol F, Robertson C. Macleod’s Clinical examination, 13th edn. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2013. A B 17.8 Differential diagnosis of finger clubbing Congenital or familial (5–10%) Acquired Thoracic (~80%) • Chronic suppurative conditions: Pulmonary tuberculosis Bronchiectasis Lung abscess Empyema Cystic fibrosis • Tumours: Lung cancer Mesothelioma Fibroma • Pulmonary fibrosis Cardiovascular • Cyanotic congenital heart disease • Infective endocarditis • Arteriovenous shunts and aneurysms Gastrointestinal • Cirrhosis • Inflammatory bowel disease • Coeliac disease Others • Thyrotoxicosis (thyroid acropachy) • Primary hypertrophic osteoarthropathy 17.9 Causes of haemoptysis Bronchial disease • Cancer* • Bronchiectasis* • Acute bronchitis* • Bronchial adenoma • Foreign body Parenchymal disease • Tuberculosis* • Suppurative pneumonia • Parasites (e.g. hydatid disease, flukes) • Lung abscess • Trauma • Actinomycosis • Mycetoma Lung vascular disease • Pulmonary infarction* • Goodpasture’s syndrome (p. 612) • Polyarteritis nodosa • Idiopathic pulmonary haemosiderosis Cardiovascular disease • Acute left ventricular failure* • Mitral stenosis • Aortic aneurysm Blood disorders • Leukaemia • Haemophilia • Anticoagulants *More common causes.

 The ‘incidental’ pulmonary nodule A pulmonary nodule may be defined as a well or poorly circumscribed, approximately rounded structure that appears on imaging as a focal opacity less than 3 cm in diameter that is surrounded by aerated lung. The increased use of helical multi-detector CT (Fig 17.12) has been accompanied by an epidemic of ‘incidental’ pulmonary nodules. Nodules must not be dismissed as ‘incidental’, however, until an important and treatable infective or malignant condition in its earliest stage is excluded or stability over at least 2 years has been demonstrated. The list of potential causes of pulmonary nodules is extensive and most are benign (Box 17.10). Features on a CT scan consistent with a benign lesion include being less than 5 mm in diameter or less than 80 mm3 in volume; diffuse, central, laminated or popcorn calcification; or the presence of macroscopic fat. In addition, perifissural lymph nodes and subpleural nodules with a lentiform or triangular shape do not require any further investigation. In cases where a benign lesion cannot be confidently assumed, further assessment depends on both the appearance of the nodule and the clinical context. These assessments may be aided by the use of computer prediction models (Box 17.11). thrombosis. Rashes, haematuria and digital infarcts point to an underlying systemic disease, such as a vasculitis, which may be associated with haemoptysis. Management In severe acute haemoptysis, the patient should be nursed upright (or on the side of the bleeding, if this is known), given high-flow oxygen and resuscitated as required. Bronchoscopy in the acute phase is difficult and often merely shows blood throughout the bronchial tree. Infusions of the antifibrinolytic agent tranexamic acid or the vasopressin precursor terlipressin may help to limit bleeding but evidence of efficacy is limited. If radiology shows an obvious central cause, then rigid bronchoscopy under general anaesthesia may allow intervention to stop bleeding; however, the source often cannot be visualised. Intubation with a divided endotracheal tube may allow protected ventilation of the unaffected lung to stabilise the patient. Bronchial arteriography and embolisation (Fig. 17.11), or even emergency surgery, can be life-saving in the acute situation. In the vast majority of cases, however, the haemoptysis itself is not life-threatening and a logical sequence of investigations can be followed: • chest X-ray, which may provide evidence of a localised lesion, including tumour (malignant or benign), pneumonia, mycetoma or tuberculosis • full blood count (FBC) and clotting screen • bronchoscopy after acute bleeding has settled, which may reveal a central lung cancer (not visible on the chest X-ray) and permit biopsy and tissue diagnosis • CTPA, which may show underlying pulmonary thromboembolic disease or alternative causes not seen on the chest X-ray (e.g. pulmonary arteriovenous malformation or small or hidden tumours). Fig. 17.11 Bronchial artery angiography. An angiography catheter has been passed via the femoral artery and aorta into an abnormally dilated right bronchial artery (arrows). Contrast is seen flowing into the lung. This patient had post-tuberculous bronchiectasis and presented with massive haemoptysis. Bronchial artery embolisation was successfully performed. Fig. 17.12 Thoracic CT scan showing a solitary pulmonary nodule identified in the right upper lobe (arrow). 17.10 Causes of pulmonary nodules Common causes • Lung cancer • Single metastasis • Localised pneumonia • Lung abscess • Tuberculoma • Pulmonary infarct Uncommon causes • Benign tumour • Lymphoma • Arteriovenous malformation • Hydatid cyst (p. 298) • Bronchogenic cyst • Rheumatoid nodule • Granulomatosis with polyangiitis (Wegener's granulomatosis) • Pulmonary sequestration • Pulmonary haematoma • 'Pseudotumour' – fluid collection in a fissure • Aspergilloma (usually surrounded by air crescent) • Cryptococcus • Aspergillus nodule

17.11 Clinical and radiographic features distinguishing benign from malignant nodules* Feature Risk of malignancy Feature Risk of malignancy Characteristics of nodule Characteristics of patient Size Nearly all > 3 cm but fewer than 1% < 4 mm are malignant Age Increases with age and is uncommon below age of 40 Margin Usually smooth in benign lesions Smoking history Increases in proportion to duration and amount smoked Spiculated suggests malignancy Other Increased by history of lung cancer in first-degree relative and by exposure to asbestos, silica, uranium and radon Calcification or fat Laminated or central deposition of calcification suggests granuloma 'Popcorn' pattern suggests hamartoma Fat may suggest hamartoma or lipoid granuloma Location

70% of lung cancers occur in upper lobes Benign lesions are equally distributed throughout upper and lower lobes *Linear or sheet-like lung opacities are unlikely to represent neoplasms and do not require follow-up. Some nodular opacities may be sufficiently typical of scarring for follow-up not to be warranted. Adapted from MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005; 237:395–400. Fig. 17.13 Recommendations on the assessment of a solid pulmonary nodule. A Initial approach to solid pulmonary nodules. The Brock model is an online calculator that can also be downloaded as an app (https://brocku.ca/lung-cancer-risk-calculator). The model integrates data on age, sex, family history of cancer, the presence of emphysema, nodule size, nodule type, nodule position, nodule count and speculation, and calculates the probability that a nodule will become malignant within a 2- to 4-year follow-up period. Herder is a similar model. *Consider positron emission tomography–computed tomography (PET-CT) for larger nodules in young patients with low risk by Brock score, as this score was developed in a screening cohort (50–75 years) and so performance in younger patients is unproven. Continues overleaf. Solid non-calcified nodule(s) on CT Previous imaging? <10% risk of malignancy* ≥10% risk of malignancy 10–70% risk of malignancy <10% risk of malignancy

> 70% risk of malignancy Consider excision or non-surgical treatment (± image-guided biopsy) CT surveillance (Fig. 17.13B) Discharge Yes Assess risk of lung cancer according to Fig. 17.13B Yes Yes No Nodule <8mm diameter or <300mm3 volume? No Assess risk using Brock model No Clear features of benign disease (e.g. hamartoma, typical perifissural nodule), or nodule <5mm diameter (or <80mm3) or patient unfit for any treatment PET-CT with risk assessment using Herder model (provided size is greater than local PET-CT threshold) Consider image-guided biopsy; other options are excision biopsy or CT surveillance guided by individual risk and patient preference A

562 • RESPIRATORY MEDICINE Baseline volumetric analysis (or diameter measurement if volumetry not available/technically impossible) ≥80mm3 volume or ≥6mm diameter 5–6mm diameter CT 1 year after baseline CT 3 months after baseline VDT ≤400 days or clear evidence of growth? VDT ≤400 days or clear evidence of growth Stable on basis of 2D non-automated diameter value Stable on basis of volumetry VDT

> 600 days VDT 400–600 days Further workup and consideration of definitive management CT 2 years after baseline VDT assessment and manage as per VDT categories at 1 year Discharge if stable Discharge Consider discharge (only if based on volumetry) or ongoing surveillance depending on patient preference Consider biopsy or further CT surveillance depending on patient preference Yes No B B Solid pulmonary nodule surveillance algorithm. (VDT = volume doubling time) From Callister ME, Baldwin DR, Akram AR, et al. British Thoracic Society Guidelines on the investigation and management of pulmonary nodules. Thorax 2015; Suppl. 2:ii1–ii54. Fig. 17.13, cont’d A variety of diagnostic approaches may

be considered, including bronchoscopy, percutaneous needle biopsy, PET, interval CT scanning or even surgical resection of the lesion. Pulmonary nodules are invariably beyond the vision of the bronchoscope and, with the notable exception of pulmonary infection (e.g. tuberculosis), the yield from blind washings is low, although this may improve as advances in endobronchial imaging are adopted. If the nodule is favourably located and of sufficient size, percutaneous needle biopsy under ultrasound or CT guidance may be employed. The risk of pneumothorax is approximately 15% and around 7% require intercostal drainage, so this should be contemplated only in individuals with an FEV1 of more than 35% predicted. Haemorrhage into the lung or pleural space, air embolism and tumour seeding are rare but recognised complications. Where clinical suspicion remains high despite a benign or indeterminate biopsy or where a nodule is considered to be of sufficiently high risk for malignancy to merit proceeding straight to surgery, then surgical resection may be the best management, as surgery remains the best chance of curing lung cancer. It is important for the logic underlying this approach to be discussed with the patient and the consequences of resection of a benign lesion explained. PET scanning provides useful information about nodules of at least 1 cm in diameter. The presence of high metabolic activity is strongly suggestive of malignancy, while an inactive 'cold' nodule is consistent with benign disease. However, a high SUV is a marker of glucose metabolism, not malignancy, and PET has significant limitations in regions with high endemic rates of infectious or granulomatous disease. False-negative results may occur with neuro-endocrine tumours and minimally invasive lepidic adenocarcinoma. Detection of neuro-endocrine tumours may be improved by the use of 68Ga-Dotatoc in place of FDG. If the nodule is small and inaccessible, interval CT scanning may be employed. A repeat CT scan at 3 months will reliably detect growth in larger nodules and may also demonstrate resolution. Further interval scans may be arranged, depending on the clinical context (Fig. 17.13). Particular care must be taken with subsolid nodules, particularly if further imaging demonstrates the development of a new solid component, as these may represent a pre-malignant or an early invasive form of adenocarcinoma. In cases where the probability of cancer is low, the potential risk of further scanning must be considered. Subsequent scans often detect further nodules, increase the risk of false-positive findings and lead to unnecessary patient anxiety while exposing the individual to increased radiation. Pleural effusion The accumulation of serous fluid within the pleural space is termed pleural effusion. The accumulation of frank pus is termed empyema (p. 564), that of blood is haemothorax, and that of chyle is a chylothorax. In general, pleural fluid accumulates as a result of either increased hydrostatic pressure or decreased osmotic pressure ('transudative' effusion, as seen in cardiac, liver or renal failure), or from increased microvascular pressure due to disease of the pleura or injury in the adjacent lung ('exudative'

17.13 Pleural effusion: main causes and features Cause Appearance of fluid Type of fluid Predominant cells in fluid Other diagnostic features Tuberculosis Serous, usually amber-coloured Exudate Lymphocytes (occasionally polymorphs) Positive tuberculin test Isolation of Mycobacterium tuberculosis from pleural fluid (20%) Positive pleural biopsy (80%) Raised adenosine deaminase Malignant disease Serous, often blood-stained Exudate Serosal cells and lymphocytes Often clumps of malignant cells Positive pleural biopsy (40%) Evidence of malignancy elsewhere Cardiac failure Serous, strawcoloured Transudate Few serosal cells Other signs of cardiac failure Response to diuretics Pulmonary infarction Serous or blood-stained Exudate (rarely transudate) Red blood cells Eosinophils Evidence of pulmonary infarction Obvious source of embolism Factors predisposing to venous thrombosis Rheumatoid disease Serous Turbid if chronic Exudate Lymphocytes (occasionally polymorphs) Rheumatoid arthritis: rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies Cholesterol in chronic effusion; very low glucose in pleural fluid Systemic lupus erythematosus (SLE) Serous Exudate Lymphocytes and serosal cells Other signs of SLE Antinuclear factor or anti-DNA positive Acute pancreatitis Serous or blood-stained Exudate No cells predominate Higher amylase in pleural fluid than in serum Obstruction of thoracic duct Milky Chyle None Chylomicrons *May cause bilateral effusions. 17.12 Causes of pleural effusion Common causes • Pneumonia (‘parapneumonic effusion’) • Tuberculosis • Pulmonary infarction* • Malignant disease • Cardiac failure* • Subdiaphragmatic disorders (subphrenic abscess, pancreatitis etc.) Uncommon causes • Hypoproteinaemia* (nephrotic syndrome, liver failure, malnutrition) • Connective tissue diseases* (particularly systemic lupus erythematosus and rheumatoid arthritis) • Post-myocardial infarction syndrome • Acute rheumatic fever • Meigs’ syndrome (ovarian tumour plus pleural effusion) • Myxoedema* • Uraemia* • Asbestos-related benign pleural effusion effusion). The causes of the majority of pleural effusions (Boxes 17.12 and 17.13) are identified by a thorough history, examination and relevant investigations. Clinical assessment Symptoms (pain on inspiration and coughing) and signs of pleurisy (a pleural rub) often precede the development of an effusion, especially in patients with underlying pneumonia, pulmonary infarction or connective tissue disease. When breathlessness is the only symptom, however, the onset may be insidious, depending on the size and rate of accumulation. The physical signs are detailed on page 547. Investigations Radiological investigations The classical appearance of pleural fluid on the erect PA chest film is of a curved shadow at the lung base, blunting the costophrenic angle and ascending towards the axilla (p. 547). Fluid appears to track up the lateral chest wall. In fact, fluid surrounds the whole lung at this level but casts a radiological shadow only where the X-ray beam passes tangentially across the fluid against the lateral chest wall. Around 200 mL of fluid is required in order for it to be detectable on a PA chest X-ray. Previous scarring or adhesions in the pleural space can cause localised effusions. Pleural fluid localised below the lower lobe (‘subpulmonary effusion’) simulates an elevated hemidiaphragm. Pleural fluid localised within an oblique fissure may produce a rounded opacity that may be mistaken for a tumour. Ultrasound is more accurate than plain chest X-ray for determining the presence of fluid. A clear hypoechoic space is consistent with a transudate and the presence of moving, floating densities suggests an exudate. The presence of septation most likely indicates an evolving empyema or resolving haemothorax. CT scanning is indicated where malignant disease i s suspected. Pleural aspiration and biopsy In some conditions (e.g. left ventricular failure), it should not be necessary to sample fluid unless atypical features are present; appropriate treatment should be administered and the effusion re-evaluated. In most other circumstances, however, diagnostic sampling is required. Simple aspiration provides information on the colour and texture of fluid and these alone may immediately suggest an empyema or chylothorax. The presence of blood is consistent with pulmonary infarction or malignancy but may result from a traumatic tap. Biochemical analysis allows classification into

 Fig. 17.14 Chest X-ray showing a ‘D’-shaped shadow in the left mid-zone, consistent with an empyema. In this case, an intercostal chest drain has been inserted but the loculated collection of pus remains. 17.15 Clinical features of empyema Systemic features • Pyrexia, usually high and remittent • Rigors, sweating, malaise and weight loss • Polymorphonuclear leucocytosis, high C-reactive protein Local features • Pleural pain; breathlessness; cough and sputum, usually because of underlying lung disease; copious purulent sputum if empyema ruptures into a bronchus (bronchopleural fistula) • Clinical signs of pleural effusion 17.14 Light’s criteria for distinguishing pleural transudate from exudate Exudate is likely if one or more of the following criteria are met: • Pleural fluid protein:serum protein ratio > 0.5 • Pleural fluid LDH:serum LDH ratio > 0.6 • Pleural fluid LDH > two-thirds of the upper limit of normal serum LDH (LDH = lactate dehydrogenase) transudate and exudate (Box 17.14) and Gram stain may suggest parapneumonic effusion. The predominant cell type provides useful information and cytological examination is essential. A low pH suggests infection but may also be seen in rheumatoid arthritis, ruptured oesophagus or advanced malignancy. Ultrasound- or CT-guided pleural biopsy provides tissue for pathological and microbiological analysis. Where necessary, video-assisted thoracoscopy allows visualisation of the pleura and direct guidance of a biopsy. Management Therapeutic aspiration may be required to palliate breathlessness but removing more than 1.5 L at a time is associated with a small risk of re-expansion pulmonary oedema. An effusion should never be drained to dryness before establishing a diagnosis, as biopsy may be precluded until further fluid accumulates. Treatment of the underlying cause – e.g. heart failure, pneumonia, pulmonary embolism or subphrenic abscess – will often be followed by resolution of the effusion. The management of pleural effusion in pneumonia, tuberculosis and malignancy is dealt with below. Empyema This is a collection of pus in the pleural space, which may be as thin as serous fluid or so thick that it is impossible to aspirate, even through a wide-bore needle. Microscopically, neutrophil leucocytes are present in large numbers. An empyema may involve the whole pleural space or only part of it (‘loculated’ or ‘encysted’ empyema) and is usually unilateral. It is always secondary to infection in a neighbouring structure, usually the lung, most commonly due to the bacterial pneumonias and tuberculosis. Over 40% of patients with community-acquired pneumonia develop an associated pleural effusion (‘parapneumonic’ effusion) and about 15% of these become secondarily infected. Other causes are infection of a haemothorax following trauma or surgery, oesophageal rupture, and rupture of a subphrenic abscess through the diaphragm. Both pleural surfaces are covered with a thick, shaggy, inflammatory exudate. The pus in the pleural space is often under considerable pressure, and if the condition is not adequately treated, pus may rupture into a bronchus, causing a bronchopleural fistula and pyopneumothorax, or track through the chest wall with the formation of a subcutaneous abscess or sinus, so-called empyema necessitans. Clinical assessment An empyema should be suspected in patients with pulmonary infection if there is severe pleuritic chest pain or persisting or recurrent pyrexia, despite appropriate antibiotic treatment. In other cases, the primary infection may be so mild that it passes unrecognised and the first definite clinical features are due to the empyema itself. Once an empyema has developed, systemic features are prominent (Box 17.15). Investigations Chest X-ray appearances may be indistinguishable from those of pleural effusion, although pleural adhesions may confine the empyema to form a ‘D’-shaped shadow against the inside of the chest wall (Fig. 17.14). When air is present as well as pus (pyopneumothorax), a horizontal ‘fluid level’ marks the air/liquid interface.

Ultrasound shows the position of the fluid, the extent of pleural thickening and whether fluid is in a single collection or multiloculated, containing fibrin and debris (Fig. 17.15). CT provides information on the pleura, underlying lung parenchyma and patency of the major bronchi. Ultrasound or CT is used to identify the optimal site for aspiration, which is best performed using a wide-bore needle. If the fluid is thick and turbid pus, empyema is confirmed. Other features suggesting empyema are a fluid glucose of less than 3.3 mmol/L (60 mg/dL), lactate dehydrogenase (LDH) of more than 1000 IU/L, or a fluid pH of less than 7.0 (H^+ > 100 nmol/L). However, pH measurement should be avoided if pus is thick, as it damages blood gas machines. The pus is frequently sterile on culture if antibiotics have already been given. The distinction between tuberculous and non-tuberculous disease can be difficult and may require pleural biopsy, histology, culture and/or a NAAT.

preventing re-expansion of the lung. Surgery is also necessary if a bronchopleural fistula develops. Despite the widespread availability of antibiotics that are effective against pneumonia, empyema remains a significant cause of morbidity and mortality. Respiratory failure The term ‘respiratory failure’ is used when pulmonary gas exchange fails to maintain normal arterial oxygen and carbon dioxide levels. Its classification into types I and II is defined by the absence or presence of hypercapnia (raised $PaCO_2$). Pathophysiology When disease impairs ventilation of part of a lung (e.g. in asthma or pneumonia), perfusion of that region results in hypoxic and CO_2laden blood entering the pulmonary veins. Increased ventilation of neighbouring regions of normal lung can increase CO_2 excretion, correcting arterial CO_2 to normal, but cannot augment oxygen uptake because the haemoglobin flowing through these normal regions is already fully saturated. Admixture of blood from the under-ventilated and normal regions thus results in hypoxia with normocapnia, which is called ‘type I respiratory failure’. Diseases causing this include all those that impair ventilation locally with sparing of other regions (Box 17.16). Arterial hypoxia with hypercapnia (type II respiratory failure) is seen in conditions that cause generalised, severe ventilation– perfusion mismatch, leaving insufficient normal lung to correct $PaCO_2$, or any disease that reduces total ventilation. The latter includes not just diseases of the lung but also disorders affecting any part of the neuromuscular mechanism of ventilation (Box 17.16). Management of acute respiratory failure Prompt diagnosis and management of the underlying cause is crucial. In type I respiratory failure, high concentrations of oxygen (40–60% by mask) will usually relieve hypoxia by increasing the alveolar PO_2 in poorly ventilated lung units. Occasionally, however (e.g. severe pneumonia affecting several lobes), mechanical ventilation may be needed to relieve hypoxia. Patients who need high concentrations of oxygen for more than a few hours should receive humidified oxygen. Management An empyema will heal only if infection is eradicated and the empyema space is obliterated, allowing apposition of the visceral and parietal pleural layers. This can only occur if re-expansion of the compressed lung is secured at an early stage by removal of all the pus from the pleural space. When the pus is sufficiently thin, this is most easily achieved by the insertion of a wide-bore intercostal tube into the most dependent part of the empyema space. If the initial aspirate reveals turbid fluid or frank pus, or if loculations are seen on ultrasound, the tube should be put on suction (−5 to −10 cmH_2O) and flushed regularly with 20 mL normal saline. If the organism causing the empyema can be identified, the appropriate antibiotic should be given for 2–4 weeks. Empirical antibiotic treatment (e.g. intravenous co-amoxiclav or cefuroxime with metronidazole) should be used if the organism is unknown. Intrapleural fibrinolytic therapy is of no benefit. An empyema can often be aborted if these measures are started early, but if the intercostal tube is not providing adequate drainage – e.g. when the pus is thick or loculated – surgical intervention is required to clear the empyema cavity of pus and break down any adhesions. Surgical ‘decortication’ of the lung may also be required if gross thickening of the visceral pleura is Fig. 17.15 Pleural ultrasound showing septation. Courtesy of Dr P. Sivasothy, Department of Respiratory Medicine, Addenbrooke’s Hospital, Cambridge. 17.16 How to interpret blood gas abnormalities in respiratory failure Type I Type II Hypoxia (PaO_2 < 8.0 kPa (60 mmHg)) Normal or low $PaCO_2$ (≤ 6 kPa (45 mmHg)) Hypoxia (PaO_2 < 8.0 kPa (60 mmHg)) Raised $PaCO_2$ (> 6 kPa (45 mmHg)) Acute Chronic Acute Chronic H^+ → → ↑ → or ↑ Bicarbonate → → → ↑ Causes Acute asthma Pulmonary oedema Pneumonia Lobar collapse Pneumothorax Pulmonary embolus ARDS COPD Lung fibrosis Lymphangitic carcinomatosis Right-to-left shunts Acute severe asthma Acute exacerbation of COPD Upper airway obstruction Acute neuropathies/paralysis Narcotic drugs Primary alveolar hypoventilation Flail chest injury COPD Sleep apnoea Kyphoscoliosis Myopathies/muscular dystrophy Ankylosing spondylitis (ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease)

 due to COPD may not appear distressed, despite being critically ill with severe hypoxaemia, hypercapnia and acidaemia. While the physical signs of CO_2 retention (delirium, flapping tremor, bounding pulses and so on) can be helpful if present, they may not be, so measurement of arterial blood gases is mandatory in the assessment of initial severity and response to treatment. Management The principal aims of treatment in acute on chronic type II respiratory failure are to achieve a safe PaO_2 (> 7.0 kPa (52 mmHg)) without increasing $PaCO_2$ and acidosis, while identifying and treating the precipitating condition. In these patients, it is not necessary to achieve a normal PaO_2; even a small increase will greatly improve tissue oxygen delivery, since their PaO_2 values are often on the steep part of the oxygen dissociation curve (see Fig. 10.9, p. 191). The risks of worsening hypercapnia and coma must be balanced against those of severe hypoxaemia, which include potentially fatal arrhythmias and hypoxic brain damage. Immediate treatment is shown in Box 17.17. Patients who are conscious and have adequate respiratory drive may benefit from non-invasive ventilation (NIV), which has been shown to reduce the need for intubation and shorten hospital stay in acidotic exacerbations of COPD. Patients who are drowsy and have low respiratory drive require an urgent decision regarding intubation and ventilation, as this is likely to be the only effective treatment, even though weaning off the ventilator may be difficult in severe disease. The decision is challenging, and important factors to consider include patient and family wishes, presence of a potentially remediable precipitating condition, prior functional Acute type II respiratory failure is an emergency requiring immediate intervention. It is useful to distinguish between patients with high ventilatory drive (rapid respiratory rate and accessory muscle recruitment) who cannot move sufficient air, and those with reduced or inadequate respiratory effort. In the former, particularly if inspiratory stridor is present, acute upper airway obstruction from foreign body inhalation or laryngeal obstruction (angioedema, carcinoma or vocal cord paralysis) must be considered, as the Heimlich manœuvre (p. 625), immediate intubation or emergency tracheostomy may be life-saving. More commonly, the problem is in the lungs, with severe generalised bronchial obstruction from COPD or asthma, acute respiratory distress syndrome (ARDS) arising from a variety of insults (p. 198), or occasionally tension pneumothorax (p. 625). In all such cases, high-concentration (e.g. 60%) oxygen should be administered, pending a rapid examination of the respiratory system and measurement of arterial blood gases. Patients with the trachea deviated away from a silent and resonant hemithorax are likely to have tension pneumothorax, and air should be aspirated from the pleural space and a chest drain inserted as soon as possible. Patients with generalised wheeze, scanty breath sounds bilaterally or a history of asthma or COPD should be treated with salbutamol 2.5 mg nebulised with oxygen, repeated until bronchospasm is relieved. Failure to respond to initial treatment, declining conscious level and worsening respiratory acidosis (H^+ > 50 nmol/L (pH < 7.3), $PaCO_2$ > 6.6 kPa (50 mmHg)) on blood gases are all indications that supported ventilation is required (p. 202). A small percentage of patients with severe chronic COPD and type II respiratory failure develop abnormal tolerance to raised $PaCO_2$ and may become dependent on hypoxic drive to breathe. In these patients only, lower concentrations of oxygen (24–28% by Venturi mask) should be used to avoid precipitating worsening respiratory depression (see below). In all cases, regular monitoring of arterial blood gases is important to assess progress. Patients with acute type II respiratory failure who have reduced drive or conscious level may be suffering from sedative poisoning, CO_2 narcosis or a primary failure of neurological drive (e.g. following intracerebral haemorrhage or head injury). History from a witness may be invaluable, and reversal of specific drugs with (for example) opiate antagonists is occasionally successful, but should not delay intubation and supported mechanical ventilation in appropriate cases. Chronic and 'acute on chronic' type II respiratory failure The most common cause of chronic type II respiratory failure is severe COPD. Although $PaCO_2$ may be persistently raised, there is no persisting acidaemia because the kidneys retain bicarbonate, correcting arterial pH to normal. This 'compensated' pattern, which may also occur in chronic neuromuscular disease or kyphoscoliosis, is maintained until there is a further acute illness (Box 17.16), such as an exacerbation of COPD that precipitates an episode of 'acute on chronic' respiratory failure, with acidaemia and initial respiratory distress followed by drowsiness and eventually coma. These patients have lost their chemosensitivity to elevated $PaCO_2$, and so they may paradoxically depend on hypoxia for respiratory drive and are at risk of respiratory depression if given high concentrations of oxygen, e.g. during ambulance transfers or in emergency departments. Moreover, in contrast to acute severe asthma, some patients with 'acute on chronic' type II respiratory failure 17.17 Assessment and management of 'acute on chronic' type II respiratory failure Initial assessment Patient may not appear distressed, despite being critically ill • Conscious level (response to commands, ability to cough) • CO_2 retention (warm periphery, bounding pulses, flapping tremor) • Airways obstruction (wheeze, prolonged expiration, hyperinflation, intercostal indrawing, pursed lips) • Cor pulmonale (peripheral oedema, raised jugular venous pressure, hepatomegaly, ascites) • Background functional status and quality of life • Signs of precipitating cause (see Box 17.15) Investigations • Arterial blood gases (severity of hypoxaemia, hypercapnia, acidaemia, bicarbonate) • Chest X-ray Management • Maintenance of airway • Treatment of specific precipitating cause • Frequent physiotherapy ± pharyngeal suction • Nebulised bronchodilators • Controlled oxygen therapy: Start with 24% Venturi mask Aim for a PaO_2 > 7 kPa (52 mmHg) (a PaO_2 < 5 (37 mmHg) is dangerous) • Antibiotics if evidence of infection • Diuretics if evidence of fluid overload Progress • If $PaCO_2$ continues to rise or a safe PaO_2 cannot be achieved without severe hypercapnia and acidaemia, mechanical ventilatory support may be required

irradiation are employed to treat obliterative bronchiolitis but late organ failure remains a significant problem. The major factor limiting the availability of lung transplantation is the shortage of donor lungs. To improve organ availability, techniques to recondition the lungs in vitro after removal from the donor are being developed. Obstructive pulmonary diseases Asthma Asthma is a chronic inflammatory disorder of the airways, in which many cells and cellular elements play a role. Chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible, either spontaneously or with treatment. The prevalence of asthma increased steadily over the latter part of last century. As asthma affects all age groups, it is one of the most common and important long-term respiratory conditions in terms of global years lived with disability (Fig. 17.16). The development and course of asthma and the response to treatment are influenced by genetic determinants, while the rapid rise in prevalence implies that environmental factors are critically important in the development and expression of the disease. The potential role of indoor and outdoor allergens, microbial exposure, diet, vitamins, breastfeeding, tobacco smoke, air pollution and obesity have been explored but no clear consensus has emerged. capacity and quality of life. The various types of non-invasive (via a face or nasal mask) or invasive (via an endotracheal tube) ventilation are detailed on page 202. Respiratory stimulant drugs, such as doxapram, have been superseded by intubation and mechanical ventilation in patients with CO2 narcosis. Home ventilation for chronic respiratory failure NIV is of great value in the long-term treatment of respiratory failure due to spinal deformity, neuromuscular disease and central alveolar hypoventilation. Some patients with advanced lung disease, e.g. cystic fibrosis, also benefit from NIV for respiratory failure. In these conditions, type II respiratory failure can develop slowly and insidiously. Morning headache (due to elevated PaCO2) and fatigue are common symptoms but, in many cases, the diagnosis is revealed only by sleep studies or morning blood gas analysis. In the initial stages, ventilation is insufficient for metabolic needs only during sleep, when there is a physiological decline in ventilatory drive. Over time, however, CO2 retention becomes chronic, with renal compensation of acidosis. Treatment by home-based NIV overnight is often sufficient to restore the daytime PCO2 to normal, and to relieve fatigue and headache. In advanced disease (e.g. muscular dystrophies or cystic fibrosis), daytime NIV may also be required. Lung transplantation Lung transplantation is an established treatment for carefully selected patients with advanced lung disease unresponsive to medical treatment (Box 17.18). Single-lung transplantation may be used for selected patients with advanced emphysema or lung fibrosis. This is contraindicated in patients with chronic bilateral pulmonary infection, such as cystic fibrosis and bronchiectasis, because the transplanted lung is vulnerable to cross-infection in the context of post-transplant immunosuppression, and for these individuals bilateral lung transplantation is the standard procedure. Combined heart–lung transplantation is still occasionally needed for patients with advanced congenital heart disease, such as Eisenmenger’s syndrome, and is preferred by some surgeons for the treatment of primary pulmonary hypertension unresponsive to medical therapy. The prognosis following lung transplantation is improving steadily with modern immunosuppressive drugs: over 50% 10-year survival in some UK centres. Chronic rejection with obliterative bronchiolitis continues to afflict some recipients, however. Glucocorticoids are used to manage acute rejection, but drugs that inhibit cell-mediated immunity specifically, such as ciclosporin, mycophenolate and tacrolimus (p. 89), are used to prevent chronic rejection. Azithromycin, statins and total lymphoid 17.18 Indications for lung transplantation Parenchymal lung disease • Cystic fibrosis • Emphysema • Pulmonary fibrosis • Obliterative bronchiolitis • Langerhans cell histiocytosis (p. 613) • Lymphangioleiomyomatosis (p. 613) Pulmonary vascular disease • Primary pulmonary hypertension • Thromboembolic pulmonary hypertension • Veno-occlusive disease • Eisenmenger’s syndrome (p. 532) Fig. 17.16 The burden of asthma, measured by disability life years (DALYs) per 100 000 population. The burden of asthma is greatest in children approaching adolescence and the elderly. The burden is similar in males and females at ages below 30–34 but at older ages the burden is higher in males. From The Global Asthma Report 2014. Copyright 2014 The Global Asthma Network. 80+ 70–74 75–79 65–69 60–64 55–59 50–54 45–49 40–44 35–39 30–34 25–29 20–24 15–19 10–14 5–9 1–4 DALYs (per 100000)

Females Males Years

 With increasing severity and chronicity of the disease, remodelling of the airway may occur, leading to fibrosis of the airway wall, fixed narrowing of the airway and a reduced response to bronchodilator medication. Clinical features Typical symptoms include recurrent episodes of wheezing, chest tightness, breathlessness and cough. Asthma is commonly mistaken for a cold or a persistent chest infection (e.g. longer than 10 days). Classical precipitants include exercise, particularly in cold weather, exposure to airborne allergens or pollutants, and viral upper respiratory tract infections. Wheeze apart, there is often very little to find on examination. An inspection for nasal polyps and eczema should be performed. Rarely, a vasculitic rash may suggest eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss syndrome; p. 1043). Patients with mild intermittent asthma are usually asymptomatic between exacerbations. Individuals with persistent asthma report ongoing breathlessness and wheeze but these are variable, with symptoms fluctuating over the course of one day, or from day to day or month to month. Asthma characteristically displays a diurnal pattern, with symptoms and lung function being worse in the early morning. Particularly when poorly controlled, symptoms such as cough and wheeze disturb sleep. Cough may be the dominant symptom in some patients, and the lack of wheeze or breathlessness may lead to a delay in reaching the diagnosis of so-called ‘cough-variant asthma’. Some patients with asthma have a similar inflammatory response in the upper airway. Careful enquiry should be made as to a history of sinusitis, sinus headache, a blocked or runny nose and loss of sense of smell. Although the aetiology of asthma is often elusive, an attempt should be made to identify any agents that may contribute to the appearance or aggravation of the condition. Particular enquiry should be made about potential allergens, such as exposure to a pet cat, guinea pig, rabbit or horse, pest infestation, exposure to moulds following water damage to a home or building, and any potential occupational agents (p. 613). In some circumstances, the appearance of asthma is triggered by medications. Beta-blockers, even when administered topically Pathophysiology Airway hyper-reactivity (AHR) – the tendency for airways to narrow excessively in response to triggers that have little or no effect in normal individuals – is integral to the diagnosis of asthma and appears to be related, although not exclusively, to airway inflammation (Fig. 17.17). Other factors likely to be important in the behaviour of airway smooth muscle include the degree of airway narrowing and neurogenic mechanisms. The relationship between atopy (the propensity to produce IgE) and asthma is well established and in many individuals there is a clear relationship between sensitisation and allergen exposure, as demonstrated by skin-prick reactivity or elevated serum-specific IgE. Common examples of allergens include house dust mites, pets such as cats and dogs, pests such as cockroaches, and fungi. Inhalation of an allergen into the airway is followed by an early and late-phase bronchoconstrictor response (Fig. 17.18). Allergic mechanisms are also implicated in some cases of occupational asthma (p. 613). In cases of aspirin-sensitive asthma, the ingestion of salicylates results in inhibition of the cyclo-oxygenase enzymes, preferentially shunting the metabolism of arachidonic acid through the lipoxygenase pathway with resultant production of the asthmogenic cysteinyl leukotrienes. In exercise-induced asthma, hyperventilation results in water loss from the pericellular lining fluid of the respiratory mucosa, which, in turn, triggers mediator release. Heat loss from the respiratory mucosa may also be important. In persistent asthma, a chronic and complex inflammatory response ensues, characterised by an influx of numerous inflammatory cells, the transformation and participation of airway structural cells, and the secretion of an array of cytokines, chemokines and growth factors. Examination of the inflammatory cell profile in induced sputum samples demonstrates that, although asthma is predominantly characterised by airway eosinophilia, neutrophilic inflammation predominates in some patients while in others scant inflammation is observed: so-called 'paucigranulocytic' asthma. Fig. 17.17 Airway hyper-reactivity in asthma. This is demonstrated by bronchial challenge tests with sequentially increasing concentrations of either histamine, or methacholine or mannitol. The reactivity of the airways is expressed as the concentration or dose of either chemical required to produce a specific decrease (usually 20%) in the forced expired volume in 1 second (FEV1) (PC20 or PD20, respectively).

Reduction in FEV1 (%) Increasing concentration of histamine Severe asthma Moderate asthma Mild asthma Normal Fig. 17.18 Changes in peak flow following allergen challenge. A similar biphasic response is observed following a variety of different challenges. Occasionally, an isolated late response is seen with no early reaction. Time (hours) Peak flow (L/min)

Early reaction (type I) Pre-formed mediator release Late reaction (type II) Inflammatory cell recruitment and activation

Challenge, e.g. allergen

available, a peak flow meter may be used. Symptomatic patients should be instructed to record peak flow readings after rising in the morning and before retiring in the evening. A diurnal variation in PEF of more than 20% (the lowest values typically being recorded in the morning) is considered diagnostic, and the magnitude of variability provides some indication of disease severity (Fig. 17.20). A trial of glucocorticoids (e.g. 30 mg daily for 2 weeks) may be useful in establishing the diagnosis, by demonstrating an improvement in either FEV1 or PEF. It is not uncommon for patients whose symptoms are suggestive of asthma to have normal lung function. In these circumstances, the demonstration of AHR by challenge tests may be useful to confirm the diagnosis (see Fig. 17.17). AHR has a high negative predictive value but positive results may be seen in other conditions, such as COPD, bronchiectasis and cystic fibrosis. The use of exercise tests is useful when symptoms are predominantly related to exercise (Fig. 17.21). The diagnosis may be supported by the presence of atopy demonstrated by skin-prick tests or measurement of total and allergen-specific IgE, an FENO (a surrogate of eosinophilic airway inflammation) of ≥ 40 parts per billion in a glucocorticoid-naïve adult, or a peripheral blood eosinophilia. Chest X-ray appearances are often normal but lobar collapse may be seen if mucus occludes a large bronchus and, if accompanied by the presence of flitting infiltrates, may suggest that asthma has been complicated by allergic bronchopulmonary aspergillosis (p. 596). A high-resolution CT scan (HRCT) may be useful to detect bronchiectasis. Management Setting goals Asthma is a chronic condition but may be controlled with appropriate treatment in the majority of patients. The goal of treatment should be to obtain and maintain complete control (Box 17.20) but aims may be modified according to the circumstances as eye drops, may induce bronchospasm, as may aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). The classical aspirin-sensitive patient is female and presents in middle age with asthma, rhinosinusitis and nasal polyps. Aspirin-sensitive patients may also report symptoms following alcohol and foods containing salicylates. Other medications implicated include the oral contraceptive pill, cholinergic agents and prostaglandin F2α. Betel nuts contain arecoline, which is structurally similar to methacholine and can aggravate asthma. An important minority of patients develop a particularly severe form of asthma and this appears to be more common in women. Allergic triggers are less important and airway neutrophilia predominates. Diagnosis The diagnosis of asthma is predominantly clinical and is based on the combination of the history, lung function and ‘other’ tests, which allows high, intermediate or low probability of asthma to emerge. The approach may vary from patient to patient and may need to be re-evaluated following the introduction of treatment. Supportive evidence is provided by the demonstration of variable airflow obstruction, preferably by using spirometry (Box 17.19) to measure FEV1 and FVC. This identifies the obstructive defect, defines its severity, and provides a baseline for bronchodilator reversibility (Fig. 17.19). If spirometry is not 17.19 How to make a diagnosis of asthma Compatible clinical history plus either/or: • FEV1 ≥ 12% (and 200 mL) increase following administration of a bronchodilator/trial of glucocorticoids. Greater confidence is gained if the increase is > 15% and > 400 mL • > 20% diurnal variation on ≥ 3 days in a week for 2 weeks on PEF diary • FEV1 ≥ 15% decrease after 6 mins of exercise (FEV1 = forced expiratory volume in 1 sec; PEF = peak expiratory flow) Fig. 17.19 Reversibility test. Forced expiratory manœuvres before and 20 minutes after inhalation of a β2-adrenoceptor agonist. Note the increase in forced expiratory volume in 1 second (FEV1) from 1.0 to 2.5 L.

Time (seconds)

Volume expired (L) FEV1 FEV1 20 mins after bronchodilator drug administered 2.5

Before bronchodilator drug administered Fig. 17.20 Serial recordings of peak expiratory flow (PEF) in a patient with asthma. Note the sharp overnight fall (morning dip) and subsequent rise during the day. Following the introduction of glucocorticoids, there is an improvement in PEF rate and reduction of morning dipping.

am am Peak flow (L/min)

pm pm am am pm pm am am pm

Time (days)

Glucocorticoids commenced

570 • RESPIRATORY MEDICINE pet, may effect improvement. House dust mite exposure may be minimised by replacing carpets with floorboards and using miteimpermeable bedding. So far, improvements in asthma control following such measures have been difficult to demonstrate. Many patients are sensitised to several ubiquitous aeroallergens, making avoidance strategies largely impractical. Measures to reduce fungal exposure may be applicable in specific circumstances and medications known to precipitate or aggravate asthma should be avoided. Smoking cessation (p. 94) is particularly important, as smoking not only encourages sensitisation but also induces a relative glucocorticoid resistance in the airway. The stepwise approach to the management of

asthma See Figure 17.22. Step 1: Occasional use of inhaled short-acting β2-adrenoreceptor agonist bronchodilators A variety of different inhaled devices are available and the choice of device should be guided by patient preference and competence Fig. 17.21 Exercise-induced asthma. Serial recordings of forced expiratory volume in 1 second (FEV1) in a patient with bronchial asthma before and after 6 minutes of strenuous exercise. Note initial rise on completion of exercise, followed by sudden fall and gradual recovery. Adequate warm-up exercise or pre-treatment with a β2-adrenoceptor agonist, nedocromil sodium or a leukotriene antagonist can protect against exercise-induced symptoms. 3.5 Time (minutes)

FEV1 (L) 3.0 2.5 2.0 Exercise and the patient. Unfortunately, surveys consistently demonstrate that the majority of individuals with asthma report suboptimal control, perhaps reflecting the poor expectations of patients and their clinicians. Whenever possible, patients should be encouraged to take responsibility for managing their own disease. A full explanation of the nature of the condition, the relationship between symptoms and inflammation, the importance of key symptoms such as nocturnal waking, the different types of medication and, if appropriate, the use of PEF to guide management decisions should be given. A variety of tools/questionnaires have been validated to assist in assessing asthma control. Written action plans can be helpful in developing self-management skills. Avoidance of aggravating factors This is particularly important in the management of occupational asthma (p. 613) but may also be relevant in atopic patients, when removing or reducing exposure to relevant antigens, such as a 17.21 Asthma in pregnancy • Clinical course: women with well-controlled asthma usually have good pregnancy outcomes. Pregnancy in women with more severe asthma can precipitate worsening control and lead to increased maternal and neonatal morbidity. • Labour and delivery: 90% have no symptoms. • Safety data: good for β2-agonists, inhaled glucocorticoids, theophyllines, oral prednisolone, and chromones. • Oral leukotriene receptor antagonists: no evidence that these harm the fetus and they should not be stopped in women who have previously demonstrated significant improvement in asthma control prior to pregnancy. • Glucocorticoids: women on maintenance prednisolone > 7.5 mg/ day should receive hydrocortisone 100 mg 3–4 times daily during labour. • Prostaglandin F2α: may induce bronchospasm and should be used with extreme caution. • Breastfeeding: use medications as normal. • Uncontrolled asthma: associated with maternal (hyperemesis, hypertension, pre-eclampsia, vaginal haemorrhage, complicated labour) and fetal (intrauterine growth restriction and low birth weight, preterm birth, increased perinatal mortality, neonatal hypoxia) complications. Characteristic Controlled Partly controlled (any present in any week) Uncontrolled Daytime symptoms None (≤ twice/week)

> twice/week ≥ 3 features of partly controlled asthma present in any week Limitations of activities None Any Nocturnal symptoms/awakening None Any Need for rescue/‘reliever’ treatment None (≤ twice/week) twice/week Lung function (PEF or FEV1) Normal < 80% predicted or personal best (if known) on any day Exacerbation None ≥ 1/year 1 in any week (FEV1 = forced expiratory volume in 1 sec; PEF = peak expiratory flow) } 17.20 Levels of asthma control

Fig. 17.22 Management approach in adults based on asthma control. (ICS = inhaled corticosteroids (glucocorticoids); LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; SR = sustained-release) From British Thoracic Society and SIGN guideline 153: British guideline on the management of asthma (2016). Move down to find and maintain lowest controlling therapy Move up to improve control as needed Consider monitored initiation of treatment with low-dose ICS Infrequent, short-lived wheeze Low-dose ICS Short-acting β2 agonists as required – consider moving up if using three doses a week or more Evaluation: • assess symptoms, measure lung function, check inhaler technique and adherence • adjust dose • update self-management plan • move up and down as appropriate Asthma – suspected Asthma – diagnosed Diagnosis and assessment Consider trials of: Increasing ICS up to high dose Addition of a fourth drug, eg LTRA, SR theophylline, beta agonist tablet, LAMA Use daily steroid tablet in the lowest dose providing adequate control Maintain high-dose ICS Consider other treatments to minimize use of steroid tablets Regular preventer Initial add-on therapy Additional add-on therapies High-dose therapies Continuous frequent use of oral steroids Add inhaled LABA to low-dose ICS (normally as a combination inhaler) No response to LABA – stop LABA and consider increased dose of ICS If benefit from LABA but control still inadequate – continue LABA and increase ICS to medium dose If benefit from LABA but control still inadequate – continue LABA and ICS and consider trial of other therapy – LTRA, SR theophylline, LAMA Refer patient for specialist care Refer patient for specialist care Fig. 17.23 How to use a metered-dose inhaler. • Remove the cap and shake the inhaler • Breathe out gently and place the mouthpiece into the mouth • Incline the head backwards to minimise oropharyngeal deposition • Simultaneously, begin a slow deep inspiration, depress the canister and continue to inhale • Hold the breath for 10 seconds (BUD), fluticasone, mometasone or ciclesonide) should be started in addition to inhaled β2-agonists taken on an as-required basis for any patient who: • has experienced an exacerbation of asthma in the last 2 years • uses inhaled β2-agonists three times a week or more • reports symptoms three times a week or more • is awakened by asthma one night per week. For adults, a reasonable starting dose is 400 μg beclometasone dipropionate (BDP) or equivalent per day in adults, although higher doses may be required in smokers. Alternative but much less effective preventive agents include chromones, leukotriene receptor antagonists and theophyllines. Step 3: Add-on therapy If a patient remains poorly controlled despite regular use of an inhaled glucocorticoid, a thorough review should be undertaken of adherence, inhaler technique and ongoing exposure to modifiable aggravating factors. A further increase in the dose of inhaled glucocorticoid may benefit some patients but, in general, add-on therapy should be considered in adults taking 800 μg/day BDP (or equivalent). The addition of a long-acting β2-agonist (LABA) to an inhaled glucocorticoid provides more effective asthma control compared with increasing the dose of inhaled glucocorticoid alone. Fixedcombination inhalers of glucocorticoids and LABAs have been developed; these are more convenient, increase adherence and prevent patients using a LABA as monotherapy – the latter may be accompanied by an increased risk of life-threatening attacks in its use. The metered-dose inhaler remains the most widely prescribed (Fig. 17.23). For patients with mild intermittent asthma (symptoms less than once a week for 3 months and fewer than two nocturnal episodes per month), it is usually sufficient to prescribe an inhaled short-acting β2-agonist, such as salbutamol or terbutaline, to be used as required. However, many patients (and their physicians) under-estimate the severity of asthma. A history of a severe exacerbation should lead to a step-up in treatment. Step 2: Introduction of regular preventer therapy Regular anti-inflammatory therapy (preferably inhaled glucocorticoids (ICS), such as beclometasone, budesonide not necessary, unless glucocorticoid has been given for more than 3 weeks. Indications for 'rescue' courses include: • symptoms and PEF progressively worsening day by day, with a fall of PEF below 60% of the patient's personal best recording • onset or worsening of sleep disturbance by asthma • persistence of morning symptoms until midday • progressively diminishing response to an inhaled bronchodilator • symptoms that are sufficiently severe to require treatment with nebulised or injected bronchodilators. Management of acute severe asthma Box 17.22 highlights the immediate assessment requirements in acute asthma. Measurement of PEF is mandatory, unless the patient is too ill to cooperate, and is most easily interpreted when expressed as a percentage of the predicted normal or of the previous best value obtained on optimal treatment (Fig. 17.24). Arterial blood gas analysis is essential to determine the $PaCO_2$, a normal or elevated level being particularly dangerous. A chest X-ray is not immediately necessary, unless pneumothorax is suspected. Treatment includes the following measures: • Oxygen. High concentrations (humidified if possible) should be administered to maintain the oxygen saturation above 92% in adults. The presence of a high $PaCO_2$ should not be taken as an indication to reduce oxygen concentration but as a warning sign of a severe or life-threatening attack. Failure to achieve appropriate oxygenation is an indication for assisted ventilation. • High doses of inhaled bronchodilators. Short-acting β_2-agonists are the agent of choice. In hospital, they are most conveniently given via a nebuliser driven by oxygen, but delivery of multiple doses of salbutamol via a metered-dose inhaler through a spacer device provides equivalent bronchodilatation and can be used in primary care. Ipratropium bromide provides further bronchodilator therapy and should be added to salbutamol in acute severe or life-threatening attacks. or asthma death. The onset of action of formoterol is similar to that of salbutamol such that, in carefully selected patients, a fixed combination of budesonide and formoterol may be used as both rescue and maintenance therapy. Oral leukotriene receptor antagonists (e.g. montelukast 10 mg daily) are generally less effective than LABAs as add-on therapy but may facilitate a reduction in the dose of inhaled glucocorticoid and control exacerbations. Step 4: Poor control on moderate dose of inhaled glucocorticoid and add-on therapy: addition of a fourth drug In adults, the dose of inhaled glucocorticoid may be increased to 2000 µg BDP/BUD (or equivalent) daily. A nasal glucocorticoid preparation should be used in patients with prominent upper airway symptoms. Leukotriene receptor antagonists, long-acting antimuscarinic agents, theophyllines or a slow-release β_2-agonist may be considered. If the trial of add-on therapy is ineffective, it should be discontinued. Step 5: Continuous or frequent use of oral glucocorticoids At this stage, prednisolone therapy (usually administered as a single daily dose in the morning) should be prescribed in the lowest amount necessary to control symptoms. Patients who are on long-term glucocorticoid tablets (> 3 months) or are receiving more than three or four courses per year will be at risk of systemic side-effects (p. 670). The risk of osteoporosis in this group can be reduced by giving bisphosphonates (p. 1047). In patients who continue to experience symptoms and asthma exacerbation and demonstrate impaired lung function despite step 5 treatment, omalizumab, a monoclonal antibody directed against IgE, should be considered for those with a prominent atopic phenotype, and mepolizumab, a monoclonal antibody that blocks the binding of IL-5 to its receptor on eosinophils, should be considered in those with eosinophilic-mediated disease. The use of immunosuppressants, such as methotrexate, ciclosporin or oral gold, is less common nowadays, as the response is variable and the limited benefits may be easily offset by side-effects. Step-down therapy Once asthma control is established, the dose of inhaled (or oral) glucocorticoid should be titrated to the lowest dose at which effective control of asthma is maintained. Decreasing the dose of glucocorticoid by around 25–50% every 3 months is a reasonable strategy for most patients. Exacerbations of asthma The course of asthma may be punctuated by exacerbations with increased symptoms, deterioration in lung function, and an increase in airway inflammation. Exacerbations are most commonly precipitated by viral infections but moulds (Alternaria and Cladosporium), pollens (particularly following thunderstorms) and air pollution are also implicated. Most attacks are characterised by a gradual deterioration over several hours to days but some appear to occur with little or no warning: so-called brittle asthma. An important minority of patients appear to have a blunted perception of airway narrowing and fail to appreciate the early signs of deterioration. Management of mild to moderate exacerbations Doubling the dose of inhaled glucocorticoids does not prevent an impending exacerbation. Short courses of ‘rescue’ glucocorticoids (prednisolone 30–60 mg daily) are therefore often required to regain control. Tapering of the dose to withdraw treatment is 17.22 Immediate assessment of acute severe asthma Acute severe asthma • PEF 33–50% predicted (< 200 L/min) • Heart rate ≥ 110 beats/min • Respiratory rate ≥ 25 breaths/min • Inability to complete sentences in 1 breath Life-threatening features • PEF < 33% predicted (< 100 L/min) • SpO_2 < 92% or PaO_2 < 8 kPa (60 mmHg) (especially if being treated with oxygen) • Normal or raised $PaCO_2$ • Silent chest • Cyanosis • Feeble respiratory effort • Bradycardia or arrhythmias • Hypotension • Exhaustion • Delirium • Coma Near-fatal asthma • Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures (PEF = peak expiratory flow)

patient, contributes to delay in delivering appropriate therapy and to under-treatment. Prior to discharge, patients should be stable on discharge medication (nebulised therapy should have been discontinued for at least 24 hours) and the PEF should have reached 75% of predicted or personal best. The acute attack should prompt a look for and avoidance of any trigger factors, the delivery of asthma education and the provision of a written self-management plan. The patient should be offered an appointment with a GP or asthma nurse within 2 working days of discharge, and follow-up at a specialist hospital clinic within a month. Chronic obstructive pulmonary disease Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways • Systemic glucocorticoids. These reduce the inflammatory response and hasten the resolution of an exacerbation. They should be administered to all patients with an acute severe attack. They can usually be administered orally as prednisolone but intravenous hydrocortisone may be used in patients who are vomiting or unable to swallow. There is no evidence base for the use of intravenous fluids but many patients are dehydrated due to high insensible water loss and will probably benefit. Potassium supplements may be necessary, as repeated doses of salbutamol can lower serum potassium. If patients fail to improve, a number of further options may be considered. Intravenous magnesium may provide additional bronchodilatation in patients whose presenting PEF is below 30% predicted. Some patients appear to benefit from the use of intravenous aminophylline but cardiac monitoring is recommended. PEF should be recorded every 15–30 minutes and then every 4–6 hours. Pulse oximetry should ensure that SaO_2 remains above 92%, but repeat arterial blood gases are necessary if the initial $PaCO_2$ measurements were normal or raised, the PaO_2 was below 8 kPa (60 mmHg) or the patient deteriorates. Box 17.23 lists the indications for endotracheal intubation and intermittent positive pressure ventilation (IPPV). Prognosis The outcome from acute severe asthma is generally good but a considerable number of deaths occur in young people and many are preventable. Failure to recognise the severity of an attack, on the part of either the assessing physician or the Fig. 17.24 Immediate treatment of patients with acute severe asthma. • Check with senior medical staff • Prednisolone 40 mg daily for 5 days • Start or double inhaled glucocorticoids • Return immediately if worse • Appointment with GP within 48 hours • Usual treatment • Return immediately if worse • Appointment with GP within 48 hours Usual inhaled bronchodilator Wait 60 mins Wait 30 mins • Administer repeat salbutamol 5 mg + ipratropium bromide 500 μg by oxygen-driven nebuliser • Consider continuous salbutamol nebuliser 5–10 mg/hr • Consider intravenous magnesium sulphate 1.2–2.0 g over 20 mins, or aminophylline 5 mg/kg loading dose over 20 mins followed by a continuous infusion at 1 mg/kg/hr • Correct fluid and electrolytes (especially K^+) Arterial blood gas Nebulised salbutamol 5 mg or terbutaline 2.5 mg Oxygen–high-flow/60% Prednisolone 40 mg orally PEF $< 60\%$ predicted PEF $> 60\%$ predicted Life-threatening/acute severe MEASURE PEAK EXPIRATORY FLOW Convert PEF to % best or % predicted 0% 50% 51% 75% 76% 100% Mild Moderate Measure PEF Home Admit Home Intravenous access, chest X-ray, plasma theophylline level, plasma K^+ Arterial blood gas Nebulised salbutamol 5 mg or terbutaline 2.5 mg 6–12 times daily or as required Oxygen–high-flow/60% Prednisolone 40 mg orally (or hydrocortisone 200 mg IV) Did patient receive nebulised therapy before PEF recorded? Yes No 17.23 Indications for assisted ventilation in acute severe asthma • Coma • Respiratory arrest • Deterioration of arterial blood gas tensions despite optimal therapy: $PaO_2 < 8$ kPa (60 mmHg) and falling $PaCO_2 > 6$ kPa (45 mmHg) and rising pH low and falling (H^+ high and rising) • Exhaustion, delirium, drowsiness

 affecting pulmonary and chest wall compliance. Pulmonary hyperinflation also results, which flattens the diaphragmatic muscles and leads to an increasingly horizontal alignment of the intercostal muscles, placing the respiratory muscles at a mechanical disadvantage. The work of breathing is therefore markedly increased – first on exercise, when the time for expiration is further shortened, but then, as the disease advances, at rest. and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Related diagnoses include chronic bronchitis (cough and sputum for at least 3 consecutive months in each of 2 consecutive years) and emphysema (abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis). Extrapulmonary effects include weight loss and skeletal muscle dysfunction (Fig. 17.25). Commonly associated co-morbid conditions include cardiovascular disease, cerebrovascular disease, the metabolic syndrome (p. 730), osteoporosis, depression and lung cancer. The prevalence of COPD is directly related to the prevalence of risk factors in the community, such as tobacco smoking, coal dust exposure or the use of biomass fuels, and to the age of the population being studied. Those with the most severe disease bear the greatest personal impact of the condition and contribute to its significant social and economic consequences on society. It is predicted that, by 2030, COPD will represent the seventh leading cause of disability and fourth most common cause of death worldwide. Risk factors are shown in Box 17.24. Cigarette smoking represents the most significant risk factor for COPD and the risk of developing the condition relates to both the amount and duration of smoking. It is unusual to develop COPD with less than 10 pack years (1 pack year = 20 cigarettes/day/year) and not all smokers develop the condition, suggesting that individual susceptibility factors are important. Pathophysiology COPD has both pulmonary and systemic components (Fig. 17.25). The presence of airflow limitation combined with premature airway closure leads to gas trapping and hyperinflation, adversely Fig. 17.25 The pulmonary and systemic features of chronic obstructive pulmonary disease. Altered fat metabolism contributing to weight loss Enlargement of mucus-secreting glands and increase in number of goblet cells, accompanied by an inflammatory cell infiltrate, result in increased sputum production leading to chronic bronchitis Loss of elastic tissue, inflammation and fibrosis in airway wall result in premature airway closure, gas trapping and dynamic hyperinflation leading to changes in pulmonary and chest wall compliance Unopposed action of proteases and oxidants leading to destruction of alveoli and appearance of emphysema Pulmonary vascular remodelling and impaired cardiac performance Muscular weakness reflecting deconditioning and cellular changes in skeletal muscles Impaired salt and water excretion leading to peripheral oedema ↑ Prevalence of osteoporosis Increased circulating inflammatory markers Pulmonary Systemic 17.24 Risk factors for development of chronic obstructive pulmonary disease Environmental factors • Tobacco smoke: accounts for 95% of cases in the UK • Indoor air pollution: cooking with biomass fuels in confined areas in developing countries • Occupational exposures, such as coal dust, silica and cadmium • Low birth weight: may reduce maximally attained lung function in young adult life • Lung growth: childhood infections or maternal smoking may affect growth of lung during childhood, resulting in a lower maximally attained lung function in adult life • Infections: recurrent infection may accelerate decline in FEV1; persistence of adenovirus in lung tissue may alter local inflammatory response, predisposing to lung damage; HIV infection is associated with emphysema • Low socioeconomic status • Cannabis smoking Host factors • Genetic factors: α1-antitrypsin deficiency; other COPD susceptibility genes are likely to be identified • Airway hyper-reactivity (FEV1 = forced expiratory volume in 1 sec)

particularly if there is coexisting sleep apnoea or thromboembolic disease (‘cor pulmonale’). However, even in the absence of heart failure, COPD patients often have pitting oedema from salt and water retention caused by renal hypoxia and hypercapnia. The term ‘cor pulmonale’ is a misnomer in such patients, as they do not have heart failure. Fatigue, anorexia and weight loss may point to the development of lung cancer or tuberculosis, but are common in patients with severe COPD and the body mass index (BMI) is of prognostic significance. Depression and anxiety are also common and contribute to morbidity. Two classical phenotypes have been described: ‘pink puffers’ and ‘blue bloaters’. The former are typically thin and breathless, and maintain a normal $PaCO_2$ until the late stage of disease. The latter develop (or tolerate) hypercapnia earlier and may develop oedema and secondary polycythaemia. In practice, these phenotypes often overlap. Investigations Although there are no reliable radiographic signs that correlate with the severity of airflow limitation, a chest X-ray is essential to identify alternative diagnoses such as cardiac failure, other complications of smoking such as lung cancer, and the presence of bullae. A blood count is useful to exclude anaemia or document polycythaemia, and in younger patients with predominantly basal emphysema α1-antitrypsin should be assayed. The diagnosis requires objective demonstration of airflow obstruction by spirometry and is established when the postbronchodilator FEV1/FVC is < 70%. The severity of COPD may be defined in relation to the post-bronchodilator FEV1 (Box 17.26). Measurement of lung volumes provides an assessment of hyperinflation. This is generally performed by helium dilution technique (p. 515); however, in patients with severe COPD, and in particular large bullae, body plethysmography is preferred because the use of helium may under-estimate lung volumes. The presence of emphysema is suggested by a low gas transfer (p. 515). Exercise tests provide an objective assessment of exercise tolerance and provide a baseline on which to judge the response to bronchodilator therapy or rehabilitation programmes; they may also be valuable when assessing prognosis. Pulse oximetry may prompt referral for a domiciliary oxygen assessment if less than 93%. The assessment of health status by the St George's Respiratory Questionnaire (SGRQ) is commonly used for research. In practice, the COPD Assessment Test and the COPD Control Questionnaire are easier to administer. HRCT is likely to play an increasing role in the assessment of COPD, as it allows the detection, Fig. 17.26 The pathology of emphysema. A Normal lung. B Emphysematous lung, showing gross loss of the normal surface area available for gas exchange. B, Courtesy of the British Lung Foundation. A B Emphysema (Fig. 17.26) may be classified by the pattern of the enlarged airspaces: centriacinar, panacinar and paraseptal. Bullae form in some individuals. This results in impaired gas exchange and respiratory failure. Clinical features COPD should be suspected in any patient over the age of 40 years who presents with symptoms of chronic bronchitis and/or breathlessness. Depending on the presentation, important differential diagnoses include chronic asthma, tuberculosis, bronchiectasis and congestive cardiac failure. Cough and associated sputum production are usually the first symptoms, and are often referred to as a 'smoker's cough'. Haemoptysis may complicate exacerbations of COPD but should not be attributed to COPD without thorough investigation. Breathlessness usually prompts presentation to a health professional. The level should be quantified for future reference, often by documenting what the patient can manage before stopping; scales such as the modified Medical Research Council (MRC) dyspnoea scale may be useful (Box 17.25). In advanced disease, enquiry should be made as to the presence of oedema (which may be seen for the first time during an exacerbation) and morning headaches (which may suggest hypercapnia). Physical signs (p. 546) are non-specific, correlate poorly with lung function, and are seldom obvious until the disease is advanced. Breath sounds are typically quiet; crackles may accompany infection but, if persistent, raise the possibility of bronchiectasis. Finger clubbing is not a feature of COPD and should trigger further investigation for lung cancer or fibrosis. Right heart failure may develop in patients with advanced COPD, 17.25 Modified Medical Research Council (MRC) dyspnoea scale Grade Degree of breathlessness related to activities

No breathlessness, except with strenuous exercise

Breathlessness when hurrying on the level or walking up a slight hill

Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace

Stops for breath after walking about 100 m or after a few minutes on level ground

Too breathless to leave the house, or breathless when dressing or undressing

 smokers, and cessation (p. 94) remains the only strategy that impacts favourably on the natural history of COPD. Complete cessation is accompanied by an improvement in lung function and deceleration in the rate of FEV1 decline (Fig. 17.28). In regions where the indoor burning of biomass fuels is important, the introduction of non-smoking cooking devices or alternative fuels should be encouraged. Bronchodilators Bronchodilator therapy is central to the management of breathlessness. The inhaled route is preferred and a number of different agents delivered by a variety of devices are available. Choice should be informed by patient preference and inhaler assessment. Short-acting bronchodilators may be used for patients with mild disease but longer-acting bronchodilators are usually more appropriate for those with moderate to severe disease. Significant improvements in breathlessness may be reported despite minimal changes in FEV1, probably reflecting improvements in lung emptying that reduce dynamic hyperinflation and ease the work of breathing. Oral bronchodilator therapy, such as theophylline preparations, may be contemplated in patients who cannot use inhaled devices efficiently but their use may be limited by side-effects, unpredictable metabolism and drug interactions; hence the requirement to monitor plasma levels. Orally active, highly selective phosphodiesterase inhibitors remain under appraisal. Combined inhaled glucocorticoids and bronchodilators The fixed combination of an inhaled glucocorticoid and a LABA improves lung function, reduces the frequency and severity of exacerbations and improves quality of life. These advantages may be accompanied by an increased risk of pneumonia, particularly in the elderly. LABA/inhaled glucocorticoid combinations are frequently given with a long-acting muscarinic antagonist (LAMA). LAMAs should be used with caution in patients with significant heart disease or a history of urinary retention. Oral glucocorticoids Oral glucocorticoids are useful during exacerbations but maintenance therapy contributes to osteoporosis and impaired skeletal muscle function, and should be avoided. Oral characterisation and quantification of emphysema (Fig. 17.27) and is more sensitive than the chest X-ray at detecting bullae. It is also used to guide lung volume reduction surgery. Assessment of severity The severity of COPD has traditionally been defined in relation to the FEV% predicted. However, assessing the impact of COPD on individual patients in terms of the symptoms and limitations in activity that they experience and whether they suffer frequent or significant exacerbations may provide a more clinically relevant assessment and help guide management. Management The management of COPD focuses on improving breathlessness, reducing the frequency and severity of exacerbations, and improving health status and prognosis. Reducing exposure to noxious particles and gases Sustained smoking cessation in mild to moderate COPD is accompanied by a reduced decline in FEV1 compared to persistent Fig. 17.27 Gross emphysema. High-resolution computed tomogram showing emphysema, most evident in the right lower lobe. R L 17.26 Spirometric classification of COPD severity based on post-bronchodilator FEV1 PD FEV1/ FVC FEV1% predicted Severity of airflow obstruction post-bronchodilator ATS/ERS (2004) GOLD (2008) NICE Clinical Guideline 101 (2010) < 0.7 ≥ 80% Mild Stage I – mild Stage I – mild1 < 0.7 50–79% Moderate Stage II – moderate Stage II – moderate < 0.7 30–49% Severe Stage III – severe Stage III – severe < 0.7 < 30% Very severe Stage IV – very severe2 Stage IV – very severe2 1Mild COPD should not be diagnosed on lung function alone if the patient is asymptomatic. 2Or FEV1 < 50% with respiratory failure. (ATS/ERS = American Thoracic Society/European Respiratory Journal; FEV1 = forced expiratory volume in 1 sec; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PD = post-bronchodilator) Adapted from National Institute for Health and Care Excellence (NICE) CG101 – Chronic obstructive pulmonary disease in over 16s: diagnosis and management; 2010. Fig. 17.28 Model of annual decline in FEV1 with accelerated decline in susceptible smokers. When smoking is stopped, subsequent loss is similar to that in healthy non-smokers. (FEV1 = forced expiratory volume in 1 second)

Age (years) Smoked regularly and susceptible to its effects Stopped smoking at 45 Stopped smoking at 65 Never smoked or not susceptible to smoke FEV1 (% of value at age 25) Disability Death

Prognosis COPD has a variable natural history but is usually progressive. The prognosis is inversely related to age and directly related to the post-bronchodilator FEV1. Additional poor prognostic indicators include weight loss and pulmonary hypertension. A composite score (BODE), comprising the body mass index (B), the degree of airflow obstruction (O), a measurement of dyspnoea (D) and exercise capacity (E) may assist in predicting death from respiratory and other causes (Box 17.28). Respiratory failure, cardiac disease and lung cancer represent common modes of death. Acute exacerbations of COPD Acute exacerbations of COPD are characterised by an increase in symptoms and deterioration in lung function and health status. They become more frequent as the disease progresses and are usually triggered by bacteria, viruses or a change in air quality. They may be accompanied by the development of respiratory failure and/or fluid retention and represent an important cause of death. Many patients can be managed at home with the use of increased bronchodilator therapy, a short course of oral glucocorticoids and, if appropriate, antibiotics. The presence of cyanosis, peripheral oedema or an alteration in consciousness should prompt referral to hospital. In other patients, consideration of comorbidity and social circumstances may influence decisions regarding hospital admission. Oxygen therapy In patients with an exacerbation of severe COPD, high concentrations of oxygen may cause respiratory depression and worsening acidosis (p. 566). Controlled oxygen at 24% or 28% should be used with the aim of maintaining a PaO_2 of more than 8 kPa (60 mmHg) (or an SaO_2 of more than 90%) without worsening acidosis. Bronchodilators Nebulised short-acting β_2-agonists combined with an anticholinergic agent (e.g. salbutamol and ipratropium) should be administered. With careful supervision it is usually safe to drive nebulisers with oxygen, but if concern exists regarding oxygen sensitivity, they may be driven by compressed air and supplemental oxygen delivered by nasal cannula. glucocorticoid trials assist in the diagnosis of asthma but do not predict response to inhaled glucocorticoids in COPD. Pulmonary rehabilitation Exercise should be encouraged at all stages and patients reassured that breathlessness, while distressing, is not dangerous. Multidisciplinary programmes that incorporate physical training, disease education and nutritional counselling reduce symptoms, improve health status and enhance confidence. Most programmes include two to three sessions per week, last between 6 and 12 weeks, and are accompanied by demonstrable and sustained improvements in exercise tolerance and health status. Oxygen therapy Long-term domiciliary oxygen therapy (LTOT) improves survival in selected patients with COPD complicated by severe hypoxaemia (arterial PaO_2 < 7.3 kPa (55 mmHg); Box 17.27). It is most conveniently provided by an oxygen concentrator and patients should be instructed to use oxygen for a minimum of 15 hours/ day; greater benefits are seen in those who use it for more than 20 hours/day. The aim of therapy is to increase the PaO_2 to at least 8 kPa (60 mmHg) or SaO_2 to at least 90%. Ambulatory oxygen therapy should be considered in patients who desaturate on exercise and show objective improvement in exercise capacity and/or dyspnoea with oxygen. Oxygen flow rates should be adjusted to maintain SaO_2 above 90%. Surgical intervention Bullectomy may be considered when large bullae compress surrounding normal lung tissue. Patients with predominantly upper lobe emphysema, preserved gas transfer and no evidence of pulmonary hypertension may benefit from lung volume reduction surgery (LVRS), in which peripheral emphysematous lung tissue is resected with the aim of reducing hyperinflation and decreasing the work of breathing. Both bullectomy and LVRS can be performed thoracoscopically, minimising morbidity. Lung transplantation may benefit carefully selected patients with advanced disease (p. 567). Other measures Patients with COPD should be offered an annual influenza vaccination and, as appropriate, pneumococcal vaccination. Obesity, poor nutrition, depression and social isolation should be identified and, if possible, improved. Mucolytic agents are occasionally used but evidence of benefit is limited. Palliative care Addressing end-of-life needs is an important, yet often ignored, aspect of care in advanced disease. Morphine preparations may be used for palliation of breathlessness in advanced disease and benzodiazepines in low dose may reduce anxiety. Decisions regarding resuscitation should be addressed in advance of critical illness. 17.27 Prescription of long-term oxygen therapy in COPD Arterial blood gases are measured in clinically stable patients on optimal medical therapy on at least two occasions 3 weeks apart: • $PaO_2 < 7.3$ kPa (55 mmHg) irrespective of $PaCO_2$ and $FEV_1 <$ 1.5 L • PaO_2 7.3–8 kPa (55–60 mmHg) plus pulmonary hypertension, peripheral oedema or nocturnal hypoxaemia • the patient has stopped smoking Use at least 15 hrs/day at 2–4 L/min to achieve a $PaO_2 > 8$ kPa (60 mmHg) without unacceptable rise in $PaCO_2$ 17.28 Calculation of the BODE index Variable Points on BODE index

FEV_1 ≥ 65 50–64 36–49 ≤ 35 Distance walked in 6 mins (m) ≥ 350 250–349 150–249 ≤ 149 MRC dyspnoea scale* 0–1

Body mass index

> 21 ≤ 21 A patient with a BODE score of 0–2 has a mortality rate of around 10% at 52 months, whereas a patient with a BODE score of 7–10 has a mortality rate of around 80% at 52 months. *See Box 17.25. (BODE – see text; FEV_1 = forced expiratory volume in 1 sec)

578 • RESPIRATORY MEDICINE Discharge Discharge from hospital may be contemplated once patients are clinically stable on their usual maintenance medication. Hospital at-home teams may provide short-term nebuliser loan, improving discharge rates and providing additional support for the patient. Bronchiectasis Bronchiectasis means abnormal dilatation of the bronchi. Chronic suppurative airway infection with sputum production, progressive scarring and lung damage occur, whatever the cause. Aetiology and pathology Bronchiectasis may result from a congenital defect affecting airway ion transport or ciliary function, such as cystic fibrosis (see below), or may be acquired secondary to damage to the airways by a destructive infection, inhaled toxin or foreign body. The result is chronic inflammation and infection in the airways. Box 17.30 shows the common causes, of which tuberculosis is the most common worldwide. Localised bronchiectasis may occur due to the accumulation of pus beyond an obstructing bronchial lesion, such as enlarged tuberculous hilar lymph nodes, a bronchial tumour or an inhaled foreign body (e.g. an aspirated peanut). The bronchiectatic cavities may be lined by granulation tissue, squamous epithelium or normal ciliated epithelium. There may also be inflammatory changes in the deeper layers of the bronchial wall and hypertrophy of the bronchial arteries. Chronic inflammatory and fibrotic changes are usually found in the surrounding lung tissue, resulting in progressive destruction of the normal lung architecture in advanced cases. Clinical features The symptoms are shown in Box 17.31. Physical signs in the chest may be unilateral or bilateral. If the bronchiectatic airways do not contain secretions and there is no associated lobar collapse, there are no abnormal physical signs. When there are large amounts of sputum in the bronchiectatic spaces, numerous coarse crackles may be heard over the affected areas. Collapse with retained secretions blocking a proximal bronchus may lead to locally diminished breath sounds, while advanced disease may cause scarring and overlying bronchial Glucocorticoids Oral prednisolone reduces symptoms and

improves lung function. Doses of 30 mg for 10 days are currently recommended but shorter courses may be acceptable. Prophylaxis against osteoporosis should be considered in patients who receive repeated courses of glucocorticoids (p. 670). Antibiotic therapy The role of bacteria in exacerbations remains controversial and there is little evidence for the routine administration of antibiotics. They are currently recommended for patients reporting an increase in sputum purulence, sputum volume or breathlessness. In most cases simple regimens are advised, such as an aminopenicillin, a tetracycline or a macrolide. Co-amoxiclav is only required in regions where β-lactamase-producing organisms are known to be common. Non-invasive ventilation Non-invasive ventilation is safe and effective in patients with an acute exacerbation of COPD complicated by mild to moderate respiratory acidosis ($H^+ \geq 45$ nmol/L, $pH < 7.35$), and should be considered early in the course of respiratory failure to reduce the need for endotracheal intubation, treatment failure and mortality. It is not useful in patients who cannot protect their airway. Mechanical ventilation may be contemplated when there is a reversible cause for deterioration (e.g. pneumonia) or when no prior history of respiratory failure has been noted. Additional therapy Exacerbations may be accompanied by the development of peripheral oedema; this usually responds to diuretics. There has been a vogue for using an infusion of intravenous aminophylline but evidence for benefit is limited and attention must be paid to the risk of inducing arrhythmias and drug interactions. The use of the respiratory stimulant doxapram has been largely superseded by the development of NIV but it may be useful for a limited period in selected patients with a low respiratory rate. 17.29 Obstructive pulmonary disease in old age • Asthma: may appear de novo in old age, so airflow obstruction should not always be assumed to be due to COPD. • Peak expiratory flow recordings: older people with poor vision have difficulty reading PEF meters. • Perception of bronchoconstriction: impaired by age, so an older patient’s description of symptoms may not be a reliable indicator of severity. • Stopping smoking: the benefits on the rate of loss of lung function decline with age but remain valuable up to the age of 80. • Metered-dose inhalers: many older people cannot use these because of difficulty coordinating and triggering the device. Even mild cognitive impairment virtually precludes their use. Frequent demonstration and re-instruction in the use of all devices are required. • Mortality rates for acute asthma: higher in old age, partly because patients under-estimate the severity of bronchoconstriction and also develop a lower degree of tachycardia and pulsus paradoxus for the same degree of bronchoconstriction. • Treatment decisions: advanced age in itself is not a barrier to intensive care or mechanical ventilation in an acute episode of asthma or COPD, but this decision may be difficult and should be shared with the patient (if possible), the relatives and the GP. 17.30 Causes of bronchiectasis Congenital • Cystic fibrosis • Ciliary dysfunction syndromes: Primary ciliary dyskinesia (immotile cilia syndrome) Kartagener’s syndrome (sinusitis and transposition of the viscera) • Primary hypogammaglobulinaemia (p. 79) Acquired: children • Severe infections in infancy (especially whooping cough, measles) • Primary tuberculosis • Inhaled foreign body Acquired: adults • Suppurative pneumonia • Pulmonary tuberculosis • Allergic bronchopulmonary aspergillosis complicating asthma (p. 596) • Bronchial tumours

Management In patients with airflow obstruction, inhaled bronchodilators and glucocorticoids should be used to enhance airway patency. Physiotherapy Patients should be shown how to perform regular daily physiotherapy to assist the drainage of excess bronchial secretions. Efficiently executed, this is of great value both in reducing the amount of cough and sputum, and in preventing recurrent episodes of bronchopulmonary infection. Patients should lie in a position in which the lobe to be drained is uppermost. Deep breathing, followed by forced expiratory manœuvres (the 'active cycle of breathing' technique), helps to move secretions in the dilated bronchi towards the trachea, from which they can be cleared by vigorous coughing. Devices that increase airway pressure either by a constant amount (positive expiratory pressure mask) or in an oscillatory manner (flutter valve) aid sputum clearance in some patients and a variety of techniques should be tried to find the one that suits the individual. The optimum duration and frequency of physiotherapy depend on the amount of sputum but 5–10 minutes twice daily is a minimum for most patients. Antibiotic therapy For most patients with bronchiectasis, the appropriate antibiotics are the same as those used in COPD (p. 578) but larger doses and longer courses are required, and resolution of symptoms is often incomplete. When secondary infection occurs with staphylococci and Gram-negative bacilli, in particular Pseudomonas species, antibiotic therapy becomes more challenging and should be guided by the microbiological sensitivities. For Pseudomonas, oral ciprofloxacin (500–750 mg twice daily) or an intravenous anti-pseudomonal β-lactam (e.g. piperacillin–tazobactam or ceftazidime) will be required. Haemoptysis in bronchiectasis often responds to treatment of the underlying infection, although percutaneous embolisation of the bronchial circulation by an interventional radiologist may be necessary in severe cases. Surgical treatment Excision of bronchiectatic areas is indicated in only a small proportion of cases. These are usually patients in whom the bronchiectasis is confined to a single lobe or segment on CT. Unfortunately, many of those in whom medical treatment proves unsuccessful are also unsuitable for surgery because of either extensive bilateral bronchiectasis or coexisting severe airflow obstruction. In progressive forms of bronchiectasis, resection of destroyed areas of lung that are acting as a reservoir of infection should be considered only as a last resort. Prognosis The disease is progressive when associated with ciliary dysfunction and cystic fibrosis, and eventually causes respiratory failure. In other patients, the prognosis can be relatively good if physiotherapy is performed regularly and antibiotics are used aggressively. Prevention As bronchiectasis commonly starts in childhood following measles, whooping cough or a primary tuberculous infection, adequate prophylaxis for and treatment of these conditions are essential. Early recognition and treatment of bronchial obstruction are also important. Fig. 17.29 Computed tomogram of bronchiectasis. Extensive dilatation of the bronchi, with thickened walls (arrows) in both lower lobes. R L 17.31 Symptoms of bronchiectasis • Cough: chronic, daily, persistent • Sputum: copious, continuously purulent • Pleuritic pain: when infection spreads to involve pleura, or with segmental collapse due to retained secretions • Haemoptysis: Streaks of blood common, larger volumes with exacerbations of infection Massive haemoptysis requiring bronchial artery embolisation sometimes occurs • Infective exacerbation: increased sputum volume with fever, malaise, anorexia • Halitosis: frequently accompanies purulent sputum • General debility: difficulty maintaining weight, anorexia, exertional breathlessness breathing. Acute haemoptysis is an important complication of bronchiectasis; management is described on page 560. Investigations In addition to common respiratory pathogens, sputum culture may reveal Pseudomonas aeruginosa and Staphylococcus aureus, fungi such as Aspergillus and various mycobacteria. Frequent cultures are necessary to ensure appropriate treatment of resistant organisms. Bronchiectasis, unless very gross, is not usually apparent on a chest X-ray. In advanced disease, thickened airway walls, cystic bronchiectatic spaces and associated areas of pneumonic consolidation or collapse may be visible. CT is much more sensitive and shows thickened, dilated airways (Fig. 17.29). A screening test can be performed in patients suspected of having a ciliary dysfunction syndrome by measuring the time taken for a small pellet of saccharin placed in the anterior chamber of the nose to reach the pharynx, at which point the patient can taste it. This time should not exceed 20 minutes but is greatly prolonged in patients with ciliary dysfunction. Ciliary beat frequency may also be assessed from biopsies taken from the nose. Structural abnormalities of cilia can be detected by electron microscopy.

 Clinical features The lungs are macroscopically normal at birth, but bronchiolar inflammation and infections usually lead to bronchiectasis in childhood. At this stage, the lungs are most commonly infected with Staph. aureus; however, in adulthood, many patients become colonised with P. aeruginosa, Stenotrophomonas maltophilia or other Gram-negative bacilli. Recurrent exacerbations of bronchiectasis, initially in the upper lobes but subsequently throughout both lungs, cause progressive lung damage, resulting ultimately in death from respiratory failure. Other clinical manifestations are shown in Box 17.32. Most men with CF are infertile due to failure of development of the vas deferens, but microsurgical sperm aspiration and in vitro fertilisation are possible. Genotype is a poor predictor of disease severity in individuals; even siblings with matching genotypes may have different phenotypes. This suggests that other ‘modifier genes’, as yet unidentified, influence clinical outcome. Management Treatment of CF lung disease The management of CF lung disease is that of severe bronchiectasis. All patients with CF who produce sputum should perform chest physiotherapy daily, and more frequently during exacerbations. While infections with Staph. aureus can often be managed with oral antibiotics, intravenous treatment (frequently self-administered at home through an implanted subcutaneous vascular access device) is usually needed for Pseudomonas infections. Unfortunately, the bronchi of many patients with CF eventually become colonised with pathogens that are resistant to most antibiotics. Resistant strains of P. aeruginosa, Stenotrophomonas maltophilia and Burkholderia cepacia are the main culprits and may require prolonged treatment with unusual combinations of antibiotics. Aspergillus and non-tuberculous mycobacteria are also frequently found in the sputum of patients with CF but in most cases these behave as benign ‘colonisers’ of the bronchiectatic airways and do not require specific therapy. An Cystic fibrosis Genetics, pathogenesis and epidemiology Cystic fibrosis (CF) is the most common fatal genetic disease in Caucasians, with autosomal recessive inheritance, a carrier rate of 1 in 25, and an incidence of about 1 in 2500 live births (pp. 40 and 48). It is much less common in people of African descent and rarer still in Asians. CF is the result of mutations affecting a gene on the long arm of chromosome 7, which codes for a chloride channel known as cystic fibrosis transmembrane conductance regulator (CFTR); this influences salt and water movement across epithelial cell membranes. The most common CFTR mutation in northern European and American populations is ΔF508 but over 2000 mutations of this gene have now been identified. The genetic defect causes increased sodium and chloride content in sweat and increased resorption of sodium and water from respiratory epithelium (Fig. 17.30). Relative dehydration of the airway epithelium is thought to predispose to chronic bacterial infection and ciliary dysfunction, leading to bronchiectasis. The gene defect also causes disorders in the gut epithelium, pancreas, liver and reproductive tract (see below). In the 1960s, few patients with CF survived childhood, yet with aggressive treatment of airway infection and nutritional support, life expectancy has improved dramatically, so that there are now more adults than children with CF in many developed countries. Until recently, the diagnosis was most commonly made from the clinical picture (bowel obstruction, failure to thrive, steatorrhoea and/or chest symptoms in a young child), supported by sweat electrolyte testing and genotyping. Patients with unusual phenotypes were commonly missed, however, and late diagnosis led to poorer outcomes. Neonatal screening for CF using immunoreactive trypsin and genetic testing of newborn blood samples is now routine in the

UK and should reduce delayed diagnosis and improve outcomes. Pre-implantation and/or prenatal testing may be offered to those known to be at high risk (p. 56). Fig. 17.30 Cystic fibrosis: basic defect in the pulmonary epithelium. A The cystic fibrosis gene (CFTR) codes for a chloride channel (1) in the apical (luminal) membrane of epithelial cells in the conducting airways. This is normally controlled by cyclic adenosine monophosphate (cAMP) and indirectly by β-adrenoceptor stimulation, and is one of several apical ion channels that control the quantity and solute content of airway-lining fluid. Normal channels appear to inhibit the adjacent epithelial sodium channels (2). B In cystic fibrosis, one of many cystic fibrosis gene defects causes absence or defective function of this chloride channel (3). This leads to reduced chloride secretion and loss of inhibition of sodium channels, with excessive sodium resorption (4) and dehydration of the airway lining. The resulting abnormal airway-lining fluid predisposes to infection by mechanisms still to be fully explained. cAMP Chloride ion Sodium ion Chloride ion Sodium ion Water cAMP Chloride ion Sodium ion Chloride ion Sodium ion Water Basal surface

Airway lumen Apical surface EPITHELIAL CELL β2-adrenoceptor Cystic fibrosis Normal A B

eventually develops in over 25% of patients and often requires insulin therapy. Osteoporosis secondary to malabsorption and chronic ill health should be sought and treated. Novel therapies for cystic fibrosis Small molecules designed to correct the function of particular CFTR defects are being developed. One such drug, ivacaftor (a CFTR ‘potentiator’), is now an established oral treatment for the 5% of patients with the G551D mutation, causing sustained improvements in FEV1 and weight, and normalising the sweat test. The combination of ivacaftor and lumacaftor (a CFTR ‘corrector’) has been found to have modest short-term benefit in patients with DF508 mutations. Improved versions of these treatments may soon offer similar benefits for these patients. Somatic gene therapy for CF is also under development. Manufactured normal copies of the CF gene are ‘packaged’ in liposomes or virus vectors and administered to the airways by aerosol inhalation. Trials are under way but more efficient gene delivery methods are needed to make this practical. Infections of the respiratory system Infections of the upper and lower respiratory tract are a major cause of morbidity and mortality, particularly in patients at the extremes of age and those with pre-existing lung disease or immune suppression. Upper respiratory tract infection Upper respiratory tract infections (URTIs), such as coryza (the common cold), acute pharyngitis and acute tracheobronchitis, are the most common of all communicable diseases and represent the most frequent cause of short-term absenteeism from work and school. The vast majority are caused by viruses (p. 249) and, in adults, are usually short-lived and rarely serious. Acute coryza is the most common URTI and is usually the result of rhinovirus infection. In addition to general malaise, acute coryza typically causes nasal discharge, sneezing and cough. Involvement of the pharynx results in a sore throat, and that of exception is Mycobacterium abscessus, which is multi-resistant, may be transmissible between patients with CF and can cause progressive lung destruction that is hard to treat. Some patients have coexistent asthma, which is treated with inhaled bronchodilators and glucocorticoids; allergic bronchopulmonary aspergillosis (p. 596) also occurs occasionally in CF. Four maintenance treatments have been shown to cause modest rises in lung function and/or to reduce the frequency of chest exacerbations in patients with CF (Box 17.33). Individual responses are variable and should be carefully monitored to avoid burdening patients with treatments that prove ineffective. For advanced CF lung disease, home oxygen and NIV may be necessary to treat respiratory failure. Ultimately, lung transplantation can produce dramatic improvements but is limited by donor organ availability. Treatment of non-respiratory manifestations of CF There is a clear link between good nutrition and prognosis in CF. Malabsorption occurs in 85% of patients due to exocrine pancreatic failure and is treated with oral pancreatic enzymes and vitamin supplements. The increased calorie requirements of patients with CF are met by supplemental feeding, including nasogastric or gastrostomy tube feeding if required. Diabetes 17.33 Treatments that reduce chest exacerbations and/or improve lung function in cystic fibrosis Therapy Patients treated Nebulised recombinant human DNase 2.5 mg daily Age ≥ 5, FVC > 40% predicted Nebulised tobramycin 300 mg twice daily, given in alternate months Patients colonised with Pseudomonas aeruginosa Regular oral azithromycin 500 mg 3 times a week Patients colonised with P. aeruginosa Nebulised hypertonic saline 4 mL 7%, twice daily Age ≥ 6, FEV1 > 40% predicted (FEV1 = forced expiratory volume in 1 sec; FVC = forced vital capacity) 17.32 Complications of cystic fibrosis Respiratory • Progressive airway obstruction • Infective exacerbations of bronchiectasis • Respiratory failure • Spontaneous pneumothorax • Haemoptysis • Lobar collapse due to secretions • Pulmonary hypertension • Nasal polyps Gastrointestinal and hepatic • Malabsorption and steatorrhoea • Distal intestinal obstruction syndrome • Biliary cirrhosis • Portal hypertension, varices and splenomegaly • Gallstones Others • Diabetes (25% of adults) • Delayed puberty • Male infertility • Stress incontinence due to repeated forced cough • Psychosocial problems • Osteoporosis • Arthropathy • Cutaneous vasculitis 17.34 Cystic fibrosis in adolescence Issues for the patient • Move to adult CF centre – loss of trusted paediatric team • Feelings of being different from peers due to chronic illness • Demanding treatments that conflict with social and school life • Pressure to take responsibility for self-care • Relationship/fertility concerns Issues for the patient's parents • Loss of control over patient's treatment – feeling excluded • Loss of trusted paediatric team • Need to develop trust in adult team • Feelings of helplessness when adolescent rebels or will not take treatment Issues for the CF team • Reluctance or refusal by patient to engage with transition • Management of deterioration due to non-adherence • Motivation of adolescents to self-care • Provision of adolescent-friendly health-care environment

 most common infecting agent, and thereafter the likelihood that other organisms may be involved depends on the age of the patient and the clinical context. Viral infections are recognised as important causes of CAP in children and their contribution to adult CAP is increasingly recognised. The common causative organisms are shown in Box 17.36. Clinical features Pneumonia, particularly lobar pneumonia, usually presents as an acute illness. Systemic features, such as fever, rigors, shivering and malaise, predominate and delirium may be present. The appetite is invariably lost and headache frequently reported. Pulmonary symptoms include cough, which at first is characteristically short, painful and dry, but later is accompanied by the expectoration of mucopurulent sputum. Rust-coloured sputum may be produced by patients with Strep. pneumoniae infection and the occasional patient may report haemoptysis. the larynx a hoarse or lost voice. If complicated by a tracheitis or bronchitis, chest tightness and wheeze typical of asthma occur. Specific investigation is rarely warranted and treatment with simple analgesics, antipyretics and decongestants is all that is required. Symptoms usually resolve quickly, but if repeated URTIs 'go to the chest', a more formal diagnosis of asthma ought to be considered. A variety of viruses causing URTI may also trigger exacerbations of asthma or COPD and aggravate other lung diseases. Bordetella pertussis, the cause of whooping cough, is an important source of URTI. It is highly contagious and is notifiable in the UK. Vaccination confers protection and is usually offered in infancy, but its efficacy wanes in adult life and the infection is easily spread.

Adults usually experience a mild illness similar to acute coryza but some individuals develop paroxysms of coughing that can persist for weeks to months, earning whooping cough the designation of ‘the cough of 100 days’. The diagnosis may be confirmed by bacterial culture, polymerase chain reaction (PCR) from a nasopharyngeal swab or serological testing. If the illness is recognised early in the clinical course, macrolide antibiotics may ameliorate the course. Rhinosinusitis typically causes a combination of nasal congestion, blockage or discharge and may be accompanied by facial pain/pressure or loss of smell. Examination usually confirms erythematous swollen nasal mucosa and pus may be evident. Nasal polyps should be sought and dental infection excluded. Treatment with topical glucocorticoids, nasal decongestants and regular nasal douching is usually sufficient and, although bacterial infection is often present, antibiotics are indicated only if symptoms persist for more than 5 days. Persistent symptoms or recurrent episodes should prompt a referral to an ear, nose and throat specialist. Influenza is discussed on page 240. Pneumonia Pneumonia is as an acute respiratory illness associated with recently developed radiological pulmonary shadowing that may be segmental, lobar or multilobar. The context in which pneumonia develops is highly suggestive of the likely organism(s) involved; therefore, pneumonias are usually classified as community- or hospital-acquired, or those occurring in immunocompromised hosts. ‘Lobar pneumonia’ is a radiological and pathological term referring to homogeneous consolidation of one or more lung lobes, often with associated pleural inflammation; bronchopneumonia refers to more patchy alveolar consolidation associated with bronchial and bronchiolar inflammation, often affecting both lower lobes. Community-acquired pneumonia Figures from the UK suggest that an estimated 5–11/1000 adults suffer from community-acquired pneumonia (CAP) each year, accounting for around 5–12% of all lower respiratory tract infections. CAP may affect all age groups but is particularly common at the extremes of age; for example, worldwide, CAP continues to kill more children than any other illness and the propensity to ease the passing of the debilitated and the elderly led to designation of pneumonia as the ‘old man’s friend’. Most cases are spread by droplet infection, and while CAP may occur in previously healthy individuals, several factors may impair the effectiveness of local defences and predispose to CAP (Box 17.35). Streptococcus pneumoniae (Fig. 17.31) remains the Fig. 17.31 Gram stain of sputum showing Gram-positive diplococci characteristic of Streptococcus pneumoniae (arrows). 17.36 Organisms causing community-acquired pneumonia Bacteria • Streptococcus pneumoniae • Mycoplasma pneumoniae • Legionella pneumophila • Chlamydia pneumoniae • Haemophilus influenzae • Staphylococcus aureus • Chlamydia psittaci • Coxiella burnetii (Q fever) • Klebsiella pneumoniae (Freidländer’s bacillus) Viruses • Influenza, parainfluenza • Measles • Herpes simplex • Varicella • Adenovirus • Cytomegalovirus • Coronaviruses (SARS-CoV and MERS-CoV) (MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome) 17.35 Factors that predispose to pneumonia • Cigarette smoking • Upper respiratory tract infections • Alcohol • Glucocorticoid therapy • Old age • Recent influenza infection • Pre-existing lung disease • HIV • Indoor air pollution

identify the development of complications. While many cases of mild to moderate CAP can be successfully managed without identification of the organism, a range of microbiological tests should be performed on patients with severe CAP. Management The most important aspects of management include oxygenation, fluid balance and antibiotic therapy. In severe or prolonged illness, nutritional support may be required. Oxygen Oxygen should be administered to all patients with tachypnoea, hypoxaemia, hypotension or acidosis with the aim of maintaining the PaO2 ≥ 8 kPa (60 mmHg) or SaO2 ≥ 92%. High concentrations (≥ 35%), preferably humidified, should be used in all patients who do not have hypercapnia associated with COPD. Continuous positive airway pressure (CPAP) should be considered in those who remain hypoxic despite high-concentration oxygen therapy, and these patients should be managed in a high-dependency or intensive care environment where mechanical ventilation may be rapidly employed. Indications for ITU referral are summarised in Box 17.39. Fluid balance Intravenous fluids should be considered in those with severe illness, in older patients and those with vomiting. It may be appropriate to discontinue hypertensive agents temporarily. Otherwise, an adequate oral intake of fluid should be encouraged. Inotropic support may be required in patients with shock (p. 204). Pleuritic chest pain may be a presenting feature and on occasion may be referred to the shoulder or anterior abdominal wall. Upper abdominal tenderness is sometimes apparent in patients with lower lobe pneumonia or those with associated hepatitis. Less typical presentations may be seen in the very young and the elderly. While different organisms often give rise to a similar clinical and radiological picture, it may be possible to infer the likely agent from the clinical context. Mycoplasma pneumoniae is more common in young people and rare in the elderly, whereas Haemophilus influenzae is more common in the elderly, particularly if underlying lung disease is present. Legionella pneumophila occurs in local outbreaks centred on contaminated cooling towers in hotels, hospitals and other industries. Staph. aureus is more common following an episode of influenza. Klebsiella pneumonia has a specific association with alcohol abuse and often presents with a particularly severe bacteraemic illness. Recent foreign travel raises the possibility of infections that may otherwise be unusual in the UK, e.g. MERS-coronavirus (Middle East; p. 249), melioidosis caused by Burkholderia pseudomallei (South-east Asia and northern Australia; p. 261) and endemic fungal infection (North, Central or South America; p. 301). Certain occupations may be associated with exposure to specific bacteria (p. 618). Clinical examination should first focus on the respiratory and pulse rates, blood pressure and an assessment of the mental state, as these are important in forming a judgement as to severity of the illness (Fig. 17.32). Chest signs (p. 547) vary, depending on the inflammatory response, which proceeds through stages of acute exudation, red and then grey hepatisation, and finally resolution. When consolidated, the lung is typically dull to percussion and, as conduction of sound is enhanced, auscultation reveals bronchial breathing and whispering pectoriloquy; crackles are heard throughout. An assessment of the state of nutrition is important, particularly in the elderly. The presence of herpes labialis may point to streptococcal infection, as may the finding of 'rusty' sputum. The differential diagnosis of pneumonia is shown in Box 17.37. Investigations The object of investigations, which are summarised in Box 17.38, is to confirm the diagnosis, assess the severity and Fig. 17.32 Hospital CURB-65. *Defined as a mental test score of 8 or less, or new disorientation in person, place or time. (ICU = intensive care unit; urea of 7 mmol/L ≅ 20 mg/dL) Consider hospital-supervised treatment Options may include • Short-stay inpatient • Hospital-supervised outpatient Likely to be suitable for home treatment Manage in hospital as severe pneumonia Assess for ICU admission, especially if CURB-65 score = 4 or 5 3 or more 0 or 1 Any of: • Confusion* • Urea > 7 mmol/L • Respiratory rate > 30/min • Blood pressure (systolic < 90 mmHg or diastolic < 60 mmHg) • Age > 65 years CURB-65 score

Score 1 point for each feature present 17.37 Differential diagnosis of pneumonia • Pulmonary infarction • Pulmonary/pleural tuberculosis • Pulmonary oedema (can be unilateral) • Pulmonary eosinophilia (p. 611) • Malignancy: bronchoalveolar cell carcinoma • Cryptogenic organising pneumonia/bronchiolitis obliterans organising pneumonia (COP/BOOP) (p. 606)

 Treatment of pleural pain It is important to relieve pleural pain in order to allow the patient to breathe normally and cough efficiently. For the majority, simple analgesia with paracetamol, co-codamol or NSAIDs is sufficient. In some patients, opiates may be required but must be used with extreme caution in individuals with poor respiratory function. Physiotherapy Physiotherapy is not usually indicated in patients with CAP, although it may be helpful to assist expectoration in patients who suppress cough because of pleural pain. Antibiotic treatment Prompt administration of antibiotics improves the outcome. The initial choice of antibiotic is guided by clinical context, severity assessment, local knowledge of antibiotic resistance patterns and, at times, epidemiological information. Current regimens are detailed in Box 17.40. In most patients with uncomplicated pneumonia a 5-day course is adequate, although treatment is usually required for longer in patients with Legionella, staphylococcal or Klebsiella pneumonia. Oral antibiotics are usually adequate unless the patient has a severe illness, impaired consciousness, loss of swallowing reflex or functional or anatomical reasons for malabsorption. Fig. 17.33 Pneumonia of the right middle lobe. A Posteroanterior view: consolidation in the right middle lobe with characteristic opacification beneath the horizontal fissure and loss of normal contrast between the right heart border and lung. B Lateral view: consolidation confined to the anteriorly situated middle lobe. A B 17.39 Indications for referral to ITU • CURB score of 4–5 (see Fig. 17.32), failing to respond rapidly to initial management • Persisting hypoxia (PaO2 < 8 kPa (60 mmHg)), despite high concentrations of oxygen • Progressive hypercapnia • Severe acidosis • Circulatory shock • Reduced conscious level 17.38 Investigations in community-acquired pneumonia Blood Full blood count • Very high (> 20 × 109/L) or low (< 4 × 109/L) white cell count: marker of severity • Neutrophil leucocytosis > 15 × 109/L: suggests bacterial aetiology • Haemolytic anaemia: occasional complication of Mycoplasma Urea and electrolytes • Urea > 7 mmol/L (~20 mg/dL): marker of severity • Hyponatraemia: marker of severity Liver function tests • Abnormal if basal pneumonia inflames liver • Hypoalbuminaemia: marker of severity Erythrocyte sedimentation rate/C-reactive protein • Non-specifically elevated Blood culture • Bacteraemia: marker of severity Cold agglutinins • Positive in 50% of patients with Mycoplasma Arterial blood gases • Measure when SaO2 < 93% or when clinical features are severe, to assess ventilatory failure or acidosis Sputum Sputum samples • Gram stain (see Fig. 17.31), culture and antimicrobial sensitivity testing Oropharynx swab • Polymerase chain reaction for Mycoplasma pneumoniae and other atypical pathogens Urine • Pneumococcal and/or Legionella antigen Chest X-ray Lobar pneumonia • Patchy opacification evolves into homogeneous consolidation of affected lobe • Air bronchogram (air-filled bronchi appear lucent against consolidated lung tissue) may be present (Fig. 17.33) Bronchopneumonia • Typically patchy and segmental shadowing Complications • Para-pneumonic effusion, intrapulmonary abscess or empyema Staphylococcus aureus • Suggested by multilobar shadowing, cavitation, pneumatoceles and abscesses Pleural fluid • Always aspirate and culture when present in more than trivial amounts, preferably with ultrasound guidance

Prevention Current smokers should be advised to stop. Influenza and pneumococcal vaccination should be considered in patients at highest risk of pneumonia (e.g. those over 65 or with chronic lung, heart, liver or kidney disease, diabetes or immunosuppression). Because of the mode of spread, Legionella pneumophila has important public health implications and usually requires notification to the appropriate health authority for investigation of potential sources. In resource-poor settings, tackling malnourishment and indoor air pollution, and encouraging immunisation against measles, pertussis and Haemophilus influenzae type b are particularly important in children. Hospital-acquired pneumonia Hospital-acquired pneumonia (HAP) or nosocomial pneumonia refers to a new episode of pneumonia occurring at least 2 days after admission to hospital. It is the second most common hospital-acquired infection (HAI) and the leading cause of HAIassociated death. The elderly are particularly at risk, as are patients in intensive care units, especially when mechanically ventilated; here, the term ventilator-associated pneumonia (VAP) is applied. Health-care-associated pneumonia (HCAP) refers to the development of pneumonia in a person who has spent at least 2 days in hospital within the last 90 days, or has attended a haemodialysis unit, or received intravenous antibiotics, or been resident in a nursing home or other long-term care facility. The factors predisposing to the development of pneumonia in a hospitalised patient are listed in Box 17.42. Clinical features and investigation The diagnosis should be considered in any hospitalised or ventilated patient who develops purulent sputum (or endotracheal secretions), new radiological infiltrates, an otherwise unexplained increase in oxygen requirement, a core temperature > 38.3°C, and a leucocytosis or leucopenia. The clinical features and radiographic signs are variable and non-specific, however, raising a broad differential diagnosis that includes pulmonary embolism, ARDS, pulmonary oedema, pulmonary haemorrhage and drug toxicity. Therefore, in contrast to CAP, microbiological confirmation should Prognosis Most patients respond promptly to antibiotic therapy. Fever may persist for several days, however, and the chest X-ray often takes several weeks or even months to resolve, especially in old age. Delayed recovery suggests either that a complication has occurred (Box 17.41) or that the diagnosis is incorrect (see Box 17.37). Alternatively, the pneumonia may be secondary to a proximal bronchial obstruction or recurrent aspiration. The mortality rate of adults with non-severe pneumonia is very low (< 1%); hospital death rates are typically between 5% and 10% but may be as high as 50% in severe illness. Discharge and follow-up The decision to discharge a hospitalised patient depends on the home circumstances and the likelihood of complications. A chest X-ray need not be repeated before discharge in patients making a satisfactory clinical recovery. Clinical review by GP or hospital should be arranged around 6 weeks later and a chest X-ray obtained if there are persistent symptoms, physical signs or reasons to suspect underlying malignancy. 17.42 Factors predisposing to hospital-acquired pneumonia Reduced host defences against bacteria • Reduced immune defences (e.g. glucocorticoid treatment, diabetes, malignancy) • Reduced cough reflex (e.g. post-operative) • Disordered mucociliary clearance (e.g. anaesthetic agents) • Bulbar or vocal cord palsy Aspiration of nasopharyngeal or gastric secretions • Immobility or reduced conscious level • Vomiting, dysphagia (N.B. stroke disease), achalasia or severe reflux • Nasogastric intubation Bacteria introduced into lower respiratory tract • Endotracheal intubation/tracheostomy • Infected ventilators/nebulisers/bronchoscopes • Dental or sinus infection Bacteraemia • Abdominal sepsis • Intravenous cannula infection • Infected emboli 17.41 Complications of pneumonia • Para-pneumonic effusion – common • Empyema (p. 564) • Retention of sputum causing lobar collapse • Deep vein thrombosis and pulmonary embolism • Pneumothorax, particularly with Staphylococcus aureus • Suppurative pneumonia/lung abscess • ARDS, renal failure, multi-organ failure (p. 198) • Ectopic abscess formation (Staph. aureus) • Hepatitis, pericarditis, myocarditis, meningoencephalitis • Arrhythmias (e.g. atrial fibrillation) • Pyrexia due to drug hypersensitivity (ARDS = acute respiratory distress syndrome) *Antibiotic use in individual patients should take into account local guidance and antibiotic sensitivity patterns. 17.40 Antibiotic treatment for community-acquired pneumonia* Uncomplicated CAP • Amoxicillin 500 mg 3 times daily orally If patient is allergic to penicillin • Clarithromycin 500 mg twice daily orally or Erythromycin 500 mg 4 times daily orally If Staphylococcus is cultured or suspected • Flucloxacillin 1–2 g 4 times daily IV plus • Clarithromycin 500 mg twice daily IV If Mycoplasma or Legionella is suspected • Clarithromycin 500 mg twice daily orally or IV or Erythromycin 500 mg 4 times daily orally IV plus • Rifampicin 600 mg twice daily IV in severe cases Severe CAP • Clarithromycin 500 mg twice daily IV or Erythromycin 500 mg 4 times daily IV plus • Co-amoxiclav 1.2 g 3 times daily IV or Ceftriaxone 1–2 g daily IV or Cefuroxime 1.5 g 3 times daily IV or • Amoxicillin 1 g 4 times daily IV plus flucloxacillin 2 g 4 times daily IV Adapted from British Thoracic Society Guidelines.

 aid expectoration in the immobile and elderly, and adequate nutritional support is often required. Prevention Despite appropriate management, the mortality from HAP is high (approximately 30%), mandating prevention whenever possible. Good hygiene is paramount, particularly with regard to hand-washing and any equipment used. Steps should be taken to minimise the chances of aspiration and to limit the use of stress ulcer prophylaxis with proton pump inhibitors. Oral antiseptic (chlorhexidine 2%) may be used to decontaminate the upper airway and some intensive care units employ selective decontamination of the digestive tract when the anticipated requirement for ventilation will exceed 48 hours. Suppurative pneumonia, aspiration pneumonia and pulmonary abscess These conditions are considered together, as their aetiology and clinical features overlap. Suppurative pneumonia is characterised by destruction of the lung parenchyma by the inflammatory process. Although microabscess formation is a characteristic histological feature, ‘pulmonary abscess’ is usually taken to refer to lesions in which there is a large localised collection of pus, or a cavity lined by chronic inflammatory tissue, from which pus has escaped by rupture into a bronchus. Suppurative pneumonia and pulmonary abscess often develop after the inhalation of septic material during operations on the nose, mouth or throat, under general anaesthesia, or of vomitus during anaesthesia or coma, particularly if oral hygiene is poor. Additional risk factors for aspiration pneumonia include bulbar or vocal cord palsy, achalasia or oesophageal reflux, and alcoholism. Aspiration tends to localise to dependent areas of the lung, such as the apical segment of the lower lobe in a supine patient. These conditions may also complicate local bronchial obstruction from a neoplasm or foreign body. Infections are usually due to a mixture of anaerobes and aerobes in common with the typical flora encountered in the mouth and upper respiratory tract. Isolates of Prevotella melaninogenica, Fusobacterium necrophorum, anaerobic or microaerophilic cocci, and Bacteroides fragilis may be identified. When suppurative pneumonia or a pulmonary abscess occurs in a previously healthy lung, the most likely infecting organisms are Staph. aureus or K. pneumoniae. Actinomyces infections (mostly A. israelii) cause chronic suppurative pulmonary infections, which may be associated with poor dental hygiene. Actinomycosis presents a particular diagnostic challenge because of the slow growth of actinomycetes. Bacterial infection of a pulmonary infarct or a collapsed lobe may also produce a suppurative pneumonia or lung abscess. The organism(s) isolated from the sputum include Strep. pneumoniae, Staph. aureus, Streptococcus pyogenes, H. influenzae and, in some cases, anaerobic bacteria. In many cases, however, no pathogen can be isolated, particularly when antibiotics have been given. Some strains of community-acquired MRSA (CA-MRSA) produce the cytotoxin Panton–Valentine leukocidin. The organism is mainly responsible for suppurative skin infection but may be associated with rapidly progressive severe necrotising pneumonia. Lemierre’s syndrome is a rare cause of pulmonary abscesses. The usual causative agent is the anaerobe Fusobacterium necrophorum. The illness typically commences as a sore throat, be sought whenever possible. Adequate sputum samples may be difficult to obtain in the frail elderly person and physiotherapy should be considered to aid expectoration. In patients who are mechanically ventilated, bronchoscopy-directed protected brush specimens, bronchoalveolar lavage (BAL) or endotracheal aspirates may be obtained. Management The principles of management are similar to those of CAP, focusing on adequate oxygenation, appropriate fluid balance and antibiotics. The choice of empirical antibiotic therapy is considerably more challenging, however, given the diversity of pathogens and the potential for drug resistance. The organisms implicated in early-onset HAP (occurring within 4–5 days of admission) are similar to those involved in CAP. In patients who have received no previous antibiotics, co-amoxiclav or cefuroxime represents a sensible choice. If the patient has received a course of recent antibiotics, then piperacillin/tazobactam or a third-generation cephalosporin should be considered. Late-onset HAP is more often attributable to Gram-negative bacteria (e.g. Escherichia coli, Pseudomonas aeruginosa, Klebsiella spp. and Acinetobacter baumannii), Staph. aureus (including meticillin-resistant Staph. aureus (MRSA)) and anaerobes, and the choice of antibiotics ought to cover these possibilities. Antipseudomonal cover may be provided by a carbapenem (meropenem), an anti-pseudomonal cephalosporin or piperacillin–tazobactam. MRSA cover may be provided by glycopeptides such as vancomycin or linezolid. A. baumannii is usually sensitive to carbapenems but resistant cases may require nebulised and/or intravenous colistin. The choice of agents is most appropriately guided by knowledge of local patterns of microbiology and antibiotic resistance. It is sensible to commence broad-based cover, discontinuing less appropriate antibiotics as culture results become available. In the absence of good evidence, the duration of antibiotic therapy remains a matter for clinical judgement. Physiotherapy is important to 17.43 Respiratory infection in old age • Increased risk of and from respiratory infection: because of reduced immune responses, increased closing volumes, reduced respiratory muscle strength and endurance, altered mucus layer, poor nutritional status and the increased prevalence of chronic lung disease. • Predisposing factors: other medical conditions may predispose to infection, e.g. swallowing difficulties due to stroke increase the risk of aspiration pneumonia. • Atypical presentation: older patients often present with delirium, rather than breathlessness or cough. • Mortality: the vast majority of deaths from pneumonia in developed countries occur in older people. • Influenza: has a much higher complication rate, and morbidity and mortality. Vaccination significantly reduces morbidity and mortality in old age but uptake is poor. • Tuberculosis: most cases in old age represent reactivation of previous, often unrecognised, disease and may be precipitated by glucocorticoid therapy, diabetes mellitus and the factors above. Cryptic miliary tuberculosis is an occasional alternative presentation. Older people more commonly suffer adverse effects from antituberculous chemotherapy and require close monitoring.

Pneumonia in the immunocompromised patient Patients immunocompromised by drugs or disease (particularly human immunodeficiency virus (HIV) infection; p. 318) are at increased risk of pulmonary infection and pneumonia is the most common cause of death in this group. The majority of infections are caused by the same pathogens that cause pneumonia in immunocompetent individuals, but in patients with more profound immunosuppression less common organisms, or those normally considered to be of low virulence or non-pathogenic, may become ‘opportunistic’ pathogens. Depending on the clinical context, clinicians should consider the possibility of Gram-negative bacteria, especially P. aeruginosa, viruses, fungi, mycobacteria, and less common organisms such as Nocardia spp. Infection is often due to more than one organism. Clinical features

These typically include fever, cough and breathlessness but are influenced by the degree of immunosuppression, and the presentation may be less specific in the more profoundly immunosuppressed. The onset of symptoms tends to be swift in those with a bacterial infection but more gradual in patients with opportunistic organisms such as Pneumocystis jirovecii and mycobacterial infections (p. 318). In P. jirovecii pneumonia, symptoms of cough and breathlessness can be present several days or weeks before the onset of systemic symptoms or the appearance of radiographic abnormality. The clinical features of invasive pulmonary aspergillosis are dealt with on page 597. Investigations The approach is informed by the clinical context and severity of the illness. Invasive investigations, such as bronchoscopy, BAL, transbronchial biopsy or surgical lung biopsy, are often impractical, as many patients are too ill to undergo these safely; however, 'induced sputum' (p. 554) offers a relatively safe method of obtaining microbiological samples. HRCT can be helpful: • focal unilateral airspace opacification favours bacterial infection, mycobacteria or Nocardia • bilateral opacification favours P. jirovecii pneumonia, fungi, viruses and unusual bacteria, e.g. Nocardia • cavitation may be seen with N. asteroides, mycobacteria and fungi • the presence of a 'halo sign' (a zone of intermediate attenuation between the nodule and the lung parenchyma) may suggest aspergillosis (p. 596) • pleural effusions suggest pyogenic bacterial infections and are uncommon in P. jirovecii pneumonia. Management In theory, treatment should be based on an established aetiological diagnosis; in practice, however, the causative agent is frequently unknown. Factors that favour a bacterial aetiology include neutropenia, rapid onset and deterioration. In these circumstances, broad-spectrum antibiotic therapy should be commenced immediately, e.g. a third-generation cephalosporin, or a quinolone, plus an antistaphylococcal antibiotic, or an antipseudomonal penicillin plus an aminoglycoside. Thereafter, treatment may be tailored according to the results of investigations and the clinical response. Depending on the clinical context and response to treatment, antifungal or antiviral therapies may be added. The management of P. jirovecii infection is detailed on page 318 and that of invasive aspergillosis on page 596. painful swollen neck, fever, rigor, haemoptysis and dyspnoea; spread into the jugular veins leads to thrombosis and metastatic dispersal of the organisms. Injecting drug-users are at particular risk of developing haematogenous lung abscess, often in association with endocarditis affecting the pulmonary and tricuspid valves. A non-infective form of aspiration pneumonia – exogenous lipid pneumonia – may follow the aspiration of animal, vegetable or mineral oils. The clinical features of suppurative pneumonia are summarised in Box 17.44. Investigations Radiological features of suppurative pneumonia include homogeneous lobar or segmental opacity consistent with consolidation or collapse. Abscesses are characterised by cavitation and a fluid level. Occasionally, a pre-existing emphysematous bulla becomes infected and appears as a cavity containing an air–fluid level. Management Aspiration pneumonia can usually be treated with amoxicillin and metronidazole. Co-amoxiclav also has a suitable antibiotic spectrum but increases the risk of Clostridium difficile infection. Further modification of antibiotics should be informed by clinical response and microbiological results. CA-MRSA is usually susceptible to a variety of oral non-β-lactam antibiotics, such as trimethoprim/sulfamethoxazole, clindamycin, tetracyclines and linezolid. Parenteral therapy with vancomycin or linezolid can also be considered. Fusobacterium necrophorum is highly susceptible to β-lactam antibiotics and to metronidazole, clindamycin and third-generation cephalosporins. Prolonged treatment for 4–6 weeks may be required in some patients with lung abscess. Established pulmonary actinomycosis requires 6–12 months' treatment with intravenous or oral penicillin, or with a tetracycline in penicillin-allergic patients. Physiotherapy is of great value, especially when suppuration is present in the lower lobes or when a large abscess cavity has formed. In most patients there is a good response to treatment, and although residual fibrosis and bronchiectasis are common sequelae, these seldom give rise to serious morbidity. Surgery should be contemplated if no improvement occurs despite optimal medical therapy. Removal or treatment of any obstructing endobronchial lesion is essential. 17.44 Clinical features of suppurative pneumonia Symptoms • Cough with large amounts of sputum, sometimes fetid and blood-stained • Pleural pain common • Sudden expectoration of copious amounts of foul sputum if abscess ruptures into a bronchus Clinical signs • High remittent pyrexia • Profound systemic upset • Digital clubbing may develop quickly (10–14 days) • Consolidation on chest examination; signs of cavitation rarely found • Pleural rub common • Rapid deterioration in general health, with marked weight loss if not adequately treated

 (p. 594). If these reparative processes fail, primary progressive disease ensues (Fig. 17.36). The estimated lifetime risk of developing disease after primary infection is 10%, with roughly half of this risk occurring in the first 2 years after infection. Factors predisposing to TB are summarised in Box 17.45 and the natural history of infection with TB is summarised in Box 17.46. Clinical features: pulmonary disease Primary pulmonary TB Primary TB refers to the infection of a previously uninfected (tuberculin-negative) individual. A few patients develop a selflimiting febrile illness but clinical disease occurs only if there is a hypersensitivity reaction or progressive infection (Box 17.47). Progressive primary disease may appear during the course of the initial illness or after a latent period of weeks or months. Miliary TB Blood-borne dissemination gives rise to miliary TB, which may present acutely but more frequently is characterised by 2–3 weeks of fever, night sweats, anorexia, weight loss and a Fig. 17.34 Worldwide incidence of tuberculosis (2014). Estimated new cases (all forms) per 100 000 population. From World Health Organisation. Global tuberculosis report, 20th edn. Geneva: WHO; 2015. 0–9.9 10–19 20–49 50–124 125–299 300–499 ≥500 No data Not applicable Fig. 17.35 Tuberculous granuloma. Normal lung tissue is lost and replaced by a mass of fibrous tissue with granulomatous inflammation characterised by large numbers of macrophages and multinucleate giant cells (white arrow). The central area of this focus shows caseous degeneration (black arrow). Courtesy of Dr William Wallace, Department of Pathology, Royal Infirmary of Edinburgh. Tuberculosis Epidemiology Tuberculosis (TB) is caused by infection with Mycobacterium tuberculosis (MTB), which is part of a complex of organisms including M. bovis (reservoir cattle) and M. africanum (reservoir humans). The resurgence in TB in the UK observed over the latter part of the last century has finally halted and notification of TB has fallen by around 1.5% per year since 2000. None the less, its impact on world health remains significant. An estimated 9.6 million new cases were recorded in 2014, with the majority presenting in the world's poorest nations, which struggle to cover the costs associated with management and control programmes (Fig. 17.34). In the same year, 1.5 million men, women and children died of TB, and TB continues to rank alongside HIV as a leading cause of death worldwide. Pathology and pathogenesis M. bovis infection arises mainly drinking non-sterilised milk from infected cows. M. tuberculosis is spread by the inhalation of aerosolised droplet nuclei from other infected patients. Once inhaled, the organisms lodge in the alveoli and initiate the recruitment of macrophages and lymphocytes. Macrophages undergo transformation into epithelioid and Langhans cells, which aggregate with the lymphocytes to form the classical tuberculous granuloma (Fig. 17.35). Numerous granulomas aggregate to form a primary lesion or 'Ghon focus' (a pale yellow, caseous nodule, usually a few millimetres to 1–2 cm in diameter), which is characteristically situated in the periphery of the lung. Spread of organisms to the hilar lymph nodes is followed by a similar pathological reaction, and the combination of the primary lesion and regional lymph nodes is referred to as the 'primary complex of Ranke'.

Reparative processes encase the primary complex in a fibrous capsule, limiting the spread of bacilli. If no further complications ensue, this lesion eventually calcifies and is clearly seen on a chest X-ray. Lymphatic or haematogenous spread may occur before immunity is established, however, seeding secondary foci in other organs, including lymph nodes, serous membranes, meninges, bones, liver, kidneys and lungs, which may lie dormant for years. The only clue that infection has occurred may be the appearance of a cell-mediated, delayed-type hypersensitivity reaction to tuberculin, demonstrated by tuberculin skin testing or an interferon gamma release assay (IGRA): so-called latent TB

Fig. 17.36 Primary pulmonary tuberculosis. (1) Spread from the primary focus to hilar and mediastinal lymph glands to form the ‘primary complex’, which heals spontaneously in most cases. (2) Direct extension of the primary focus – progressive pulmonary tuberculosis. (3) Spread to the pleura – tuberculous pleurisy and pleural effusion. (4) Blood-borne spread: few bacilli – pulmonary, skeletal, renal, genitourinary infection, often months or years later; massive spread – miliary pulmonary tuberculosis and meningitis.

dry cough. Hepatosplenomegaly may develop and the presence of a headache may indicate coexistent tuberculous meningitis. Auscultation of the chest is frequently normal but in more advanced disease widespread crackles are evident. Fundoscopy may show choroidal tubercles. The classical appearances on chest X-ray are of fine 1–2 mm lesions (‘millet seed’) distributed throughout the lung fields, although occasionally the appearances are coarser. Anaemia and leucopenia reflect bone marrow involvement. ‘Cryptic’ miliary TB is an unusual presentation sometimes seen in old age (Box 17.48). Post-primary pulmonary TB Post-primary disease refers to exogenous (‘new’ infection) or endogenous (reactivation of a dormant primary lesion) infection in a person who has been sensitised by earlier exposure. It is most frequently pulmonary and characteristically occurs in the apex of an upper lobe, where the oxygen tension favours survival of the strictly aerobic organism. The onset is usually insidious, developing slowly over several weeks. Systemic symptoms include fever, night sweats, malaise and loss of appetite and weight, and are accompanied by progressive pulmonary symptoms (Box 17.49). Very occasionally, this form of TB may present with one of the complications listed in Box 17.50. Radiological changes include ill-defined opacification in one or both of the upper lobes, and as progression occurs, consolidation, collapse and cavitation develop to varying degrees (Fig. 17.37). It is often difficult to distinguish active from quiescent disease on radiological criteria alone but the presence of a miliary pattern or cavitation favours active disease. In extensive disease, collapse may be marked and results in significant displacement of the trachea and mediastinum. Occasionally, a caseous lymph node may drain into an adjoining bronchus, leading to tuberculous pneumonia. 17.46 Natural history of untreated primary tuberculosis Time from infection Manifestations 3–8 weeks Primary complex, positive tuberculin skin test 3–6 months Meningeal, miliary and pleural disease Up to 3 years Gastrointestinal, bone and joint, and lymph node disease Around 8 years Renal tract disease From 3 years onwards Post-primary disease due to reactivation or re-infection Adapted from Davies PDO, ed. Clinical tuberculosis. London: Hodder Arnold; 1998. 17.45 Factors increasing the risk of tuberculosis Patient-related • Age (children > young adults < elderly) • First-generation immigrants from high-prevalence countries • Close contacts of patients with smear-positive pulmonary TB • Overcrowding (prisons, collective dormitories); homelessness (doss houses and hostels) • Chest X-ray evidence of self-healed TB • Primary infection < 1 year previously • Smoking: cigarettes, bidis (Indian cigarettes made of tobacco wrapped in temburini leaves) and cannabis Associated diseases • Immunosuppression: HIV, anti-tumour necrosis factor (TNF) and other biologic therapies, high-dose glucocorticoids, cytotoxic agents • Malignancy (especially lymphoma and leukaemia) • Diabetes mellitus • Chronic kidney disease • Silicosis • Gastrointestinal disease associated with malnutrition (gastrectomy, jejuno-ileal bypass, cancer of the pancreas, malabsorption) • Deficiency of vitamin D or A • Recent measles in children 17.47 Features of primary tuberculosis Infection (4–8 weeks) • Influenza-like illness • Skin test conversion • Primary complex Disease • Lymphadenopathy: hilar (often unilateral), paratracheal or mediastinal • Collapse (especially right middle lobe) • Consolidation (especially right middle lobe) • Obstructive emphysema • Cavitation (rare) • Pleural effusion • Miliary • Meningitis • Pericarditis Hypersensitivity • Erythema nodosum • Phlyctenular conjunctivitis • Dactylitis 17.48 Cryptic tuberculosis • Age over 60 years • Intermittent low-grade pyrexia of unknown origin • Unexplained weight loss, general debility (hepatosplenomegaly in 25–50%) • Normal chest X-ray • Blood dyscrasias; leukaemoid reaction, pancytopenia • Negative tuberculin skin test • Confirmation by biopsy with granulomas and/or acid-fast bacilli in liver or bone marrow

 distortion of the bowel, with caecal involvement predominating. Diagnosis rests on obtaining histology by either colonoscopy or mini-laparotomy. The main differential diagnosis is Crohn’s disease (p. 813). Tuberculous peritonitis is characterised by abdominal distension, pain and constitutional symptoms. The ascitic fluid is exudative and cellular, with a predominance of lymphocytes. Laparoscopy reveals multiple white ‘tubercles’ over the peritoneal and omental surfaces. Low-grade hepatic dysfunction is common in miliary disease, in which biopsy reveals granulomas. Occasionally, patients may be frankly icteric, with a mixed hepatic/cholestatic picture. Pericardial disease Disease occurs in two forms (see Fig. 17.38 and p. 542): pericardial effusion and constrictive pericarditis. Fever and night sweats are rarely prominent and the presentation is usually insidious, with breathlessness and abdominal swelling. Coexistent pulmonary disease is very rare, with the exception of pleural effusion. Pulsus paradoxus, a raised JVP, hepatomegaly, prominent ascites and peripheral oedema are common to both types. Pericardial effusion is associated with increased pericardial dullness and a globular enlarged heart on chest X-ray, and pericardial calcification occurs in around 25% of cases. Constriction is associated with an early third heart sound and, occasionally, atrial fibrillation. Diagnosis is based on the clinical, radiological and echocardiographic findings (p. 542). The effusion is frequently blood-stained. Open pericardial biopsy can be performed where there is diagnostic uncertainty. The addition of glucocorticoids to antituberculosis treatment has been shown to help both forms of pericardial disease. Fig. 17.37 Chest X-ray: major manifestations and differential diagnosis of pulmonary tuberculosis. Less common manifestations include pneumothorax, acute respiratory distress syndrome (ARDS; p. 198), cor pulmonale and localised emphysema. ‘Miliary’ diffuse shadowing Differential diagnosis • Sarcoidosis • Malignancy • Pneumoconiosis • Infection (e.g. histoplasmosis) Pleural effusion/empyema Differential diagnosis • Bacterial pneumonia • Pulmonary infarction • Carcinoma • Connective tissue disorder Cavitation Differential diagnosis • Pneumonia/lung abscess • Lung cancer • Pulmonary infarct • Granulomatosis with polyangiitis (Wegener’s granulomatosis) • Progressive massive fibrosis Consolidation/collapse Differential diagnosis • Pneumonia • Bronchial carcinoma • Pulmonary infarct *From swallowed sputum. 17.50 Complications of chronic pulmonary tuberculosis Pulmonary • Massive haemoptysis • Cor pulmonale • Fibrosis/emphysema • Atypical mycobacterial infection • Lung/pleural calcification •*

Aspergilloma/chronic aspergillosis • Obstructive airways disease • Bronchiectasis • Bronchopleural fistula Non-pulmonary • Empyema necessitans • Laryngitis • Enteritis • Anorectal disease* • Amyloidosis • Poncet's polyarthritis 17.49 Clinical presentations of pulmonary tuberculosis • Chronic cough, often with haemoptysis • Pyrexia of unknown origin • Unresolved pneumonia • Exudative pleural effusion • Asymptomatic (diagnosis on chest X-ray) • Weight loss, general debility • Spontaneous pneumothorax Clinical features: extrapulmonary disease Extrapulmonary TB accounts for 20% of cases in those who are HIV-negative but is more common in HIV-positive patients. Lymphadenitis Lymph nodes are the most common extrapulmonary site of disease. Cervical and mediastinal glands are affected most frequently, followed by axillary and inguinal, and more than one region may be involved. Disease may represent primary infection, spread from contiguous sites or reactivation. Supraclavicular lymphadenopathy is often the result of spread from mediastinal disease. The nodes are usually painless and initially mobile but become matted together with time. When caseation and liquefaction occur, the swelling becomes fluctuant and may discharge through the skin with the formation of a 'collar-stud' abscess and sinus formation. Approximately half of cases fail to show any constitutional features, such as fevers or night sweats. The tuberculin test is usually strongly positive. During or after treatment, paradoxical enlargement, development of new nodes and suppuration may all occur but without evidence of continued infection; surgical excision is rarely necessary. In non-immigrant children in the UK, most mycobacterial lymphadenitis is caused by opportunistic mycobacteria, especially of the M. avium complex. Gastrointestinal tuberculosis TB can affect any part of the bowel and patients may present with a wide range of symptoms and signs (Fig. 17.38). Upper gastrointestinal tract involvement is rare and is usually an unexpected histological finding in an endoscopic or laparotomy specimen. Ileocaecal disease accounts for approximately half of abdominal TB cases. Fever, night sweats, anorexia and weight loss are usually prominent and a right iliac fossa mass may be palpable. Up to 30% of cases present with an acute abdomen. Ultrasound or CT may reveal thickened bowel wall, abdominal lymphadenopathy, mesenteric thickening or ascites. Barium enema and small bowel enema reveal narrowing, shortening and

immunologically mediated polyarthritis that usually resolves within 2 months of starting treatment. Genitourinary disease Fever and night sweats are rare with renal tract TB and patients are often only mildly symptomatic for many years. Haematuria, frequency and dysuria are often present, with sterile pyuria found on urine microscopy and culture. In women, infertility from endometritis, or pelvic pain and swelling from salpingitis or a tubo-ovarian abscess occurs occasionally. In men, genitourinary TB may present as epididymitis or prostatitis. Investigations The presence of an otherwise unexplained cough for more than 2–3 weeks, particularly in regions where TB is prevalent, or typical chest X-ray or CT changes (Fig. 17.39) should prompt further investigation (Box 17.51). Direct microscopy of a sputum smear remains the most important first step. At least two sputum samples (including at least one obtained in the early morning) from a spontaneously produced deep cough should be obtained. Induced sputum may be used in those unable to expectorate. In selected cases, bronchoscopy and lavage or aspiration of a lymph node by EBUS may be used. Light-emitting diode fluorescent microscopy with auramine staining is increasingly replacing the more traditional standard light microscopy and Ziehl–Neelsen stain (Fig. 17.40) or the use of mercury-vapour fluorescent microscopy. A positive smear is sufficient for the presumptive diagnosis of TB but definitive Central nervous system disease Meningeal disease represents the most important form of central nervous system TB. Unrecognised and untreated, it is rapidly fatal. Even when appropriate treatment is prescribed, mortality rates of 30% have been reported, while survivors may be left with neurological sequelae. Clinical features, investigations and management are described on page 1120. Bone and joint disease The spine is the most common site for bony TB (Pott's disease), which usually presents with chronic back pain and typically involves the lower thoracic and lumbar spine (see Fig. 17.38). The infection starts as a discitis and then spreads along the spinal ligaments to involve the adjacent anterior vertebral bodies, causing angulation of the vertebrae with subsequent kyphosis. Paravertebral and psoas abscess formation is common and the disease may present with a large (cold) abscess in the inguinal region. CT or MRI is valuable in gauging the extent of disease, the amount of cord compression, and the site for needle biopsy or open exploration, if required. The major differential diagnosis is malignancy, which tends to affect the vertebral body and leave the disc intact. Important complications include spinal instability or cord compression. TB can affect any joint but most frequently involves the hip or knee. Presentation is usually insidious, with pain and swelling; fever and night sweats are uncommon. Radiological changes are often non-specific but, as disease progresses, reduction in joint space and erosions appear. Poncet's arthropathy is an Fig. 17.38 Systemic presentations of extrapulmonary tuberculosis. Exudative ascites Mesenteric adenitis Intestinal obstruction Cranial nerve palsy Lymph node enlargement Pericardial effusion Constrictive pericarditis Monoarthritis Haematuria/dysuria Infertility in women Epididymitis Anorectal ulceration Headache, vomiting, seizures, delirium Lymphocytic meningitis Hydrocephalus Space-occupying lesion (tuberculoma) Kyphosis Cord compression Abdominal mass Psoas abscess General observation

Weight loss

Fever

Night sweats Chronic back pain

592 • RESPIRATORY MEDICINE of rapid NAATs (p. 106). For example, Xpert MTB/RIF (a DNA detection-based NAAT) has the capacity to detect MTB (and rifampicin resistance) in less than 2 hours. However, while it is specific to MTB, it is not sufficiently sensitive to have replaced culture. The diagnosis of extrapulmonary TB can be more challenging. There are generally fewer organisms (particularly in meningeal or pleural fluid), so culture, histopathological examination of tissue and/or NAAT may be required. Stimulation of T cells by mycobacterial antigens leads to increased levels of adenosine deaminase in pleural, pericardial, cerebrospinal and ascitic fluid, and so may assist in confirming suspected TB. In the presence of HIV, examination of sputum may still be useful, as subclinical pulmonary disease is common. Lateral flow urinary lipoarabinomannan assay (LF-LAM) may be useful in the severely ill patient with a CD4 count of 100 cells/μL or less. Drug sensitivity testing The rapid detection of drug resistance is central both to the management of the individual with TB and to control of the disease in the population. The gold standard remains culture, in either solid or liquid media, but the use of other phenotypic tests, such as microscopically observed drug susceptibility (MODS), colorimetric redox indicator (CRI) methods and nitrate reductase assay, offer low-cost alternatives, depending on the resource and expertise available. The potential for molecular tests to provide rapid drug sensitivity testing (DST) is improving, particularly with regard to the detection of rifampicin resistance, which is important because rifampicin forms the cornerstone of 6-month chemotherapy. Rapid identification of

rifampicin resistance is provided by Xpert MTB/RIF. Line probe assays (LPAs) use PCR and reverse hybridisation to detect genetic sequences linked to resistance to both rifampicin and isoniazid, and increasingly to resistance to pyrazinamide, ethambutol and other second-line agents. Management Chemotherapy The treatment of TB is based on the principle of an initial intensive phase to reduce the bacterial population rapidly, followed by a continuation phase to destroy any remaining bacteria (Box 17.52). Standard treatment involves 6 months' treatment with isoniazid and rifampicin, supplemented in the first 2 months with diagnosis requires culture. The probability of detecting acid-fast bacilli is proportional to the bacillary burden in the sputum. Smear-negative sputum should also be cultured, as only 10–100 viable organisms are required for sputum to be culture-positive. A diagnosis of smear-negative TB may be made in advance of culture if the chest X-ray appearances are typical of TB. The slow growth of MTB on solid (typically between 4 and 6 weeks) and automated and semi-automated liquid (typically around 2 weeks) culture media has prompted the development Fig. 17.39 Typical changes of tuberculosis. The chest X-ray shows bilateral upper lobe airspace shadowing with cavitation. Fig. 17.40 Positive Ziehl–Neelsen stain. Mycobacteria (arrow) retain the red carbol fuchsin stain, despite washing with acid and alcohol. Courtesy of Adam Hill. 17.51 Diagnosis of tuberculosis Specimens required Pulmonary • Sputum* (induced with nebulised hypertonic saline if patient not expectorating) • Bronchoscopy with washings or BAL • Gastric washing* (mainly used for children) Extrapulmonary • Fluid examination (cerebrospinal, ascitic, pleural, pericardial, joint): yield classically very low • Tissue biopsy (from affected site): bone marrow/liver may be diagnostic in disseminated disease Diagnostic tests • Tuberculin skin test: low sensitivity/specificity; useful only in primary or deep-seated infection • Stain Ziehl–Neelsen Auramine fluorescence • Nucleic acid amplification • Culture Solid media (Löwenstein–Jensen, Middlebrook) Liquid media (e.g. MGIT) • Pleural fluid: adenosine deaminase • Response to empirical antituberculous drugs (usually seen after 5–10 days) Baseline blood tests • Full blood count, C-reactive protein, erythrocyte sedimentation rate, urea and electrolytes, liver function tests (BAL = bronchoalveolar lavage; MGIT = mycobacteria growth indicator tube) *At least two but preferably three, including an early morning sample.

17.52 Treatment of new tuberculosis patients (World Health Organisation recommendations) Intensive phase Continuation phase Comments Standard regimen 2 months of HRZE 4 months of HR 2 months of HRZE 4 months of HRE Applies only in countries with high levels of isoniazid resistance in new TB patients, and where isoniazid drug susceptibility testing in new patients is not done (or results are unavailable) before the continuation phase begins Dosing frequency Daily* Daily Optimal Daily* 3 times/week Acceptable alternative for any new patient receiving directly observed therapy 3 times/week 3 times/week Acceptable alternative, provided that the patient is receiving directly observed therapy and is NOT living with HIV or living in an HIV-prevalent setting *Daily (rather than 3 times weekly) intensive-phase dosing may help to prevent acquired drug resistance in TB patients starting treatment with isoniazid resistance. (H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol) Adapted from World Health Organisation. Treatment of tuberculosis guidelines, 4th edn; 2010. 17.53 Main adverse reactions of first-line antituberculous drugs Isoniazid Rifampicin Pyrazinamide Streptomycin Ethambutol Mode of action Cell wall synthesis DNA transcription Unknown Protein synthesis Cell wall synthesis Major adverse reactions Peripheral neuropathy1 Hepatitis2 Rash Febrile reactions Hepatitis Rash Gastrointestinal disturbance Hepatitis Gastrointestinal disturbance Hyperuricaemia 8th nerve damage Rash

Retrobulbar neuritis3 Arthralgia Less common adverse reactions Lupoid reactions Seizures Psychoses Interstitial nephritis Thrombocytopenia Haemolytic anaemia Rash Photosensitisation Gout Nephrotoxicity Agranulocytosis Peripheral neuropathy Rash 1The risk may be reduced by prescribing pyridoxine. 2More common in patients with a slow acetylator status and in alcoholics. 3Reduced visual acuity and colour vision may be reported with higher doses and are usually reversible. pyrazinamide and ethambutol. Fixed-dose tablets combining two or three drugs are preferred. Treatment should be commenced immediately in any patient who is smear-positive, and in those who are smear-negative but with typical chest X-ray changes and no response to standard antibiotics. Six months of therapy is appropriate for all patients with new-onset pulmonary TB and most cases of extrapulmonary TB. However, 12 months of therapy is recommended for meningeal TB, including involvement of the spinal cord in cases of spinal TB; in these cases, ethambutol may be replaced by streptomycin. Pyridoxine should be prescribed in pregnant women and malnourished patients to reduce the risk of peripheral neuropathy with isoniazid. Where drug resistance is not anticipated, patients can be assumed to be non-infectious after 2 weeks of appropriate therapy. Most patients can be treated at home. Admission to a hospital unit with appropriate isolation facilities should be considered where there is uncertainty about the diagnosis, intolerance of medication, questionable treatment adherence, adverse social conditions or a significant risk of multidrug-resistant TB (culturepositive after 2 months on treatment, or contact with known multidrug-resistant TB). Patients treated with rifampicin should be advised that their urine, tears and other secretions will develop a bright, orange/ red coloration, and women taking the oral contraceptive pill must be warned that its efficacy will be reduced and alternative contraception may be necessary. Ethambutol and streptomycin should be used with caution in renal impairment, with appropriate dose reduction and monitoring of drug levels. Adverse drug reactions occur in about 10% of patients but are significantly more common with HIV co-infection (Box 17.53). Baseline liver function and regular monitoring are important for patients treated with standard therapy. Rifampicin may cause asymptomatic hyperbilirubinaemia but, along with isoniazid and pyrazinamide, may also cause hepatitis. Mild asymptomatic increases in transaminases are common but significant hepatotoxicity only occurs in 2–5%. It is appropriate to stop treatment and allow any symptoms to subside and the liver function tests to recover before commencing a stepwise re-introduction of the individual drugs. Less hepatotoxic regimens may be considered, including streptomycin, ethambutol and fluoroquinolones. Glucocorticoids reduce inflammation and limit tissue damage; they are currently recommended when treating pericardial or meningeal disease, and in children with endobronchial disease. They may confer benefit in TB of the ureter, pleural effusions and extensive pulmonary disease, and can suppress hypersensitivity drug reactions. Surgery should be considered in cases complicated by massive haemoptysis, loculated empyema, constrictive pericarditis, lymph node suppuration, and spinal disease with cord compression, but usually only after a full course of antituberculosis treatment. The effectiveness of therapy for pulmonary TB is assessed by further sputum smear at 2 months and at 5 months. Treatment failure is defined as a positive sputum smear or culture at 5 months or any patient with a multidrug-resistant strain, regardless of

 asymptomatic contact who tests positive but has a normal chest X-ray may be treated with chemoprophylaxis to prevent infection from progressing to clinical disease. Chemoprophylaxis should be offered to adults up to the age of 65 (although age-specific cut-off varies by country). It should also be considered for HIV-infected close contacts of a patient with smear-positive disease. A course of rifampicin and isoniazid for 3 months or isoniazid for 6 months is effective. Tuberculin skin testing may be associated with false-positive reactions in those who have had a BCG vaccination and in areas where exposure to non-tuberculous mycobacteria is high. The skin tests may also be falsely negative in the setting of immunosuppression or overwhelming TB infection. IGRAs detect the release of interferon-gamma (IFN-γ) from sensitised T cells in response to antigens, such as early secretory antigenic target (ESAT)-6 or culture filtrate protein (CFP)-10, which are encoded by genes specific to Mycobacterium tuberculosis and are not shared with BCG or opportunistic mycobacteria (Fig. 17.42). IGRAs are more specific than skin testing and logistically more convenient, as they require a single blood test rather than two clinic visits. In the UK, a dual strategy of TST followed by IGRA is recommended. TST remains the first choice in children, while IGRA represents the first choice for individuals with HIV. Directly observed therapy Poor adherence to therapy is a major factor in prolonged illness, risk of relapse, and the emergence of drug resistance. Directly observed therapy (DOT) involves the supervised administration of therapy 3 times weekly to improve adherence. DOT has become an important control strategy in resource-poor nations. In the UK, it is currently recommended for patients thought unlikely to be adherent to therapy: homeless people and drifters, alcohol or Fig. 17.41 The tuberculin skin test. A The reaction to the intradermal injection of tuberculin purified protein derivative (PPD) on the inner surface of the forearm is read between 48 and 72 hours. B The diameter of the indurated area should be measured across the forearm and is positive when ≥ 5 mm. A B Fig. 17.42 The principles of interferon-gamma release assays (IGRAs). A sample of either (A) purified T cells (T-SPOT.TB test) or (B) whole blood (QuantiFERON–TB Gold test) is incubated in the presence of antigens specific to Mycobacterium tuberculosis (MTB). The release of interferon-gamma (IFN-γ) by the cells is measured by enzyme-linked immunosorbent assay (ELISA). (ELISPOT = enzyme-linked immunosorbent spot assay) Incubate in the presence of antigens specific to MTB Incubate in the presence of antigens specific to MTB Purified T lymphocytes IFN-γ released IFN-γ binds to antibody on base of ELISPOT wells Spots counted A Whole blood IFN-γ released Supernatant removed and IFN-γ measured by ELISA B whether they are smear-positive or negative. Extrapulmonary TB must be assessed clinically or radiographically, as appropriate. Control and prevention TB is preventable, particularly so in those with latent TB. Supporting the development of laboratory and health-care services to improve detection and treatment of active and latent TB is an important component of this goal. Detection of latent TB The majority of individuals exposed to MTB harbour the bacteria, which remain dormant. They do not develop any signs of active disease and are non-infectious. They are however, at risk of developing active TB disease and becoming infectious. The lifetime risk of TB disease for a person with documented latent TB infection is estimated at 5–15%, with the majority of cases occurring within the first 5 years after initial infection. Latent TB may be identified by the presence of immune responses to M. tuberculosis antigens. Contact tracing is a legal requirement in many countries. It has the potential to identify the probable index case, other cases infected by the same index patient (with or without evidence of disease), and close contacts who should receive BCG vaccination (see below) or chemotherapy. Approximately 10–20% of close contacts of patients with smear-positive pulmonary TB and 2–5% of those with smear-negative, culture-positive disease have evidence of TB infection. Cases are commonly identified using the tuberculin skin test (TST; Fig. 17.41) or an IGRA (Fig. 17.42). An otherwise

5 months and usually have the same drug susceptibility. In the absence of treatment, a patient with smear-positive TB will remain infectious for an average of 2 years; in 1 year, 25% of untreated cases will die. Death is more likely in those who are smear-positive and those who smoke. A few patients die unexpectedly soon after commencing therapy and it is possible that some have subclinical hypoadrenalism that is unmasked by a rifampicin-induced increase in glucocorticoid metabolism. HIV-positive patients have higher mortality rates and a modestly increased risk of relapse. Opportunistic mycobacterial infection Other species of environmental mycobacteria (often termed ‘atypical’) may cause human disease (Box 17.55). The sites commonly involved are the lungs, lymph nodes, skin and soft tissues. The most widely recognised of these mycobacteria, M. avium complex (MAC), is well described in severe HIV disease (CD4 count < 50 cells/mL – p. 324). However, several others (including MAC) colonise and/or infect apparently immunocompetent patients with chronic lung diseases such as COPD, bronchiectasis, pneumoconiosis, old TB, or cystic fibrosis. The clinical presentation varies from a relatively indolent course in some to an aggressive course characterised by cavitatory or nodular disease in others. Radiological appearances may be similar to classical TB, but in patients with bronchiectasis, opportunistic infection may present with lower-zone nodules. The most commonly reported organisms include M. kansasii, M. malmoense, M. xenopi and M. abscessus but geographical variation is marked. M. abscessus and M. fortuitum grow rapidly but the majority grow slowly. More rapid diagnostic systems are under development, including DNA probes, high-performance liquid chromatography (HPLC), PCR restriction enzyme analysis (PRA) and 16S rRNA gene sequence analysis. With the exception of M. kansasii, drug sensitivity testing is usually unhelpful in predicting treatment response. In the UK, these organisms are not notifiable to local public health departments as they are not normally communicable, although there is some evidence of patient-to-patient transmission of M. abscessus in cystic fibrosis. drug users, patients with serious mental illness and those with a history of non-adherence. TB and HIV/AIDS The close links between HIV and TB, particularly in sub-Saharan Africa, and the potential for both diseases to overwhelm healthcare funding in resource-poor nations have been recognised, with the promotion of programmes that link detection and treatment of TB with detection and treatment of HIV. It is recommended that all patients with TB should be tested for HIV infection. Mortality is high and TB is a leading cause of death in HIV patients. Full discussion of its presentation and management is given on page 318. Drug-resistant TB Drug-resistant TB is defined by the presence of resistance to any first-line agent. Multidrug-resistant tuberculosis (MDR-TB) is defined by resistance to at least rifampicin and isoniazid, with or without other drug resistance. Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB. In 2014, an estimated 190 000 people died of MDR-TB. Extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to at least rifampicin and isoniazid, in addition to any quinolone and at least one injectable second-line agent. An estimated 9.7% of people with MDR-TB have XDR-TB. The prevalence of MDR-TB is rising, particularly in the former Soviet Union, Central Asia and Africa. It is more common in individuals with a prior history of TB, particularly if treatment has been inadequate, and those with HIV infection. Box 17.54 lists the factors contributing to the emergence of drug-resistant TB. Diagnosis is challenging, especially in resource-poor settings, and although cure may be possible, it requires prolonged treatment with less effective, more toxic and more expensive therapies. The mortality rate from MDR-TB is high and that from XDR-TB higher still. Vaccines BCG (the Calmette–Guérin bacillus), a live attenuated vaccine derived from M. bovis, is the most established TB vaccine. It is administered by intradermal injection and is highly immunogenic. BCG appears to be effective in preventing disseminated disease, including tuberculous meningitis, in children, but its efficacy in adults is inconsistent and new vaccines are

urgently needed. Current vaccination policies vary worldwide according to incidence and health-care resources, but usually target children and other high-risk individuals. BCG is very safe, with the occasional complication of local abscess formation. It should not be administered to those who are immunocompromised (e.g. by HIV) or pregnant. Prognosis Following successful completion of chemotherapy, cure should be anticipated in the majority of patients. There is a small (< 5%) and unavoidable risk of relapse. Most relapses occur within 17.55 Site-specific opportunistic mycobacterial disease Pulmonary • M. xenopi • M. kansasii • M. malmoense • MAC • M. abscessus (in cystic fibrosis) Lymph node • MAC • M. malmoense • M. fortuitum • M. chelonei Soft tissue/skin • M. leprae • M. ulcerans (prevalent in Africa, northern Australia and South-east Asia) • M. marinum • M. fortuitum • M. chelonae Disseminated • MAC (HIV-associated) • M. haemophilum • M. genavense • M. fortuitum • M. chelonae • BCG (BCG = bacille Calmette–Guérin; MAC = Mycobacterium avium complex – M. scrofulaceum, M. intracellulare and M. avium) 17.54 Factors contributing to the emergence of drug-resistant tuberculosis • Drug shortages • Poor-quality drugs • Lack of appropriate supervision • Transmission of drug-resistant strains • Prior antituberculosis treatment • Treatment failure (smear-positive at 5 months)

 glucocorticoids; a 4-month trial is usually recommended to assess its efficacy. The use of specific anti-IgE monoclonal antibodies is under consideration. Exacerbations, particularly when associated with new chest X-ray changes, should be treated promptly with prednisolone (40–60 mg daily) and physiotherapy. If persistent lobar collapse occurs, bronchoscopy (usually under general anaesthetic) should be performed to remove impacted mucus and ensure prompt re-inflation. Chronic pulmonary aspergillosis The term chronic pulmonary aspergillosis (CPA) encompasses simple aspergilloma, chronic cavitary pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis, Aspergillus nodule and semi-invasive aspergillosis. They are uncommon conditions and challenging to diagnose and treat. Simple aspergilloma Cavities left by diseases such as TB or by damaged bronchi provide favourable conditions in which inhaled Aspergillus may lodge and germinate. At the earliest stage, CT scanning may identify an irregular mucosal wall and, as fungal growth progresses, this finally collapses into the cavity, forming a fungal ball that may be identified on imaging (Fig. 17.44). Simple aspergillomas are often asymptomatic. They can, however, give rise to a variety of non-specific symptoms, such as lethargy and weight loss, and may cause recurrent haemoptysis, which may be life-threatening. Fig. 17.43 Branching Aspergillus hyphae seen in allergic bronchopulmonary aspergillosis. The figure shows the use of calcofluor white, a non-specific fluorochrome stain that binds to fungi and fluoresces when exposed to light of the appropriate wavelength. Aspergillus fumigatus was subsequently grown on culture. Courtesy of Mr T. Russell and Dr M. Hanson, Department of Microbiology, NHS Lothian. 17.58 Features of allergic bronchopulmonary aspergillosis • Asthma (in the majority of cases) • Proximal bronchiectasis (inner two-thirds of chest CT field) • Positive skin test to an extract of Aspergillus fumigatus • Elevated total serum immunoglobulin E (IgE) > 417 kU/L (1000 ng/mL) • Elevated A. fumigatus-specific IgE or IgG • Peripheral blood eosinophilia > 0.5 × 109/L • Presence or history of chest X-ray abnormalities • Fungal hyphae of A. fumigatus on microscopic examination of sputum 17.57 Classification of bronchopulmonary aspergillosis • Allergic bronchopulmonary aspergillosis (asthmatic pulmonary eosinophilia) • Extrinsic allergic alveolitis (Aspergillus clavatus) • Intracavitary aspergilloma • Invasive pulmonary aspergillosis • Chronic and subacute pulmonary aspergillosis 17.56 Factors predisposing to pulmonary fungal disease Systemic factors • Haematological malignancy • HIV • Diabetes mellitus • Chronic alcoholism • Radiotherapy • Glucocorticoids, cytotoxic chemotherapy, biologic therapies and other immunosuppressant medication Local factors • Tissue damage by suppuration or necrosis • Alteration of normal bacterial flora by antibiotic therapy Respiratory diseases caused by fungi The majority of fungi encountered by humans are harmless saprophytes but in certain circumstances (Box 17.56) some species may cause disease by infecting human tissue, promoting damaging allergic reactions or producing toxins. 'Mycosis' is the term applied to disease caused by fungal infection. The conditions associated with Aspergillus species are listed in Box 17.57. Allergic bronchopulmonary aspergillosis Allergic bronchopulmonary aspergillosis (ABPA) occurs as a result of a hypersensitivity reaction to germinating fungal spores in the airway wall. The condition may complicate the course of asthma and cystic fibrosis, and is a recognised cause of pulmonary eosinophilia (p. 611). The prevalence of ABPA is approximately 1–2% in asthma and 5–10% in CF. A variety of human leucocyte antigens (HLAs) convey both an increased and a decreased risk of developing the condition, suggesting that genetic susceptibility is important. Clinical features Clinical features depend on the stage of the disease. Common manifestations in the early phases include fever, breathlessness, cough productive of bronchial casts and worsening of asthmatic symptoms. The appearance of radiographic infiltrates may cause ABPA to be mistaken for pneumonia but the diagnosis may also be suggested by segmental or lobar collapse on chest X-rays of patients whose asthma symptoms are stable. Diagnostic features are shown in Box 17.58 and the typical Aspergillus hyphae in Figure 17.43. If bronchiectasis develops, the symptoms and complications of that disease often overshadow those of asthma. Management ABPA is generally considered an indication for regular therapy with low-dose oral glucocorticoids (prednisolone 7.5–10 mg daily) with the aim of suppressing the immunopathological responses and preventing progressive tissue damage. In some patients, itraconazole (400 mg/day) facilitates a reduction in oral

The clinical and radiological picture is similar to CCPA but lung biopsy demonstrates invasion of lung tissue by hyphae. The development of SIA is favoured by mild immunocompromise and should be suspected in patients with diabetes mellitus, malnutrition or alcoholism, or with advanced age and in prolonged glucocorticoid use. It is also seen in the presence of COPD, non-tuberculous mycobacteria or HIV infection. SIA should be treated in a similar manner to invasive pulmonary aspergillosis. Invasive pulmonary aspergillosis Invasive pulmonary aspergillosis (IPA) is most commonly a complication of profound neutropenia caused by drugs (especially immunosuppressive agents) and/or disease (Box 17.59). Clinical features Acute IPA causes a severe necrotising pneumonia and must be considered in any immunocompromised patient who develops fever, new respiratory symptoms (particularly pleural pain or haemoptysis) or a pleural rub. Invasion of pulmonary vessels causes thrombosis and infarction, and systemic spread may occur Fig. 17.44 Computed tomogram of aspergilloma in the left upper lobe. The rounded fungal ball is separated from the wall of the cavity by an 'air crescent' (arrow). Fig. 17.45 Chronic pulmonary aspergillosis. A The chest X-ray shows pleural thickening with loss of lung volume at the left apex (arrow). B High-resolution computed tomography reveals multiple small cavities and pleural thickening with an aspergilloma and surrounding air crescent (arrow) in one of the cavities. Courtesy of Professor David Denning, National Aspergillosis Centre, Manchester, UK. A B The typical radiological picture is invariably accompanied by elevated serum precipitins/IgG to A. fumigatus. Sputum microscopy typically demonstrates scanty hyphal fragments and is usually positive on culture. Less than half exhibit skin hypersensitivity to extracts of A. fumigatus. Rarely, other filamentous fungi can cause intracavity mycetoma and are identified by culture. Asymptomatic cases do not require treatment but haemoptysis should be controlled by surgery. Tranexamic acid or bronchial artery embolisation may provide a bridge to surgery or palliate haemoptysis when surgery is not possible. Instillation of antifungal agents, such as amphotericin B, via a catheter placed into the cavity has been reported but is rarely used in the UK. Chronic cavitary pulmonary aspergillosis and chronic fibrosing pulmonary aspergillosis The features of chronic cavitary pulmonary aspergillosis (CCPA) include cough (with or without haemoptysis), weight loss, anorexia and fatigue over months or years, with associated fever, night sweats and elevated inflammatory markers. Radiological features include thick-walled cavities (predominantly apical), pulmonary infiltrates and pleural thickening (Fig. 17.45). Once again, diagnosis rests on a combination of radiological examination, histopathology, isolation of fungus from the respiratory tract and detection of Aspergillus IgG in serum. Treatment usually involves prolonged courses of itraconazole or voriconazole. Cure is unusual and the most frequent pattern is chronic relapse/remission with gradual deterioration. Surgical intervention is fraught with complications and should be avoided. Many patients are malnourished and require nutritional support. Glucocorticoids should be avoided. As CCPA progresses, fibrotic destruction of the lung results and the condition may then be referred to as chronic fibrosing pulmonary aspergillosis (CFPA). Aspergillus nodule The formation of one or more nodules is a less common manifestation of Aspergillus infection. In addition to lung cancer, the Aspergillus nodule may mimic TB but cavitation is unusual. Cryptococcosis or coccidioidomycosis should be considered in areas where these conditions are endemic. Subacute invasive aspergillosis Subacute invasive aspergillosis (SIA) was previously referred to as chronic necrotising or semi-invasive pulmonary aspergillosis.

 but the majority of patients are too ill for invasive tests, such as bronchoscopy or lung biopsy. Other investigations include detection of Aspergillus cell-wall components (galactomannan and β-1,3-glucan) in blood or BAL fluid and Aspergillus DNA by PCR. Diagnosis is often inferred from a combination of features (Box 17.60). Management and prevention IPA carries a high mortality rate, especially if treatment is delayed. The drug of choice is voriconazole. Second-line agents include liposomal amphotericin, caspofungin, posaconazole and isavuconazole. Response may be assessed clinically, radiologically and serologically (by estimation of the circulating galactomannan level). Recovery is dependent on immune reconstitution, which may be accompanied by enlargement and/or cavitation of pulmonary nodules. Patients at risk of Aspergillus (and other fungal infections) should be managed in rooms with high-efficiency particulate air (HEPA) filters and laminar airflow. In areas with high spore counts, patients are advised to wear a mask if venturing outside their hospital room. Posaconazole (200 mg 3 times daily) or itraconazole (200 mg/ day) may be prescribed for primary prophylaxis, and patients with a history of definite or probable IPA should be considered for secondary prophylaxis before further immunosuppression. Other fungal infections Mucormycosis (p. 303) may present with a pulmonary syndrome that is clinically indistinguishable from acute IPA. Diagnosis relies on histopathology (where available) and/or culture of the organism from diseased tissue. The principles of treatment are as for other forms of mucormycosis: correction of predisposing factors, antifungal therapy with high-dose lipid amphotericin B or posaconazole (second line), and surgical débridement. The endemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis and Emergomyces infection) and cryptococcosis are discussed on pages 302–304. Pneumocystis jirovecii pneumonia is described on page 318. Tumours of the bronchus and lung Lung cancer is the most common cause of death from cancer worldwide, causing 1.59 million deaths per year (Box 17.61). Tobacco use is the major preventable cause. Just as tobacco use and cancer rates are falling in some developed countries, both smoking and lung cancer are rising in Eastern Europe and in many developing countries. The great majority of tumours in the lung are primary lung cancers and, in contrast to many other tumours, the prognosis remains poor, with fewer than 30% of patients surviving at 1 year and 6–8% at 5 years. to the brain, heart, kidneys and others organs. Tracheobronchial aspergillosis involvement is characterised by the formation of fungal plaques and ulceration. HRCT characteristically shows macronodules (usually ≥ 1 cm), which may be surrounded by a 'halo' of intermediate attenuation if captured early (< 5 days). Culture or histopathological evidence of Aspergillus in diseased tissues provides a definitive diagnosis 17.59 Risk factors for invasive aspergillosis • Neutropenia: risk related to duration and degree • Solid organ or allogeneic stem cell transplantation • Prolonged high-dose glucocorticoid therapy • Leukaemia and other haematological malignancies • Cytotoxic chemotherapy • Advanced HIV disease • Severe chronic obstructive pulmonary disease • Critically ill patients on intensive care units • Chronic granulomatous disease 17.61 The burden of lung cancer • 1.8 million new cases worldwide each year • Most common cancer in men • Rates rising in women: Female lung cancer deaths outnumber male in some Nordic countries Has overtaken breast cancer in several countries • More than a threefold increase in deaths since 1950 • More than 50% of cases have metastatic disease at diagnosis 17.60 Criteria for the diagnosis of probable invasive pulmonary aspergillosis Host factors • Recent history of neutropenia (< 0.5 × 109/L for ≥ 10 days) temporally related to the onset of fungal disease • Recipient of allogeneic stem cell transplant • Prolonged use of glucocorticoids (average minimum 0.3 mg/kg/day prednisolone or equivalent) for > 3 weeks (excludes allergic bronchopulmonary aspergillosis) • Treatment with other recognised T-cell immune suppressants, such as ciclosporin, tumour necrosis factor, alpha-blockers, specific monoclonal antibodies (e.g. alemtuzumab) or nucleoside analogues during the last 90 days • Inherited severe immune deficiency, e.g. chronic granulomatous disease or severe combined immune deficiency (p. 79) Clinical criteria1 • The presence of one of the following on CT: Dense, well-circumscribed lesion(s) with or without a halo sign Air crescent sign Cavity Tracheobronchitis • Tracheobronchial ulceration, nodule, pseudomembrane, plaque or eschar seen on bronchoscopy Mycological criteria • Mould in sputum, BAL fluid or bronchial brush, indicated by one of the following: Recovery of fungal elements indicating a mould of Aspergillus Recovery by culture of a mould of Aspergillus • Indirect tests (detection of antigen or cell wall constituents) Galactomannan antigen in plasma, serum or BAL fluid β-1,3-glucan detected in serum (detects other species of fungi, as well as Aspergillus)2 (BAL = bronchoalveolar lavage) Adapted from De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organisation for Research and Treatment of Cancer/Mycoses Study Group. Clin Infect Dis 2008; 46:1813–1821. 1Must be consistent with the mycological findings and temporally related to current episode. 2May be useful as a preliminary screening tool for invasive aspergillosis.

In women, smoking prevalence and deaths from lung cancer continue to increase, and more women now die of lung cancer than breast cancer in the USA and the UK. Pathology Lung cancers arise from the bronchial epithelium or mucous glands. The common cell types are listed in Box 17.62. When the tumour occurs in a large bronchus, symptoms arise early but tumours originating in a peripheral bronchus can grow very large without producing symptoms, resulting in delayed diagnosis. Peripheral squamous tumours may undergo central necrosis and cavitation and may resemble a lung abscess on X-ray (Fig. 17.47). Lung cancer may involve the pleura directly or by lymphatic spread and may extend into the chest wall, invading the intercostal nerves or the brachial plexus and causing pain. Lymphatic spread to mediastinal and supraclavicular lymph nodes often occurs before diagnosis. Blood-borne metastases occur most commonly in liver, bone, brain, adrenals and skin. Even a small primary tumour may cause widespread metastatic deposits and this is a particular characteristic of small-cell lung cancers. Clinical features Lung cancer presents in many different ways, reflecting local, metastatic or paraneoplastic tumour effects. Cough This is the most common early symptom. It is often dry but secondary infection may cause purulent sputum. A change in the character of a smoker's cough, particularly if associated with other new symptoms, should always raise suspicion of lung cancer. Haemoptysis Haemoptysis is common, especially with central bronchial tumours. Although it may be caused by bronchitic Fig. 17.46 Mortality trends from lung cancer in UK, 1979–2013, by age and year of death. A Males. B Females. Note the decline in mortality from lung cancer in men and increase in mortality in older women towards the end of this period, reflecting changes in smoking habits. From Cancer Research UK: http://www.cancerresearchuk.org/health-professional/ cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality. Accessed January 2017. 25–49 50–59 60–69 70–79 80+

Year of diagnosis

Rate per 100000 1979–81 1980–82 1981–83 1982–84 1983–85 1984–86 1985–87 1986–88 1987–89 1988–90 1989–91 1990–92 1991–93 1992–94 1993–95 1994–96 1995–97 1996–98 1997–99 1998–00 1999–01 2000–02 2001–03 2002–04 2003–05 2004–06 2005–07 2006–08 2007–09 2008–10 2009–11 2010–12 2011–13 A

25–49 50–59 60–69 70–79 80+

Year of diagnosis

Rate per 100000 1979–81 1980–82 1981–83 1982–84 1983–85 1984–86 1985–87 1986–88 1987–89 1988–90 1989–91 1990–92 1991–93 1992–94 1993–95 1994–96 1995–97 1996–98 1997–99 1998–00 1999–01 2000–02 2001–03 2002–04 2003–05 2004–06 2005–07 2006–08 2007–09 2008–10 2009–11 2010–12 2011–13 B 17.62 Common cell types in lung cancer Cell type % Adenocarcinoma 35–40 Squamous 25–30 Small-cell

Large-cell 10–15 Primary tumours of the lung Aetiology Cigarette smoking is by far the most important cause of lung cancer. It is thought to be directly responsible for at least 90% of cases, the risk being proportional to the amount smoked and to the tar content of cigarettes. The death rate from the disease in heavy smokers is 40 times that in non-smokers. Risk falls slowly after smoking cessation but remains above that in non-smokers for many years. It is estimated that 1 in 2 smokers dies from a smoking-related disease, about half in middle age. The effect of 'passive' smoking is more difficult to quantify but is currently thought to be a factor in 5% of all lung cancer deaths. Exposure to naturally occurring radon is another risk. The incidence of lung cancer is slightly higher in urban than in rural dwellers, which may reflect differences in atmospheric pollution (including tobacco smoke) or occupation, since a number of industrial materials are associated with lung cancer (p. 1320). In recent years, the strong link between smoking and ill health has led many governments to legislate against smoking in public places, and smoking prevalence and some smoking-related diseases are already declining in these countries (p. 94). Lung cancer The incidence of lung cancer increased dramatically during the 20th century as a direct result of the tobacco epidemic (Fig. 17.46). Fig. 17.47 Large cavitated lung cancer in left lower lobe.

 Breathlessness Breathlessness may be caused by collapse or pneumonia, or by tumour causing a large pleural effusion or compressing a phrenic nerve and leading to diaphragmatic paralysis. Pain and nerve entrapment Pleural pain may indicate malignant pleural invasion, although it can occur with distal infection. Intercostal nerve involvement causes pain in the distribution of a thoracic dermatome. Cancer in the lung apex may cause Horner's syndrome (ipsilateral partial ptosis, enophthalmos, miosis and hypohidrosis of the face; p. 1091) due to involvement of the sympathetic nerves to the eye at or above the stellate ganglion. Pancoast's syndrome (pain in the inner aspect of the arm, sometimes with small muscle wasting in the hand) indicates malignant destruction of the T1 and C8 roots in the lower part of the brachial plexus by an apical lung tumour. Mediastinal spread Involvement of the oesophagus may cause dysphagia. If the pericardium is invaded, arrhythmia or pericardial effusion may occur. Superior vena cava obstruction by malignant nodes causes suffusion and swelling of the neck and face, conjunctival oedema, headache and dilated veins on the chest wall and is most commonly due to lung cancer. Involvement of the left recurrent laryngeal nerve by tumours at the left hilum causes vocal cord paralysis, voice alteration and a 'bovine' cough (lacking the normal explosive character). Supraclavicular lymph nodes may be palpably enlarged or identified using ultrasound; if so, a needle aspirate may provide a simple means of cytological diagnosis. Metastatic spread This may lead to focal neurological defects, epileptic seizures, personality change, jaundice, bone pain or skin nodules. Lassitude, anorexia and weight loss usually indicate metastatic spread. Finger clubbing Overgrowth of the soft tissue of the terminal phalanx, leading to increased nail curvature and nail bed fluctuation, is often seen (p. 546). Hypertrophic pulmonary osteoarthropathy (HPOA) This is a painful periostitis of the distal tibia, fibula, radius and ulna, with local tenderness and sometimes pitting oedema over the anterior shin. X-rays reveal subperiosteal new bone formation. While Fig. 17.48 Collapse of the right lung: effects on neighbouring structures. A Chest X-ray. B The typical abnormalities are highlighted. A B Compensatory emphysema of left lung Site of obstruction of right main bronchus Displacement of trachea, heart and other mediastinal structures to the right Position of elevated right hemidiaphragm (not seen on chest X-ray) 17.63 Causes of large bronchus obstruction Common • Lung cancer or adenoma • Enlarged tracheobronchial lymph nodes (malignant or tuberculous) • Inhaled foreign bodies (especially right lung) • Bronchial casts or plugs consisting of inspissated mucus or blood clot (especially asthma, cystic fibrosis, haemoptysis, debility) • Collections of mucus or mucopus retained in the bronchi as a result of ineffective expectoration (especially postoperative following abdominal surgery) Rare • Aortic aneurysm • Giant left atrium • Pericardial effusion • Congenital bronchial atresia • Fibrous bronchial stricture (e.g. following tuberculosis or bronchial surgery/lung transplant) infection, haemoptysis in a smoker should always be investigated to exclude a lung cancer. Occasionally, central tumours invade large vessels, causing sudden massive haemoptysis that may be fatal. Bronchial obstruction This is another common presentation. The clinical and radiological manifestations (Figs 17.48 and 17.5, p. 552; Box 17.63) depend on the site and extent of the obstruction, any secondary infection and the extent of coexisting lung disease. Complete obstruction causes collapse of a lobe or lung, with breathlessness, mediastinal displacement and dullness to percussion with reduced breath sounds. Partial bronchial obstruction may cause a monophonic, unilateral wheeze that fails to clear with coughing, and may also impair the drainage of secretions to cause pneumonia or lung abscess as a presenting problem. Pneumonia that recurs at the same site or responds slowly to treatment, particularly in a smoker, should always suggest an underlying lung cancer. Stridor (a harsh inspiratory noise) occurs when the larynx, trachea or a main bronchus is narrowed by the primary tumour or by compression from malignant enlargement of the subcarinal and paratracheal lymph nodes.

for invasive investigation, sputum cytology may reveal malignant cells, although the yield is low. In patients with pleural effusions, pleural aspiration and biopsy is the preferred investigation. Where facilities exist, thoracoscopy increases yield by allowing targeted biopsies under direct vision. In patients with metastatic disease, the diagnosis can often be confirmed by needle aspiration or biopsy of affected lymph nodes, skin lesions, liver or bone marrow. most frequently associated with lung cancer, HPOA can occur with other tumours. Non-metastatic extrapulmonary effects (Box 17.64) The syndrome of inappropriate antidiuretic hormone secretion (SIADH, p. 357) and ectopic adrenocorticotrophic hormone secretion (p. 670) are usually associated with small-cell lung cancer. Hypercalcaemia may indicate malignant bone destruction or production of hormone-like peptides by a tumour. Associated neurological syndromes may occur with any type of lung cancer. Investigations The main aims of investigation are to confirm the diagnosis, establish the histological cell type and define the extent of the disease. Imaging Lung cancer produces a range of appearances on chest X-ray, from lobar collapse (see Fig. 17.5, p. 552) to mass lesions, effusion or malignant rib destruction (Fig. 17.49). CT should be performed early, as it may reveal mediastinal or metastatic spread and is helpful for planning biopsy procedures, e.g. in establishing whether a tumour is accessible by bronchoscopy or percutaneous CT-guided biopsy. Biopsy and histopathology Over half of primary lung tumours can be visualised and sampled directly by biopsy and brushing using a flexible bronchoscope. Bronchoscopy also allows an assessment of operability, from the proximity of central tumours to the main carina (Fig. 17.50). For tumours that are too peripheral to be accessible by bronchoscope, the yield of 'blind' bronchoscopic washings and brushings from the radiologically affected area is low and percutaneous needle biopsy under CT or ultrasound guidance is a more reliable way to obtain a histological diagnosis. There is a small risk of iatrogenic pneumothorax, which may preclude the procedure if there is extensive coexisting COPD. In patients with a peripheral tumour and enlarged hilar or paratracheal lymph nodes on CT, bronchoscopy with EBUS-guided node sampling may allow both diagnosis and staging. In those who are unfit Fig. 17.49 Common radiological presentations of lung cancer. (1) Unilateral hilar enlargement suggests a central tumour or hilar glandular involvement. However, a peripheral tumour in the apex of a lower lobe can look like an enlarged hilar shadow on the posteroanterior X-ray. (2) Peripheral pulmonary opacity (p. 560) is usually irregular but well circumscribed, and may contain irregular cavitation. It can be very large. (3) Lung, lobe or segmental collapse is usually caused by tumour occluding a proximal bronchus. Collapse may also be due to compression of a bronchus by enlarged lymph glands. (4) Pleural effusion usually indicates tumour invasion of the pleural space or, very rarely, infection in collapsed lung tissue distal to a lung cancer. (5) Paratracheal lymphadenopathy may cause widening of the upper mediastinum. (6) A malignant pericardial effusion may cause enlargement of the cardiac shadow. (7) A raised hemidiaphragm may be caused by phrenic nerve palsy. Screening will show paradoxical upward movement when the patient sniffs. (8) Osteolytic rib destruction indicates direct invasion of the chest wall or metastatic spread.

17.64 Non-metastatic extrapulmonary manifestations of lung cancer Endocrine (Ch. 18) • Inappropriate antidiuretic hormone (ADH, vasopressin) secretion, causing hyponatraemia • Ectopic adrenocorticotrophic hormone secretion • Hypercalcaemia due to secretion of parathyroid hormone-related peptides • Carcinoid syndrome (p. 678) • Gynaecomastia Neurological (Ch. 25) • Polyneuropathy • Myelopathy • Cerebellar degeneration • Myasthenia (Lambert–Eaton syndrome, p. 1142) Other • Digital clubbing • Hypertrophic pulmonary osteoarthropathy • Nephrotic syndrome • Polymyositis and dermatomyositis • Eosinophilia Fig. 17.50 Bronchoscopic view of a lung cancer. There is distortion of mucosal folds, partial occlusion of the airway lumen and abnormal tumour tissue.

 Radiotherapy While much less effective than surgery, radical radiotherapy can offer long-term survival in selected patients with localised disease in whom comorbidity precludes surgery. Radical radiotherapy is usually combined with chemotherapy when lymph nodes are involved (stage III). Highly targeted (stereotactic) radiotherapy may be given in 3–5 treatments for small lesions. The greatest value of radiotherapy, however, is in the palliation of distressing complications, such as superior vena cava obstruction, recurrent haemoptysis, and pain caused by chest wall invasion or by skeletal metastatic deposits. Obstruction of the trachea and main bronchi can also be relieved temporarily. Radiotherapy can be used in conjunction with chemotherapy in the treatment of small-cell carcinoma and is particularly efficient at preventing the development of brain metastases in patients who have had a complete response to chemotherapy (p. 1331). Chemotherapy The treatment of small-cell carcinoma with combinations of cytotoxic drugs, sometimes with radiotherapy, can increase median survival from 3 months to well over a year. The use of combinations of chemotherapeutic drugs requires considerable skill and should be overseen by multidisciplinary teams of clinical oncologists and specialist nurses. Combination chemotherapy leads to better outcomes than single-agent treatment. Regular cycles of therapy, including combinations of intravenous cyclophosphamide, doxorubicin and vincristine or intravenous cisplatin and etoposide, are commonly used. In NSCLC chemotherapy is less effective, though platinumbased chemotherapy regimens offer 30% response rates and a modest increase in survival, and are widely used. Some non-small-cell lung tumours, particularly adenocarcinomas in non-smokers, carry detectable mutations, e.g. in the epidermal growth factor receptor (EGFR) gene. Tyrosine kinase inhibitors, such as erlotinib and monoclonal antibodies to EGFR (e.g. bevacizumab), show improved treatment responses in metastatic Staging to guide treatment The propensity of small-cell lung cancer to metastasise early means these patients are usually not suitable for surgical intervention. In non-small-cell lung cancer (NSCLC), treatment and prognosis are determined by disease extent, so careful staging is required. CT is used early to detect obvious local or distant spread. Enlarged upper mediastinal nodes may be sampled using an EBUSequipped bronchoscope or by mediastinoscopy. Nodes in the lower mediastinum can be sampled through the oesophageal wall using endoscopic ultrasound. Combined CT and whole-body PET (see Fig. 17.6, p. 553) is commonly used to detect occult but metabolically active metastases. Head CT, radionuclide bone scanning, liver ultrasound and bone marrow biopsy are generally reserved for patients with clinical, haematological or biochemical evidence of tumour spread to these sites. Information on tumour size and nodal and metastatic spread is then collated to assign the patient to one of seven staging groups that determine optimal management and prognosis (Fig. 17.51). Detailed physiological testing is required to assess whether respiratory and cardiac function is sufficient to allow aggressive treatment. Management Surgical resection carries the best hope of long-term survival but some patients treated with radical radiotherapy and chemotherapy also achieve prolonged remission or cure. In over 75% of cases, treatment with the aim of cure is not possible or is inappropriate due to extensive spread or comorbidity. Such patients are offered palliative therapy and best supportive care. Radiotherapy and, in some cases, chemotherapy can relieve symptoms. Surgical treatment Accurate pre-operative staging, coupled with improvements in surgical and post-operative care, now offers 5-year survival rates of over 75% in stage I disease (N0, tumour confined within visceral pleura) and 55% in stage II disease, which includes resection in patients with ipsilateral peribronchial or hilar node involvement. Fig. 17.51 Tumour stage and 5-year survival in non-small-cell lung cancer. The figure shows the relationship between tumour extent (size, lymph node status and metastases) and prognosis (% survival at 5 years for each clinical stage). Based on data from Detterbeck FC, Boffa DJ, Kim AW, Tanoue T. The eighth edition lung cancer stage classification. Chest 2017; 151:193–203. N2 (Ipsilateral mediastinal or subcarinal) N1 (Ipsilateral hilar) N0 (None) T1a (≤1 cm) T1b (>1 to ≤2 cm) T1c (>2 to ≤3 cm) T2a (>3 to ≤4 cm) T2b (>4 cm to ≤5 cm) T3 (>5 cm) M1a Lung metastasis/effusion M1b Single extrathoracic metastasis M1c Multiple extrathoracic metastases T4 (>7 cm or invading heart, vessels, oesophagus, carina etc.) IA1 (92%) IIB (53%) IIIA (36%) IVA (10%) IVB (0%) IIIB (26%) IIIB (26%) IIIC (13%) IIIA (36%) IA2 (83%) IA3 (77%) IB (68%) IIA (60%) IIB (53%) N3 (Contralateral or supraclavicular) Lymph node spread Tumour stage

other sarcomas. These secondary deposits are usually multiple and bilateral. Often there are no respiratory symptoms and the diagnosis is incidental on X-ray. Breathlessness may occur if a considerable amount of lung tissue has been replaced by metastatic tumour. Endobronchial deposits are uncommon but can cause haemoptysis and lobar collapse. Lymphatic infiltration may develop in carcinoma of the breast, stomach, bowel, pancreas or bronchus. ‘Lymphangitic carcinomatosis’ causes severe, rapidly progressive breathlessness with marked hypoxaemia. The chest X-ray shows diffuse pulmonary shadowing radiating from the hilar regions, often with septal lines, and CT shows characteristic polygonal thickened interlobular septa. Palliation of breathlessness with opiates may help (p. 1353). Tumours of the mediastinum Figure 17.52 shows the major compartments of the mediastinum and Box 17.66 lists likely causes of a mediastinal mass. NSCLC and EGFR mutations, and similar approaches are being developed to target other known genetic abnormalities. In NSCLC there is some evidence that chemotherapy given before surgery may increase survival and can effectively ‘down-stage’ disease with limited nodal spread. Post-operative chemotherapy is now proven to enhance survival rates when operative samples show nodal involvement by tumour. Nausea and vomiting are common side-effects of chemotherapy and are best treated with 5-HT3 receptor antagonists (p. 1353). Laser therapy and stenting Palliation of symptoms caused by major airway obstruction can be achieved in selected patients using bronchoscopic laser treatment to clear tumour tissue and allow re-aeration of collapsed lung. The best results are achieved in tumours of the main bronchi. Endobronchial stents can be used to maintain airway patency in the face of extrinsic compression by malignant nodes. General aspects of management The best outcomes are obtained when lung cancer is managed in specialist centres by multidisciplinary teams, including oncologists, thoracic surgeons, respiratory physicians and specialist nurses. Effective communication, pain relief and attention to diet are important. Lung tumours can cause clinically significant depression and anxiety, and these may need specific therapy. The management of non-metastatic endocrine manifestations is described in Chapter 18. When a malignant pleural effusion is present, an attempt should be made to drain the pleural cavity using an intercostal drain; provided that the lung fully re-expands, pleurodesis with a sclerosing agent, such as talc, should be performed to prevent recurrent effusion. Prognosis The overall prognosis in lung cancer is very poor, 70% of patients dying within a year of diagnosis and only 6–8% surviving 5 years after diagnosis. The best prognosis is with well-differentiated squamous cell tumours that have not metastasised and are amenable to surgical resection. The clinical features and prognosis of some less common tumours are given in Box 17.65. Secondary tumours of the lung Blood-borne metastatic deposits in the lungs may be derived from many primary carcinomas, in particular breast, kidney, uterus, ovary, testes and thyroid, and also from osteogenic and 17.65 Rare types of lung tumour Tumour Status Histology Typical presentation Prognosis Adenosquamous carcinoma Malignant Tumours with areas of unequivocal squamous and adeno-differentiation Peripheral or central lung mass Stage-dependent Neuro-endocrine (carcinoid) tumour (p. 678) Low-grade malignant Neuro-endocrine differentiation Bronchial obstruction, cough 95% 5-year survival with resection Bronchial gland adenoma Benign Salivary gland differentiation Tracheobronchial irritation/obstruction Local resection curative Bronchial gland carcinoma Low-grade malignant Salivary gland differentiation Tracheobronchial irritation/obstruction Local recurrence Hamartoma Benign Mesenchymal cells, cartilage Peripheral lung nodule Local resection curative Bronchoalveolar carcinoma Malignant Tumour cells line alveolar spaces Alveolar shadowing, productive cough Variable, worse if multifocal 17.66 Causes of a mediastinal mass Superior mediastinum • Retrosternal goitre • Persistent left superior vena cava • Prominent left subclavian artery • Thymic tumour • Dermoid cyst • Lymphoma • Aortic aneurysm Anterior mediastinum • Retrosternal goitre • Dermoid cyst • Thymic tumour • Lymphoma • Aortic aneurysm • Germ cell tumour • Pericardial cyst • Hiatus hernia through the diaphragmatic foramen of Morgagni Posterior mediastinum • Neurogenic tumour • Paravertebral abscess • Oesophageal lesion • Aortic aneurysm • Foregut duplication Middle mediastinum • Lung cancer • Lymphoma • Sarcoidosis • Bronchogenic cyst • Hiatus hernia

604 • RESPIRATORY MEDICINE Investigations A benign mediastinal tumour generally appears on chest X-ray as a sharply circumscribed mediastinal opacity encroaching on one or both lung fields (Fig. 17.53). CT (or MRI) is the investigation of choice for mediastinal tumours (e.g. see Fig. 18.12, p. 648). A malignant mediastinal tumour seldom has a clearly defined margin and often presents as a general broadening of the mediastinum. Bronchoscopy may reveal a primary lung cancer causing mediastinal lymphadenopathy. EBUS may be used to guide sampling of peribronchial masses. The posterior mediastinum can be imaged and biopsied via the oesophagus using endoscopic ultrasound (p. 553). Mediastinoscopy under general anaesthetic can be used to visualise and biopsy masses in the superior and anterior mediastinum but surgical exploration of the chest, with removal of part or all of the tumour, is often required to obtain a histological diagnosis. Benign tumours and cysts in the mediastinum are often diagnosed when a chest X-ray is undertaken for some other reason. In general, they do not invade vital structures but may cause symptoms by compressing the trachea or the superior vena cava. A dermoid cyst may very occasionally rupture into a bronchus. Malignant mediastinal tumours are distinguished by their power to invade, as well as compress, surrounding structures. As a result, even a small malignant tumour can produce symptoms, although, more commonly, the tumour has attained a considerable size before this happens (Box 17.67). The most common cause is mediastinal lymph node metastasis from lung cancer but lymphomas, leukaemia, malignant thymic tumours and germ-cell tumours can cause

similar features. Aortic and innominate aneurysms have destructive features resembling those of malignant mediastinal tumours. Fig. 17.52 The divisions of the mediastinum. (1) Superior mediastinum. (2) Anterior mediastinum. (3) Middle mediastinum. (4) Posterior mediastinum. Sites of the more common mediastinal tumours are also illustrated. From Johnson N McL. Respiratory medicine. Oxford: Blackwell Science; 1986.

Lower border of 4th thoracic vertebra Lymphoid masses Neurogenic tumour Retrosternal thyroid Thymus Lower border of manubrium sterni Teratoma Dermoid Pleuropericardial cyst 17.67 Clinical features of malignant mediastinal invasion Trachea and main bronchi • Stridor, breathlessness, cough, pulmonary collapse Oesophagus • Dysphagia, oesophageal displacement or obstruction on barium swallow examination Phrenic nerve • Diaphragmatic paralysis Left recurrent laryngeal nerve • Paralysis of left vocal cord with hoarseness and 'bovine' cough Sympathetic trunk • Horner's syndrome Superior vena cava • SVC obstruction: non-pulsatile distension of neck veins, subconjunctival oedema, and oedema and cyanosis of head, neck, hands and arms; dilated anastomotic veins on chest wall Pericardium • Pericarditis and/or pericardial effusion Fig. 17.53 Intrathoracic goitre (arrows) extending from right upper mediastinum.

They often present with cough, which is typically dry and distressing, and breathlessness, which is often insidious in onset but thereafter relentlessly progressive. Physical examination reveals the presence of inspiratory crackles and in many cases digital clubbing develops. Pulmonary function tests typically show a restrictive ventilatory defect in the presence of small lung volumes and reduced gas transfer. The typical radiographic findings include, in the earliest stages, ground glass and reticulonodular shadowing, with progression to honeycomb cysts and traction bronchiectasis. While these appearances may be seen on a 'plain' chest X-ray, they are most easily appreciated on HRCT, which has assumed a central role in the evaluation of DPLD (Fig. 17.54). The current classification is shown in Figure 17.55 and the potential differential diagnoses in Box 17.69. Idiopathic interstitial pneumonias The idiopathic interstitial pneumonias represent a major subgroup of DPLD that are grouped together as a result of their unknown aetiology (Box 17.70). They are often distinguished by the predominant histological pattern on tissue biopsy; hence they are frequently referred to by their pathological description, e.g. usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP). The most important of these is idiopathic pulmonary fibrosis. Idiopathic pulmonary fibrosis Idiopathic pulmonary fibrosis is defined as a progressive fibrosing interstitial pneumonia of unknown cause, occurring in adults and associated with the histological or radiological pattern of UIP. Important differentials include fibrosing diseases caused Management Benign mediastinal tumours should be removed surgically because most produce symptoms sooner or later. Cysts may become infected, while neural tumours have the potential to undergo malignant transformation. The operative mortality is low in the absence of coexisting cardiovascular disease, COPD or extreme age. Interstitial and infiltrative pulmonary diseases Diffuse parenchymal lung disease The diffuse parenchymal lung diseases (DPLDs) are a heterogeneous group of conditions affecting the pulmonary parenchyma (interstitium) and/or alveolar lumen, which are frequently considered collectively as they share a sufficient number of clinical physiological and radiographic similarities (Box 17.68). 17.68 Features common to the diffuse parenchymal lung diseases Clinical presentation • Cough: usually dry, persistent and distressing • Breathlessness: usually slowly progressive; insidious onset; acute in some cases

Examination findings • Crackles: typically bilateral and basal • Clubbing: common in idiopathic pulmonary fibrosis but also seen in other types, e.g. asbestosis • Central cyanosis and signs of right heart failure in advanced disease Radiology • Chest X-ray: typically small lung volumes with reticulonodular shadowing but may be normal in early or limited disease • High-resolution computed tomography: combinations of ground glass changes, reticulonodular shadowing, honeycomb cysts and traction bronchiectasis, depending on stage of disease Pulmonary function • Typically restrictive ventilatory defect with reduced lung volumes and impaired gas transfer; exercise tests assess exercise tolerance and exercise-related fall in SaO_2 Fig. 17.54 Algorithm for the investigation of patients with interstitial lung disease following initial clinical and chest X-ray examination. Clinical assessment including chest X-ray, pulmonary function tests, haematology, biochemical and immunological investigations Appearances consistent with another diffuse parenchymal lung disease, e.g. sarcoid Inconsistent clinical or CT appearances Appearances consistent with usual interstitial pneumonia High-resolution CT Further investigations, e.g. bronchoalveolar lavage, transbronchial biopsy, surgical biopsy Diagnose idiopathic pulmonary fibrosis Diagnose and treat accordingly 17.69 Conditions that mimic diffuse parenchymal lung disease Infection • Viral pneumonia • Pneumocystis jirovecii • Mycoplasma pneumoniae • Tuberculosis • Parasite, e.g. filariasis • Fungal infection Malignancy • Leukaemia and lymphoma • Lymphangitic carcinomatosis • Multiple metastases • Bronchoalveolar carcinoma Pulmonary oedema Aspiration pneumonitis

 CT scanning it may present as an incidental finding in an otherwise asymptomatic individual but more typically presents with progressive breathlessness (which may have been insidious) and a non-productive cough. Constitutional symptoms are unusual. Clinical findings include finger clubbing and the presence of bi-basal fine late inspiratory crackles likened to the unfastening of Velcro. Investigations These are summarised in Box 17.71. Established IPF will be apparent on chest X-ray as a bilateral lower lobe and subpleural reticular shadowing. The chest X-ray may be normal in individuals with early or limited disease, however. HRCT typically demonstrates a patchy, predominantly peripheral, subpleural and basal reticular pattern and, in more advanced disease, the presence of honeycombing cysts and traction bronchiectasis Fig. 17.55 Classification of diffuse parenchymal lung disease. DPLD of known cause, e.g. drugs or association with connective tissue disease Diffuse parenchymal lung disease (DPLD) Idiopathic interstitial pneumonia Granulomatous DPLD, e.g. sarcoidosis Other forms of DPLD, e.g. lymphangioleiomyomatosis, histiocytosis X etc. Idiopathic pulmonary fibrosis Idiopathic interstitial pneumonia other than idiopathic pulmonary fibrosis Desquamative interstitial pneumonia Respiratory bronchiolitis interstitial lung disease Acute interstitial pneumonia Cryptogenic organising pneumonia Non-specific interstitial pneumonia Lymphocytic interstitial pneumonia 17.70 Idiopathic interstitial pneumonias Clinical diagnosis Notes Usual interstitial pneumonia (UIP) Idiopathic pulmonary fibrosis – see text Non-specific interstitial pneumonia (NSIP) See page 608 Respiratory bronchiolitis–interstitial lung disease More common in men and smokers. Usually presents at age 40–60 years. Smoking cessation may lead to improvement. Natural history unclear Acute interstitial pneumonia Often preceded by viral upper respiratory tract infection. Severe exertional dyspnoea, widespread pneumonic consolidation and diffuse alveolar damage on biopsy. Prognosis often poor Desquamative interstitial pneumonia (DIP) More common in men and smokers. Presents at age 40–60 years. Insidious onset of dyspnoea. Clubbing in 50%. Biopsy shows increased macrophages in alveolar space, septal thickening and type II pneumocyte hyperplasia. Prognosis generally good Cryptogenic organising pneumonia (‘bronchiolitis obliterans organising pneumonia' – BOOP) Presents as clinical and radiological pneumonia. Systemic features and markedly raised erythrocyte sedimentation rate common. Finger clubbing absent. Biopsy shows florid proliferation of immature collagen (Masson bodies) and fibrous tissue. Response to glucocorticoids classically excellent Lymphocytic interstitial pneumonia (LIP) More common in women, slow onset over years. Investigate for associations with connective tissue disease or HIV. Unclear whether glucocorticoids are helpful by occupational exposure, medication or connective tissue diseases, which must be excluded by careful history, examination and investigation. The histological features of the condition are suggestive of repeated episodes of focal damage to the alveolar epithelium consistent with an autoimmune process but the aetiology remains elusive: speculation has included exposure to viruses (e.g. Epstein–Barr virus), occupational dusts (metal or wood), drugs (antidepressants) or chronic gastro-oesophageal reflux. Familial cases are rare but genetic factors that control the inflammatory and fibrotic response are likely to be important. There is a strong association with cigarette smoking. Clinical features IPF usually presents in the older adult and is uncommon before the age of 50 years. With the advent of widespread

Management The management options for IPF are improving. If the vital capacity is between 50% and 80% predicted, patients may be offered either pirfenidone (an antifibrotic agent) or nintedanib (a tyrosine kinase inhibitor). Both of these agents have been shown to reduce the rate of decline in lung function. Patients taking pirfenidone should be advised to avoid direct exposure to sunlight and use photoprotective clothing and high-protection sunscreens. Nintedanib may be accompanied by diarrhoea. Neither drug improves cough or breathlessness and treatment should be discontinued if lung function declines by more than 10% over the first year of treatment. Medication to control gastro-oesophageal reflux may improve the cough. Current smokers should be apprised of the increased risk of lung cancer and advised to stop. Influenza and pneumococcal vaccination should be recommended. Patients should be encouraged to exercise and participate in pulmonary rehabilitation using ambulatory oxygen if appropriate. Domiciliary oxygen should be considered for palliation of breathlessness in severe cases. Where appropriate, lung transplantation should be considered. The optimum treatment for acute exacerbations is unknown. Treatment is largely supportive. Broad-spectrum antibiotics may 17.71 Investigations in diffuse parenchymal lung disease Laboratory investigations • Full blood count: lymphopenia in sarcoid; eosinophilia in pulmonary eosinophilias and drug reactions; neutrophilia in hypersensitivity pneumonitis • Ca^{2+}: may be elevated in sarcoid • Lactate dehydrogenase: may be elevated in active alveolitis • Serum angiotensin-converting enzyme: non-specific indicator of disease activity in sarcoid • Erythrocyte sedimentation rate and C-reactive protein: nonspecifically raised • Autoimmune screen: anti-cyclic citrullinated peptide (anti-CCP) and other autoantibodies may suggest connective tissue disease Radiology • See Box 17.68 Pulmonary function • See Box 17.68 Bronchoscopy • Bronchoalveolar lavage: differential cell counts may point to sarcoid and drug-induced pneumonitis, pulmonary eosinophilias, hypersensitivity pneumonitis or cryptogenic organising pneumonia; useful to exclude infection • Transbronchial biopsy: useful in sarcoid and differential of malignancy or infection • Bronchial biopsy: occasionally useful in sarcoid Video-assisted thoracoscopic lung biopsy (in selected cases) • Allows pathological classification: presence of asbestos bodies may suggest asbestosis; silica in occupational fibrosing lung disease Others • Liver biopsy: may be useful in sarcoidosis • Urinary calcium excretion: may be useful in sarcoidosis (Fig. 17.56). When these features are present, HRCT has a high positive predictive value for the diagnosis of IPF and recourse to biopsy is seldom necessary. HRCT appearances may also be sufficiently characteristic to suggest an alternative diagnosis such as hypersensitivity pneumonitis (p. 616) or sarcoidosis (p. 608). The presence of pleural plaques may suggest asbestosis (p. 618). Pulmonary function tests classically show a restrictive defect with reduced lung volumes and gas transfer. However, lung volumes may be preserved in patients with concomitant emphysema. Dynamic tests are useful to document exercise tolerance and demonstrate exercise-induced arterial hypoxaemia, but as IPF advances, arterial hypoxaemia and hypocapnia are present at rest. Bronchoscopy is seldom indicated unless there is serious consideration of differential diagnoses of infection or a malignant process; lymphocytosis may suggest chronic hypersensitivity pneumonitis. The tissue samples obtained by transbronchial lung biopsy are invariably insufficient to be of value, and if tissue is required, a surgical lung biopsy should be sought. Lung biopsy should be considered in cases of diagnostic uncertainty or with atypical features. UIP is the histological pattern predominantly encountered in IPF (Fig. 17.57); however, it is also found in asbestosis, hypersensitivity pneumonitis, connective tissue diseases and drug reactions. It is not uncommon to identify a mildly positive antinuclear antibody (ANA) or anti-cyclic citrullinated peptide 2 (anti-CCP2) and repeat serological testing may be performed, as lung disease may precede the appearance of connective tissue disease. Fig. 17.56 Idiopathic pulmonary fibrosis. Typical high-resolution CT images demonstrate the bilateral, predominantly basal and peripheral reticular opacities, accompanied by honeycombing in the later stages. A Anteroposterior view. B Transverse section. Courtesy of Dr Andrew Baird, Consultant Radiologist, NHS Lothian, Edinburgh, UK. A B

 rarely affected. The tendency for sarcoid to present in the spring and summer has led to speculation about the role of infective agents, including mycobacteria, propionibacteria and viruses, but the cause remains elusive. Genetic susceptibility is supported by familial clustering; a range of class II HLA alleles confer protection from, or susceptibility to, the condition. Sarcoidosis occurs less frequently in smokers. It may be associated with common variable immunodeficiency (p. 79). Clinical features Sarcoidosis is considered with other DPLDs, as over 90% of cases affect the lungs, but the condition can involve almost any organ (Fig. 17.59 and Box 17.72). Löfgren's syndrome – an acute illness characterised by erythema nodosum, peripheral arthropathy, uveitis, bilateral hilar lymphadenopathy (BHL), lethargy and occasionally fever – is often seen in young women. Alternatively, BHL may be detected in an otherwise asymptomatic individual undergoing a chest X-ray for other purposes. Pulmonary disease may also present in a more insidious manner with cough, exertional breathlessness and radiographic infiltrates; chest auscultation is often surprisingly unremarkable. Fibrosis be combined with glucocorticoids and sometimes additional immunosuppression but there are few data to support this approach. Prognosis The natural history is usually one of steady decline; however, some patients are prone to exacerbations accompanied by an acute deterioration in breathlessness, disturbed gas exchange, and new ground glass changes or consolidation on HRCT. In advanced disease, central cyanosis is detectable and patients may develop pulmonary hypertension and features of right heart failure. A median survival of 3 years is widely quoted; the rate of disease progression varies considerably, however, from death within a few months to survival with minimal symptoms for many years. Serial lung function testing may provide useful prognostic information, relative preservation of lung function suggesting longer survival and significantly impaired gas transfer and/or desaturation on exercise heralding a poorer prognosis. The finding of high numbers of fibroblastic foci on biopsy suggests a more rapid deterioration. Non-specific interstitial pneumonia The clinical picture of fibrotic NSIP is similar to that of IPF, although patients tend to be women and younger in age. As with UIP, the condition may present as an isolated idiopathic pulmonary condition, but an NSIP pattern is often associated with connective tissue disease, certain drugs, chronic hypersensitivity pneumonitis or HIV infection and care must be taken to exclude these possibilities. As with UIP, the pulmonary condition may precede the appearance of connective tissue disease. HRCT findings are less specific than with IPF and lung biopsy may be required. The prognosis is significantly better than that of IPF, particularly in the cellular form of the condition, and the 5-year mortality rate is typically less than 15%. Sarcoidosis Sarcoidosis is a multisystem granulomatous disorder of unknown aetiology that is characterised by the presence of non-caseating granulomas (Fig. 17.58). The condition is more frequently described in colder parts of northern Europe. It also appears to be more common and more severe in those from a West Indian or Asian background; Eskimos, Arabs and Chinese are Fig. 17.57 Pathology of usual interstitial pneumonia. A Lung tissue showing subpleural scarring, most prominently down the posterior edge of the lower lobe. This distribution of fibrosis is typical of usual interstitial pneumonitis. The fibrosis may be associated with prominent cystic change known as 'honeycomb lung'. B Histology showing severe interstitial fibrosis with loss of the normal alveolar architecture and the development of 'honeycomb' cysts. Courtesy of Dr William Wallace, Department of Pathology, Royal Infirmary of Edinburgh. A B Fig. 17.58 Sarcoidosis of the lung. Histology showing non-caseating granulomas (arrows). Courtesy of Dr William Wallace, Department of Pathology, Royal Infirmary of Edinburgh.

may provide a non-specific marker of disease activity and can assist in monitoring the clinical course. Chest radiography has been used to stage sarcoid (Box 17.73). In patients with pulmonary infiltrates, pulmonary function testing may show a restrictive defect accompanied by impaired gas exchange. Exercise tests Fig. 17.59 Possible systemic involvement in sarcoidosis. Inset (Erythema nodosum): From Savin JA, Hunter JAA, Hepburn NC. Skin signs in clinical medicine. London: Mosby–Wolfe; 1997. Pachymeningitis Space-occupying lesion Diabetes insipidus Anterior uveitis Sicca syndrome Lymphadenopathy Bilateral hilar lymphadenopathy (BHL) Cardiac arrhythmia Heart block, sudden death Splenomegaly Nephrocalcinosis Hypercalciuria Renal stones Arthropathies Osteoporosis Arthropathies Osteoporosis Mononeuritis multiplex Peripheral neuropathy Skin plaques and nodules Infiltration of scars Granulomatous liver disease Phalangeal bone cysts Lacrimal gland enlargement Cranial nerve palsy Interstitial lung disease Nasal cutaneous sarcoid lesions (lupus pernio) Erythema nodosum Parotid gland enlargement 17.72 Presentation of sarcoidosis • Asymptomatic: abnormal routine chest X-ray (~30%) or abnormal liver function tests • Respiratory and constitutional symptoms (20–30%) • Erythema nodosum and arthralgia (20–30%) • Ocular symptoms (5–10%) • Skin sarcoid (including lupus pernio) (5%) • Superficial lymphadenopathy (5%) • Other (1%), e.g. hypercalcaemia, diabetes insipidus, cranial nerve palsies, cardiac arrhythmias, nephrocalcinosis occurs in around 20% of cases of pulmonary sarcoidosis and may cause a silent loss of lung function. Pleural disease is uncommon and finger clubbing is not a feature. Complications such as bronchiectasis, aspergilloma, pneumothorax, pulmonary hypertension and cor pulmonale have been reported but are rare. Investigations Lymphopenia is characteristic and liver function tests may be mildly deranged. Hypercalcaemia may be present (reflecting increased formation of calcitriol – 1,25-dihydroxyvitamin D – by alveolar macrophages), particularly if the patient has been exposed to strong sunlight. Hypercalciuria may also be seen and may lead to nephrocalcinosis. Serum angiotensin-converting enzyme (ACE) 17.73 Chest X-ray changes in sarcoidosis Stage I: BHL (usually symmetrical); paratracheal nodes often enlarged • Often asymptomatic but may be associated with erythema nodosum and arthralgia. The majority of cases resolve spontaneously within 1 year Stage II: BHL and parenchymal infiltrates • Patients may present with breathlessness or cough. The majority of cases resolve spontaneously Stage III: parenchymal infiltrates without BHL • Disease less likely to resolve spontaneously Stage IV: pulmonary fibrosis • Can cause progression to ventilatory failure, pulmonary hypertension and cor pulmonale (BHL = bilateral hilar lymphadenopathy)

610 • RESPIRATORY MEDICINE Lung diseases due to systemic inflammatory disease The acute respiratory distress syndrome See page 198. Respiratory involvement in connective tissue disorders Pulmonary complications of connective tissue disease are common, affecting the airways, alveoli, pulmonary vasculature, diaphragm and chest wall muscles, and the chest wall itself. In some instances, pulmonary disease may precede the appearance of the connective tissue disorder (Box 17.74). Indirect associations between connective tissue disorders and respiratory complications include those due to disease in other organs, e.g. thrombocytopenia causing haemoptysis; pulmonary toxic effects of drugs used to treat the connective tissue disorder (e.g. gold and methotrexate); and secondary infection due to the disease itself, neutropenia or immunosuppressive drug regimens. Rheumatoid disease Pulmonary involvement in rheumatoid disease is important, accounting for around 10–20% of the mortality associated with the condition (p. 1021). The majority of cases occur within 5 years of the rheumatological diagnosis but pulmonary manifestations may precede joint involvement in 10–20%. Pulmonary fibrosis is the most common pulmonary manifestation. All forms of interstitial disease have been described but NSIP is probably the most common. A rare variant of localised upper lobe fibrosis and cavitation is occasionally seen. Pleural effusion is common, especially in men with seropositive disease. Effusions are usually small and unilateral, but can be large and bilateral. Most resolve spontaneously. Biochemical testing shows an exudate with markedly reduced glucose levels and raised lactate dehydrogenase (LDH). Effusions that fail to resolve spontaneously may respond to a short course of oral prednisolone (30–40 mg daily) but some become chronic. Rheumatoid pulmonary nodules are usually asymptomatic and detected incidentally on imaging. They are most often multiple and subpleural in site (Fig. 17.60). Solitary nodules can mimic primary lung cancer; when multiple, the differential may reveal oxygen desaturation. Bronchoscopy may demonstrate a ‘cobblestone’ appearance of the mucosa, and bronchial and transbronchial biopsies usually show non-caseating granulomas, as may samples from the mediastinal nodes obtained by EBUS. Bronchoalveolar lavage fluid typically contains an increased CD4:CD8 T-cell ratio. Characteristic HRCT appearances include reticulonodular opacities that follow a perilymphatic distribution centred on bronchovascular bundles and the subpleural areas. PET scanning can detect extrapulmonary disease. The occurrence of erythema nodosum with BHL on chest X-ray is often sufficient for a confident diagnosis, without recourse to a tissue biopsy. Similarly, a typical presentation with classical HRCT features may also be accepted. In other instances, however, the diagnosis should be confirmed by histological examination of the involved organ. The presence of anergy (e.g. to tuberculin skin tests) may support the diagnosis. Management Patients who present with acute illness and erythema nodosum should receive NSAIDs and, on occasion, a short course of glucocorticoids. The majority of patients enjoy spontaneous remission and so, if there is no evidence of organ damage, systemic glucocorticoid therapy can be withheld for 6 months. However, prednisolone (at a starting dose of 20–40 mg/ day) should be commenced immediately in the presence of hypercalcaemia, pulmonary impairment, renal impairment and uveitis. Topical glucocorticoids may be useful in cases of mild uveitis, and inhaled glucocorticoids have been used

to shorten the duration of systemic glucocorticoid use in asymptomatic parenchymal sarcoid. Patients should be warned that strong sunlight may precipitate hypercalcaemia and endanger renal function. Features suggesting a less favourable outlook include age over 40, Afro-Caribbean ethnicity, persistent symptoms for more than 6 months, the involvement of more than three organs, lupus pernio (see Fig. 17.59) and a stage III/IV chest X-ray. In patients with severe disease, methotrexate (10–20 mg/week), azathioprine (50–150 mg/day) and specific tumour necrosis factor alpha (TNF-α) inhibitors (p. 1006) have been effective. Chloroquine, hydroxychloroquine and low-dose thalidomide may be useful in cutaneous sarcoid with limited pulmonary involvement. Selected patients may be referred for consideration of single lung transplantation. The overall mortality is low (1–5%) and usually reflects cardiac involvement or pulmonary fibrosis. 17.74 Respiratory complications of connective tissue disorders Disorder Airways Parenchyma Pleura Diaphragm and chest wall Rheumatoid arthritis Bronchitis, obliterative bronchiolitis, bronchiectasis, crico-arytenoid arthritis, stridor Pulmonary fibrosis, nodules, upper lobe fibrosis, infections Pleurisy, effusion, pneumothorax Poor healing of intercostal drain sites Systemic lupus erythematosus – Pulmonary fibrosis, 'vasculitic' infarcts Pleurisy, effusion Diaphragmatic weakness (shrinking lungs) Systemic sclerosis Bronchiectasis Pulmonary fibrosis, aspiration pneumonia – Cutaneous thoracic restriction (hidebound chest) Dermatomyositis/ polymyositis Lung cancer Pulmonary fibrosis – Intercostal and diaphragmatic myopathy Granulomatosis with polyangiitis Epistaxis, nasal discharge crusting, subglottic stenosis Pulmonary nodules that may cavitate Pleurisy, effusion –

systemic sclerosis but isolated pulmonary hypertension may develop. Other pulmonary complications include recurrent aspiration pneumonias secondary to oesophageal disease. Rarely, sclerosis of the skin of the chest wall may be so extensive and cicatrising as to restrict chest wall movement – the so-called 'hidebound chest'. Pulmonary eosinophilia and vasculitides Pulmonary eosinophilia refers to the association of radiographic (usually pneumonic) abnormalities and peripheral blood eosinophilia. The term encompasses a group of disorders of different aetiology (Box 17.75). Eosinophils are the predominant cell recovered in sputum or BAL, and eosinophil products are likely to the prime mediators of tissue damage. Acute eosinophilic pneumonia Acute eosinophilic pneumonia is an acute febrile illness (of less than 5 days' duration), characterised by diffuse pulmonary infiltrates and hypoxic respiratory failure. The pathology is usually that of diffuse alveolar damage. Diagnosis is confirmed by BAL, which characteristically demonstrates > 25% eosinophils. The condition is usually idiopathic but drug reactions should be considered. Glucocorticoids invariably induce prompt and complete resolution. Chronic eosinophilic pneumonia Chronic eosinophilic pneumonia typically presents in an insidious manner with malaise, fever, weight loss, breathlessness and unproductive cough. It is more common in middle-aged females. The classical chest X-ray appearance has been likened to the photographic negative of pulmonary oedema with bilateral, peripheral and predominantly upper lobe parenchymal shadowing. The peripheral blood eosinophil count is almost always very high, and the erythrocyte sedimentation rate (ESR) and total serum IgE are elevated. BAL reveals a high proportion of eosinophils diagnoses include pulmonary metastatic disease. Cavitation raises the possibility of TB and predisposes to pneumothorax. The combination of rheumatoid nodules and pneumoconiosis is known as Caplan's syndrome (p. 615). Bronchitis and bronchiectasis are both more common in rheumatoid patients. Rarely, the potentially fatal condition called obliterative bronchiolitis may develop. Bacterial lower respiratory tract infections are frequent. Treatments given for rheumatoid arthritis may also be relevant: glucocorticoid therapy predisposes to infections, methotrexate may cause pulmonary fibrosis, and anti-TNF therapy has been associated with the reactivation of TB. Systemic lupus erythematosus Pleuropulmonary involvement is more common in lupus than in any other connective tissue disorder and may be a presenting problem, when it is sometimes attributed incorrectly to infection or pulmonary embolism. Up to two-thirds of patients have repeated episodes of pleurisy, with or without effusions. Effusions may be bilateral and may also involve the pericardium. The most serious manifestation of lupus is an acute alveolitis that may be associated with diffuse alveolar haemorrhage. This condition is life-threatening and requires either immediate immunosuppression with glucocorticoids or a step-up in immunosuppressive treatment, if already started. Pulmonary fibrosis is a relatively uncommon manifestation of systemic lupus erythematosus (SLE). Some patients with SLE present with exertional dyspnoea and orthopnoea but without overt signs of pulmonary fibrosis. The chest X-ray reveals elevated diaphragms and pulmonary function testing shows reduced lung volumes. This condition has been described as ‘shrinking lungs’ and has been attributed to diaphragmatic myopathy. SLE patients with antiphospholipid antibodies are at increased risk of venous and pulmonary thromboembolism and require life-long anticoagulation. Systemic sclerosis Most patients with systemic sclerosis (p. 1037) eventually develop diffuse pulmonary fibrosis; at necropsy more than 90% have evidence of lung fibrosis. In some patients it is indolent, but when progressive, as in IPF, the median survival time is around 4 years. Pulmonary fibrosis is rare in the CREST variant of progressive Fig. 17.60 Rheumatoid (necrobiotic) nodules. Thoracic CT just below the level of the main carina, showing the typical appearance of peripheral pleural-based nodules (arrows). The nodule in the left lower lobe shows characteristic cavitation. 17.75 Pulmonary eosinophilia Extrinsic (cause known) • Helminths: e.g. Ascaris, Toxocara, Filaria • Drugs: nitrofurantoin, para-aminosalicylic acid (PAS), sulfasalazine, imipramine, chlorpropamide, phenylbutazone • Fungi: e.g. Aspergillus fumigatus causing allergic bronchopulmonary aspergillosis (p. 596) Intrinsic (cause unknown) • Cryptogenic eosinophilic pneumonia • Eosinophilic granulomatosis with polyangiitis (formerly Churg– Strauss syndrome), diagnosed on the basis of four or more of the following features: Asthma Peripheral blood eosinophilia > 1.5 × 109/L (or > 10% of a total white cell count) Mononeuropathy or polyneuropathy Pulmonary infiltrates Paranasal sinus disease Eosinophilic vasculitis on biopsy of an affected site • Hypereosinophilic syndrome • Polyarteritis nodosa (p. 1042; rare)

 respond to glucocorticoid treatment. The pulmonary effects of radiation (p. 1332) are exacerbated by treatment with cytotoxic drugs, and the phenomenon of ‘recall pneumonitis’ describes the appearance of radiation injury in a previously irradiated area when chemotherapy follows radiotherapy. If the patient survives, there are long-term risks of lung cancer. Drugs Drugs may cause a variety of pulmonary conditions (Box 17.76). Pulmonary fibrosis may occur in response to a variety of drugs but is seen most frequently with bleomycin, methotrexate, amiodarone and nitrofurantoin. Eosinophilic pulmonary reactions can also be caused by drugs. The pathogenesis may be an immune reaction similar to that in hypersensitivity pneumonitis, which specifically attracts large numbers of eosinophils into the lungs. This type of reaction is well described as a rare reaction to a variety of antineoplastic agents (e.g. bleomycin), antibiotics (e.g. sulphonamides), sulfasalazine and the anticonvulsants phenytoin and carbamazepine. Patients usually present with breathlessness, cough and fever. The chest X-ray characteristically shows patchy shadowing. Most cases resolve completely on withdrawal of the drug, but if the reaction is severe, rapid resolution can be obtained with glucocorticoids. Drugs may also cause other lung diseases, such as asthma, pulmonary haemorrhage, pleural effusion and, rarely, pleural thickening. An ARDS-like syndrome of acute non-cardiogenic pulmonary oedema may present with dramatic onset of breathlessness, severe hypoxaemia and signs of alveolar oedema in the lavage fluid. Response to prednisolone (20–40 mg daily) is usually dramatic. Prednisolone can usually be withdrawn after a few weeks without relapse but long-term, low-dose therapy is occasionally necessary. Tropical pulmonary eosinophilia Tropical pulmonary eosinophilia occurs as a result of a mosquitoborne filarial infection with Wuchereria bancrofti or Brugia malayi (p. 290). The condition presents with fever, weight loss, dyspnoea and asthma-like symptoms. The peripheral blood eosinophilia is marked, as is the elevation of total IgE. High antifilarial antibody titres are seen. The diagnosis may be confirmed by a response to treatment with diethylcarbamazine (6 mg/kg/day for 3 weeks). Tropical pulmonary eosinophilia must be distinguished from infection with Strongyloides stercoralis (p. 289) as, in strongyloidiasis, glucocorticoids may cause a life-threatening hyperinfection syndrome. Ascariasis (‘larva migrans’) and other hookworm infestation are covered in Chapter 11. Granulomatosis with polyangiitis Granulomatosis with polyangiitis (formerly referred to as Wegener’s granulomatosis) is a rare vasculitic and granulomatous condition (p. 1041). The lung is commonly involved in systemic forms of the disease but a limited pulmonary form may also occur. Respiratory symptoms include cough, haemoptysis and chest pain. Associated upper respiratory tract manifestations include nasal discharge and crusting, and otitis media. Fever, weight loss and anaemia are common. Radiological features include multiple nodules and cavitation that may resemble primary or metastatic carcinoma, or a pulmonary abscess. Tissue biopsy confirms the distinctive pattern of necrotising granulomas and necrotising vasculitis. Other respiratory complications include tracheal subglottic stenosis and saddle nose deformity. The differential diagnoses include mycobacterial and fungal infection and other forms of pulmonary vasculitis, including polyarteritis nodosa (pulmonary infarction), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome: marked tissue eosinophilia and association with asthma), necrotising sarcoid, bronchocentric granulomatosis and lymphomatoid granulomatosis. Goodpasture’s disease This describes the association of pulmonary haemorrhage and glomerulonephritis, in which IgG antibodies bind to the glomerular or alveolar basement membranes (p. 401). Pulmonary disease usually precedes renal involvement and includes radiographic infiltrates and hypoxia with or without haemoptysis. It occurs more commonly in men and almost exclusively in smokers. Lung diseases due to irradiation and drugs Radiotherapy Targeting radiotherapy to certain tumours is inevitably accompanied by irradiation of normal lung tissue. Although delivered in divided doses, the effects are cumulative. Acute radiation pneumonitis is typically seen within 6–12 weeks and presents with cough and dyspnoea. This may resolve spontaneously but responds to glucocorticoid treatment. Chronic interstitial fibrosis may present several months later with symptoms of exertional dyspnoea and cough. Changes are often confined to the area irradiated but may be bilateral. Established post-irradiation fibrosis does not usually 17.76 Drug-induced respiratory disease Non-cardiogenic pulmonary oedema (ARDS) • Hydrochlorothiazide • Thrombolytics (streptokinase) • Intravenous β-adrenoceptor agonists (e.g. for premature labour) • Aspirin and opiates (in overdose) Non-eosinophilic alveolitis • Amiodarone, flecainide, gold, nitrofurantoin, cytotoxic agents – especially bleomycin, busulfan, mitomycin C, methotrexate, sulfasalazine Pulmonary eosinophilia • Antimicrobials (nitrofurantoin, penicillin, tetracyclines, sulphonamides, nalidixic acid) • Drugs used in joint disease (gold, aspirin, penicillamine, naproxen) • Cytotoxic drugs (bleomycin, methotrexate, procarbazine) • Psychotropic drugs (chlorpromazine, dosulepin, imipramine) • Anticonvulsants (carbamazepine, phenytoin) • Others (sulfasalazine, nadolol) Pleural disease • Bromocriptine, amiodarone, methotrexate, methysergide • Induction of systemic lupus erythematosus – phenytoin, hydralazine, isoniazid Asthma • Pharmacological mechanisms (β-blockers, cholinergic agonists, aspirin and NSAIDs) • Idiosyncratic reactions (tamoxifen, dipyridamole) (ARDS = acute respiratory distress syndrome; NSAIDs = non-steroidal anti-inflammatory drugs)

Rare interstitial lung diseases See Box 17.78. Occupational and environmental lung disease The role of occupation and environmental exposure in lung disease is a particularly important area of respiratory medicine. Occupational lung disease is common and, in addition to the challenges of its diagnosis and management, often involves discussions about the workplace and, in some circumstances, litigation. Many countries encourage the registration of cases of occupational lung disease. Occupational airway disease Occupational asthma Occupational asthma should be considered in any individual of working age who develops new-onset asthma, particularly if the individual reports improvement in asthma symptoms during periods away from work, e.g. at weekends and on holidays. Workers in certain occupations appear to be at particularly high risk (Box 17.79) and the condition is more common in smokers and atopic individuals. Depending on the intensity of exposure, asthmatic symptoms usually develop within the first few years of employment but are classically preceded by a latent period. Symptoms of rhinoconjunctivitis often precede 17.77 Interstitial lung disease in old age • Idiopathic pulmonary fibrosis: the most common interstitial lung disease, with a poor prognosis. • Chronic aspiration pneumonitis: must always be considered in elderly patients presenting with bilateral basal shadowing on a chest X-ray. • Granulomatosis with polyangiitis (Wegener’s granulomatosis): a rare condition but more common in old age. Renal involvement is more common at presentation and upper respiratory problems are fewer. • Asbestosis: symptoms may appear only in old age because of the prolonged latent period between exposure and disease. • Drug-induced interstitial lung disease: more common, presumably because of the increased chance of exposure to multiple drugs. • Rarer interstitial disease: sarcoidosis, idiopathic pulmonary haemosiderosis, alveolar proteinosis and eosinophilic pneumonia rarely present. • Increased dyspnoea: coexistent muscle weakness, chest wall deformity (e.g. thoracic kyphosis) and deconditioning may all exacerbate dyspnoea associated with interstitial lung disease. • Surgical lung biopsy: often inappropriate in the very frail. A diagnosis therefore frequently depends on clinical and highresolution computed tomography findings alone. 17.78 Rare interstitial lung diseases Disease Presentation Chest X-ray Course Idiopathic pulmonary haemosiderosis Haemoptysis, breathlessness, anaemia Bilateral infiltrates, often perihilar Diffuse pulmonary fibrosis Rapidly progressive in children Slow progression or remission in adults Death from massive pulmonary haemorrhage or cor pulmonale and respiratory failure Alveolar proteinosis Breathlessness and cough Occasionally fever, chest pain and haemoptysis Diffuse bilateral shadowing, often more pronounced in the hilar regions Air bronchogram Spontaneous remission in one-third Whole-lung lavage or granulocyte– macrophage colony-stimulating factor (GM–CSF) therapy may be effective Langerhans cell histiocytosis (histiocytosis X) Breathlessness, cough, pneumothorax Diffuse interstitial shadowing progressing to honeycombing Course unpredictable but may progress to respiratory failure Smoking cessation may be followed by significant improvement Poor response to immunosuppressive treatment Neurofibromatosis Breathlessness and cough in a patient with multiple organ involvement with neurofibromas, including skin Bilateral reticulonodular shadowing of diffuse interstitial fibrosis Slow progression to death from respiratory failure Poor response to glucocorticoid therapy Alveolar microlithiasis May be asymptomatic

Breathlessness and cough Diffuse calcified micronodular shadowing more pronounced in the lower zones Slowly progressive to cor pulmonale and respiratory failure May stabilise in some Lymphangioleiomyomatosis Haemoptysis, breathlessness, pneumothorax and chylous effusion in females Diffuse bilateral shadowing CT shows characteristic thin-walled cysts with well-defined walls throughout both lungs Progressive to death within 10 years Oestrogen ablation and progesterone therapy of doubtful value Consider lung transplantation Pulmonary tuberous sclerosis Very similar to lymphangioleiomyomatosis, except occasionally occurs in men on the chest X-ray. This syndrome has been reported most frequently in cases of opiate overdose in drug addicts (p. 142) but also after salicylate overdose, and there are occasional reports of its occurrence after therapeutic doses of drugs, including hydrochlorothiazides and some cytotoxic agents.

 very high concentrations. Pulmonary function tests show airflow obstruction and airway hyper-reactivity, and the management is similar to that of asthma. Once developed, the condition often persists but it is common for symptoms to improve over years. Chronic obstructive pulmonary disease While tobacco smoking remains the most important preventable cause of COPD, there is increasing recognition that other noxious particles and gases can cause, or aggravate, the condition. Occupational COPD is recognised in workers exposed to coal dust, crystalline silica and cadmium. In many parts of the developing world, indoor air pollution from the burning of biomass fuels in confined spaces used for cooking contributes to the development of COPD. Byssinosis Byssinosis occurs in workers of cotton and flax mills exposed to cotton brack (dried leaf and plant debris). An acute form of the disease may occur, but more typically, byssinosis develops after 20–30 years' exposure. Typical symptoms include chest tightness or breathlessness accompanied by a drop in lung function; classically, these are most severe on the first day of the working week ('Monday fever') or on return to work following a period away. As the week progresses, symptoms improve and the fall in lung function becomes less dramatic. Continued exposure leads to the development of persistent symptoms and a progressive decline in FEV1, similar to that observed in COPD. Pneumoconiosis Pneumoconiosis may be defined as a permanent alteration of lung structure due to the inhalation of mineral dust and the tissue reactions of the lung to its presence, excluding bronchitis and emphysema (Box 17.80). Not all dusts are pathogenic. For example, silica is highly fibrogenic, whereas iron (siderosis), tin (stannosis) and barium (baritosis) are almost inert. Beryllium causes an interstitial granulomatous disease similar to sarcoidosis. In the development of asthma. When occupational asthma follows exposure to high-molecular-weight proteins, sensitisation may be demonstrated by skin testing or measurement of specific IgE to the agent in question. Confirmation of occupational asthma should be sought from lung function tests. This usually involves serial recording of peak flow at work at least four times per day for a minimum of 3 weeks and, if possible, including a period away from work (Fig. 17.61). In certain circumstances, specific challenge tests are required to confirm the diagnosis. It may be possible to remove the worker from the implicated agent, but when this cannot be done, consideration of personal protective equipment and workplace hygiene may allow the worker to retain their job and livelihood. Specialist follow-up in such situations is highly advisable. A favourable prognosis is indicated by a short history of symptoms and normal lung function at diagnosis. Where reduction or avoidance of exposure fails to bring about resolution, the management is identical to that of any patient with asthma (p. 569). Reactive airways dysfunction syndrome Reactive airways dysfunction syndrome or acute irritant-induced asthma refers to the development of a persistent asthma-like syndrome following the inhalation of an airway irritant: typically, a single, specific exposure to a gas, smoke, fume or vapour in 17.79 Occupational asthma

Most frequently reported causative agents • Isocyanates • Flour and grain dust • Colophony and fluxes • Latex • Animals • Aldehydes • Wood dust Workers most commonly reported to occupational asthma schemes • Paint sprayers • Bakers and pastry-makers • Nurses • Chemical workers Fig. 17.61 Peak flow readings in occupational asthma. In this example, an individual with suspected occupational asthma has performed serial peak flow recording both at and away from work. The maximum, mean and minimum values are plotted daily. Days at work are indicated by the shaded areas. The diurnal variation is displayed at the top. Here, a period away from work is followed by a marked improvement in peak flow readings and a reduction in diurnal variation. (PEF = peak expiratory flow)

0% 20% 50% Diurnal variation of PEF Peak flow (L/min) Weekdays m t w t f s s m t w t f s s m t w t f s s m t w t f s s m t w t f s s

Cause Occupation Description Characteristic pathological features Coal dust Coal mining Coal worker's pneumoconiosis Focal and interstitial fibrosis, centrilobular emphysema, progressive massive fibrosis Silica Mining, quarrying, stone dressing, metal grinding, pottery, boiler scaling Silicosis Asbestos Demolition, ship breaking, manufacture of fireproof insulating materials, pipe and boiler lagging Asbestos-related disease Pleural plaques, diffuse pleural thickening, acute benign pleurisy, carcinoma of lung, interstitial fibrosis, mesothelioma Iron oxide Arc welding Siderosis Mineral deposition only Tin oxide Tin mining Stannosis Tin-laden macrophages Beryllium Aircraft, atomic energy and electronics industries Berylliosis Granulomas, interstitial fibrosis } 17.80 Lung diseases caused by exposure to inorganic dusts may develop (Fig. 17.62). Enlargement of the hilar glands with an 'egg-shell' pattern of calcification is said to be characteristic but is non-specific. Silica is highly fibrogenic and the disease is usually progressive, even when exposure ceases; hence the affected worker should invariably be removed from further exposure. Individuals with silicosis are at increased risk of TB many types of pneumoconiosis, a long period of dust exposure is required before radiological changes appear and these may precede clinical symptoms. The most important pneumoconioses include coal worker's pneumoconiosis, silicosis and asbestosis. Coal worker's pneumoconiosis Coal worker's pneumoconiosis (CWP) follows prolonged inhalation of coal dust. Dust-laden alveolar macrophages aggregate to form macules in or near the centre of the secondary pulmonary lobule and a fibrotic reaction ensues, resulting in the appearance of scattered discrete fibrotic lesions. Classification is based on the size and extent of radiographic nodularity. Simple coal worker's pneumoconiosis (SCWP) refers to the appearance of small radiographic nodules in an otherwise asymptomatic individual. SCWP does not impair lung function and, once exposure ceases, will seldom progress. Progressive massive fibrosis (PMF) refers to the formation of conglomerate masses (mainly in the upper lobes), which may cavitate. The development of PMF is usually associated with cough, sputum that may be black (melanoptysis) and breathlessness. The chest X-ray appearances may be confused with lung cancer, TB and granulomatosis with polyangiitis. PMF may progress, even after coal dust exposure ceases, and in extreme cases leads to respiratory failure and right ventricular failure. Caplan's syndrome describes the coexistence of rheumatoid arthritis and rounded fibrotic nodules 0.5–5 cm in diameter. They show pathological features similar to a rheumatoid nodule, including central necrosis, palisading histiocytes, and a peripheral rim of lymphocytes and plasma cells. This syndrome may also occur in other types of pneumoconiosis. Silicosis Silicosis results from the inhalation of crystalline silica, usually in the form of quartz, by workers cutting, grinding and polishing stone. Classic silicosis is most common and usually manifests after 10–20 years of continuous silica exposure, during which time the patient remains asymptomatic. Accelerated silicosis is associated with a much shorter duration of dust exposure (typically 5–10 years), may present as early as after 1 year of exposure and, as the name suggests, follows a more aggressive course. Intense exposure to very fine crystalline silica dust can cause a more acute disease: silicoproteinosis, similar to alveolar proteinosis (see Box 17.78). Radiological features are similar to those of CWP, with multiple well-circumscribed 3–5 mm nodular opacities predominantly in the mid- and upper zones. As the disease progresses, PMF Fig. 17.62 Silicosis. A A chest X-ray from a patient with silicosis, showing the presence of small rounded nodules, predominantly seen in the upper zones. B High-resolution computed tomogram from the same patient, demonstrating conglomeration of nodules with posterior bias. A B

 Hypersensitivity pneumonitis Hypersensitivity pneumonitis (HP; also called extrinsic allergic alveolitis) results from the inhalation of a wide variety of organic antigens that give rise to a diffuse immune complex reaction in the walls of alveoli and bronchioles. Common causes include farmer's lung and bird fancier's lung. Other examples are shown in Box 17.81. HP is not exclusively occupational or environmental and other important causes include medications (see Box 17.76). The pathology of HP is consistent with both type III and type IV immunological mechanisms (p. 83). Precipitating IgG antibodies may be detected in the serum and a type III Arthus reaction is believed to occur in the lung, where the precipitation of immune complexes results in activation of complement and an inflammatory response in the alveolar walls, characterised by the influx of mononuclear cells and foamy histiocytes. The presence of poorly formed non-caseating granulomas in the alveolar walls suggests that type IV responses are also important. The distribution of the inflammatory infiltrate is predominantly peribronchiolar. Chronic forms of the disease may be accompanied by fibrosis. For reasons that remain uncertain, there is a lower incidence of HP in smokers compared to non-smokers. Clinical features The presentation of HP varies from an acute form to a more indolent pattern in accordance with the antigen load. For example, the farmer exposed to mouldy hay, as occurs when the hay is gathered and stored damp during a wet summer, or the pigeon fancier cleaning a large pigeon loft will, within a few hours, report influenza-like symptoms accompanied by cough, breathlessness and wheeze. The individual with low-level antigen exposure, however, such as the owner of an indoor pet bird, will typically present in a more indolent fashion with slowly progressive breathlessness; in some cases, established fibrosis may be present by the time the disease is recognised. Chest auscultation typically reveals widespread end-inspiratory crackles and squeaks. Investigations In cases of acute HP, the chest X-ray typically shows ill-defined patchy airspace shadowing, which, given the systemic features, may be confused with pneumonia. HRCT is more likely to show bilateral ground-glass shadowing and areas of consolidation superimposed on small centrilobar nodular opacities with an upper and middle lobe predominance (Fig. 17.63). In more chronic disease, features of fibrosis, such as volume loss, linear opacities and architectural distortion, appear. In common with other fibrotic diseases, pulmonary function tests show a restrictive ventilatory defect with reduced lung volumes and impaired gas transfer, dynamic tests may detect oxygen desaturation and, in more advanced disease, type I respiratory failure is present at rest. Diagnosis The diagnosis of HP is usually based on the characteristic clinical and radiological features, together with the identification of a potential source of antigen at the patient's home or place of work (Box 17.82). It may be supported by a positive serum precipitin test or by more sensitive serological investigations. It is important, however, to be aware that the presence of precipitins in the absence of other features does not make the diagnosis; the great majority of farmers with positive precipitins do not have farmer's lung, and up to 15% of pigeon breeders may have positive serum precipitins yet remain healthy. (silicotuberculosis), lung cancer and COPD; associations with renal and connective tissue disease have also been described. Berylliosis Exposure to beryllium is encountered in the aerospace, engineering, telecommunications and biomedical industries. The presence of cough, progressive breathlessness, night sweats and arthralgia in a worker exposed to dusts, fumes or vapours containing beryllium should raise suspicion of berylliosis. The radiographic appearances are similar in type and distribution to those of sarcoid and biopsy shows sarcoid-like granulomas. The diagnosis may be confirmed by specialised tests of lymphocyte function. Less common pneumoconioses Siderosis refers to the development of a benign iron oxide pneumoconiosis in welders and other iron foundry workers. Baritosis may be seen in barium process workers and stannosis in tin refining. Haematite lung occurs in iron ore miners and resembles silicosis but stains the lung red. Diamond polishers may develop hard metal disease, which is similar to UIP but the pathology shows a giant-cell interstitial pneumonia. Workers exposed to aluminium oxide develop bauxite pneumoconiosis, sometimes referred to as shaver's disease. Popcorn worker's lung is a form of obliterative bronchiolitis following ingestion of diacetyl used in butter flavouring. Lung diseases due to organic dusts A wide range of organic agents may cause respiratory disorders (Box 17.81). Disease results from a local immune response to animal proteins or fungal antigens in mouldy vegetable matter. Hypersensitivity pneumonitis is the most common of these conditions. 17.81 Examples of lung diseases caused by organic dusts Disorder Source Antigen/agent Farmer's lung* Mouldy hay, straw, grain Saccharopolyspora rectivirgula (formerly Micropolyspora faeni) Aspergillus fumigatus Bird fancier's lung* Avian excreta, proteins and feathers Avian serum proteins Malt worker's lung* Mouldy maltings Aspergillus clavatus Cheese worker's lung* Mouldy cheese Aspergillus clavatus Penicillium casei Maple bark stripper's lung* Bark from stored maple Cryptostroma corticale Saxophone player's lung* Reed of any wind instrument Fusarium spp. Penicillium spp. Cladosporium spp. Byssinosis Textile industries Cotton, flax, hemp dust Inhalation ('humidifier') fever Contamination of air conditioning Thermophilic actinomycetes *Presents as hypersensitivity pneumonitis.

hobbies (e.g. pigeon breeders). Dust masks with appropriate filters may minimise exposure and may be combined with methods of reducing levels of antigen (e.g. drying hay before storage). In acute cases, prednisolone should be given for 3–4 weeks, starting with an oral dose of 40 mg per day. Severely hypoxaemic patients may require high-concentration oxygen therapy initially. Most patients recover completely, but if unchecked, fibrosis may progress to cause severe respiratory disability, hypoxaemia, pulmonary hypertension, cor pulmonale and eventually death. Inhalation ('humidifier') fever Inhalation fever shares similarities with HP. It occurs as a result of contaminated humidifiers or air-conditioning units that release a fine spray of microorganisms into the atmosphere. The illness is characterised by self-limiting fever and breathlessness; permanent sequelae are unusual. An identical syndrome can also develop after disturbing an accumulation of mouldy hay, compost or mulch. So-called 'hot tub lung' appears to be attributable to Mycobacterium avium. Outbreaks of HP in workers using metalworking fluids appear to be linked to Acinetobacter or Ochrobactrum. Asbestos-related lung and pleural diseases Asbestos is a naturally occurring silicate. Asbestos fibres may be classified as either chrysotile (white asbestos), which accounts for 90% of the world's production, or serpentine (crocidolite or blue asbestos, and amosite or brown asbestos). The favourable thermal and chemical insulation properties led to its extensive use by the shipbuilding and construction industries throughout the latter part of the 20th century. Exposure to asbestos may be followed, after a lengthy latent period, by the development of both pleural and pulmonary disease. Pleural plaques Pleural plaques are the most common manifestation of past asbestos exposure, being discrete circumscribed areas of hyaline fibrosis situated on the parietal pleura of the chest wall, Where HP is suspected but the cause is not readily apparent, a visit to the patient's home or workplace should be arranged. Occasionally, such as when an agent previously unrecognised as causing HP is suspected, provocation testing may be necessary to prove the diagnosis; if positive, inhalation of the relevant antigen is followed after 3–6 hours by pyrexia and a reduction in vital capacity and gas transfer factor. BAL fluid usually shows an increase in the number of CD8+ T lymphocytes and transbronchial biopsy can occasionally provide sufficient tissue for a confident diagnosis; however, open lung biopsy may be necessary. Management If it is practical, the patient should cease exposure to the inciting agent. In some cases this may be difficult, however, because of either implications for livelihood (e.g. farmers) or addiction to Fig. 17.63 Hypersensitivity pneumonitis. A High-resolution computed tomogram showing typical patchy ground-glass opacification. B Histology shows evidence of an interstitial inflammatory infiltrate in the lung, and expanding alveolar walls, with a peribronchial distribution. Within the infiltrate, there are foci of small, poorly defined non-caseating granulomas (inset), which often lie adjacent to the airways. In this case, there is little in the way of established lung fibrosis but this can be marked. A, Courtesy of Dr S. Jackson, Western General Hospital, Edinburgh. B, Courtesy of Dr William Wallace, Dept of Pathology, Royal Infirmary of Edinburgh. B A 17.82 Predictive factors in the identification of hypersensitivity pneumonitis • Exposure to a known offending antigen • Positive precipitating antibodies to offending antigen • Recurrent episodes of symptoms • Inspiratory crackles on examination • Symptoms occurring 4–8 hours after exposure • Weight loss Fig. 17.64 Asbestos-related benign pleural plaques. Chest X-ray showing extensive calcified pleural plaques ('candle wax' appearance – arrows), particularly marked on the diaphragm and lateral pleural surfaces.

 performed, asbestosis may be diagnosed when alveolar septal fibrosis is accompanied by an average of at least two asbestos bodies per square centimetre of lung tissue. In some cases, asbestos fibre counts may be performed on lung biopsy material to establish the diagnosis. Asbestosis is usually slowly progressive and has a better prognosis than IPF, but in advanced cases respiratory failure, pulmonary hypertension and cor pulmonale may still develop. About 40% of patients (who usually smoke) develop lung cancer and 10% may develop mesothelioma. Mesothelioma Mesothelioma is a malignant tumour affecting the pleura or, less commonly, the peritoneum. Its occurrence almost invariably suggests past asbestos exposure, which may be low-level. There is typically a long latent interval between first exposure and the onset of clinical manifestations, and this accounts for the continued increasing incidence many years after control measures have been implemented. Around 1 in 170 of all British men born in the 1940s will die of mesothelioma. Pleural mesothelioma typically presents with increasing breathlessness resulting from pleural effusion or unremitting chest pain, reflecting involvement of the chest wall. As the tumour progresses, it encases the underlying lung and may invade the parenchyma, the mediastinum and the pericardium. Metastatic disease, although not often clinically detectable in life, is a common finding on postmortem. Mesothelioma is almost invariably fatal. Highly selected patients may be considered for radical surgery but, in the majority of patients, therapy is invariably directed towards palliation of symptoms. The use of chemotherapy may improve quality of life and is accompanied by a small survival benefit, typically regarded as being around 3 months. Radiotherapy can be used to control pain and limit the risk of tumour seeding at biopsy sites. Pleural effusions are managed with drainage and pleurodesis. Typical figures for survival from onset of symptoms are around 16 months for epithelioid tumours, 10 months for sarcomatoid tumours and 15 months for biphasic tumours, with only a minority of patients surviving for longer periods. Occupational lung cancer Individuals exposed to substantial quantities of asbestos are at increased risk of lung cancer, particularly if they smoke tobacco. Increased risks of lung cancer have also been reported in workers who develop silicosis and those exposed to radon gas, beryllium, diesel exhaust fumes, cadmium, chromium, and dust and fumes from coke plants. Occupational pneumonia Occupational and environmental exposures may be linked to the development of pneumonia. Pneumococcal vaccine is recommended for welders. Farm workers, abattoir workers and hide factory workers may be exposed to Coxiella burnetii, the causative agent of Q fever. The organisms are excreted from milk, urine, faeces and amniotic fluid; they may be transmitted by cattle ticks or contaminated dust from the milking floor, or by drinking milk that is inadequately pasteurised. Birds (often parrots) or budgerigars infected with Chlamydia psittaci can cause psittacosis. Sewage workers, farmers, animal handlers and vets run an increased risk of leptospiral pneumonia, and contact diaphragm, pericardium or mediastinum. They are virtually always asymptomatic, usually being identified as an incidental finding on a chest X-ray (Fig. 17.64) or thoracic CT scan, particularly when partially calcified. They do not cause impairment of lung function and are benign. Acute benign asbestos pleurisy Benign asbestos pleurisy is estimated to occur in around 20% of asbestos workers but many episodes are subclinical and pass unreported. When symptomatic, patients present with features of pleurisy, including mild fever and systemic disturbance. The diagnosis therefore necessitates the exclusion of other known causes of pleurisy and pleural effusion. Repeated episodes may be followed by the development of diffuse (visceral) pleural thickening. Diffuse pleural thickening Diffuse pleural thickening (DPT) refers to thickening of the visceral pleura. In contrast to pleural plaques, if this is sufficiently extensive, it may cause restrictive lung function impairment, exertional breathlessness and, occasionally, persistent chest pain. The typical appearances of DPT on chest X-ray include thickening of the pleura along the chest wall and obliteration of the costophrenic angles. Earlier manifestations detected by CT scanning include parenchymal bands (Fig. 17.65) and ‘round atelectasis’. There is no treatment and the condition may be progressive in around one-third of individuals. In exceptionally severe cases, surgical decortication may be considered. A pleural biopsy may be required to exclude mesothelioma. Fig. 17.65 Thoracic CT scan showing right-sided pleural thickening and an associated parenchymal band. Asbestosis Fibrosis of the lung following asbestos exposure generally requires substantial exposure over several years and is rarely associated with low-level or bystander exposure. In common with other fibrosing lung diseases, asbestosis usually presents with exertional breathlessness and fine, late inspiratory crackles over the lower zones. Finger clubbing may be present. Pulmonary function tests and HRCT appearances are similar to those of UIP. These features, accompanied by a history of substantial asbestos exposure, are generally sufficient to establish the diagnosis and lung biopsy is rarely necessary. When biopsy is

Clinical features The diagnosis of pulmonary embolism (PE) may be aided by asking three questions: • Is the clinical presentation consistent with PE? • Does the patient have risk factors for

PE? • Are there any alternative diagnoses that can explain the patient's presentation? Clinical presentation varies, depending on number, size and distribution of emboli and on underlying cardiorespiratory reserve (Box 17.83). A recognised risk factor is present in 80–90% (see Box 23.65, p. 975). The presence of one or more risk factors increases the risk further still. Investigations A variety of non-specific radiographic appearances have been described (Fig. 17.66) but the chest X-ray is most useful in with rabbits, hares, muskrats and ground squirrels is associated with tularaemic pneumonia, caused by Francisella tularensis. Anthrax (wool-sorter's disease) may occur in workers exposed to infected hides, hair, bristle, bonemeal and animal carcases. Pulmonary vascular disease Pulmonary embolism The majority of pulmonary emboli arise from the propagation of lower limb deep vein thrombosis (p. 186). Rare causes include septic emboli (from endocarditis affecting the tricuspid or pulmonary valves), tumour (especially choriocarcinoma), fat following fracture of long bones such as the femur, air, and amniotic fluid, which may enter the mother's circulation following delivery. 17.83 Features of pulmonary thromboemboli Acute massive PE Acute small/medium PE Chronic PE Pathophysiology Major haemodynamic effects: ↓cardiac output; acute right heart failure Occlusion of segmental pulmonary artery → infarction ± effusion Chronic occlusion of pulmonary microvasculature, right heart failure Symptoms Faintness or collapse, crushing central chest pain, apprehension, severe dyspnoea Pleuritic chest pain, restricted breathing, haemoptysis Exertional dyspnoea Late: symptoms of pulmonary hypertension or right heart failure Signs Major circulatory collapse: tachycardia, hypotension, ↑JVP, RV gallop rhythm, loud P2, severe cyanosis, ↓urinary output Tachycardia, pleural rub, raised hemidiaphragm, crackles, effusion (often blood-stained), low-grade fever Early: may be minimal Later: RV heave, loud P2 Terminal: signs of right heart failure Chest X-ray Usually normal; may be subtle oligaemia Pleuropulmonary opacities, pleural effusion, linear shadows, raised hemidiaphragm Enlarged pulmonary artery trunk, enlarged heart, prominent right ventricle Electrocardiogram S1Q3T3 anterior T-wave inversion, RBBB Sinus tachycardia RV hypertrophy and strain Arterial blood gases Markedly abnormal with ↓PaO_2 and ↓$PaCO_2$, metabolic acidosis May be normal or ↓PaO_2 or ↓$PaCO_2$ Exertional ↓PaO_2 or desaturation on formal exercise testing Alternative diagnoses Myocardial infarction, pericardial tamponade, aortic dissection Pneumonia, pneumothorax, musculoskeletal chest pain Other causes of pulmonary hypertension (JVP = jugular venous pressure; PE = pulmonary embolism; RBBB = right bundle branch block; RV = right ventricular) Fig. 17.66 Features of pulmonary thromboembolism/infarction on chest X-ray. Pulmonary opacities (any size or shape, rarely lobar or segmental, can cavitate) Elevated hemidiaphragm Horizontal linear opacities (bilateral and usually in lower zones) Pleural effusion (usually blood-stained on aspiration) Wedge-shaped opacity Oligaemia of lung field Enlarged pulmonary artery

 Colour Doppler ultrasound of the leg veins may be used in patients with suspected PE, particularly if there are clinical signs in a limb, as many will have identifiable proximal thrombus in the leg veins. Bedside echocardiography is extremely helpful in the differential diagnosis and assessment of acute circulatory collapse (p. 199). Acute dilatation of the right heart is usually present in massive PE, and thrombus (embolism in transit) may be visible. Important differential diagnoses, including left ventricular failure, aortic dissection and pericardial tamponade, can also be identified. Conventional pulmonary angiography is still useful in selected settings or for the delivery of catheter-based therapies. Management General measures Prompt recognition and treatment are potentially life-saving. Sufficient oxygen should be given to hypoxaemic patients to maintain arterial oxygen saturation above 90%. Circulatory shock should be treated with intravenous fluids or plasma expander, but inotropic agents are of limited value as the hypoxic dilated right ventricle is already close to maximally stimulated by endogenous catecholamines. Diuretics and vasodilators should also be avoided, as they will reduce cardiac output. Opiates may be necessary to relieve pain and distress but should be used with caution excluding key differential diagnoses, e.g. pneumonia or pneumothorax. Normal appearances in an acutely breathless and hypoxaemic patient should raise the suspicion of PE, as should bilateral changes in anyone presenting with unilateral pleuritic chest pain. The ECG is often normal but is useful in excluding other important differential diagnoses, such as acute myocardial infarction and pericarditis. The most common findings in PE include sinus tachycardia and anterior T-wave inversion but these are non-specific; larger emboli may cause right heart strain revealed by an S1Q3T3 pattern, ST-segment and T-wave changes, or the appearance of right bundle branch block. Arterial blood gases typically show a reduced PaO_2 and a normal or low $PaCO_2$, and an increased alveolar–arterial oxygen gradient, but may be normal in a significant minority. A metabolic acidosis may be seen in acute massive PE with cardiovascular collapse. An elevated D-dimer (see Fig. 10.6, p. 187) is of limited value, as it may be raised in a variety of other conditions, including myocardial infarction, pneumonia and sepsis. However, low levels, particularly in the context of a low clinical risk, have a high negative predictive value and further investigation is usually unnecessary (Fig. 17.67). The result of the D-dimer assay should be disregarded in high-risk patients, as further investigation is mandatory even when normal. The serum troponin I (see Box 10.3, p. 179) may be elevated, reflecting right heart strain. CTPA is the first-line diagnostic test (Fig. 17.68). It has the advantage of visualising the distribution and extent of the emboli or highlighting an alternative diagnosis, such as consolidation, pneumothorax or aortic dissection. The sensitivity of CT scanning may be increased by simultaneous visualisation of the femoral and popliteal veins, although this is not widely practised. As the contrast media may be nephrotoxic, care should be taken in patients with renal impairment, and CTPA avoided in those with a history of allergy to iodinated contrast media. In these cases, either $\dot{V}/\dot{Q}$ scanning or ventilation/perfusion single photon emission computed tomography ($\dot{V}/\dot{Q}$ SPECT) may be considered. Fig. 17.67 Algorithm for the investigation of patients with suspected pulmonary thromboembolism. Clinical risk is based on the presence of risk factors for venous thromboembolism and the probability of another diagnosis. (DVT = deep vein thrombosis; PE = pulmonary embolism) • Ultrasound leg veins ± • CT pulmonary

angiogram or • V/Q scan (no previous cardiopulmonary disease) D-dimer –ve Risk high Assess clinical risk Measure D-dimer levels Venous thromboembolism suspected D-dimer –ve Risk low Not DVT/PE D-dimer +ve Risk low . . Risk high Treat Confirm diagnosis Fig. 17.68 CT pulmonary angiogram. The arrow points to a saddle embolism in the bifurcation of the pulmonary artery. 17.84 Pulmonary embolism in pregnancy • Maternal mortality: venous thromboembolism is the leading direct cause in the UK. • CT pulmonary angiography: may be performed safely (0.01– 0.06 mGy). It is important to consider the risk of radiation to breast tissue (particularly if there is a family history of breast carcinoma). • $\dot{V}/\dot{Q}$ scanning: greater radiation dose to fetus (0.11–0.22 mGy) but significantly less to maternal breast tissue. • In utero radiation exposure: estimated incidence of childhood malignancy is about 1 in 16 000 per mGy. • Warfarin: teratogenic, so pulmonary embolism should be treated with low-molecular-weight heparin during pregnancy.

Clinical features PH presents insidiously and is often diagnosed late. Typical symptoms include breathlessness, chest pain, fatigue, palpitation and syncope. Important signs include elevation of the JVP (with a prominent ‘a’ wave if in sinus rhythm), a parasternal heave (right ventricular hypertrophy), accentuation of the pulmonary component of the second heart sound and a right ventricular third heart sound. Signs of interstitial lung disease or cardiac, liver or connective tissue disease may suggest the underlying cause. Investigations PH is suspected if an ECG shows a right ventricular ‘strain’ pattern or a chest X-ray shows enlarged pulmonary arteries, peripheral pruning and right ventricle enlargement (Fig. 17.69). Doppler assessment of the tricuspid regurgitant jet by transthoracic echocardiography provides a non-invasive estimate of the PAP, which is equal to 4 × (tricuspid regurgitation velocity)2. Further assessment should be by right heart catheterisation to assess pulmonary haemodynamics, measure vasodilator responsiveness and thus guide further therapy. Management Specialist centres should direct the management of PH. Diuretic therapy should be prescribed for patients with right heart failure. Supplemental oxygen should be given to maintain resting PaO_2 in the hypotensive patient. External cardiac massage may be successful in the moribund patient by dislodging and breaking up a large central embolus. Anticoagulation The main principle of treatment for PE is anticoagulation, which is discussed for PE and other forms of VTE on page 975. Thrombolytic and surgical therapy Thrombolysis is indicated in any patient presenting with acute massive PE accompanied by cardiogenic shock. In the absence of shock, the benefits are less clear but thrombolysis may be considered in those presenting with right ventricular dilatation and hypokinesis or severe hypoxaemia. Patients must be screened carefully for haemorrhagic risk, as there is a high risk of intracranial haemorrhage. Surgical pulmonary embolectomy may be considered in selected patients but carries a high mortality. Caval filters A patient in whom anticoagulation is contraindicated, who has suffered massive haemorrhage on anticoagulation, or recurrent VTE despite anticoagulation, should be considered for an inferior vena caval filter. Retrievable caval filters are particularly useful in individuals with temporary risk factors. The caval filter should be used only until anticoagulation can be safely initiated, at which time the filter should be removed if possible. Prognosis Immediate mortality is greatest in those with echocardiographic evidence of right ventricular dysfunction or cardiogenic shock. Once anticoagulation is commenced, however, the risk of mortality rapidly falls. The risk of recurrence is highest in the first 6–12 months after the initial event, and at 10 years around one-third of individuals will have suffered a further event. Pulmonary hypertension Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) of at least 25 mmHg at rest, as measured by right heart catheterisation. The definition may be further refined by consideration of the pulmonary wedge pressure (PWP), the cardiac output and the transpulmonary pressure gradient (mean PAP − mean PWP). The clinical classification of PH is shown in Box 17.85. Further classification is based on the degree of functional disturbance, assessed using the New York Heart Association (NYHA) grades I–IV. Although respiratory failure due to intrinsic pulmonary disease is the most common cause of PH, severe PH may occur as a primary disorder, as a complication of connective tissue disease (e.g. systemic sclerosis), or as a result of chronic thromboembolic events. Primary pulmonary hypertension (PPH) is a rare but important disease that predominantly affects women aged between 20 and 30 years. Familial disease is rarer still but is known to be associated with mutations in the gene encoding type II bone morphogenetic protein receptor (BMPR2), a member of the transforming growth factor beta (TGF-β) superfamily. Mutations in this gene have been identified in some patients with sporadic PH. Pathological features include hypertrophy of both the media and the intima of the vessel wall and a clonal expansion of endothelial cells, which take on the appearance of plexiform lesions. There is marked narrowing of the vessel lumen and this, together with the frequently observed in situ thrombosis, leads to an increase in pulmonary vascular resistance and PH. Adapted from Dana Point 2008. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54:S43–S54. 17.85 Classification of pulmonary hypertension Pulmonary arterial hypertension • Primary pulmonary hypertension: sporadic and familial • Secondary to: connective tissue disease (limited cutaneous systemic sclerosis), congenital systemic to pulmonary shunts, portal hypertension, HIV infection, exposure to various drugs or toxins, and persistent pulmonary hypertension of the newborn Pulmonary venous hypertension • Left-sided atrial or ventricular heart disease • Left-sided valvular heart disease • Pulmonary veno-occlusive disease • Pulmonary capillary haemangiomatosis Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia • Chronic obstructive pulmonary disease • Diffuse parenchymal lung disease • Sleep-disordered breathing • Alveolar hypoventilation disorders • Chronic exposure to high altitude • Neonatal lung disease • Alveolar capillary dysplasia • Severe kyphoscoliosis Pulmonary hypertension caused by chronic thromboembolic disease • Thromboembolic obstruction of the proximal pulmonary arteries • In situ thrombosis • Sickle-cell disease Miscellaneous • Inflammatory conditions • Extrinsic compression of central pulmonary veins

 This is a worldwide problem, however, which may be aggravated during harvest seasons. Perennial allergic rhinitis may be a specific reaction to antigens derived from house dust, fungal spores or animal dander, but similar symptoms can be caused by physical or chemical irritants, e.g. pungent odours or fumes, including strong perfumes, cold air and dry atmospheres. The phrase ‘vasomotor rhinitis’ is often used in this context, as the term ‘allergic’ is a misnomer. Clinical features In the seasonal type, there are frequent sudden attacks of sneezing, with profuse watery nasal discharge and nasal obstruction. These attacks last for a few hours and are often accompanied by smarting and watering of the eyes and conjunctival irritation. In perennial rhinitis, the symptoms are similar but more continuous and usually less severe. Skin hypersensitivity tests with the relevant antigen are usually positive in seasonal allergic rhinitis but are less useful in perennial rhinitis. Management In those sensitised to house dust, simple measures, such as thorough dust removal from the bed area, leaving a window open and renewing old pillows, are often helpful. Avoidance of pollen and antigens from domestic pets, however desirable and beneficial, is usually impractical. The following medications, singly or in combination, are usually effective in both seasonal and perennial allergic rhinitis: • an antihistamine such as loratadine • sodium cromoglicate nasal spray • glucocorticoid nasal spray, e.g. beclometasone dipropionate, fluticasone, mometasone or budesonide. When symptoms are very severe, resistant to usual treatments and seriously interfering with school, business or social activities, immunotherapy (desensitisation) is also used but carries the risk of serious reactions and must be managed in specialist centres. Vasomotor rhinitis is often difficult to treat but may respond to ipratropium bromide, administered into each nostril 3 times daily. Sleep-disordered breathing A variety of respiratory disorders affect sleep or are affected by sleep. Cough and wheeze disturbing sleep are characteristic of asthma, while the hypoventilation that accompanies normal sleep can precipitate respiratory failure in patients with disordered ventilation due to kyphoscoliosis, diaphragmatic paralysis or muscle disease (e.g. muscular dystrophy). In contrast, a small but important group of disorders cause problems only during sleep. Patients may have normal lungs and daytime respiratory function, but during sleep have either abnormalities of ventilatory drive (central sleep apnoea) or upper airway obstruction (obstructive sleep apnoea). Of these, the obstructive sleep apnoea/hypopnoea syndrome is by far the most common and important. When this coexists with COPD, severe respiratory failure can result, even if the COPD is mild. The sleep apnoea/hypopnoea syndrome Recurrent upper airway obstruction during sleep, sufficient to cause sleep fragmentation and daytime sleepiness, is thought to affect 2% of women and 4% of men aged 30–60 in Caucasian populations. Daytime sleepiness, especially in monotonous situations, results in a threefold increased risk of road traffic accidents and a ninefold increased risk of single-vehicle accidents. above 8 kPa (60 mmHg). Anticoagulation should be considered unless there is an increased risk of bleeding. Digoxin may be useful in patients who develop atrial tachyarrhythmias. Pregnancy carries a very high risk of death and women of child-bearing age should be counselled appropriately. Excessive physical activity that leads to distressing symptoms should be avoided but otherwise patients should be encouraged to remain active. Pneumococcal and influenza vaccination should be recommended. Nitrates should be avoided owing to the risk of hypotension, and β-blockers are poorly tolerated. Cyclizine can aggravate PH and should also be avoided. Disease-targeted strategies have focused on replacing endogenous prostacyclins with infusions of epoprostenol or treprostinil or nebulised iloprost; blocking endothelin-mediated vasoconstriction with agents such as bosentan, ambrisentan or macitentan; or enhancing endogenous nitric oxide-mediated vasodilatation with phosphodiesterase V inhibitors, such as sildenafil or tadalafil, or the guanylate cyclase stimulator riociguat. High-dose calcium channel blockers may be appropriate in those with an acute vasodilator response. Selected patients are referred for double-lung transplantation, and pulmonary thrombo-endarterectomy may be contemplated in those with chronic proximal pulmonary thromboembolic disease. Atrial septostomy (the creation of a right-to-left shunt) decompresses the right ventricle and improves haemodynamic performance; it may be used as a bridge to transplantation or as a palliative measure. Diseases of the upper airway Diseases of the nasopharynx Allergic rhinitis This is a disorder in which there are episodes of nasal congestion, watery nasal discharge and sneezing. It may be seasonal or perennial, and is due to an immediate hypersensitivity reaction in the nasal mucosa. Seasonal antigens include pollens from grasses, flowers, weeds or trees. Grass pollen is responsible for hay fever, the most common type of seasonal allergic rhinitis in northern Europe, which is at its peak between May and July. Fig. 17.69 Chest X-ray showing the typical appearance in pulmonary hypertension.

threshold for diagnosing moderate sleep apnoea/hypopnoea syndrome is 15 or more apnoeas/hypopnoeas per hour of sleep, where an apnoea is defined as a 10-second or longer breathing pause and a hypopnoea a 10-second or longer 50% reduction in breathing. Several other conditions can cause daytime sleepiness but can usually be excluded by a careful history (Box 17.87). Narcolepsy is a rare cause of sudden-onset sleepiness, occurring in 0.05% of the population (p. 1105). Idiopathic hypersomnolence occurs in younger individuals and is characterised by long nocturnal sleeps. Management The major hazard to patients and those around them is traffic accidents, so drivers must be strongly advised not to drive until treatment has relieved their sleepiness. In a minority, relief of nasal obstruction or the avoidance of alcohol may prevent obstruction. Advice to obese patients to lose weight is often unheeded and the majority of patients need to use continuous Aetiology Sleep apnoea results from recurrent occlusion of the pharynx during sleep, usually at the level of the soft palate. Inspiration results in negative pressure within the pharynx. During wakefulness, upper airway dilating muscles, including palatoglossus and genioglossus, contract actively during inspiration to preserve airway patency. During sleep, muscle tone declines, impairing the ability of these muscles to maintain pharyngeal patency. In a minority of people, a combination of an anatomically narrow palatopharynx and under-activity of the dilating muscles during sleep results in inspiratory airway obstruction. Incomplete obstruction causes turbulent flow, resulting in snoring (44% of men and 28% of women aged 30–60 snore). More severe obstruction triggers increased inspiratory effort and transiently wakes the patient, allowing the dilating muscles to re-open the airway. These awakenings are so brief that patients have no recollection of them. After a series of loud deep breaths that may wake their bed partner, the patient rapidly returns to sleep, snores and becomes apnoeic once more. This cycle of apnoea and awakening may repeat itself many hundreds of times per night and results in severe sleep fragmentation and secondary variations in blood pressure, which may predispose over time to cardiovascular disease. Predisposing factors to the sleep apnoea/hypopnoea syndrome include male gender, which doubles the risk, and obesity, which is found in about 50% because parapharyngeal fat deposits tend to narrow the pharynx. Nasal obstruction or a recessed mandible can further exacerbate the problem. Acromegaly and hypothyroidism also predispose by causing submucosal infiltration and narrowing of the upper airway. Sleep apnoea is often familial, where the maxilla and mandible are back-set, narrowing the upper airway. Alcohol and sedatives predispose to snoring and apnoea by relaxing the upper airway dilating muscles. As a result of marked sympathetic activation during apnoea, sleep-disordered breathing is associated over time with sustained hypertension and an increased risk of coronary events and stroke. Associations have also been described with insulin resistance, the metabolic syndrome and type 2 diabetes. Treatment of sleep apnoea reduces sympathetic drive and blood pressure, and may also improve these associated metabolic disorders. Clinical features Excessive daytime sleepiness is the principal symptom and snoring is virtually universal. The patient usually feels that he or she has been asleep all night but wakes unrefreshed. Bed partners report loud snoring in all body positions and often have noticed multiple breathing pauses (apnoeas). Difficulty with concentration, impaired cognitive function and work performance, depression, irritability and nocturia are other features. Investigations Provided that the sleepiness does not result from inadequate time in bed or from shift work, anyone who repeatedly falls asleep during the day when not in bed, who complains that his or her work is impaired by sleepiness, or who is a habitual snorer with multiple witnessed apnoeas should be referred for a sleep assessment. A more quantitative assessment of daytime sleepiness can be obtained by questionnaire (Box 17.86). Overnight studies of breathing, oxygenation and sleep quality are diagnostic (Fig. 17.70) but the level of investigation depends on local resources and the probability of the diagnosis. The current 17.86 Epworth sleepiness scale How likely are you to doze off or fall asleep in the situations described below? Choose the most appropriate number for each situation from the following scale: 0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing • Sitting and reading • Watching TV • Sitting inactive in a public place (e.g. a theatre or a meeting) • As a passenger in a car for an hour without a break • Lying down to rest in the afternoon when circumstances permit • Sitting and talking to someone • Sitting quietly after a lunch without alcohol • In a car, while stopped for a few minutes in the traffic Normal subjects average 5.9 (SD 2.2) and patients with severe obstructive sleep apnoea average 16.0 (SD 4.4). Fig. 17.70 Sleep apnoea/hypopnoea syndrome: overnight oxygen saturation trace. The left-hand panel shows the trace of a patient who had 53 apnoeas plus hypopnoeas/hour, 55 brief awakenings/hour and marked oxygen desaturation. The right-hand panel shows the effect of continuous positive airway pressure (CPAP) of 10 cm H_2O delivered through a tight-fitting nasal mask: it abolished his breathing irregularity and awakenings, and improved oxygenation. Courtesy of Professor N.J. Douglas. ;PTLOYZ ;PTLOYZ 6_`NLU ZH[\YH[PVU the left recurrent laryngeal nerve, usually left-sided. One or both recurrent laryngeal nerves may be damaged by thyroidectomy, carcinoma of the thyroid or anterior neck injury. Rarely, the vagal trunk itself is involved by tumour, aneurysm or trauma. Clinical features and management Hoarseness always accompanies laryngeal paralysis, whatever its cause. Paralysis of organic origin is seldom reversible, but when only one vocal cord is affected, hoarseness may improve or even disappear after a few weeks, as the normal cord compensates by crossing the midline to approximate with the paralysed cord on phonation. ‘Bovine cough’ is a characteristic feature of organic laryngeal paralysis, and lacks the explosive quality of normal coughing because the cords fail to close the glottis. Sputum clearance may also be impaired. A normal cough in patients with partial loss of voice or aphonia virtually excludes laryngeal paralysis. Stridor is occasionally present but seldom severe, except when laryngeal paralysis is bilateral. Laryngoscopy is required to establish the diagnosis of laryngeal paralysis. The paralysed cord lies in the so-called ‘cadaveric’ position, midway between abduction and adduction. The cause should be treated, if possible. In unilateral paralysis, persistent dysphonia may be improved by the injection of Teflon into the affected vocal cord. In bilateral organic paralysis, tracheal intubation, tracheostomy or plastic surgery on the larynx may be necessary. Psychogenic hoarseness and aphonia Psychogenic causes of hoarseness or aphonia may be suggested by associated symptoms in the history (p. 1187). Laryngoscopy may be necessary, however, to exclude a physical cause. In psychogenic aphonia, only the voluntary movement of adduction of the vocal cords is seen to be impaired. Speech therapy may be helpful. Laryngeal obstruction Laryngeal obstruction is more liable to occur in children than in adults because of the smaller size of the glottis. Important causes are given in Box 17.89. Sudden complete laryngeal obstruction by a foreign body produces the clinical picture of acute asphyxia: positive airway pressure (CPAP) delivered by a nasal mask every night to splint the upper airway open. When CPAP is tolerated, the effect is often dramatic (Fig. 17.70), with relief of somnolence and improved daytime performance, quality of life and survival. Unfortunately, 30–50% of patients do not tolerate CPAP. Mandibular advancement devices that fit over the teeth and hold the mandible forward, thus opening the pharynx, are an alternative that is effective in some patients. There is no evidence that palatal surgery is of benefit. Laryngeal disorders The larynx is commonly affected by acute self-limiting infections (p. 581). Other disorders include chronic laryngitis, laryngeal tuberculosis, laryngeal paralysis and laryngeal obstruction. Tumours of the larynx are relatively common, particularly in smokers. For further details, the reader should refer to an otolaryngology text. Chronic laryngitis The common causes are listed in Box 17.88. The chief symptoms are hoarseness or loss of voice (aphonia). There is irritation of the throat and a spasmodic cough. The disease pursues a chronic course, frequently uninfluenced by treatment, and the voice may become permanently impaired. Other causes of chronic hoarseness include use of inhaled glucocorticoid treatment, tuberculosis, laryngeal paralysis or tumour. In some patients, a chest X-ray may reveal an unsuspected lung cancer or pulmonary tuberculosis. If these are not found, laryngoscopy should be performed to exclude a local structural cause. When no specific treatable cause is found, the voice must be rested completely. This is particularly important in public speakers and singers. Smoking should be avoided. Some benefit may be obtained from frequent inhalations of medicated steam. Laryngeal paralysis Interruption of the motor nerve supply of the larynx is nearly always unilateral and, because of the intrathoracic course of 17.87 Differential diagnosis of persistent sleepiness Lack of sleep • Inadequate time in bed • Extraneous sleep disruption (e.g. babies/children) • Shift work • Excessive caffeine intake •

Physical illness (e.g. pain) Sleep disruption • Sleep apnoea/hypopnoea syndrome • Periodic limb movement disorder (recurrent limb movements during non-REM sleep, frequent nocturnal awakenings; p. 1106) Sleepiness with relatively normal sleep • Narcolepsy • Idiopathic hypersomnolence (rare) • Neurological lesions (e.g. hypothalamic or upper brainstem infarcts or tumours) • Drugs Psychological/psychiatric • Depression 17.89 Causes of laryngeal obstruction • Inflammatory or allergic oedema, or exudate • Spasm of laryngeal muscles • Inhaled foreign body • Inhaled blood clot or vomitus in an unconscious patient • Tumours of the larynx • Bilateral vocal cord paralysis • Fixation of both cords in rheumatoid disease 17.88 Causes of chronic laryngitis • Repeated attacks of acute laryngitis • Excessive use of the voice, especially in dusty atmospheres • Heavy tobacco smoking • Mouth-breathing from nasal obstruction • Chronic infection of nasal sinuses

the mediastinum, such as carcinoma or lymphoma, eroding both the trachea and oesophagus to produce a communication between them. Swallowed liquids enter the trachea and bronchi through the fistula and provoke coughing. Surgical closure of a congenital fistula, if undertaken promptly, is usually successful. There is usually no curative treatment for malignant fistulae, and death from overwhelming pulmonary infection rapidly supervenes. Pleural disease Pleurisy, pleural effusion, empyema and asbestos-associated pleural disease have been described above. Pneumothorax Pneumothorax is the presence of air in the pleural space, which can either occur spontaneously, or result from iatrogenic injury or trauma to the lung or chest wall (Box 17.90). Primary spontaneous pneumothorax occurs in patients with no history of lung disease. Smoking, tall stature and the presence of apical subpleural blebs are risk factors. Secondary pneumothorax affects patients with pre-existing lung disease and is associated with higher mortality rates (Fig. 17.71). Where the communication between the airway and the pleural space seals off as the lung deflates and does not re-open, the violent but ineffective inspiratory efforts with indrawing of the intercostal spaces and the unsupported lower ribs, accompanied by cyanosis. Unrelieved, the condition progresses to coma and death within a few minutes. When, as in most cases, the obstruction is incomplete at first, the main clinical features are progressive breathlessness accompanied by stridor and cyanosis. Urgent treatment to prevent complete obstruction is needed. Management Transient laryngeal obstruction due to exudate and spasm, which may occur with acute pharyngitis in children and with whooping cough, is potentially dangerous but can usually be relieved by steam inhalation. Laryngeal obstruction from all other causes carries a high mortality and demands prompt treatment. When a foreign body causes laryngeal obstruction in children, it can often be dislodged by turning the patient head downwards and squeezing the chest vigorously. In adults, a sudden forceful compression of the upper abdomen (Heimlich manœuvre) may be effective. Otherwise, the cause of the obstruction should be investigated by direct laryngoscopy, which may also permit the removal of an unsuspected foreign body or the insertion of a tube past the obstruction into the trachea. Tracheostomy must be performed without delay if these procedures fail to relieve obstruction but, except in dire emergencies, this should be performed in theatre by a surgeon. In diphtheria, antitoxin should be administered, and for other infections the appropriate antibiotic should be given. In angioedema, complete laryngeal occlusion can usually be prevented by treatment with adrenaline (epinephrine; 0.5–1 mg (0.5–1 mL of 1 : 1000) IM), chlorphenamine maleate (10–20 mg by slow intravenous injection) and intravenous hydrocortisone sodium succinate (200 mg). Tracheal disorders Tracheal obstruction External compression by lymph nodes containing metastases, usually from a lung cancer, is a more frequent cause of tracheal obstruction than primary benign or malignant tumours. The trachea may also be compressed by a retrosternal goitre (see Fig. 18.12, p. 648). Rare causes include an aneurysm of the aortic arch and (in children) tuberculous mediastinal lymph nodes. Tracheal stenosis is an occasional complication of tracheostomy, prolonged intubation, granulomatosis with polyangiitis (Wegener’s granulomatosis; p. 1041) or trauma. Clinical features and management Stridor can be detected in every patient with severe tracheal narrowing. Bronchoscopic examination of the trachea should be undertaken without delay to determine the site, degree and nature of the obstruction. Localised tumours of the trachea can be resected but reconstruction after resection may be technically difficult. Endobronchial laser therapy, bronchoscopically placed tracheal stents, chemotherapy and radiotherapy are alternatives to surgery. The choice of treatment depends on the nature of the tumour and the general health of the patient. Benign tracheal strictures can sometimes be dilated but may require resection. Tracheo-oesophageal fistula This may be present in newborn infants as a congenital abnormality. In adults, it is usually due to malignant lesions in 17.90 Classification of pneumothorax Spontaneous Primary • No evidence of overt lung disease; air escapes from the lung into the pleural space through rupture of a small pleural bleb, or the pulmonary end of a pleural adhesion Secondary • Underlying lung disease, most commonly chronic obstructive pulmonary disease and tuberculosis; also seen in asthma, lung abscess, pulmonary infarcts, lung cancer and all forms of fibrotic and cystic lung disease Traumatic • Iatrogenic (e.g. following thoracic surgery or biopsy) or chest wall injury Fig. 17.71 Bimodal age distribution for hospital admissions for pneumothorax in England. The incidence of primary spontaneous pneumothorax peaks in males aged 15–30 years. Secondary spontaneous pneumothorax occurs mainly in males over 55 years.

Patient age (years) Male Female Rate per million population

 pneumothorax. CT is used in difficult cases to avoid misdirected attempts at aspiration. X-rays may also show the extent of any mediastinal displacement and reveal any pleural fluid or underlying pulmonary disease. Management Primary pneumothorax, in which the lung edge is less than 2 cm from the chest wall and the patient is not breathless, normally resolves without intervention. In young patients presenting with a moderate or large spontaneous primary pneumothorax, percutaneous needle aspiration of air is a simple and well-tolerated alternative to intercostal tube drainage, with a 60–80% chance of avoiding the need for a chest drain (Fig. 17.73). In patients with significant underlying chronic lung disease, however, secondary pneumothorax may cause respiratory distress. In these individuals, the success rate of aspiration is much lower, and intercostal tube drainage and inpatient observation are usually required, particularly in those over 50 years old and those with respiratory compromise. If there is a tension pneumothorax, immediate release of the positive pressure by insertion of a blunt cannula into the pleural space may be beneficial, allowing time to prepare for chest drain insertion. When needed, intercostal drains are inserted in the fourth, fifth or sixth intercostal space in the mid-axillary line, connected to an underwater seal or one-way Heimlich valve, and secured firmly pneumothorax is referred to as ‘closed’ (Fig. 17.72A). The mean pleural pressure remains negative, spontaneous reabsorption of air and re-expansion of the lung occur over a few days or weeks, and infection is uncommon. This contrasts with an ‘open’ pneumothorax, where the communication fails to seal and air continues to pass freely between the bronchial tree and pleural space (Fig. 17.72B). An example of the latter is a bronchopleural fistula, which can facilitate the transmission of infection from the airways into the pleural space, leading to empyema. An open pneumothorax is commonly seen following rupture of an emphysematous bulla, tuberculous cavity or lung abscess into the pleural space. Occasionally, the communication between the airway and the pleural space acts as a one-way valve, allowing air to enter the pleural space during inspiration but not to escape on expiration. This is a tension pneumothorax. Large amounts of trapped air accumulate progressively in the pleural space and the intrapleural pressure rises to well above atmospheric levels. This causes mediastinal displacement towards the opposite side, with compression of the opposite normal lung and impairment of systemic venous return, causing cardiovascular compromise (Fig. 17.72C). Clinical features The most common symptoms are sudden-onset unilateral pleuritic chest pain or breathlessness. In those individuals with underlying lung disease, breathlessness can be severe and may not resolve spontaneously. In patients with a small pneumothorax, physical examination may be normal. A larger pneumothorax (> 15% of the hemithorax) results in decreased or absent breath sounds (p. 547). The combination of absent breath sounds and a resonant percussion note is diagnostic of pneumothorax. By contrast, in tension pneumothorax there is rapidly progressive breathlessness associated with a marked tachycardia, hypotension, cyanosis and tracheal displacement away from the side of the silent hemithorax. Occasionally, tension pneumothorax may occur without mediastinal shift, if malignant disease or scarring has splinted the mediastinum. Investigations The chest X-ray shows the sharply defined edge of the deflated lung with complete translucency (no lung markings) between this and the chest wall (p. 547). Care must be taken to differentiate between a large pre-existing emphysematous bulla and a Fig. 17.72 Types of spontaneous pneumothorax. A Closed type. B Open type. C Tension (valvular) type. Tension type Mean pleural pressure positive, mediastinal shift to opposite side Closed type Mean pleural pressure negative Open type Mean pleural pressure atmospheric A B C 17.91 Pleural disease in old age • Spontaneous pneumothorax: invariably associated with underlying lung disease in old age and has a significant mortality. Surgical or chemical pleurodesis is advised in all such patients. • Rib fracture: common cause of pleural-type pain; may be spontaneous (due to coughing), traumatic or pathological. Underlying osteomalacia may contribute to poor healing, especially in the housebound with no exposure to sunlight. • Tuberculosis: should always be considered and actively excluded in any elderly patient presenting with a unilateral pleural effusion. • Mesothelioma: more common in older individuals than younger people due to a long latency period between asbestos exposure (often more than 20 years) and the development of disease. • Analgesia: frail older people are particularly sensitive to the respiratory depressant effects of opiate-based analgesia and careful monitoring is required when using these agents for pleural pain.

by pleural abrasion or parietal pleurectomy at thoracotomy or thoracoscopy. Diseases of the diaphragm and chest wall Disorders of the diaphragm Congenital disorders Diaphragmatic hernias Congenital defects of the diaphragm can allow herniation of abdominal viscera. Posteriorly situated hernias through the foramen of Bochdalek are more common than anterior hernias through the foramen of Morgagni. Eventration of the diaphragm Abnormal elevation or bulging of one hemidiaphragm, more often the left, results from total or partial absence of muscular development of the septum transversum. Most eventrations are asymptomatic and are detected by chance on X-ray in adult life but severe respiratory distress can be caused in infancy if the diaphragmatic muscular defect is extensive. Acquired disorders Elevation of a hemidiaphragm may result from paralysis or other structural causes (Box 17.92). The phrenic nerve may be damaged by lung cancer, disease of cervical vertebrae, tumours of the cervical cord, shingles, trauma (including road traffic and birth injuries), surgery, and stretching of the nerve by mediastinal masses and aortic aneurysms. Idiopathic diaphragmatic paralysis occasionally occurs in otherwise fit patients. Paralysis of one hemidiaphragm results in loss of around 20% of ventilatory capacity but may not be noticed by otherwise healthy individuals. Ultrasound screening can be used to demonstrate paradoxical upward movement of the paralysed hemidiaphragm on sniffing. CT of the chest and neck is the best way to exclude occult disease affecting the phrenic nerve. Bilateral diaphragmatic weakness occurs in peripheral neuropathies of any type, including Guillain–Barré syndrome (p. 1140); in disorders affecting the anterior horn cells, e.g. poliomyelitis (p. 1123); in muscular dystrophies; and in connective tissue disorders, such as SLE and polymyositis (pp. 1034 and 1039). Hiatus hernia is common (p. 791). Diaphragmatic rupture is usually caused by a crush injury and may not be detected until years later. Respiratory disorders that cause pulmonary hyperinflation, e.g. emphysema, and those that result in small stiff lungs, e.g. diffuse pulmonary fibrosis, compromise diaphragmatic function and predispose to fatigue. to the chest wall. Clamping of an intercostal drain is potentially dangerous and rarely indicated. The drain should be removed the morning after the lung has fully re-inflated and bubbling has stopped. Continued bubbling after 5–7 days is an indication for surgery. If bubbling in the drainage bottle stops before full re-inflation, the tube is either blocked or kinked or displaced. Supplemental oxygen may speed resolution, as it accelerates the rate at which nitrogen is reabsorbed by the pleura. Patients with a closed pneumothorax should be advised not to fly, as the trapped gas expands at altitude. After complete resolution, there is no clear evidence to indicate how long patients should avoid flying for, although British Thoracic Society guidelines suggest that waiting 1–2 weeks, with confirmation of full inflation prior to flight, is prudent. Patients should also be advised to stop smoking and informed about the risks of a recurrent pneumothorax. Diving is potentially dangerous after pneumothorax, unless a surgical pleurodesis has sealed the lung to the chest wall. Recurrent spontaneous pneumothorax After primary spontaneous pneumothorax, recurrence occurs within a year of either aspiration or tube drainage in approximately 25% of patients and should prompt definitive treatment. Surgical pleurodesis is recommended in all patients following a second pneumothorax and should be considered following the first episode of secondary pneumothorax if low respiratory reserve makes recurrence hazardous. Pleurodesis can be achieved Fig. 17.73 Management of spontaneous pneumothorax. (1) Immediate decompression prior to insertion of the intercostal drain. (2) Aspirate in the second intercostal space anteriorly in the mid-clavicular line using a 16 F cannula; discontinue if resistance is felt, the patient coughs excessively, or more than 2.5 L of air are removed. (3) The post-aspiration chest X-ray is not a reliable indicator of whether a pleural leak remains, and all patients should be told to attend again immediately in the event of deterioration. Mediastinal shift and/or hypotension (tension pneumothorax) Chronic lung disease Pneumothorax

> 15% of hemithorax or significant dyspnoea 50 years of age Observe patient for 6 hours Outpatient follow-up3 Intercostal tube drainage attached to underwater seal device Percutaneous needle aspiration2 2.5 L air aspirated or pneumothorax persists Yes1 Yes No No No No No Yes Yes Yes 17.92 Causes of elevation of a hemidiaphragm • Phrenic nerve paralysis • Eventration of the diaphragm • Decrease in volume of one lung (e.g. lobectomy, unilateral pulmonary fibrosis) • Severe pleuritic pain • Pulmonary infarction • Subphrenic

> abscess • Large volume of gas in the stomach or colon • Large tumours or cysts of the liver

628 • RESPIRATORY MEDICINE curved inwards. The heart is displaced to the left and may be compressed between the sternum and the vertebral column but only rarely is there associated disturbance of cardiac function. The deformity may restrict chest expansion and reduce vital capacity. Operative correction is rarely performed, and then only for cosmetic reasons. Pectus carinatum Pectus carinatum (pigeon chest) is frequently caused by severe asthma during childhood. Very occasionally, this deformity can be produced by rickets or be idiopathic. Further information Websites brit-thoracic.org.uk British Thoracic Society: access to guidelines on a range of respiratory conditions. ersnet.org European Respiratory Society: provides information on education and research, and patient information. ginasthma.com Global Initiative for Asthma: comprehensive overview of asthma. goldcopd.org Global Initiative for Chronic Obstructive Lung Disease: comprehensive overview of COPD. thoracic.org American Thoracic Society: provides information on education and research, and patient information. Deformities of the chest wall Thoracic kyphoscoliosis Abnormalities of alignment of the dorsal spine and their consequent effects on thoracic shape may be caused by: • congenital abnormality • vertebral disease, including tuberculosis, osteoporosis and ankylosing spondylitis • trauma • neuromuscular disease, such as poliomyelitis. Simple kyphosis (increased anterior curvature of the thoracic spine) causes less pulmonary embarrassment than kyphoscoliosis (anteroposterior and lateral curvature). Kyphoscoliosis, if severe, restricts and distorts expansion of the chest wall and impairs diaphragmatic function, causing ventilation–perfusion mismatch in the lungs. Patients with severe deformity may develop type II respiratory failure (initially manifest during sleep), pulmonary hypertension and right ventricular failure. They can often be successfully treated with non-invasive ventilatory support (p. 202). Pectus excavatum Pectus excavatum (funnel chest) is an idiopathic condition in which the body of the sternum, usually only the lower end, is

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