Chapter | **7** |

Occupational, environmental and iatrogenic lung disease

7.1 Occupational disease

This chapter deals with the pneumoconioses, occupational asthma, occupational fevers and the effects o£ toxic fume and gases. Occupational diseases of the lung considered elsewhere include the effects of atmospheric pressure changes (see p. 368), extrinsic allergic alveolitis (see p. 279), carcinoma of the lung (see p. 534) and asbestos-induced pleural disease (see pp. 714–729). Dusty occupations in general are also associated with an increased risk of chronic obstructive pulmonary disease.[1,2]

PNEUMOCONIOSIS: GENERAL FEATURES

Definition of pneumoconiosis

The term 'pneumoconiosis' is an abbreviation (and etymological corruption) of Zenker's pneumonokoniosis,[3] which derives from *pneumon* (lung) and *konis* (dust) and therefore translates as dusty lung;

in practice the term is confined to the effects of mineral dust on the lungs. Diseases caused by organic dusts are not included among the pneumoconioses and, in medicolegal practice at least, the presence of dust alone is insufficient to indicate pneumoconiosis: for compensation to be considered, the mineral dust must alter the structure of the lung and cause disability. The British Industrial Injuries Advisory Council defined pneumoconiosis as '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'.[4] Parkes recommends that cancer and asthma caused by mineral dust should also be excluded from the definition, an opinion with which we concur.[5]

Dust deposition in the lung

To reach the lung, dust particles have to be very small. Particle density and shape also affect the aerodynamic properties of dust. Host factors such as airflow characteristics, airway branching patterns and airway disease also affect dust deposition. Three deposition mechanisms are recognised (Fig. 7.1.1):

1. Inertial impaction: When air streams change direction or velocity, the inertia of the entrained particles causes them to maintain their original direction for a distance that depends upon their density and the square of their diameter. The same rules govern a car approaching a bend too fast: the car crashes into the outside of the bend.
2. Sedimentation (gravitational settlement): Under the influence of gravity, particles settle with a speed that is proportional to their density and the square of their diameter.
3. Diffusion: Very small airborne particles acquire a random motion as a result of bombardment by the surrounding gas molecules.

Inhaled dust particles are liable to sediment out in the alveoli if they have a diameter in the range of 1–5 μm, are roughly spherical in shape, and in density approximate to that of water. Larger or denser particles impact or precipitate on the walls of the conductive airways and are rapidly removed by ciliary action. Smaller particles may reach the alveoli but do not sediment so readily and many are therefore exhaled. Very small particles are deposited on the walls of alveoli by diffusion but because they are so small the total amount of dust deposited in this way is insignificant compared with that deposited by sedimentation (Fig. 7.1.2). Direct measurement shows that most lung dust (96%) has a particle diameter less than 2.5 μm.[6]

Fibrous dust particles behave differently. Fibres over 100 μm in length may reach the alveoli if they are very thin and remain aligned with the air stream. Fibre penetration is inversely related to path length and the number of bifurcations.[7] Tall people have longer conductive airways and experience more deposition in these sites than short people who have greater alveolar deposition for the same level of exposure.[8]

Slightly more dust is deposited in the right lung than the left, probably because the right main bronchus is more in line with the trachea, and is broader and shorter than the left, and carries 55% of the inhaled air.[9,10]

Dust clearance from the lung

Inhaled dust that settles in the conductive airways is removed within a day or two by ciliary action. Only dust that reaches the alveoli is liable to cause pneumoconiosis and much of this is also removed, but the clearance rate here is much slower: many coalminers continue to expectorate mine dust years after retirement. Alveolar clearance is
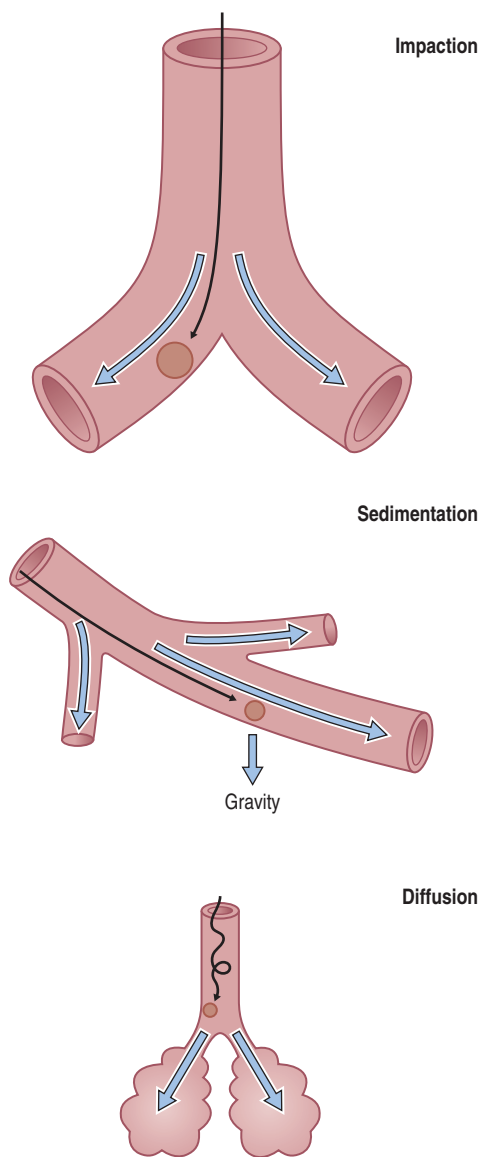
Figure 7.1.1 Mechanisms of particle deposition in the respiratory tract.

largely effected by macrophages, principally via the airways to the pharynx but also via lymphatics to the regional lymph nodes. The airway and interstitial routes interconnect at the bronchiolar level[11] where some dust-laden macrophages leave the interstitium for the air space.[12] This interconnection is probably the route utilised by circulating macrophages clearing other parts of the body of endogenous or exogenous particulate matter via the lung.[13] Long asbestos fibres present a particular problem to macrophage clearance. Some minerals, notably chrysotile asbestos, undergo slow physicochemical dissolution in the lungs.

Only a small fraction of the inhaled dust gains access to the interstitium, a necessary step if it is to cause pneumoconiosis. Some free dust enters through the bronchus-associated lymphoid tissue[11,12] and some is taken up by, or pierces, the alveolar epithelium (Fig. 1.34, p. 21).[14–16] Some of this is transported within hours to the hilar lymph nodes.[17] So rapid is this translocation that it is thought not to involve
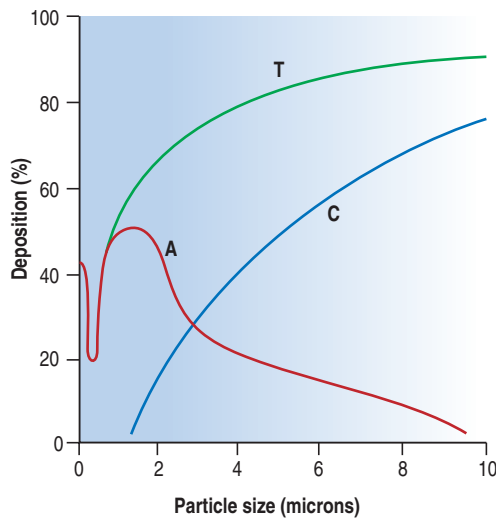
Figure 7.1.2 Percentage dust deposition in the respiratory tract according to particle diameter. The major alveolar impact is that of particles 1–3 μm diameter. Submicron particles are of negligible mass. T, total dust deposition; C, deposition on the ciliated epithelium; A, alveolar deposition.

phagocytes, although interstitial macrophages are undoubtedly important in continuing the transportation of dust to the nodes. Ultrafine dust particles are particularly liable to be transported across the alveolar epithelium.[11] The integrity of the alveolar epithelium is very important to dust translocation from the air spaces to the interstitium. Much more dust reaches the interstitium if the epithelium is damaged.[18,19]

It is widely thought that macrophages that have left the interstitium for the alveolar space never return,[17,20] but this is probably untrue.[21] Heavily laden macrophages accumulate in alveoli bordering the terminal and respiratory bronchioles, eventually filling them completely. Erosion of the alveolar epithelium permits re-entry of these macrophages into the interstitium,[22] very close to foci of bronchial mucosa-associated lymphoid tissue (MALT), which are found near the terminal bronchioles.[23] These aggregates guard the mouths of lymphatics, which commence at this point; alveoli are devoid of lymphatics. Dust-laden interstitial macrophages accumulate in and around the bronchial MALT, which Macklin therefore referred to as dust sumps.[24] Most pneumoconiotic lesions are found in the region of the dust sumps and are therefore focal. Asbestosis is diffuse rather than focal because the long asbestos fibres are not readily mobilised and cannot be concentrated in the centriacinar dust sumps. This is also seen on occasion with platy non-fibrous dusts such as talc, mica, kaolinite and feldspar.[25–33] Within the dust sumps the dust particles are not static. They are constantly being freed and reingested by interstitial macrophages and, because these cells are mobile, successively inhaled dusts soon become intimately mixed.[34] Macrophages play an important role in pneumoconiosis and if the dust is fibrogenic the repeated phagocytosis of indestructible mineral particles results in constant fibroblast stimulation.

The zonal distribution of pneumoconiosis

Pneumoconiosis affects both lungs but seldom evenly and some pneumoconioses show characteristic patterns of lung involvement. In most, the lesions are more numerous and better developed in the upper lobes than the bases but the reverse is true of asbestosis. The reasons for this are complex but undoubtedly involve the dust deposition:clearance ratio for the effect of the dust will depend upon both its amount and the duration of its stay in the lungs. There are well-recognised regional differences in the distribution and clearance of inhaled material, which in turn are dependent upon man's upright posture, the consequent gravitational forces being maximal at the apices.[35] When standing at rest, the apices of the lungs are hardly perfused, so that lymph formation and clearance are much better at the bases.[36–38] Similarly, the apices are relatively less well aerated; alveoli in the lower lobes receive more air than those in the upper lobes.[37,39] The greater respiratory excursions at the bases are thought to promote macrophage mobility there. It is to be expected therefore that the bases would both receive and clear more dust than the apices, rendering it difficult to predict on theoretical grounds which parts of the lungs carry the heaviest dust burden. In fact, more dust of all types is found in the upper lobes, the part most severely affected by every type of pneumoconiosis except asbestosis.[40,41] The predilection of asbestos to affect the periphery of the lower lobes is attributed to the dangerous long asbestos fibres preponderating there.[41,42]

Pulmonary reactions to mineral dust

The main tissue reaction to mineral dust is fibrosis. Silica is highly fibrogenic and is therefore very likely to cause pneumoconiosis. Carbon is non-fibrogenic and therefore, unless there are complications, coal pneumoconiosis causes little disability. Tin too is harmless, and stannosis therefore unimportant, although the chest radiograph is highly abnormal because tin is very radiopaque. Stannosis is one of several terms that specify pneumoconiosis due to a particular mineral, the best known being silicosis, asbestosis and anthracosis. Table 7.1.1 summarises the various pulmonary reactions to mineral dust.

Identification of the dust

The blackness of carbon and red-brown colour of iron give ample evidence, both naked-eye and microscopically, of the type and amount of these dusts when they are present in the lung (Fig. 7.1.3), but other inorganic dusts may be more difficult to identify. However, a flick-out substage condenser and Polaroid filters to test for refractility and birefringence respectively are useful adjuncts that are too often neglected by the histopathologist. Crystalline silica is traditionally regarded as being only weakly birefringent, in contrast to silicates which generally show up brightly with simple crossed Polaroid filters.[43] However, with modern microscope lamps, if the light source is set at high intensity when using Polaroid filters, both silica and silicates are birefringent.[44] Mineralogists use polarising microscopy for analysis, but only by studying large polished crystals with controlled orientation of the light. The small dust particles found in tissue sections are too small to permit analysis by this technique but it is nevertheless very useful for detecting their presence (Fig. 7.1.4).

Particle shape gives a useful indication of mineral type but appearances are sometimes deceptive: the plate-like crystals of talc are seldom observed as such, usually being viewed edge-on, when they appear to be needle-shaped. Occasionally, stains can be used to identify minerals, e.g. a modified Perls' reaction for inhaled iron, and Irwin's aluminon stain for aluminium, but these too have largely been replaced by modern analytical techniques.

Table 7.1.1 Pulmonary reactions to mineral dust

Pulmonary reaction	Examples
Macrophage accumulation with a little reticulin deposition	Anthracosis Siderosis Stannosis Baritosis Coal pneumoconiosis (macules) Aluminium pneumoconiosis (granular aluminium)
Nodular or massive fibrosis	Silicosis Mixed-dust pneumoconiosis Coal pneumoconiosis (nodules)
Diffuse fibrosis	Asbestosis Hard-metal pneumoconiosis Aluminium pneumoconiosis (aluminium fume and stamped aluminium)
Epithelioid and giant cell granulomas	Chronic berylliosis
Alveolar lipoproteinosis	'Acute' silicosis, but also seen with heavy exposure to other dusts (see p. 317)
Small-airway disease	Various dusts (see p. 123)

Microincineration combined with dark-field microscopy can also be used to demonstrate small particles. Incombustible mineral particles that cannot be seen with bright-field or polarising microscopy are rendered visible by this technique and their position on the slide can be compared with tissue reactions evident in a serial section that has not been incinerated. Microincineration has, however, also been largely replaced by modern analytical techniques that will now be considered.

Analytical electron microscopy is very helpful in identifying minerals, whether applied to lung digests or tissue sections.[45–48] Scanning electron microscopy permits the examination of thicker sections than transmission electron microscopy but does not detect very small particles. However, scanning electron microscopy allows more tissue to be examined and avoids the difficulty of cutting mineral particles with an ultramicrotome.

Mineral particles in a 5-µm thick deparaffinised section can be recognised in a scanning electron microscope set to collect the back-scattered electrons.[46] The instrument can then be focused on points of potential interest and switched to X-ray diffraction, which provides information on crystal structure (Fig. 7.1.5). Alternatively, elemental analysis may be undertaken with either energy-dispersive or wavelength-dispersive X-ray spectroscopy. With energy-dispersive X-ray spectroscopy, all elements of atomic number above 11 are identified, whilst with wavelength-dispersive X-ray spectroscopy the section can be scanned for one particular element. With the former technique different elements are shown graphically as individual
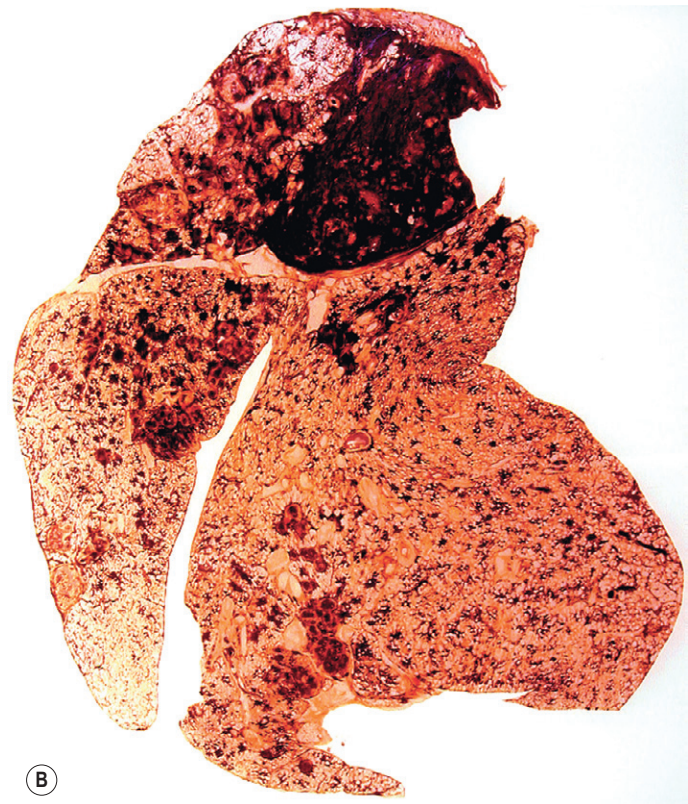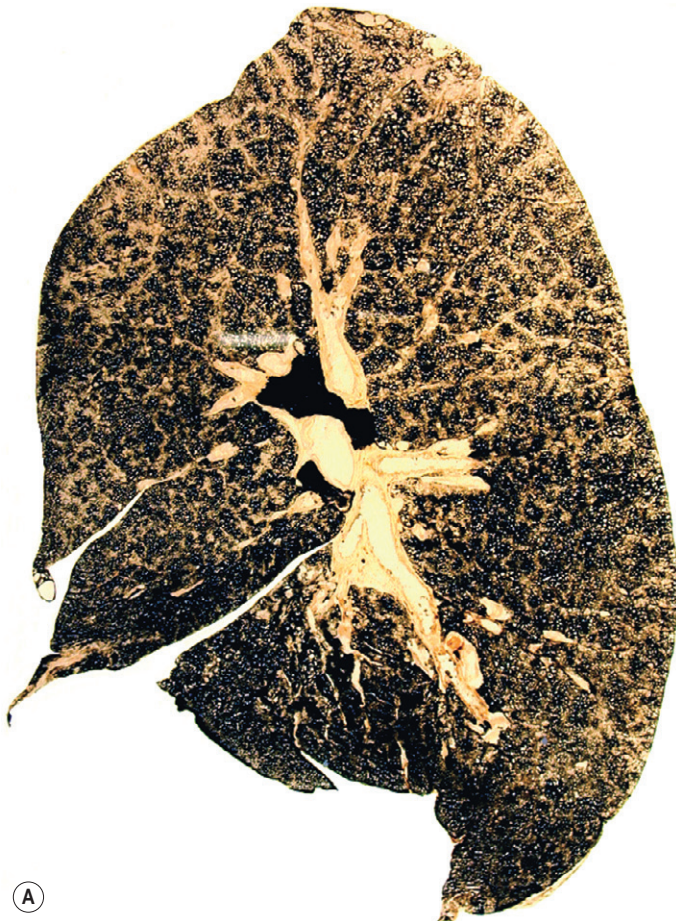
Figure 7.1.3 (A) Coal and (B) haematite miner's lungs. The respective black and red colours of these lungs give a good indication of their mineral content. Paper-mounted whole-lung sections. *(Courtesy of WGJ Edwards, London, UK.)*
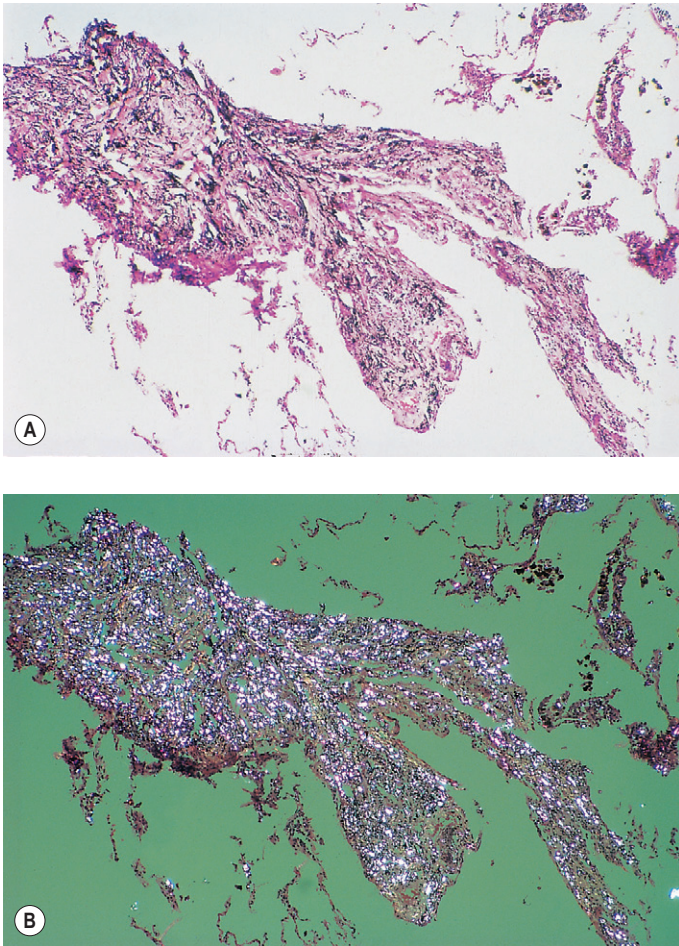
Figure 7.1.4 Talc pneumoconiosis. Only carbon is evident when the lesions are viewed with (A) non-polarised light, whereas the abundant talc particles are readily seen when (B) polarised light is employed.

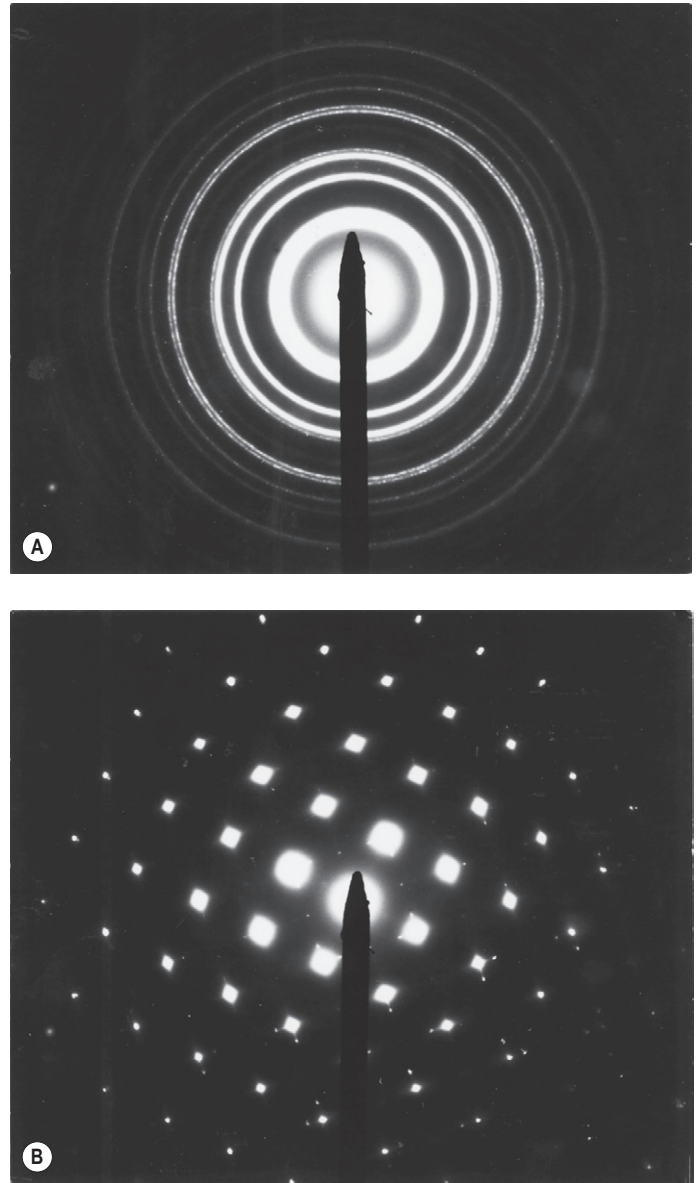**Figure 7.1.5** Electron diffraction patterns of gold, used for calibration purposes. The ring pattern (A) indicates that the material is polycrystalline and the spot pattern (B) indicates that it is a single crystal: amorphous materials give no regular pattern. The spacing of the rings gives information on crystalline structure and can be usefully applied to distinguish the various crystalline forms of silica (quartz, tridymite, cristobalite) for example. *(Courtesy of Dr M Wineberg, London, UK.)*

peaks, the heights of which are proportional to the amounts of the different elements within the particle studied, thereby giving information on probable molecular formula (Fig. 7.1.6). Thus, different silicates can be distinguished from each other and also from silica, which registers as pure silicon, oxygen (atomic number 8) not being detected. The fact that the elements of low atomic number that constitute organic chemicals are not detected means that any minerals present (except beryllium, atomic number 4) can be recognised easily in tissue sections. Only particles can be analysed however: elements present in only molecular amounts cannot be detected by X-ray analysis.

The detection of trace amounts of substances such as beryllium requires bulk chemical analysis or techniques that are not widely available such as atomic absorption spectrometry, neutron activation analysis and microprobe mass spectrometry.[49,50] The last of these techniques can also provide molecular (as opposed to elemental) analysis of organic as well as inorganic particles.[51] Another analytical technique of interest is microscopic infrared spectroscopy which provides data on the compound nature of microscopic particles in tissue sections (Fig. 7.1.7). Micro-Raman spectroscopy is also useful in this respect. Some metals cause hypersensitivity, which can be identified by exposing the patient's lymphocytes to metals and measuring their reaction in vitro.[52]

Radiological grading of pneumoconiosis

A scheme for grading pneumoconiosis radiologically by comparison with standard radiographs has been adopted by the International Labour Organisation (ILO) and is widely used.[53] Small opacities (up to 1 cm diameter) are graded by their profusion, 1, 2 and 3 indicating
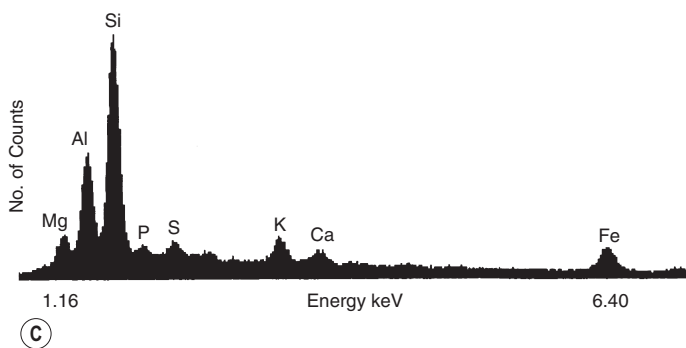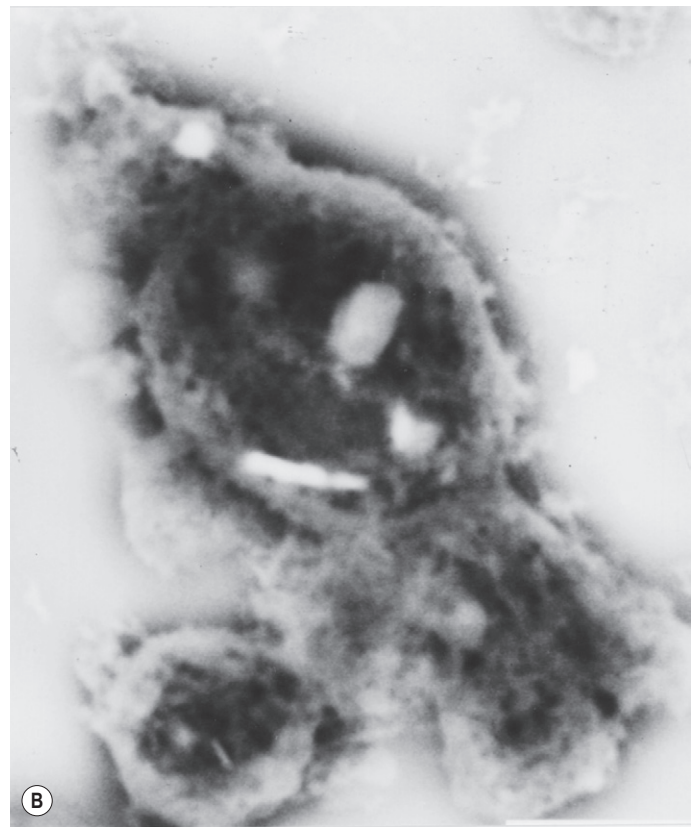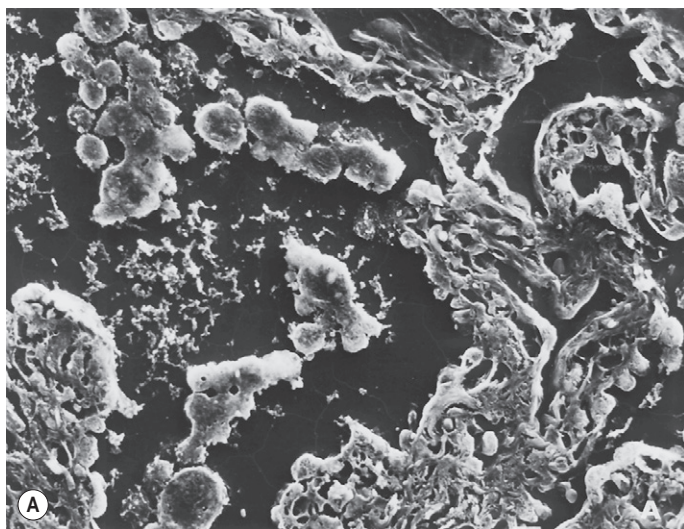
Figure 7.1.6 Dust particles in the lung: electron microprobe analysis. (A) The secondary (scanning) electron microscopic image of a deparaffinised 5-μm-thick section of lung showing clumps of macrophages in an alveolar lumen. (B) Back-scattered scanning electron microscopic image showing three of the macrophages at higher power: several bright particles worthy of further attention are evident. (C) X-ray energy spectrum of one of the particles showing it to be a silicate. The section had been transferred from a glass to a Perspex slide to avoid background signals, glass being siliceous. Each element emits a unique energy pattern when bombarded by electrons while the number of counts is in proportion to the amount of the particular element that is present in the particle. *(Courtesy of Professor DA Levison, Dundee, UK.)*
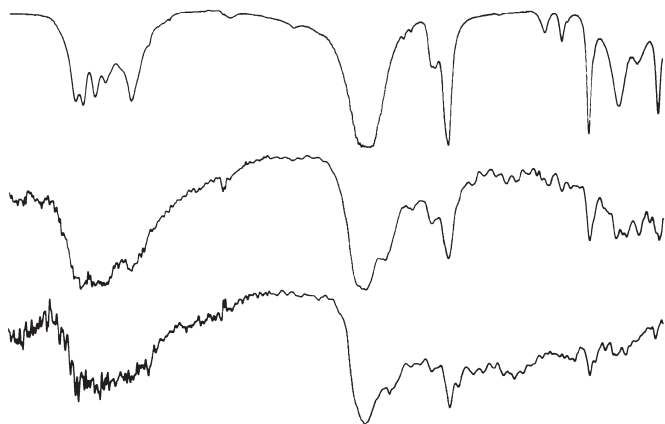
Figure 7.1.7 Infrared spectra of calcium oxalate. Top, reference standard; centre and bottom, crystals in human tissue sections. *(Courtesy of Professor DA Levison, Dundee, UK.)*

increasing numbers, and by their size, increasing through p, q and r if rounded and s, t and u if irregular. Type p opacities are described as punctiform and measure up to 1.5 mm in diameter; larger lesions up to 3 mm in diameter (type q) are described as micronodular or miliary; and those over 3 mm and up to 1 cm in diameter (type r) are described as nodular. Irregular opacities cannot be sized so accurately, s, t and u indicating fine, medium and coarse respectively. Large opacities (over 1 cm diameter) are graded by their combined size, increasing through A, an opacity measuring between 1 and 5 cm in diameter; B, one or more opacities whose combined area does not exceed the equivalent of one-third of the area of the right lung field (when they are regrouped in the mind's eye or measured with a transparent ruler); and C, one or more opacities whose combined area exceeds one-third of the area of the right lung field (when similarly regrouped). In coalworkers, small opacities (up to 1 cm diameter) correspond to simple coalworker's pneumoconiosis and large opacities (over 1 cm diameter) to complicated coalworker's pneumoconiosis, which is also known as progressive massive fibrosis.

SILICOSIS[43]

Mineralogy

Silicosis is caused by the inhalation of silica (silicon dioxide, SiO_2), which is to be distinguished from the silicates, these being more complex compounds in which silicon and oxygen form an anion combined with cations such as aluminium and magnesium: talc, for example, is a hydrated magnesium silicate with the formula $Mg_3Si_4O_{10}(OH)_2$. The element silicon is also to be distinguished from the synthetic organic polymer silicone, used in implants.

Crystalline silica is highly fibrogenic whereas amorphous silica and silicates other than asbestos are relatively inert. Silica exists in several crystalline forms, of which quartz, cristobalite and tridymite are the most important: tridymite is the most fibrogenic and cristobalite more so than quartz.[43,54]

Occupations at risk

Silicotic lesions have been identified in the lungs of Egyptian mummies, and the injurious effects on the lungs of inhaling mine dust have been recognised for more than 400 years. As long ago as the sixteenth century in Joachimsthal, Bohemia (now Jachymov, Czech Republic), diseases of miners' lungs were attributed to the dust the miners breathed. Silicosis, tuberculosis and lung cancer are all now known to have been prevalent among the miners in this region, the cancer being largely attributable to the high level of radioactivity in the mines.

Silicosis was recognised in the UK soon after the discovery in 1720 that the addition of calcined flint to the clay from which china is made produced a finer, whiter and tougher ware. The preparation and use of this flint powder were highly dangerous, causing the condition known as potter's rot, one of the first of the many trade names by which silicosis has since been known. Aluminium oxide (alumina) now provides a safe, effective substitute for flint in this industry.

In 1830 it was noted that Sheffield fork grinders who used a dry grindstone died early, and amongst other preventive measures it was recommended that the occupation should be confined to criminals: fortunately for them, the substitution of carborundum (silicon carbide) for sandstone was effective enough. However, silicosis still occurs in some miners, tunnellers, quarrymen, stone dressers and metal workers.

Silica in one form or another is used in many trades – in the manufacture of glass and pottery, in the moulds used in iron foundries, as an abrasive in grinding and sandblasting, and as a furnace lining that is refractory to high temperatures. Rocks such as granite and sandstone are siliceous and their dusts are encountered in many mining and quarrying operations. In coal mining in the UK the highest incidence of the disease was in pits where the thinness of the coal seams required the removal of a large amount of siliceous rock, a process known as 'hard heading'. In South Africa, silicosis causes a high mortality among the gold miners on the Witwatersrand, where the metallic ore is embedded in quartz. Slate is a metamorphic rock that contains both silica and silicates, and slateworkers develop both silicosis and mixed-dust pneumoconiosis.[55,56] Nor are rural industries immune from the disease, particularly if ventilation is inadequate, as it is in certain African huts where stone implements are used to pound meal and the occupants develop mixed-dust pneumoconiosis.[57] Silicosis and mixed-dust pneumoconiosis have also been reported in dental technicians.[58]

Desert sand is practically pure silica but the particles are generally too large to reach the lungs. However, silicosis has been reported in inhabitants of the Sahara, Libyan and Negev deserts and those living in windy valleys high in the Himalayan mountains,[59–65] whilst in California the inhalation of dust raised from earth has led to silicate pneumoconiosis in farm workers,[66] horses[67] and a variety of zoo animals.[68]

The silica in rocks such as granite, slate and sandstone is largely in the form of quartz and this is therefore the type of silica encountered in most of the industries considered above. Cristobalite and tridymite, which are possibly even more fibrogenic than quartz, are more likely to be encountered in the ceramic, refractory and diatomaceous earth industries where processing involves high temperatures.

Clinical features

Many workers with silicosis are asymptomatic. As a general rule, exposure to silica dust extends over many years, often 20 or more, before the symptoms of silicosis first appear: by the time the disease becomes overt clinically, much irreparable damage has been inflicted on the lungs. The initial symptoms are cough and breathlessness. From then onwards, respiratory disability progresses, even if the patient is no longer exposed to silica dust. Ultimately, there may be distressing dyspnoea with even the slightest exercise.

Silicosis sometimes develops more rapidly, perhaps within a year or so of first exposure. Such 'acute silicosis' was observed in the scouring powder industry in the 1930s when these cleansing agents consisted of ground sandstone mixed with a little soap and washing soda.[69,70] The additives were considered to have rendered the silica in the sandstone more dangerous but it is possible that the rapidity of onset of the disease merely reflected the intensity of the dust cloud to which the packers were exposed. Confusingly, the term 'acute silicosis' has since been applied to a further effect of heavy dust exposure in tunnellers, sand blasters and silica flour workers, namely pulmonary alveolar lipoproteinosis (see below),[71,72] whilst the terms 'accelerated silicosis' or 'cellular phase silicosis' have been substituted for 'acute silicosis' in referring to the rapid development of early cellular lesions.[43,73]

The time from first exposure to the development of symptoms (the latency period) is inversely proportional to the exposure level. However, it is evident that a certain amount of silica can be tolerated in the lungs without fibrosis developing, indicating either a time factor in the pathogenetic process or a threshold dust load that has to be reached before fibrosis develops.

Pathological findings

Silica particles that are roughly spherical in shape and of a diameter in the range of 1–5 μm sediment out in the alveoli and are concentrated within macrophages at Macklin's dust sumps, as explained previously (see p. 27). Early lesions, as seen in so-called accelerated or cellular phase silicosis, consist of collections of macrophages separated by only an occasional wisp of collagen. The early lesions have been likened to granulomas and on occasion have been mistaken for Langerhans cell histiocytosis or a storage disorder, but Langerhans cells are scanty and the histiocytes contain dust particles rather than accumulated lipid or polysaccharide. The macrophages of the early lesion are gradually replaced by fibroblasts and collagen is laid down in a characteristic pattern. The mature silicotic nodule is largely acellular and consists of hyaline collagen arranged in a whorled pattern, the whole lesion being well demarcated (Fig. 7.1.8) and sometimes calcified. Small numbers of birefringent crystals are generally evident within the nodules when polarising filters are used, but these mainly represent silicates such as mica and talc, inhaled with the silica. Silica particles are generally considered to be only weakly birefringent,[43] but fairly strong birefringence is evident in strong light (see above).[44]
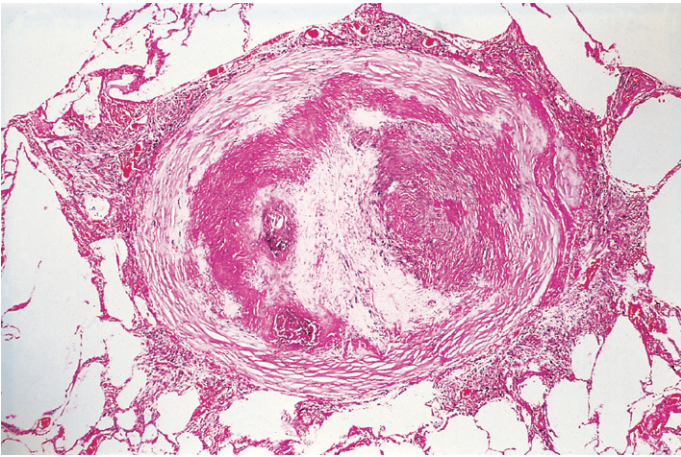
Figure 7.1.8 A silicotic nodule consisting of hyaline collagen arranged in a whorled pattern.

The silicotic nodules are situated in the centres of the pulmonary acini and are more numerous in the upper zones than the bases (Fig. 7.1.9A). They measure up to 5 mm across and are hard and easily palpable. They are grey if caused by relatively pure silica but black in coalminers and red in haematite miners.

Silicotic nodules develop first in the hilar lymph nodes and are generally better developed there than in the lungs.[74–76] Indeed, silicotic nodules are occasionally found in the hilar lymph nodes of persons who have no occupational history of exposure to silica and whose lungs are free of such lesions, the silica in the nodes being presumed to represent inhaled particles derived from quartz-rich soil.[77] Severely affected lymph nodes often calcify peripherally, giving a characteristic eggshell-like radiographic pattern. This is sometimes the only radiological abnormality.[76] Such enlarged lymph nodes may occasionally press upon and obstruct adjacent large bronchi[78] or result in a left recurrent laryngeal nerve palsy,[79] so simulating malignancy.[80] Sometimes the nodules develop within the walls of major bronchi, occasionally causing a middle-lobe syndrome (see p. 92).[81] Silicotic nodules are also found along the lines of the pleural lymphatics[75,82] where they have been likened to drops of candle wax on the visceral pleura. Very rarely, silica-induced fibrosis is more pronounced in the pleura than in the lungs.[83]

Lung tissue between the nodules is often quite normal and not until the process is very advanced is there any disability (Fig. 7.1.9B). In severe cases large masses of fibrous tissue are formed, which may undergo central necrosis and cavitation (Fig. 7.1.10).[84] On close inspection it is evident that these consist of conglomerations of many silicotic nodules closely packed together. In such severe cases cor pulmonale develops. Occasionally, silicotic nodules develop in the abdominal as well as the thoracic lymph nodes, and in the liver, spleen, peritoneum and bone marrow.[85–89]

In about 10% of cases, the typical pulmonary nodules that predominantly affect the upper lobes are accompanied by diffuse fibrosis that is maximal in the lower lobes.[27,33,90–92] The latter may show 'honeycombing' and closely resemble idiopathic pulmonary fibrosis. The association is too common to be explained by chance and the diffuse fibrosis is therefore regarded as a further manifestation of the pneumoconiosis, possibly due to an interaction between the dust and the immunological factors discussed below.

Pathogenesis

The pathogenesis of silicosis has excited much interest and many different theories have been advanced over the years. An early theory held
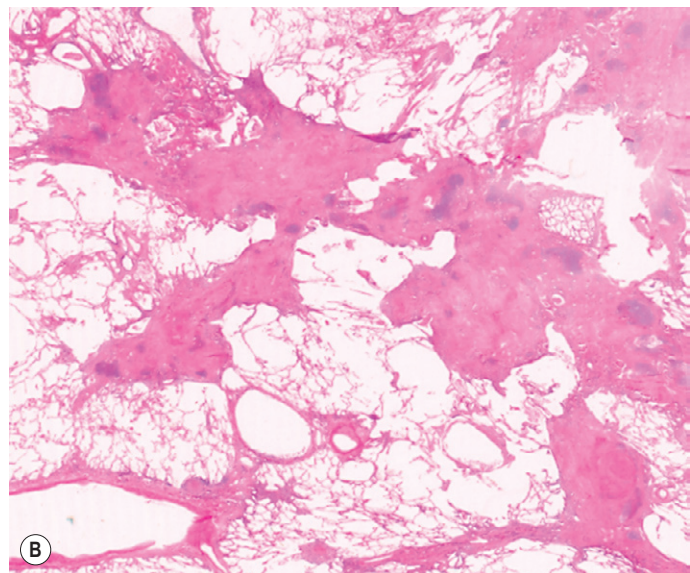
Figure 7.1.9 Silicosis. (A) The nodules are most numerous in the upper part of the lung where there is a conglomerate silicotic mass at one point. Paper-mounted whole-lung section. (B) Microscopy shows silicotic nodules scattered throughout otherwise normal lung tissue.

that the hardness of the silica was responsible, but this was discounted by the observation that silicon carbide (carborundum) is harder than silica but is non-fibrogenic. Theories based on the piezoelectric property and on the solubility of silica were successively abandoned although the latter had a long period of popularity. It gained
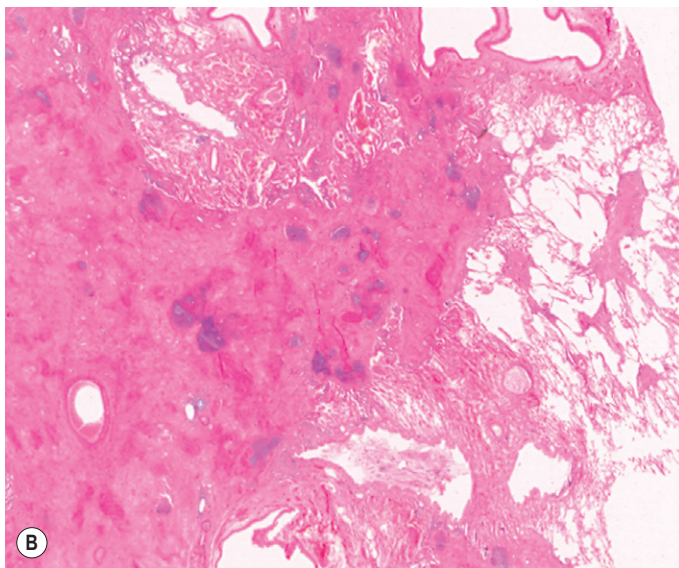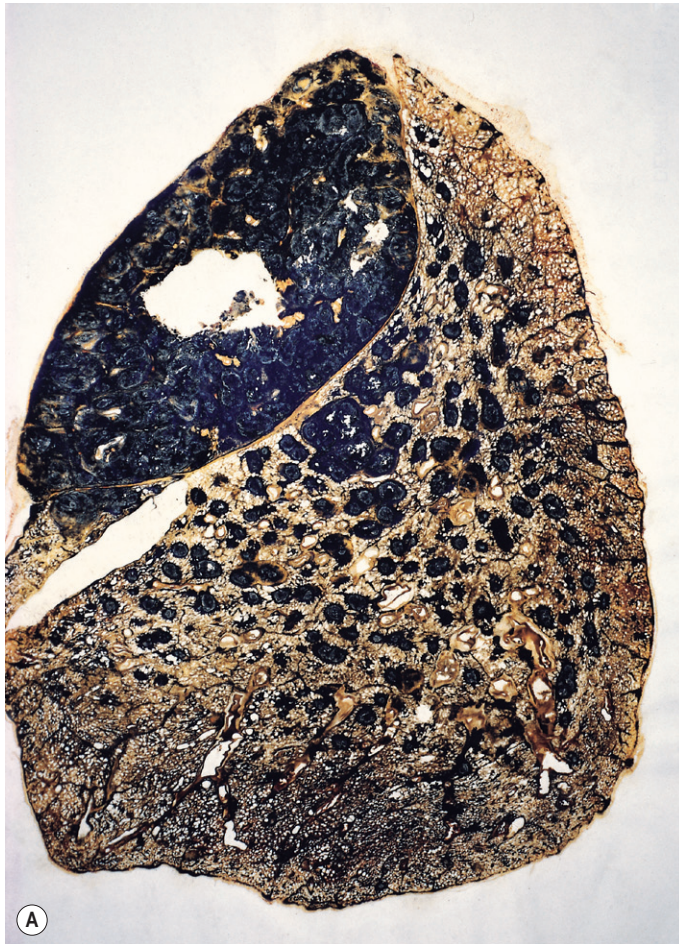
Figure 7.1.10 Silicosis. (A) The nodules are larger than in Figure 7.1.9a and have fused together. Cavitating conglomerate silicosis destroys most of the upper lobe. Paper-mounted whole-lung section. (B) Microscopy of conglomerate silicosis.

support from Kettle's experiments which showed that fibrosis developed about chambers placed in an animal's peritoneal cavity if the chambers contained silica powder sealed in by a collodion membrane through which solutes such as silicic acid could pass. However, it was later shown that the pores in a collodion membrane are quite irregular in size and when the experiments were repeated using chambers guarded by millipore membranes, no fibrosis developed, despite solutes being able to diffuse out.[93] The solubility theory also fails to take account of the differing fibrogenicity of the various forms of silica despite them being of similar solubility.[54] Furthermore, if the outer, more soluble layer of the particles is removed by etching, fibrogenicity is increased although solubility is decreased. In line with this, freshly fractured crystalline silica is more pathogenic in every respect than its aged equivalent,[94] which may partly explain the severity of silicosis in trades such as sandblasting. These observations suggest that the fibrogenicity of silica is connected with its surface configuration.

It is now known that uptake of the silica by macrophages is necessary for silicosis to develop. If silica and macrophages are enclosed together in peritoneal millipore chambers, a soluble product of the macrophages diffuses out and causes fibrosis. This observation led to the realisation that the fibrogenicity of the various crystalline forms of silica correlated well with their toxicity to macrophages and for a time macrophage death was thought to be necessary.[95] It is now considered that before the macrophages are killed by the ingested silica, they are stimulated to secrete factors that both damage other constituents of the lung and promote fibrosis.[96–102] Transforming growth factor-β is one fibrogenic factor that has been implicated in the pathogenesis of silicosis.[103–105]

Toxic damage to macrophages is due to silica particles injuring the phagolysosomal membranes, so releasing acid hydrolases into the cytoplasm.[95] It is important in the pathogenesis of the disease indirectly because when the macrophage crumbles, the silica particles are taken up by fresh macrophages and the fibrogenic process continues. It has been suggested that early involvement of the hilar lymph nodes in the fibrogenic process promotes the development of the disease in the lung by delaying dust clearance.[74]

Immunological aspects of silicosis

Immunological factors have been implicated in the pathogenesis of silicosis because many patients with silicosis have polyclonal hypergammaglobulinaemia, rheumatoid factor or antinuclear antibodies, and because there is a well-recognised association between autoimmune diseases such as systemic sclerosis and rheumatoid disease and exposure to silica.[43,106–109] The relation of immunity to dust exposure appears to be a reciprocal one: on the one hand, the presence of dust results in rheumatoid lesions in the lungs being more florid (see Caplan's syndrome, p. 341), whilst on the other, non-specific immunisation of rabbits with horse serum results in experimental silicotic lesions being larger and more collagenous.[110] It is doubtful whether pneumoconiosis and autoimmune disease play a causative role in each other but one seems to aggravate the other and may lead to its earlier development.

Tuberculosis complicating silicosis (silicotuberculosis)

One of the commonest and most feared complications of silicosis is chronic respiratory tuberculosis.[109] Once this infection has been added to the silicosis, the prognosis rapidly worsens. It is thought that in the presence of silica, the tubercle bacilli proliferate more rapidly because the ingested silica particles damage phagolysosomal membranes and thereby interfere with the defensive activity of the macrophages. The synergistic action of silica dust has long been held responsible for the inordinately high incidence of respiratory tuberculosis in mining

communities. Many former South African gold miners now have acquired immunodeficiency syndrome (AIDS) as well as silicosis and tuberculosis has consequently reached almost epidemic proportions amongst these men. Phagocyte damage by ingested dust particles may also cause some cases of chronic necrotising aspergillosis complicating pneumoconiosis.[111]

Silica-induced lung cancer

A series of studies suggesting that there might be a link between silica inhalation and lung cancer was reviewed by the International Agency for Research on Cancer in 1987, leading to the conclusion that the evidence for carcinogenicity of crystalline silica in experimental animals was sufficient, while in humans it was limited.[112] Subsequent epidemiological publications were reviewed in 1996, when it was concluded that the epidemiological evidence linking exposure to silica to the risk of lung cancer had become somewhat stronger[113] but that in the absence of lung fibrosis remained scanty.[113] The pathological evidence in humans is also weak in that premalignant changes around silicotic nodules are seldom evident.[114] Nevertheless, on this rather insubstantial evidence, lung cancer in the presence of silicosis (but not coal or mixed-dust pneumoconiosis) has been accepted as a prescribed industrial disease in the UK since 1992.[115] Some subsequent studies have provided support for this decision.[116] In contrast to the sparse data on classic silicosis, the evidence linking carcinoma of the lung to the rare diffuse pattern of fibrosis attributed to silica and mixed dusts is much stronger and appears incontrovertible.[33,92]

Alveolar lipoproteinosis in response to heavy dust exposure

A further complication of exposure to silica is the development of alveolar lipoproteinosis (see p. 317).[71,72,117,118] Very heavy experimental exposure to silica, and indeed other dusts, stimulates hypersecretion of alveolar surfactant to such an extent that the normal clearance mechanism is overwhelmed.[119–125] Alveolar macrophages are enlarged by numerous phagolysosomes distended by lamellar bodies that represent ingested surfactant. The alveoli are filled by such cells and, having a foamy cytoplasm, they produce the appearances of endogenous lipid pneumonia, similar to that more usually encountered as part of an obstructive pneumonitis distal to a bronchial tumour. The macrophages gradually disintegrate and the free denatured surfactant slowly becomes compacted, during which time its staining with both eosin and the periodic acid–Schiff reagents intensifies until the appearances are finally those of alveolar lipoproteinosis. This process prevents the aggregation and concentration of the dust in the usual foci and thereby hinders the development of silicosis. Lipoproteinosis and silicosis may be seen in conjunction but, more often, different areas of the lung show one or the other. The lipoproteinosis has its own severe impact on lung function, but, unlike silicosis, is potentially reversible (by massive alveolar lavage).

Silica-induced renal disease

Occasional patients exposed to silica develop renal disease.[126–129] Two mechanisms appear to operate. First, translocation of silica particles from the lungs leads to their deposition in the renal interstitium with resultant nephrotoxicity. Second, silica stimulates an autoimmune response characterised by the formation of various antibodies, notably rheumatoid factor and antinuclear antibodies, which leads to the development of immune complex-mediated glomerulonephritis.[128,129]
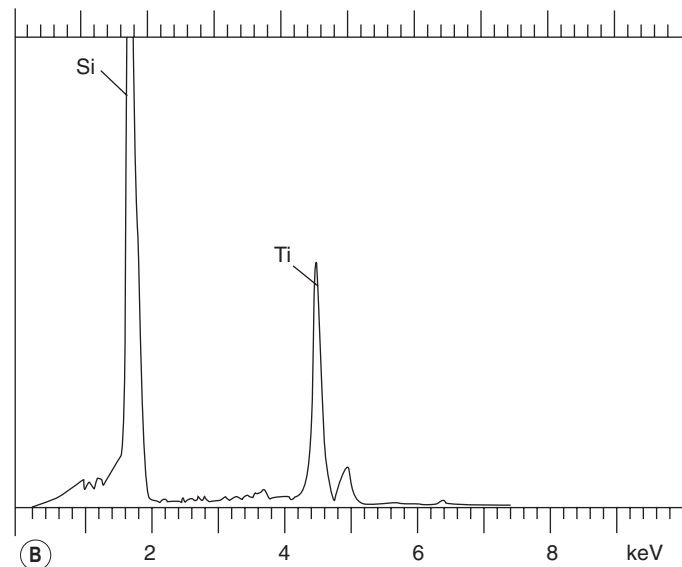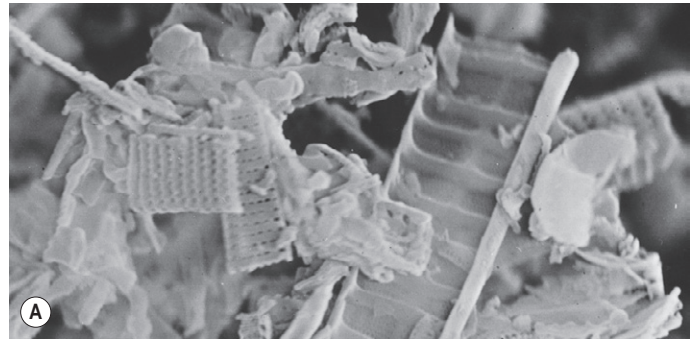
Figure 7.1.11 Diatomaceous earth. (A) Scanning electron micrograph showing the calcified diatoms, ×15 000. (B) Electron microprobe analysis shows only silicon (Si); the oxygen with which silicon is combined in silica (silicon dioxide, SiO_2) is of too low an atomic number to register. The titanium (Ti) peak derives from the sample holder. *(Courtesy of Dr D Dinsdale, Leicester, UK and Professor B Nemery, Leuven, Belgium.)*

Amorphous silica

Manmade submicron forms of silica, variously known as amorphous, vitreous, colloidal, synthetic or precipitated silica, are widely used in industry. They consist of pure non-crystalline silicon dioxide. Particle size ranges from 5 to 200 nm but aggregates of the particles measure from 1 to 10 μm. Industrial surveys suggest that inhalation of such dust is harmless, observations that are in accord with the results of animal experiments.[54]

Diatomaceous earth (keiselguhr)

An amorphous silica is the principal component of the fossilised remains of diatoms that constitute the sedimentary rock, diatomite (Fig. 7.1.11). This is generally obtained by open-cast mining, following which the rock is crushed and calcined. The calcined product is used in filters, insulation material and as a filler. Being amorphous, the silica in diatomite is harmless, but calcining (>1000°C) results in its conversion to crystalline forms of silica. Diatomaceous earth pneumoconiosis is unusual and its risk appears to be related to the amount of cristobalite and tridymite (two forms of crystalline silica) produced in the calcining process.[130]

SILICATES[43]

The silicates are complex compounds in which silicon and oxygen form an anion combined with cations such as aluminium and magnesium: talc, for example, is a hydrated magnesium silicate with the formula $Mg_3Si_4O_{10}(OH)_2$. Silicates include fibrous forms (asbestos and the zeolites), plate-like forms (talc and mica) and clays (kaolinite and fuller's earth). In histological sections, the platy talc and mica particles are generally cut tangentially and therefore appear needle-shaped (see Fig. 7.1.4). They are strongly birefringent whereas the clays are only weakly so. Talc particles in the lung exceeding 5 µm in length should arouse suspicion of intravenous drug abuse.[131]

Of the fibrous silicates, zeolite is used as a building material in certain communities, notably in central Turkey. Pneumoconiosis is not a problem but zeolites are of medical interest because, like asbestos, they present a mesothelioma risk. Asbestos is dealt with separately (see below).

Pneumoconiosis has been described with various non-fibrous silicates, notably in the rubber industry, which uses talc and, less commonly, mica as lubricants. Other occupations posing a risk include the extraction of kaolinite from china clay (kaolin),[27,132,133] and in the open-cast and underground mining of fuller's earth (montmorillonite, bentonite and attapulgite clays, which were originally used in 'fulling' (degreasing) wool).[134,135] However, all these substances are commonly contaminated with silica, asbestos or both, and it has been questioned whether in pure state they are at all fibrogenic. The modifying effect of inert substances such as iron on that of silica is well known (see mixed-dust pneumoconiosis, below) and it has been suggested that talc, mica and fuller's earth act in a similar way in regard to their more fibrogenic contaminants, the pneumoconioses attributed to them in reality representing mixed-dust pneumoconiosis or asbestosis. Contrary evidence comes from reports of pulmonary fibrosis in persons heavily exposed to pure talc, mica or kaolin.[32]

All these silicates are evident in the tissues as plate-like birefringent crystals which often provoke a foreign-body giant cell reaction (see Fig. 7.1.3) and may result in fibrotic nodules. Large focal lesions resembling the progressive massive fibrosis of coalworkers may be produced, and also a diffuse 'asbestosis-like' form of pneumoconiosis, the latter attributed to poor macrophage mobilisation of the plate-like particles.[27–32,132–138] It would appear therefore that silicates are indeed fibrogenic if enough is inhaled; they appear to vary in fibrogenicity but in all cases they are less fibrogenic than silica.

INERT DUSTS

Inert dusts are non-fibrogenic and therefore of little clinical consequence, although elements of high atomic number can give rise to a striking chest radiograph.[139] It should be noted however that inert or lowly fibrogenic materials may be associated with substances of medical importance, for example, kaolin, bentonite and barytes (barite) may all be contaminated with silica[27,134,140] and talc may be contaminated with asbestos.

The best known of the inhaled inert mineral dusts is carbon while, of the remainder, iron is the most widespread. Others include tin and barium. With all these dusts, particles retained in the lung are gathered at Macklin's dust sumps by heavily laden macrophages which are lightly bound together there by a few reticulin fibres. Collagen is not formed and the worker suffers no ill-effects. The lungs take on the colour of the dust and in siderosis assume a deep brick-red hue.

Carbon deposition is commonly found in the lungs, particularly those of city dwellers and tobacco smokers. It is also the principal constituent of coal, which is dealt with separately below, and large amounts of pure carbon may be inhaled by workers involved in the manufacture of carbon black, carbon electrodes and charcoal.[141–144] Although carbon is regarded as being non-fibrogenic, the very heavy lung burdens encountered in industries such as these may lead to the complicated form of pneumonconiosis known as progressive massive fibrosis that is more commonly encountered in coal workers (see p. 340). Heavy pure carbon deposition may also be acquired domestically when wood is burnt in buildings devoid of a chimney, so-called 'hut lung',[145] a term that is also applied to the domestic acquisition of carbon mixed with silica or silicates, resulting in forms of mixed-dust pneumoconiosis.[57,64,65]

Anthracofibrosis is a term introduced by Chinese bronchoscopists for bronchial stenosis or obliteration associated with carbon pigmentation of the mucosa.[146] Although the original description incriminated tuberculosis, mixtures of various mineral dusts acquired at work or domestically are a more likely cause.[147–150]

Iron dust in the lungs was first described by Zenker in 1867, when he also introduced the terms siderosis and pneumonokoniosis.[3] Zenker was describing a woman who coloured paper with iron oxide powder ('rouge'), a substance which is still encountered by some workers engaged in polishing silver, glass, stone and cutlery. Siderosis is also found in welders, iron foundry fettlers, steel workers, boiler scalers and haematite miners and crushers. Iron dust particles are reddish-brown but in the lung may be masked by carbon[151]: when evident, or revealed by microincineration, they resemble haemosiderin and generally give a positive Perls' reaction, but particularly with haematite, heat (60–80°C) and concentrated (12N) hydrochloric acid may be necessary.[152]

Haematite miners in both the UK (Cumbria) and France (Lorraine) have an increased risk of bronchial carcinoma, but radon gas rather than haematite is the suspected carcinogen. Radon is a decay product of uranium. Minute amounts are present in all rocks but local concentrations occur and these are liable to build up in mines if ventilation is limited.

Silver, as well as iron, is found in the lungs of silver polishers, where it stains elastin in alveolar walls and pulmonary vessels grey. Such argyrosiderosis is as harmless as siderosis.

Tin miners are subject to silicosis but not stannosis because the ore, which is found in association with siliceous rocks, contains only low concentrations of the metal. Tin smelters, on the other hand, and factory workers exposed to high concentrations of tin dust or fume, are liable to inhale large amounts of this inert metal and develop the striking chest radiograph of stannosis. They remain in good health however for tin is completely non-fibrogenic. Tin particles in the lung resemble carbon but are strongly birefringent and remain after microincineration: microprobe analysis provides positive identification.

Other inert dusts include barium, which also has a high atomic number and is therefore radiopaque,[139] and minerals of low radio-density such as limestone, marble and cement (all chiefly composed of calcium carbonate) and gypsum (hydrated calcium sulphate). However, the extraction of barium ore (almost entirely in the form of barium sulphate, which is known as barytes in Europe and barite in the USA) may entail exposure to silica and silicates. Pure baritosis resembles stannosis and siderosis.

MIXED-DUST PNEUMOCONIOSIS

The term 'mixed-dust pneumoconiosis' refers to the changes brought about by inhaling a mixture of silica and some other less fibrogenic substance such as iron, carbon, kaolin or mica.[33,151,153–155] The proportion of silica is usually less than 10%. Typical occupations include

foundry work and welding and the mining of coal, haematite, slate, shale and china clay.

The action of the silica is modified and, although fibrotic nodules are formed, they lack the well-demarcated outline and concentric pattern of classic silicosis. The lesions are found in a centriacinar position and are stellate in outline with adjacent scar emphysema. They are firm and generally measure no more than 5 mm in diameter. They closely resemble the fibrotic nodules of simple coal pneumoconiosis (see below). Confluent lesions also occur on occasions. These resemble the progressive massive fibrosis of coalworkers and appear to represent a single large lesion rather than a conglomeration of individual nodules, as in advanced silicosis. Abundant dust is generally evident in lesions of all sizes; this consists of black carbon or brown iron mixed with crystals of varying degrees of birefringence, silicates generally being strongly birefringent and silica weakly so. Calcification is unusual. Mixed-dust pneumoconiosis carries an increased risk of pulmonary tuberculosis, but not to the same degree as silicosis. In some cases the stellate nodules are accompanied by diffuse fibrosis, as in silicosis and again possibly involving interactions between the dust and immunological factors. Involvement of the bronchi with consequent stenosis (so-called anthracofibrosis) is described above.

COAL PNEUMOCONIOSIS[156]

The term 'anthracosis' was initially applied to changes observed in a coalminer's lung[157] but is now often extended to include the common carbon pigmentation of city dwellers' lungs, and the term 'coal pneumoconiosis' is more appropriate to a special form of pneumoconiosis to which coalworkers are subject, particularly those who work underground. The principal constituent of coal, carbon, is non-fibrogenic, so suspicion has naturally fallen on the ash content of mine dust, some of which derives from the coal, some from adjacent rock strata and some from stone dust laid in the roadways to minimise the risk of coal dust explosions. Coal itself appears to be the responsible agent because coal-trimmers, working in the docks and not exposed to rock dust, also develop the disease.[158] Coalminers encountering siliceous rock are, of course, also liable to develop silicosis like other underground workers.

Mineralogy

Coal consists largely of elemental carbon, oxygen and hydrogen with traces of iron ore and clays such kaolinite, muscovite and illite, but no silica. The mineral content varies with the type and rank (calorific value) of the coal. All coal derives from peat, the youngest type being lignite and the oldest anthracite, with bituminous (house) coal in between. As it ages, the oxygen and mineral constituents diminish and the coal hardens. Lignite is soft and said to be of low rank, anthracite hard and of high rank, with bituminous coal intermediate.

Although high-rank coal is of low mineral content, its dust is more toxic to macrophages in vitro and is cleared more slowly in vivo. This observation may explain why, in the UK, high-rank coal is associated with a higher prevalence of coal pneumoconiosis.

The low mineral content of high-rank coal is reflected in the mineral content of the lungs of those who hew such coal in the UK, but in the Ruhr, in Germany, and in Pennsylvania, in the USA, anthracite miners' lungs contain more silica than those who hew bituminous coal, the silica presumably deriving from other sources. Not surprisingly, the presence of silica is reflected in the tissue reaction to the inhaled dust, resulting in a more fibrotic reaction very analogous to mixed-dust pneumoconiosis. A spectrum of changes is therefore encountered in coalminers' lungs, ranging from coal pneumoconiosis through mixed-dust pneumoconiosis to silicosis; the findings in any individual depend upon the nature of the coal being mined and the type of work undertaken.

In high-rank British collieries the development of coal pneumoconiosis appears to depend on the total mass of dust inhaled, whereas in low-rank British collieries the mineral content of the lung dust appears to be more important.[159] This may explain apparently contrary data drawn from different coalfields – data based on coals of different composition that are not strictly comparable. Some workers have stressed the importance of silica in the dust whereas others, particularly in the high-rank coalfields of south Wales, have been unable to detect any association between silica and the level of pneumoconiosis. Both findings may be correct, but only for the particular group of miners examined in each case.[160]

Pathology

The lesions of coal pneumoconiosis are generally focal and fall into one or other of two major types, simple and complicated, depending upon whether the lesions measure up to or over 1 cm; simple corresponds to categories 1–3 of the ILO grading system (see p. 331) and complicated, which is also known as progressive massive fibrosis, to ILO categories A–C. More diffuse interstitial fibrosis has been reported in about 16% of Welsh and West Virginian coalminers, usually involving those carrying a particularly heavy dust burden; it runs a more benign course than non-occupational interstitial fibrosis (idiopathic pulmonary fibrosis).[161] Similar findings have been reported from France.[162]

Simple coal pneumoconiosis consists of focal dust pigmentation of the lungs, which may be associated with a little fibrosis and varying degrees of emphysema. Its clinical effects are relatively minor. Some degree of black pigmentation (anthracosis) of the lungs is common in the general urban population, especially in industrial areas, but much denser pigmentation is seen in coalminers, whose lungs at necropsy are black or slate-grey. Black pigment is evident in the visceral pleura along the lines of the lymphatics and on the cut surface where it outlines the interlobular septa and is concentrated in Macklin's centriacinar dust sumps (Fig. 7.1.12). The dust is generally more plentiful in the upper parts of the lungs and in the hilar lymph nodes, possibly due to poorer perfusion and consequently poorer lymphatic drainage there (see p. 21).[162]

Two forms of coal dust foci are recognised, macules and nodules, the former being soft and impalpable and the latter hard due to substantial amounts of collagen. Both lesions are typically stellate but the more fibrotic the nodules, the more rounded they become, until it is difficult to distinguish them macroscopically from those of silicosis. In these circumstances reliance has to be placed on the whorled pattern of the collagen that is evident microscopically in silicosis. The stellate nodules are analogous to those seen in mixed-dust pneumoconiosis caused by mixtures of silica and inert dusts other than carbon (see above). With polarising filters, small numbers of birefringent crystals may be seen in both macules and nodules, usually representing mica or kaolinite derived from rock that bordered the coal.

Macules consist of closely packed dust particles, free or within heavily laden macrophages, so that the lesion appears black throughout (Fig. 7.1.13). Appropriate stains show that the dust-laden macrophages and free dust are lightly bound by reticulin. Very little collagen is evident. Although striking in their appearance, dust macules are thought to have little effect on lung function.

Nodules contain substantial amounts of collagen and are thought to have an adverse, but limited, effect on respiration. They vary from a heavily pigmented, stellate lesion, which apart from its collagen content resembles the dust macule (Fig. 7.1.14), to one that is less

Figure 7.1.12 A coalminer's lung showing heavy dust deposition in the centres of the acini (Macklin's dust sumps). On palpation the dust deposits felt soft and were consequently described as macules rather than nodules. Despite the heavy dust deposition, there is minimal pneumoconiosis. Part of a paper-mounted whole-lung section.

pigmented and more circumscribed. The stellate, heavily pigmented type of nodule is seen in lungs that have a relatively low ash content whilst the more rounded and less pigmented nodule is seen in lungs with relatively high ash loads.[163]

Radiologically (see p. 321), p-type opacities correspond to macules, q-type opacities to the stellate nodules that resemble those of mixed-dust pneumoconiosis and r-type opacities to the rounded nodules that resemble those of silicosis.[53,164] Thus, the radiological changes of simple coalworker's pneumoconiosis are due to the dust and the small amount of collagen present and do not reflect any emphysema that may also be present. However, pulmonary dust foci are often associated with emphysema (Fig. 7.1.15) and the severity of the emphysema appears to correlate with the dust load. The prevalence of chronic bronchitis and emphysema is high in the coal industry and it has long been debated whether occupation or cigarette smoking is the major factor contributing to emphysema in coalminers.[165–168] As well as mineral dust, nitrous fumes from shot-firing form another occupational hazard of coal mining.

Heppleston made a special study of the emphysema found in coalminers, claiming that it differs from centriacinar emphysema, as seen in smokers in the general population, and attributing it to the dust.[169] He introduced the term 'focal emphysema of coalworkers' to describe this special process. Others find it very difficult to identify any convincing difference between the emphysema of coalworkers and that encountered outside the industry but Heppleston based his claims on the study of serial sections. By this means he showed that, although both forms affect respiratory bronchioles, the focal emphysema of coalworkers affects more proximal orders of these airways and is not associated with the bronchiolitis seen with centriacinar emphysema. Furthermore, focal emphysema is a dilatation lesion whereas
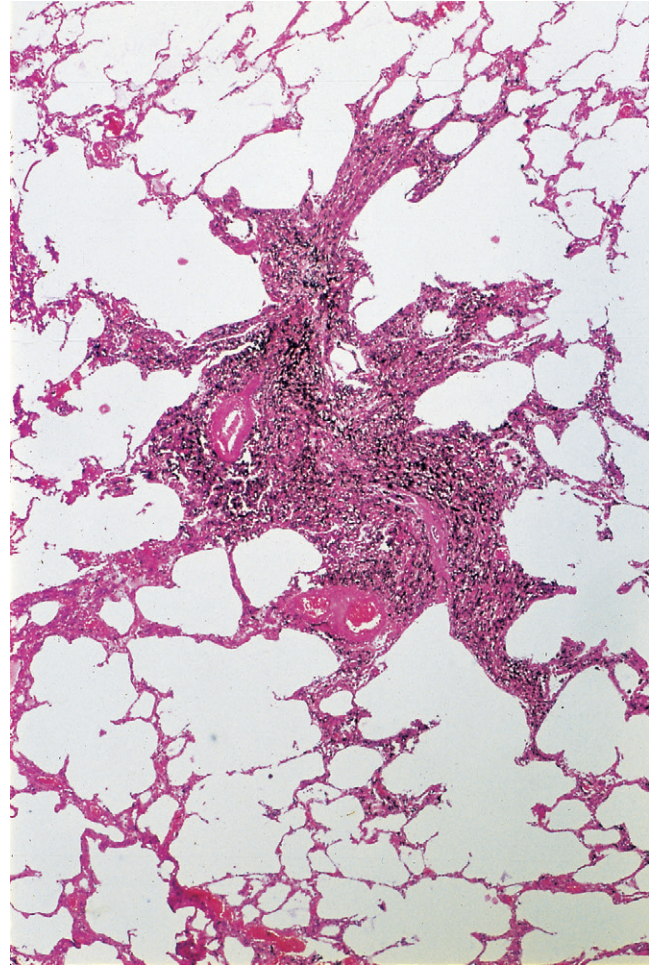
Figure 7.1.13 Coal macule. A centriacinar dust deposit of stellate outline consisting of macrophages heavily laden with coal dust and bound together by only a little reticulin. Collagen is not a feature.
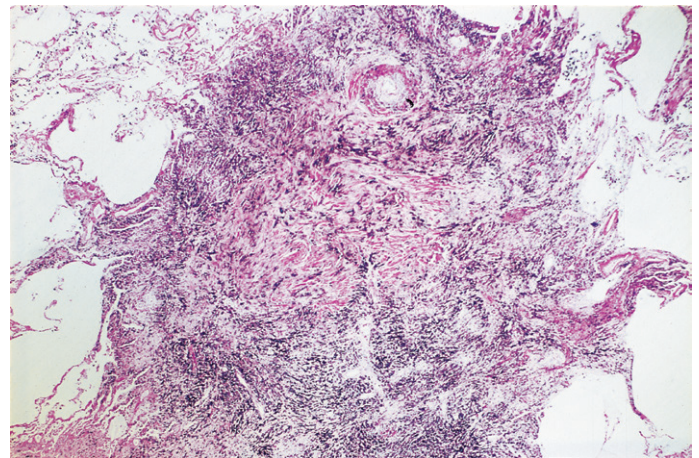
Figure 7.1.14 Coal nodule. A centriacinar dust nodule of stellate outline in which coal dust-laden macrophages are mixed with moderate amounts of collagen.

Figure 7.1.15 Coalworker's pneumoconiosis – simple type, consisting of coal macules and nodules associated with focal emphysema. Paper-mounted whole-lung section.

Figure 7.1.16 Coal pneumoconiosis – complicated type. In addition to the focal dust deposits there is a large area of progressive massive fibrosis in the upper lobe. Paper-mounted whole-lung section.

centriacinar emphysema involves destruction of adjacent alveolar walls. By definition, therefore, focal emphysema is not a true emphysema at all (see p. 102). However, it has been shown that mineral dusts cause elastin and collagen breakdown in the rat lung.[170] Focal emphysema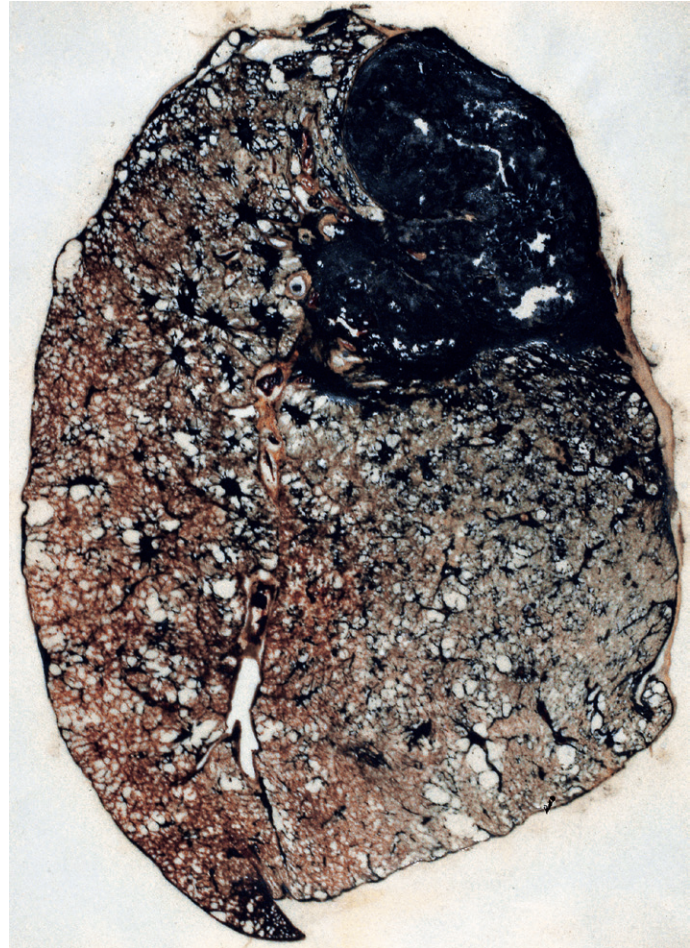 may progress to the destructive centriacinar form and this has strengthened claims that mine dust plays a causal role in centriacinar emphysema.[1,171–176] In the UK, these claims have been accepted and chronic bronchitis and emphysema in coalminers and metal production workers have been accepted as prescribed industrial diseases since 1992.[177] In Germany too, chronic obstructive pulmonary disease is now compensatable as an occupational disease. The conditions for compensation in the UK were initially:

- underground coal mining for a minimum of 20 years in aggregate
- forced expiratory volume in 1 second at least 1 litre below that expected or less than 1 litre in total
- radiological category of at least 1/1.

However the last of these criteria has now been dropped. The inclusion of a time element and the omission of some estimate of dust load (such as radiological category) have been criticised, with some justification.[178] As with lung cancer caused by chromates benefit is paid irrespective of smoking habits.

Whereas simple coal pneumoconiosis, particularly the macular variety, has little effect on lung function, complicated coal pneumo-coniosis, also known as progressive massive fibrosis, can have very serious consequences. Particularly when the lesions are large, it is associated with productive cough, breathlessness, significant impairment of lung function and premature death. The major factor accounting for the development of progressive massive fibrosis appears to be the sheer bulk of coal dust in the lung, rather than coal rank or the silica content of the mine dust.[179] Progressive massive fibrosis has occasionally been recorded in dockers loading silica-free coal into the holds of ships[158] and in workers exposed to pure carbon in the manufacture of carbon black and carbon electrodes.[141–143]

Progressive massive fibrosis is characterised by large (over 1 cm) black masses, situated anywhere in the lungs but most common in the upper lobes. The lesions may be solitary or multiple and very large, occupying most of the lobe and even crossing an interlobar fissure to involve an adjacent lobe (Figs 7.1.3B, 7.1.16). They cut fairly easily, often with the release from a central cavity of black fluid flecked by cholesterol crystals. For many years it was believed that the condition was the result of synergism between mycobacterial infection and dust but the failure of the attack rate to decrease as tuberculosis declined negated this view.[180] Today, more emphasis is placed on total dust load for the lesions tend to affect lungs that carry an unduly heavy dust burden. If the remainder of the lung shows little evidence of dust accumulation, the possibility of the masses representing Caplan-type lesions (see below) should be considered.

Microscopically, the lesions consist of dust and connective tissue intermixed in a random fashion. Central necrosis and cavitation commonly occur. The necrosis is thought to be ischaemic.[181] It is amorphous or finely granular, and eosinophilic apart from abundant dust particles and cholesterol crystal clefts. The fibrotic component in a complicated pneumoconiotic lesion is rich in fibronectin, with collagen only more abundant at the periphery.[182] Two types of progressive massive fibrosis are recognisable, corresponding to the two types of nodule described in simple coal pneumoconiosis.[163] The first appears to have arisen by enlargement of a single nodule, whereas the second is a conglomeration of individual lesions, each of which corresponds to the more circumscribed type of nodule seen in simple coal pneumoconiosis. The ash content of the lungs bearing these two types of progressive massive fibrosis varies in the same way as with the two types of simple pneumoconiotic nodules, the enlarged single lesion being found in lungs with a relatively low ash content, and the conglomerate lesion in lungs with a relatively high ash content. The second type resembles the conglomerate nodules of large silicotic lesions but lacks the characteristic whorled pattern of the latter.

The diffuse interstitial fibrosis found in a minority of coalworkers is associated with heavy dust deposition. It may progress to honeycombing but, as with the focal forms and unlike idiopathic interstitial fibrosis, it is better developed in the upper zones, the reasons for which are discussed above (see the zonal distribution of pneumoconiosis, p. 329).

Pathogenesis

The pathogenesis of coal pneumoconiosis has much in common with that of silicosis, and indeed many other pneumoconioses. It involves the promotion of fibrogenic factor synthesis and release by cells phagocytosing the inhaled dust. Several such factors have now been identified, the degree of fibrosis produced varying with the amount of dust inhaled and the ability of its constituents to promote the production of the responsible cytokines. These include platelet-derived growth factor, insulin-like growth factors 1 and 6, transforming growth factor-β and tumour necrosis factor-α.[101,183,184] As with other minerals, the indestructability of the dust perpetuates the process.

As in silicosis, immunological factors appear to be involved, for there is an increased prevalence of rheumatoid arthritis[185] and of circulating autoantibodies[186–188] in miners with coal pneumoconiosis. Rheumatoid factor has also been demonstrated within the lung lesions.[189] These abnormalities are generally more pronounced in miners with complicated pneumoconiosis but are also found in those with the simple variety. It is also possibly pertinent to the immunological basis of coal pneumoconiosis that some of the pulmonary manifestations of rheumatoid disease are more pronounced in coalminers. This was first pointed out by Caplan and will be considered next.

Pneumoconiosis and rheumatoid disease (Caplan's syndrome)

Caplan described distinctive radiographic opacities in the lungs of coalminers with rheumatoid disease,[190] and it is now recognised that similar lesions may develop in rheumatoid patients exposed to siliceous dusts. The development of such rheumatoid pneumoconiosis does not correlate with the extrapulmonary or serological activity of the rheumatoid process. Nor is there a strong relation to dust burden: Caplan lesions are characteristically seen in chest radiographs that show little evidence of simple coal pneumoconiosis.
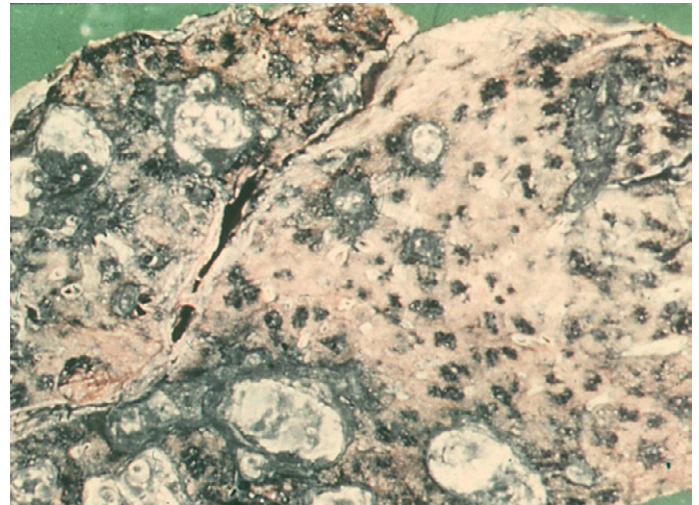
Figure 7.1.17 Caplan lesions in a coalminer's lung, which characteristically shows only light dust deposition. *(Courtesy of Dr R Seal, formerly of Penarth, UK.)*
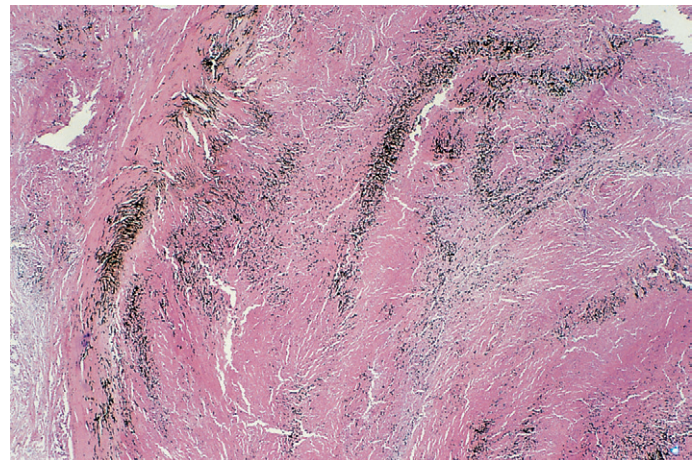
Figure 7.1.18 A Caplan lesion, characterised by successive bands of dust within the centre of a large necrobiotic nodule.

Pathologists recognise the lesions as particularly large necrobiotic nodules similar to those seen in rheumatoid patients who are not exposed to dust (Fig. 7.1.17). However, because of their large size (up to 5 cm diameter) they may be confused with progressive massive fibrosis undergoing central ischaemic necrosis (see above) or silicosis complicated by caseating tuberculosis. Such errors will be less likely if the radiological evolution of the lesions is considered for they tend to cavitate and undergo rapid remission, only to be succeeded by others. They are also well demarcated radiologically. Pathologically, they resemble rheumatoid nodules in showing peripheral palisading but differ in their large size and the presence of dust.[191] The dust accumulates in circumferential bands or arcs within the necrotic centres of the lesion (Fig. 7.1.18), an arrangement that suggests periodic episodes of inflammatory activity. Caplan lesions differ from tuberculosis in lacking satellite lesions and tubercle bacilli, and from progressive massive fibrosis in showing characteristic bands of dust pigmentation (Table 7.1.2) and only light dust deposition in the surrounding lung.

Table 7.1.2 Histological features of Caplan lesions, silicotuberculosis and progressive massive fibrosis

	Caplan lesions	Silicotuberculosis	Progressive massive fibrosis
Palisading	+	−	−
Dust banding	+	−	−
Satellite tubercles	−	+	−
Necrosis	+	+	+
Cholesterol crystals	+	±	+
Calcification	+	+	±
+ present; ± poorly represented; − absent.			

Table 7.1.3 Asbestos production by country, 2000[194]

Country	Tons
Russia	752 000
China	350 000
Canada	320 000
Brazil	209 000
Kazakhstan	179 000
Zimbabwe	152 000
Others	88 000

ASBESTOSIS

Asbestosis is defined as diffuse interstitial fibrosis of the lung caused by exposure to asbestos dust.[192,193] It does not cover asbestos-induced carcinoma of the lung or asbestos-induced pleural disease. The development of asbestosis depends on the presence of fairly large dust burdens: this is in contrast to mesothelioma and other forms of asbestos-induced pleural disease, which, although also dose-related, occur following the inhalation of far smaller amounts of asbestos dust.

Asbestos types and production

Asbestos is a generic term for more than 30 naturally occurring fibrous silicates, fibre being defined as an elongated particle with a length-to-breadth (aspect) ratio of at least 3. Asbestos fibres have a high aspect ratio, generally over 8. Based on their physical configuration they can be divided into two major groups, serpentine and amphibole. The physical dimensions and configuration of asbestos fibres are strongly linked to their pathogenicity.

Chrysotile (white asbestos) is the only important serpentine form. It accounts for most of the world production of asbestos of all types (Table 7.1.3).[194] Being a serpentine mineral, chrysotile consists of long, curly fibres that can be carded, spun and woven like cotton (Fig. 7.1.19). The curly chrysotile fibres are carried into the lungs less readily than the straight amphibole asbestos fibres, and once there undergo physicochemical dissolution and are cleared more readily.

Figure 7.1.19 A sample of Quebec chrysotile showing the fibrous nature of the ore.

They readily fragment into short particles that are easily ingested by macrophages and in the acidic environment of the macrophage phagolysosome they are particularly unstable. The half-life of chrysotile in the lungs is estimated to be in the order of only a few months.[195,196] Not surprisingly therefore chrysotile is the least harmful type of asbestos in respect of all forms of asbestos-induced pleuropulmonary disease.[197–199] It may nevertheless cause pulmonary fibrosis if sufficient is inhaled.[200,201]

In contrast to chrysotile, amphibole forms of asbestos consist of straight rigid fibres that are stable within the lung. They do not fragment, they are insensitive to chemical attack and their clearance half-lives are in the order of decades rather than months.[196] The main amphibole forms of asbestos of commercial importance are crocidolite (blue asbestos) and amosite (brown asbestos). Crocidolite, reputedly the most dangerous in regard to all forms of asbestos-related disease, was formerly mined in Western Australia (Wittenoom) and South Africa (Cape Province and the Transvaal); it was the principal amphibole used in the UK. Amosite, the name of which derives from the acronym for the former Asbestos Mines of South Africa company in the Transvaal, was the principal amphibole used in North America. Amphiboles are no longer imported by the developed countries but much remains in old lagging and presents a considerable dust hazard when this is removed. Tremolite, a further amphibole asbestos, contaminates Quebec chrysotile deposits, Montana vermiculite and many forms of commercial (non-cosmetic) talc and is responsible for much of the asbestos-related disease in chrysotile miners and millers.[202] Another amphibole asbestos, anthophyllite, was formerly mined in Finland. It causes pleural plaques (see p. 716) but not lung disease, possibly because its fibres are relatively thick (Fig. 7.1.20).[203]

Erionite is a zeolite rather than a type of asbestos but is comparable in form to amphibole asbestos and is also biopersistent. It is found
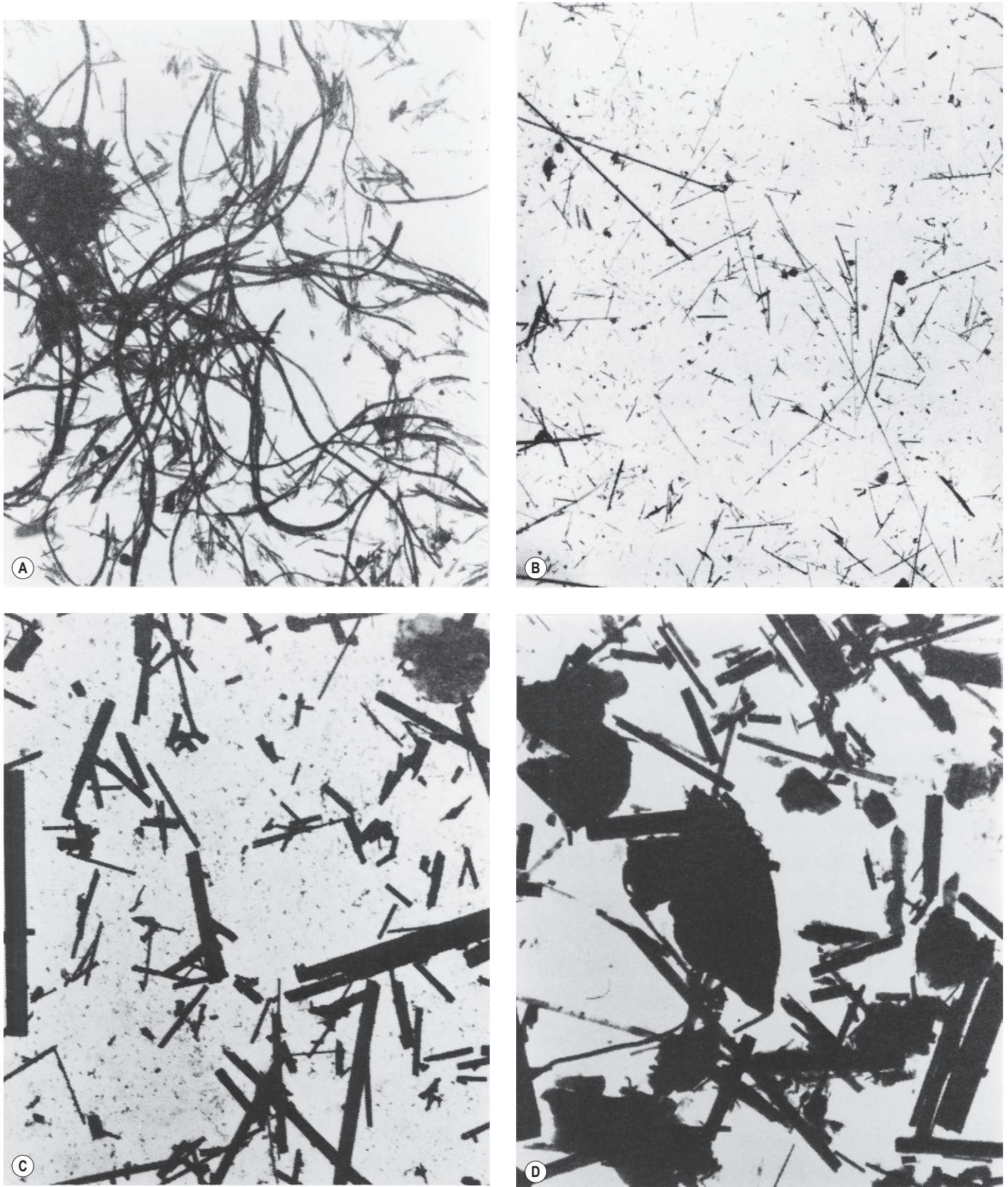
Figure 7.1.20 Electron micrographs of dispersed samples of asbestos. (A) Chrysotile; (B) crocidolite; (C) amosite; (D) anthophyllite, all ×2800, the bar representing 10 μm. *(Reproduced from Wagner et al. (1980)[203] by permission of Professor FD Pooley and the British Medical Bulletin.)*

Table 7.1.4 Asbestos consumption by country, 2000[194]		
Country	**Tons**	**kg/capita/year**
Russia	447 000	3.4
China	410 000	0.4
Brazil	182 000	1.3
India	125 000	0.2
Thailand	121 000	3.0
Japan	99 000	1.5
Indonesia	55 000	0.3
South Korea	29 000	1.9
Mexico	27 000	0.4
Others	178 000	

in parts of central Turkey where it causes both mesothelioma and a pattern of interstitial pulmonary fibrosis that is comparable to asbestosis.[204,205]

Asbestos use and exposure

Exposure to asbestos occurs in countries where it is extracted (Table 7.1.3), which is mostly by the open-cast method, and in those countries that continue to use this mineral (Table 7.1.4). The developed nations have largely ceased to use asbestos but countries keen to develop their industrial base and less concerned with health issues continue to use considerable amounts in a vast range of trades. Asbestos is used particularly for fireproofing, in heat and sound insulation and for strengthening plastics and cement. Thus, unless adequate precautions are taken, exposure is experienced by dockers unloading asbestos in the close confines of a ship's hold, by thermal insulation workers (laggers and strippers) in shipyards, power stations, train maintenance depots, factories and other large buildings, by construction workers such as carpenters cutting asbestos building panels, and by workers making asbestos products such as fireproof textiles, brake and clutch linings, and specialised cement.

As well as such direct exposure, exposure may also be:

- indirect, as experienced by the families of asbestos workers
- paraoccupational, as experienced by those working alongside an asbestos worker
- neighbourhood, as experienced by those living downwind of an asbestos works or mine
- ambient, as experienced by those living or working in a building containing asbestos.

Exposure to asbestos incorporated in the structure of a building carries a negligible health risk if the asbestos material is well maintained to prevent shedding of dust. Stripping asbestos out is more dangerous than maintaining it in situ, but maintenance is sometimes neglected. The near indestructibility of asbestos accentuates the health problems that its ubiquity poses.

Asbestos bodies

Because of their aerodynamic properties, fibres of 100 μm or more in length may reach the finer bronchioles and alveoli. Once impacted, the sharp asbestos fibres become coated with a film of protein that is rich in iron. The coating is thickest at the ends of the fibres, giving a

dumb-bell appearance. In time, a distinctive segmentation of this outer layer develops (Fig. 7.1.21). These coated structures are termed 'asbestos bodies'. Because other fibres may gain a similar coat, the non-specific term 'ferruginous body' has been advocated. However, coated carbon fibres (so-called coal bodies) are easily recognised as such by their black core.[206] In practice, ferruginous bodies with the appearance of asbestos bodies almost always prove to have an asbestos core.[207,208] Long fibres are more likely to be coated than short ones, which are cleared more quickly: in one study few fibres less than 5 μm in length were coated and few fibres over 40 μm in length were uncoated.[209] Amphiboles form bodies more readily than chrysotile. A comparison of light and electron microscopic fibre counts found that 0.14% of chrysotile, 5% of crocidolite and 26.5% of amosite formed bodies.[210] Nevertheless, sufficient chrysotile fibres are coated to permit recognition of asbestosis by standard histological criteria (diffuse fibrosis and asbestos bodies), even if chrysotile is the only asbestos present.[211] Despite the biodegradability of chrysotile, asbestos body numbers do not materially diminish with time.[212] Very occasionally however a patient with diffuse pulmonary fibrosis and a history of asbestos exposure has no evident asbestos bodies but analysis shows a fibre burden within the range found in asbestosis, justifying fibre analysis in such cases.[212a]

There is evidence that alveolar macrophages are involved in the coating of asbestos fibres to form asbestos bodies and that the bodies are less harmful to the macrophages than uncoated fibres.[213] Asbestos bodies give a Prussian blue reaction for iron when stained by Perls' method and their yellow-brown colour makes them easily recognisable in unstained films of sputum or in unstained histological sections. Sections may be cut 30 μm thick to increase the yield and help identify bodies that lie at an angle to the microtome blade. There is a good correlation between the numbers of asbestos bodies seen in lung sections and those in tissue digests.[214,215] The bodies may be found singly or in irregular clumps or stellate clusters. They are unevenly distributed but in well-established asbestosis they are easily found. If they are not evident, asbestos burden may be assessed quantitatively in tissue digests (see below). Their presence in lung tissue, sputum or bronchoalveolar lavage fluid merely confirms exposure, not the presence of disease. However, the number of asbestos bodies in lavage fluid correlates well with lung asbestos burden[216,217] and the number in sputum correlates with the duration and intensity of exposure.[216–218]

Fibre counts[193,208,219–223]

Quantitation is desirable in certain circumstances (Box 7.1.1), in which case it is best effected on 2-cm³ blocks of fixed or fresh lung tissue obtained from three different sites, avoiding tumour and thickened pleura. The tissue blocks are digested with caustic soda or bleach, following which the fibres may be collected on a millipore membrane or viewed in suspension in a red blood cell-counting chamber. If phase contrast optics are used both coated and uncoated fibres can be assessed.[219] Alternatively, dark ground illumination can be used to demonstrate uncoated fibres.[221] However, electron microscopy is to be preferred as it detects far more fibres than are visible by light microscopy and can also provide information on fibre type. It is important that the laboratory is well practised in fibre analysis and has established its own control range for the general population as well as asbestosis as most lungs contain some asbestos.

Ambient fibres are generally shorter than 5 μm and some workers therefore confine their counts to fibres that are at least as long as this.[224] Justification for this comes from animal experiments demonstrating that long fibres cause more inflammation, chromosomal damage, fibrosis, lung tumours and mesotheliomas than short fibres,[225–228] and from studies in humans suggesting that long fibres
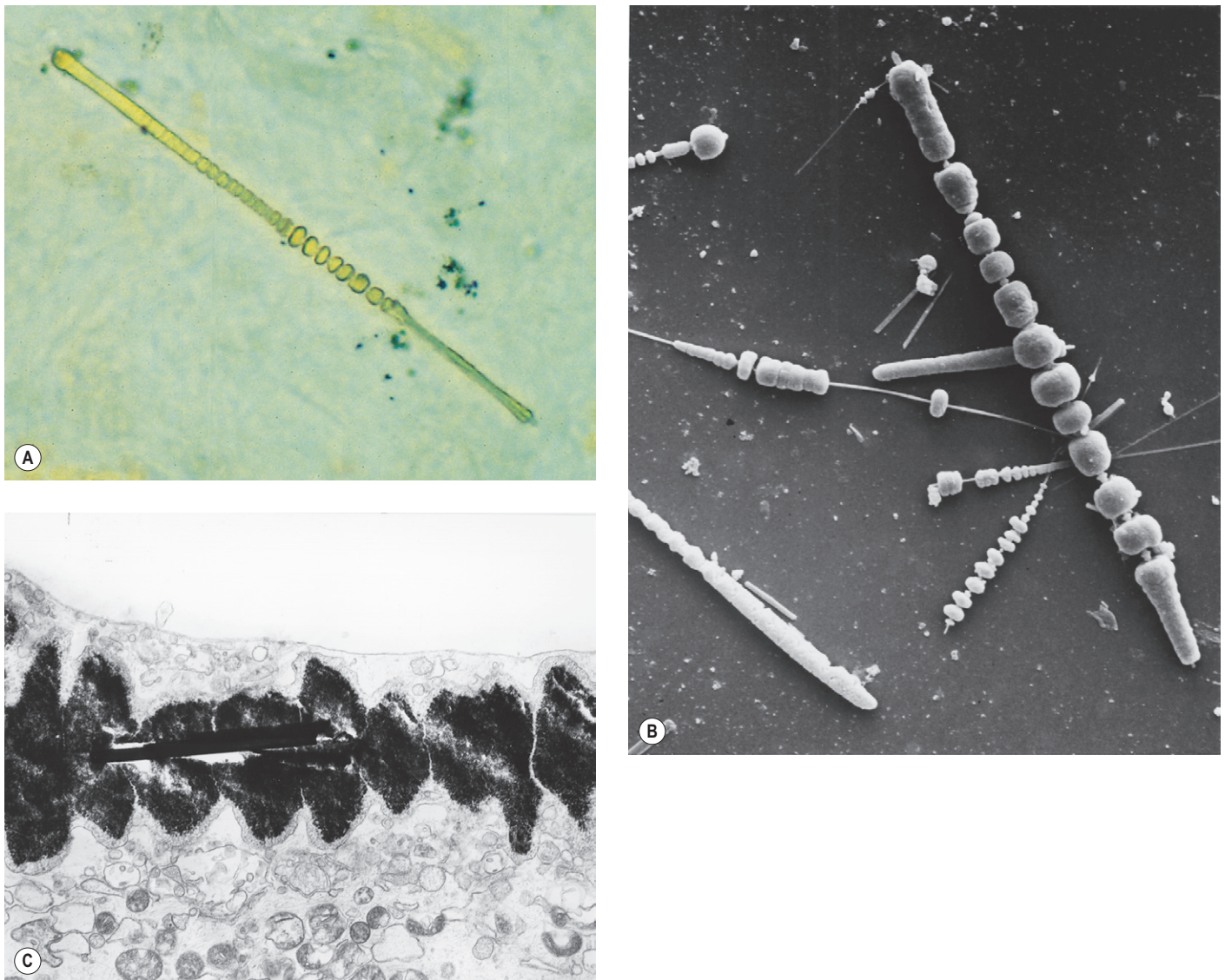
Figure 7.1.21 Asbestos bodies seen by light microscopy in (A) an unstained 30-µm-thick paraffin section; (B) by scanning electron microscopy in the digest of an asbestos worker's lung and (C) by transmission electron microscopy in lung tissue. The asbestos fibres have acquired the iron-protein coating that characterises an asbestos body. In most places the coating has become segmented, giving rise to bead-like formations, a change accompanying ageing of the bodies. *((B) Courtesy of Dr B Fox, London, UK and (C) courtesy of Miss A Dewar, Brompton, UK.)*

Box 7.1.1 Circumstances in which asbestos fibre counts are desirable

Quantitation desirable	Quantitation unnecessary
Mesothelioma if exposure is disputed and asbestos bodies are not evident	Mesothelioma if there is a history of exposure or asbestos bodies are evident
Pulmonary fibrosis (with or without carcinoma of the lung) in an asbestos worker but asbestos bodies are not evident	If there is obvious asbestosis
Carcinoma of the lung in an asbestos worker if there is no fibrosis	

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are responsible for asbestosis.[229] Other human studies have shown that, although asbestos load is maximal in the upper lobes, more long fibres are found at the bases, where fibrosis is most marked.[41,230] A further reason for limiting attention to the longer fibres is that the shorter ones are cleared more easily and their number therefore varies with the time lapsed since last exposure. For these reasons asbestos regulations in many countries now limit attention to fibres that are over 5 µm in length and have a length-to-diameter (aspect) ratio greater than 3: such fibres have become known as regulatory or World Health Organization (WHO) fibres.

Values are best expressed as fibres/g dry lung. By light microscopy, normal values range up to 50 000: over 20 000 is seen with mesotheliomas, and over 1 000 000 in asbestosis (Table 7.1.5).[216,224,231,232] However, compared with electron microscopy, light microscopy is relatively insensitive, showing only 26.5% of the amosite, 5% of the crocidolite and 0.14% of the chrysotile.[210] Light microscopic counts correlate poorly with severity of asbestosis[219] and electron microscopy

Table 7.1.5 Lung asbestos fibre counts per gram of dried lung

	Light microscopy	Electron microscopy
Normal city dwellers	Up to 50 000	Up to 5 000 000
Mesothelioma	Over 20 000	Over 1 000 000
Asbestosis (minimal)	Over 100 000	Over 10 000 000
Asbestosis (established)	Over 1 000 000	Over 100 000 000

The light microscopic counts include total fibres (coated and uncoated). The electron microscopic counts include only amphibole asbestos. Results from different laboratories vary and these figures, derived from several sources,[216,231,232] provide only a general guide. Reliable results depend upon counts being made regularly and the normal range from that laboratory being ascertained. Ratios of counts obtained by electron and light microscopy vary greatly but approximate to 100.

Box 7.1.2 **Molecular formulae of various forms of asbestos. When subjected to microprobe analysis, the total counts recorded for each element (see Fig. 7.1.6c) are proportional to the numbers of their atoms in the molecule. Thus, with tremolite the silicon peak would be four times as high as that for calcium and a little less than twice as high as that for magnesium**

Chrysotile	$Mg_3(Si_2O_5)(OH)_4$
Crocidolite	$Na_2Fe_5(Si_8O_{22})(OH)_2$
Amosite	$(Fe,Mg)_7(Si_8O_{22})(OH)_2$
Tremolite	$Ca_2Mg_5(Si_8O_{22})(OH)_2$

Table 7.1.6 Mean percentage lung fibre type by diagnostic category in a group of British asbestos factory workers compared to local controls[199]

Fibre type	Controls	Asbestosis	Carcinoma of the lung	Pleural mesothelioma
Crocidolite	2.8	60.1	56.7	20.2
Amosite	2.6	17.7	30.4	39.3
Chrysotile	25.9	4.0	6.9	17.0
Other (mainly fly ash)	68.7	18.2	6.0	23.5

Figure 7.1.22 At high magnification chysotile fibres are seen to be tubular. Transmission electron micrograph ×51 000. *(Courtesy of Miss A Dewar, Brompton, UK.)*

Non-asbestos fibres commonly found in the lung include mullite, which derives from fly ash. This may constitute up to 70% of the total fibre burden (see Table 7.1.6) and is thought to be harmless. There is no firm evidence that manmade fibres present a health hazard[237] but in certain localities natural non-asbestos mineral fibres, zeolites for example, are important causes of mesothelioma (see p. 718) and also cause interstitial pulmonary fibrosis.[204]

Clinical and radiological features

In contrast to the first half of the twentieth century, much of the asbestosis encountered today is asymptomatic, identified radiologically or histologically in lungs resected for carcinoma or removed at autopsy. Symptomatic cases are characterised by an insidious onset of breathlessness, a dry cough and crackles over the lower lung fields. Finger clubbing is a variable feature. Lung function tests show a restrictive respiratory defect. Radiology initially shows small irregular basal opacities that gradually coalesce to become linear, coarsen and eventually progress to a honeycomb pattern of small cysts.

The principal differential diagnosis, both clinically and pathologically, is from idiopathic pulmonary fibrosis. This is aided by the slow progression of asbestosis, which often extends over 20 years, as opposed to an average course of 2–3 years from presentation to death for the idiopathic condition.

Most cases of asbestosis are diagnosed solely on the occupational history and these clinicoradiological features. Recourse to histology is unusual but biopsy (preferably as a wedge of lung) may be undertaken if the clinical features are atypical. Histology also arises when the pathologist samples lung parenchyma remote from a resected carcinoma (the universal importance of which cannot be overemphasised).

is better in this respect.[197–199] By transmission electron microscopy, values may range up to 5 000 000 in controls, with asbestosis generally above 100 000 000 and mesotheliomas found at any level down to 1 000 000, all these figures representing amphibole fibres/g dried lung (see Table 7.1.5).[216,231,232] It should be noted that counts from different parts of the same lung may vary widely;[42,231–235] caution should therefore be exercised in interpreting a count obtained on a single sample. There is also wide discrepancy between laboratories, even when analysing the same sample.[234] Results obtained in an individual case therefore have to be evaluated against a standard set of values unique to that laboratory.

Electron microscopy also provides valuable information on the type of fibre. Chrysotile differs physically from the amphiboles in two respects: its fibres are both curved and hollow (Figs 7.1.20 and 7.1.22). With an electron microscope equipped for microprobe analysis, the various forms of asbestos may also be distinguished from other fibres and from each other (Box 7.1.2),[230,236] an important point as the amphibole forms of asbestos are far more dangerous than chrysotile (Table 7.1.6).[197–199]

Figure 7.1.23 Asbestosis. Fine interstitial fibrosis is evident beneath the pleura at the base of the lung. Barium sulphate-impregnated specimen.

Coroners require autopsy verification of the diagnosis in all suspected cases and this also necessitates hystology.

Morbid anatomy

When the lungs from a patient with asbestosis are seen at autopsy, pleural fibrosis is often found, and although this may also be attributable to asbestos exposure it is to be regarded as an independent process and not part of the asbestosis: it is dealt with separately on page 715.

Slicing the lung affected by asbestosis shows a fine subpleural fibrosis, especially of the lower lobes (Fig. 7.1.23). In severe cases the fibrosis often extends upwards to involve the middle lobe and lingula, and sometimes the upper lobes also. Microcystic change associated with the fibrosis develops in advanced cases and in severe disease there may be cysts over 1 cm in diameter. However, these classic changes are seldom seen in developed countries today. Following decades of dust suppression in asbestos factories, current patients have mild to moderate asbestosis and are dying of related cancer or of non-pulmonary disease.[238] In some of these cases the asbestosis is only detectable microscopically. Fixation of the lungs through the bronchi and the use of Heard's barium sulphate impregnation technique facilitate demonstration of the fibrosis (see p. 757 and Fig. 7.1.23). The mild degree of asbestosis currently encountered is of little functional significance but is often critical in determining whether an associated carcinoma of the lung should be attributed to asbestos exposure (see below).

Histological appearances

The histological diagnosis of asbestosis requires an appropriate pattern of interstitial fibrosis associated with the presence of asbestos

bodies. Both components must be present. The fibrosis is paucicellular, lacking any significant degree of inflammation and being collagenous rather than fibroblastic.

It is generally considered that asbestosis begins about the respiratory bronchioles and alveolar ducts where most of the asbestos fibres impact.[15] Alveolar walls attached to these bronchioles show fine interstitial fibrosis. However, this early lesion has to be interpreted with caution because it is not specific to asbestos, being found with other inhaled mineral dusts[239,240] and even in many cigarette smokers who have not been so exposed.[241] It more likely represents a non-specific reaction to a variety of inhaled particles. It may cause mild airflow obstruction but is not associated with the radiographic, clinical or restrictive changes of classic asbestosis.

As the disease progresses, the focal changes join up so that the basal subpleural regions show widespread interstitial fibrosis and eventually complete destruction of the alveolar architecture. In severe cases there may be honeycombing and metaplastic changes in the alveolar and bronchiolar epithelium. Apart from the presence of asbestos bodies the changes resemble those of non-specific interstitial pneumonia, or more rarely usual interstitial pneumonia. Fibroblastic foci may be found but they are uncommon. There is often an increase in alveolar macrophages but the desquamative interstitial pneumonia that has been reported in association with asbestos[242,243] is not to be regarded as a variant of asbestosis[192]; concomitant smoking is a more likely cause.[241] A variety of other non-specific inflammatory processes such as organising pneumonia have been reported in asbestos workers and if localised some have been suspected of representing malignancy until biopsied.[244]

Several schemes have been proposed for grading the extent and severity of asbestosis. These are of value in epidemiological studies but should only be applied to cases meeting the histopathological criteria for a diagnosis of asbestosis. One such scheme is shown in Box 7.1.3.[193,245,246]

In well-established asbestosis asbestos bodies are numerous and easy to find, aggregates of them sometimes forming clumps (Fig. 7.1.24). In earlier lesions a detailed search may be necessary, in which
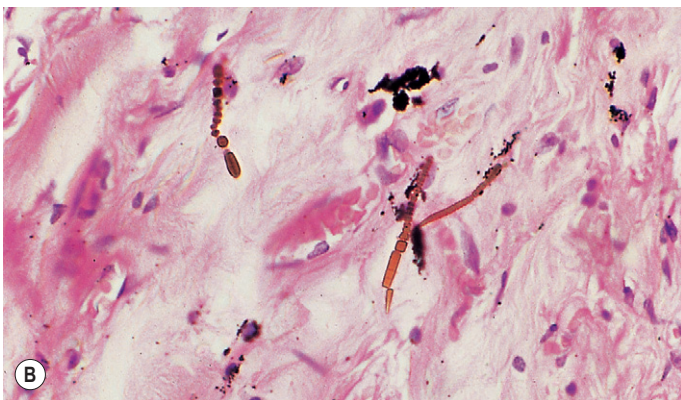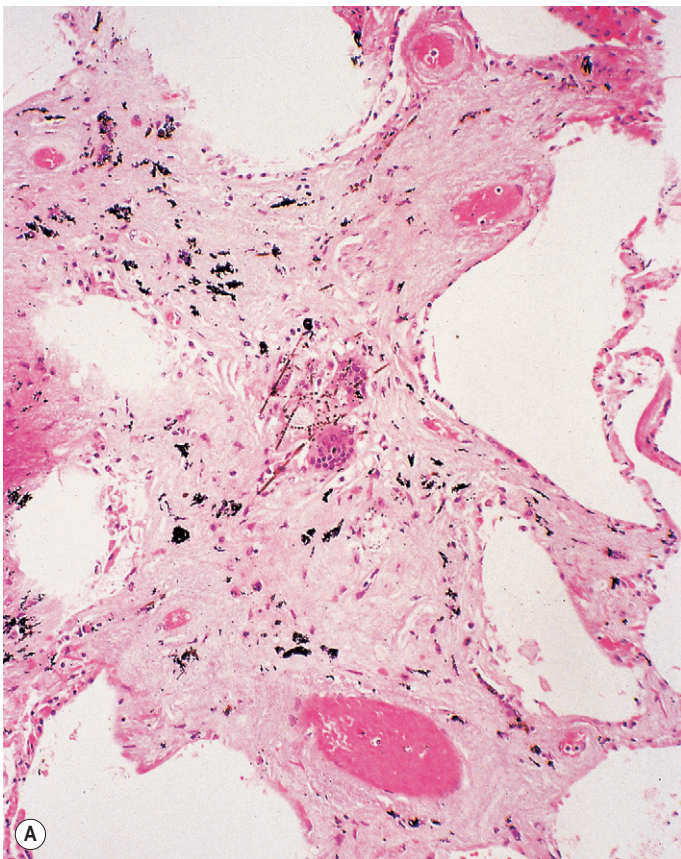
Figure 7.1.24 **Asbestosis.** Interstitial fibrosis is associated with many asbestos bodies (A), which are shown in detail in (B).

Figure 7.1.25 Cytoplasmic hyaline in asbestosis. (A) Eosinophilic inclusions are seen in the cytoplasm of several hyperplastic type II pneumocytes. Haematoxylin & eosin. *(Courtesy of Professor VL Roggli, Durham, USA.)* (B) Electron microscopy shows that the inclusions represent a tangle of microfilaments. *(Courtesy of Professor D Henderson, Adelaide, Australia.)* *(Both images reproduced by permission of the publishers of* Archives of Pathology and Laboratory Medicine.[193])

case the examination of unstained or Perls-stained sections facilitates their identification. Minimum criteria for the diagnosis of asbestosis require the identification of diffuse interstitial fibrosis in well-inflated lung tissue remote from a lung cancer or other mass lesion and the presence of either two or more asbestos bodies in tissue with a section area of 1 cm² or a count of uncoated asbestos fibres that falls in the range recorded for asbestosis by the same laboratory.[192,193] There are marked variations in the concentration of asbestos fibres between samples from the same lung[216,235] and it is therefore recommended that at least three areas be sampled, the apices of the upper and lower lobes and the base of the lower lobe.[223]

The equivalent of Mallory's alcoholic hyalin of the liver has been described in the lungs in asbestosis,[193,247] and subsequently in other pulmonary conditions.[248–251]It is seen as small eosinophilic cytoplasmic inclusions within hyperplastic type II alveolar epithelial cells (Fig. 7.1.25A). Electron microscopy shows that the inclusions consist of a tangle of tonofilaments (Fig. 7.1.25B) and by immunocytochemistry a positive reaction is obtained with antibodies to cytokeratin, both these features being typical of Mallory's hyalin in the liver. The inclusions also react for ubiquitin, the accumulation of which is indicative of cellular damage, in particular faulty proteinolysis.[251]

Differential diagnosis

The differential diagnosis of asbestosis includes pulmonary fibrosis due to many other causes, any of which may of course affect an asbes-

tos worker as much as members of the general population. The proportion of diffuse pulmonary fibrosis in asbestos workers that is not attributable to asbestos has been estimated to be as high as 5% and likely to rise as the risk of asbestosis diminishes with better industrial hygiene.[252]

The principal differential diagnosis of asbestosis is from idiopathic pulmonary fibrosis. Both diseases affect the bases and periphery of the lungs predominantly. In the late stages, cystic change is more evident in idiopathic pulmonary fibrosis but this criterion is not totally reliable. Nor is the presence of pleural fibrosis, although it is usually present in asbestosis and is seldom found in idiopathic pulmonary fibrosis. Asbestosis seldom progresses or does so very slowly after exposure ceases[253,254] whereas idiopathic pulmonary fibrosis typically proves fatal within 3–4 years from onset. The fibrosis of asbestosis is generally paucicellular: inflammation is not a feature and the fibroblastic foci that characterise the usual interstitial pneumonia pattern of fibrosing alveolitis are seldom observed in asbestosis.

Very often the distinction from idiopathic pulmonary fibrosis has to be based on the amount of asbestos in the lung and, if asbestos bodies are not readily identifiable, this has to depend on fibre counts. Errors are made both by overlooking substantial numbers of asbestos bodies completely and by ascribing undue importance to scanty bodies. If considering the possibility of minimal asbestosis (to justify attributing carcinoma of the lung to asbestos, for example) it should be remembered that a little peribronchiolar fibrosis is also characteristic of smokers' lungs, centriacinar emphysema and early mixed-dust pneumoconiosis.[239–241,255] As described above, at least two asbestos bodies/cm^2 in the presence of interstitial fibrosis distant from any lung cancer or other mass lesion is required for a diagnosis of asbestosis.[192]

Pathogenesis

Although the causes of asbestosis and idiopathic pulmonary fibrosis are very different, they resemble each other in several ways, suggesting that similar pathogenetic mechanisms may operate.[105,256–258] In both these diseases there is degeneration of the alveolar epithelium and capillary endothelium, with patchy loss of the former,[256] and bronchoalveolar lavage shows an increase in macrophages that might perpetuate the damage by releasing lysosomal enzymes, nitric oxide and hydroxyl radicals.[257,259–261] Both diseases are also characterised by an increased prevalence of circulating non-organ-specific autoantibodies.[262] Experimentally, asbestos exposure leads to the activation of a variety of fibrogenic cytokines at sites of lung injury.[105,263–268]

Inhaled asbestos activates a complement-dependent chemoattractant for macrophages[269] and macrophage stimulation involves the secretion of fibroblast stimulating factors,[270–272] asbestos being intermediate between haematite and silica in regard to macrophage-mediated fibrogenicity.[273] The epithelial damage could be mediated directly by the needle-like asbestos fibres or indirectly through enhanced phagocyte generation of free radicals (which is much greater with amphibole asbestos than with either chrysotile or silica).[268,274] Fibrogenic cytokines released by activated pulmonary phagocytes and regenerating alveolar epithelial cells in asbestosis include tumour necrosis factor-α and transforming growth factor-β,[268] as in idiopathic pulmonary fibrosis.

Asbestos-induced lung cancer

As a result of better industrial hygiene, asbestosis is less severe today than in earlier years when it followed much heavier exposure, with the consequence that death from respiratory failure and cor pulmonale is less common and sufferers are surviving longer. There is therefore now a greater risk of asbestos-related cancer eventually developing.

Table 7.1.7 Excess mortality from carcinoma of the lung attributable to asbestos exposure and cigarette smoking in insulation workers.[278] Together, these factors have a multiplicative rather than additive effect

Group	Mortality ratio
Non-smoking controls	1
Non-smoking asbestos workers	5
Cigarette-smoking controls	11
Cigarette-smoking asbestos workers	53

Asbestos exposure predisposes to two varieties of malignant neoplasm, carcinoma of the lung and mesothelioma of the pleura and peritoneum. The risk of malignancy increases with dose but the relative risk of carcinoma is much smaller than that of mesothelioma. For example, with heavy exposure, as in lagging, the risk of mesothelioma is increased 1000-fold whereas it is increased only fivefold for lung cancer. Hence, with light exposure there is a substantial risk of mesothelioma but only a small risk of lung cancer. Asbestosis requires heavy exposure and in one group of patients with asbestosis, 39% died of pulmonary carcinoma, 10% of mesothelioma and 19% of other respiratory diseases.[238] Although there were many earlier reports, the link with carcinoma of the lung may be considered to have been firmly established by 1955,[275] that between crocidolite asbestos and mesothelioma by 1960,[276] and that between amosite asbestos and mesothelioma by 1972.[277] Mesothelioma is considered on page 717.

In regard to carcinoma of the lung, asbestos is not such a potent pulmonary carcinogen as cigarette smoke but together their effects are multiplicative rather than additive (Table 7.1.7).[278,279] However, the risk attributable to asbestos is the same regardless of smoking history, being increased fivefold in both smokers and non-smokers. There is usually a latent period in excess of 20 years between first exposure to asbestos and the development of lung cancer and the risk increases the greater the cumulative exposure. The increased risk involves carcinomas of all the histological types encountered in the lung, although adenocarcinoma has been disproportionately overrepresented.[245,280–285]

It is uncertain[114] whether the increased risk of carcinoma is caused by the asbestos[192,286–291] or the asbestosis.[292–299] The latter view envisages the carcinoma arising in the foci of alveolar epithelial hyperplasia and dysplasia that commonly accompany any interstitial fibrosis (see carcinoma complicating idiopathic pulmonary fibrosis, p. 275). However, most carcinomas complicating asbestosis arise in the bronchi rather than the alveolar tissue. On the other hand, more arise in the sites worst affected by asbestosis, the lower lobes and the periphery of the lung, than in the general population (Fig. 7.1.26).[238,245,281–285]

The majority view has been that asbestosis is a necessary precursor of the carcinoma but evidence to the contrary is finding increasing support (Table 7.1.8).[192] In the UK, industrial compensation was formerly only awarded to an asbestos worker for carcinoma of the lung if there was also asbestosis or diffuse pleural fibrosis but new rules were introduced in 2006. Asbestosis remains a sufficient criterion but diffuse pleural thickening is not and asbestosis is no longer a necessary criterion: asbestos is deemed to have been responsible if the patient worked in asbestos textile manufacture, spraying, lagging or gas mask manufacture for at least 5 years before 1975 or 10 years after 1975. The basis for these changes is the premise that heavy asbestos exposure is sufficient in itself to account for carcinoma of the lung.
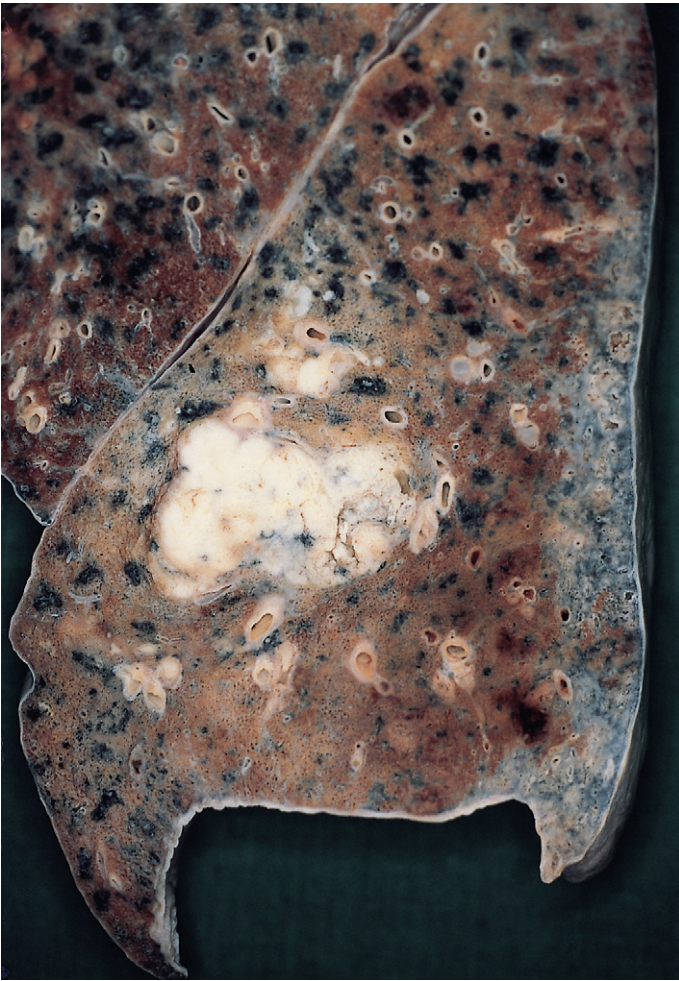
Figure 7.1.26 Asbestosis associated with carcinoma of the lung. The asbestosis has been highlighted by barium sulphate impregnation and is seen as a grey subpleural band to the right of the picture. Although the carcinoma has arisen in the same lobe as the asbestosis it has not obviously arisen in an area affected by asbestosis.

Lung fibre counts in the asbestosis range (see Table 7.1.5) provide valuable evidence of such exposure. Compensation standards for asbestos-associated lung cancer in different countries are shown in Box 7.1.4.[192,289]

Asbestos-induced airway disease

Although asbestosis causes a restrictive respiratory defect, airflow limitation is also seen in this disease. Much of the airflow limitation is attributable to cigarette smoking but it is also seen in non-smoking asbestos workers and is worse in those with asbestosis.[300] The pathological basis of this appears to be small-airways disease (see p. 123).[301] It is possibly a non-specific reaction to inhaled dust or cigarette smoke.[302] Because it is not established that this lesion progresses to interstitial alveolar fibrosis (asbestosis) the term 'asbestos airways disease' is suggested.[302] Fibrosis limited to the bronchioles is specifically excluded from the definition of asbestosis in the latest guidelines (although these retain grade 0 for fibrosis limited to the bronchiolar walls).[193] It should also be noted that, although emphysema is considered to be a destructive rather than fibrotic condition, a little focal

Table 7.1.8 Requirements for attributing carcinoma of the lung to asbestos

The traditional view that the carcinoma complicates asbestosis	The Helsinki criteria,[192] which are based upon substantial exposure
1. Asbestosis and 2. A minimum lag time of 20 years	1. Asbestosis diagnosed clinically, radiologically or histologically or A minimum count of 5000 asbestos bodies per gram dry lung tissue (/g dry), or an uncoated asbestos fibre burden of 2 million amphibole fibres more than 5 μm in length/g dry, or 5 million amphibole fibres more than 1 μm in length/g dry or Estimated cumulative exposure to asbestos of at least 25 fibres/ml-years or An occupational history of 1 year of heavy exposure to asbestos (e.g. manufacture of asbestos products, asbestos spraying) or 5–10 years of moderate exposure (e.g. construction or ship-building) and 2. A minimum lag time of 10 years

Box 7.1.4 **Compensation standards for asbestos-associated lung cancer in different countries[289]**

Government standards vary considerably and in the civil courts claims are often based on lesser evidence. Some examples of government standards are:

UK

Asbestosis or employment in a specified industry for a specified time (see text)

USA

The presence of asbestos-related bilateral pleural plaques or asbestos-related bilateral pleural thickening and occupational exposure and a lag time of at least 12 years

Germany

The presence of asbestosis or pleural plaques or diffuse pleural thickening or fibre-years of exposure

Denmark

Only fibre-years of exposure are taken into account

Finland

Exposure, at least 10 years' latency and asbestos-related pleural or parenchymal changes

Sweden

Asbestosis is not required but smoking is taken into consideration

Norway

Attempts are made to quantify separately the attributability to asbestos, smoking and other factors (e.g. radon)

fibrosis is generally evident in this common condition[255] and does not necessarily indicate early asbestosis.

ALUMINIUM

Aluminium has been implicated in the development of respiratory disease during the refining of its principal ore, bauxite, to yield various aluminium oxides (aluminas), in the preparation of the metal by smelting alumina, in the production of corundum abrasive and in the production of special aluminium powders used in explosives.

Refining of bauxite

Bauxite is a mixture of various aluminium oxides, hydroxides and silicates, iron oxide and titanium dioxide. The oxides of aluminium are obtained by differential heating of the ore and the respiratory effects of this work appear to be no more than mild airway irritation. It is generally accepted that aluminium oxide is inert.

Aluminium smelting

Aluminium is prepared by the electrolytic reduction of its oxide dissolved in sodium aluminium fluoride (cryolite), a process releasing a considerable amount of fluoride-rich effluent. Exposed workers have complained of what is termed pot-room asthma. The pathology of this condition is not well described but the pathogenesis is thought to involve irritation rather than allergy.[303]

Abrasive manufacture

The abrasive corundum is formed from bauxite mixed with coke and iron heated in an electric arc furnace, a process in which workers may be exposed to the fumes of alumina and free silica. In the past some of these workers developed diffuse pulmonary fibrosis (Shaver's disease)[369] and, although this was initially attributed to the aluminium, it is now agreed that the free silica was the responsible agent. The exposure to free silica has been reduced and the disease is now regarded as historic.

Aluminium powder

Aluminium powder holds a paradoxical position in regard to lung disease. In certain industries it has caused very severe pulmonary fibrosis, yet in others it has proved harmless. Indeed, at one time Canadian miners breathed aluminium dust before work, in the belief that this would reduce the danger of silica in the mine dust[304] and more recently silicosis has been treated by such means in France.[305] It is questionable whether this practice is effective but it at least appears to cause no harm. The explanation for these contradictory observations probably lies in differing methods of manufacture of aluminium powder.

Aluminium metal appears to be an inert substance but this is only because it has a high affinity for oxygen and the surface layer of aluminium oxide so formed is firmly bound to the underlying metal, unlike ferric oxide which permits further rusting of iron. Granular aluminium powders, produced in a ball mill or from a jet of molten aluminium, therefore acquire a protective coat of surface oxide and are inert. With stamped aluminium powders, however, surface oxidation is prevented by lubricants added to aid the separation of these flake-like particles. The usual lubricant (stearin) contains stearic acid and this polar compound combines with the underlying metal, which is thereby protected from both atmospheric oxidation and the action of body fluids when such dust is inhaled. In certain circumstances, however, non-polar lubricants in the form of mineral oils have been substituted for stearin. This happened in Germany during the Second World War when munition production was stepped up but stearin was difficult to obtain,[306,307] and in the UK in the 1950s to make the powder darker for purely commercial reasons.[308] In vitro, oil-coated stamped aluminium powder reacts with water to produce aluminium hydroxide, which affords the underlying metal no protection against further attack, so that aluminium hydroxide continues to be formed.[309] This substance is a protein denaturant, once used in the tanning industry, and it is believed that this property underlies the very exceptional cases of severe pulmonary fibrosis that have occurred in connection with stamped aluminium powder produced with mineral oil rather than stearin.[309,310] The fibrosis has a very characteristic pattern, affecting the upper lobes and progressing rapidly, the interval from onset of symptoms to death being as short as 2 years.[308] There is marked shrinkage of the lungs with gross elevation of the diaphragm and buckling of the trachea (Fig. 7.1.27). The lungs are grey (Fig. 7.1.28) and microscopically, numerous small black jagged particles are seen. These can be shown to contain aluminium with Irwin's aluminon stain or by microprobe analysis.[311]

What appears to be a different pathological effect of aluminium dust on the lungs is the rare development of granulomatous disease resembling sarcoidosis and berylliosis.[312,313] This represents hypersensitivity to the metal, amenable to confirmation with a lymphocyte transformation test similar to that used to diagnosis berylliosis (see below).

Aluminium welding

Rare cases of desquamative interstitial pneumonia and pulmonary fibrosis have been reported in aluminium welders.[311,314]

RARE EARTH (CERIUM) PNEUMOCONIOSIS

Elements with atomic numbers from 57 (lanthanum) to 71 (lutetium) are known as the lanthanides or rare earth metals. They are used in many manufacturing processes, including the production of high-temperature ceramics and the grinding of optical lenses. Carbon arc lamps used in reproduction photography emit appreciable quantities of oxidised lanthanides, particularly cerium oxide, and there are reports of pneumoconiosis in exposed individuals.[315] The pathological changes reported have varied from granulomatous nodules to diffuse interstitial fibrosis indistinguishable from the idiopathic variety except for the presence of rare earth elements (usually cerium) detected by polarising light microscopy and electron microprobe analysis.[315]

HARD-METAL DISEASE (COBALT LUNG)

Hard metal is a tungsten alloy containing small amounts of cobalt, titanium, molybdenum and nickel. It is exceptionally tough and once formed can only be worked with diamond. It is used in the tips of drill bits, on abrasive wheels and discs, and in armaments. Interstitial lung disease is liable to arise in its manufacture or in those using hard metal as an abrasive.[316] Experimental work suggests that cobalt is the dangerous constituent[317] but this element is soluble and, unless industrial contact has been recent, analysis of lung tissue usually shows tungsten and titanium but no cobalt. The role of cobalt is also
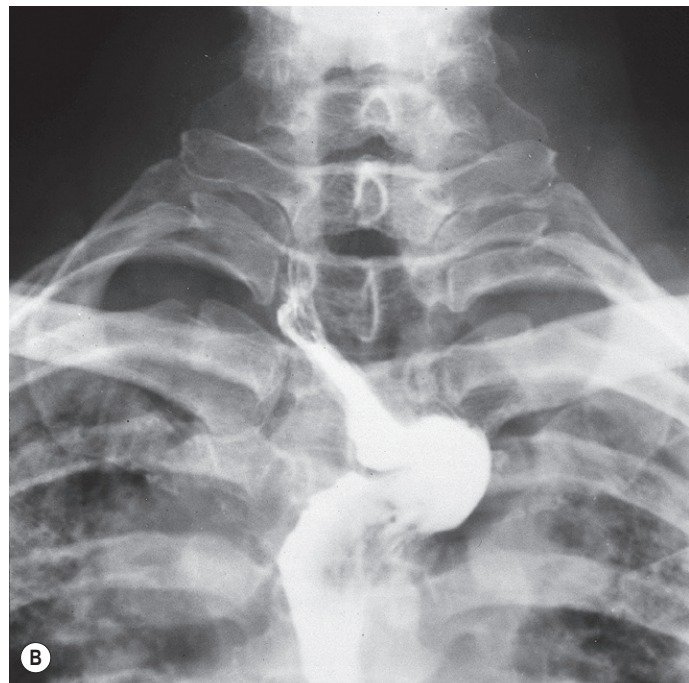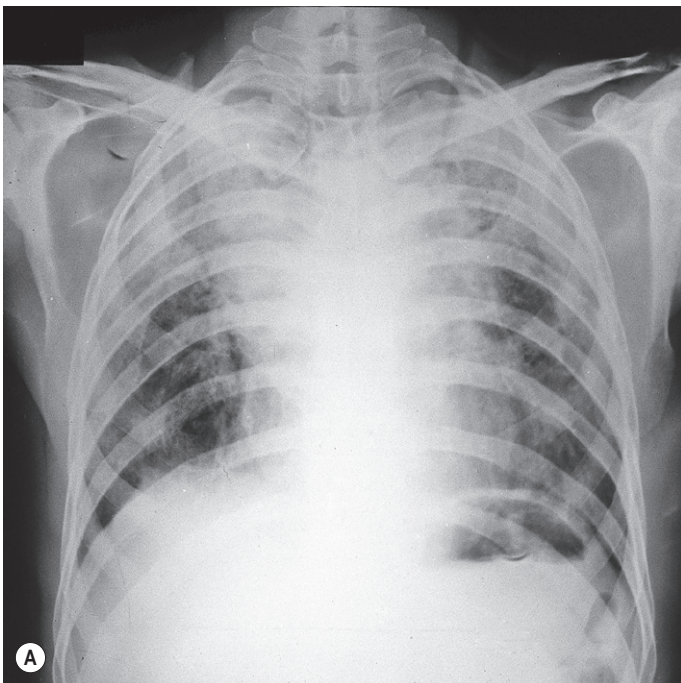
Figure 7.1.27 Aluminium pneumoconiosis. (A) A chest radiograph showing opacification of the lung apices. (B) A barium swallow showing severe buckling of the oesophagus due to fibrous contracture of the lung apices and adjacent mediastinal tissues, as seen in Figure 7.1.B. *(Courtesy of the late Professor RE Lane, Manchester, UK.)*
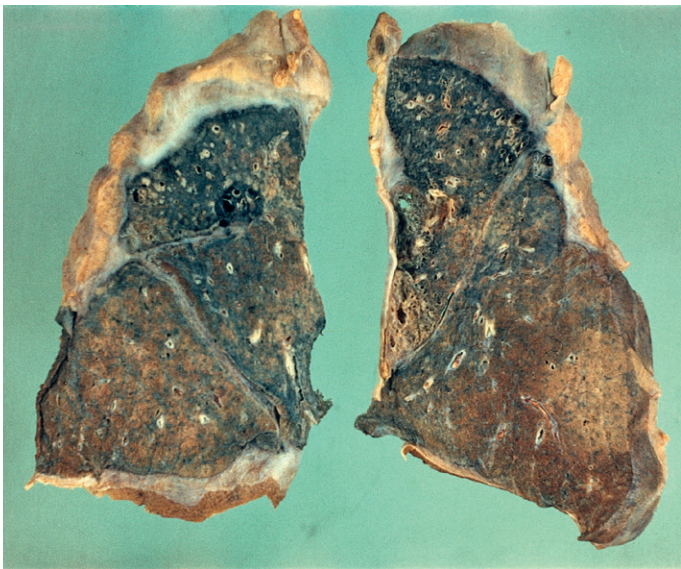
Figure 7.1.28 Aluminium pneumoconiosis. The lungs postmortem show severe fibrosis of the apex and overlying pleura. *(Courtesy of the late Dr G Manning, Bolton, UK.)*

indicated by the development of similar interstitial lung disease in diamond polishers using high-speed polishing discs made with a diamond-cobalt surface that lacked tungsten carbide and the other constituents of hard metal.[318,319]

Hard-metal lung disease and cobalt lung take two forms, an industrial asthma and interstitial fibrosis. The latter has a diffuse lower zonal distribution and the appearances mimic idiopathic pulmonary fibrosis. However, an unusual feature is the presence of moderate, or perhaps only small numbers, of giant cells (Fig. 7.1.29A, B).[316,320] Not only are there multinucleate alveolar macrophages but syncytial cell forms develop in the alveolar epithelium. Electron microscopy confirms that these are multinucleate type II pneumocytes (Fig. 7.1.29C).[316] Such epithelial changes are well known in measles pneumonia but the viral inclusion bodies that characterise this infection are not found in hard-metal pneumoconiosis. The changes are those initially described as a particular pattern of idiopathic interstitial pneumonia termed giant cell interstitial pneumonia or GIP (see p. 264). Elemental analysis shows that many, but not all, cases of GIP represent hard-metal disease. The exceptions seldom give a history of cobalt exposure and must be presumed to represent true idiopathic cases. Conversely, epithelial giant cells are not always found in hard-metal pneumoconiosis and so their presence, although highly characteristic, is neither totally specific nor totally sensitive.

BERYLLIOSIS

Beryllium is the lightest of metals. It has an atomic weight of 4 and special properties that make it especially useful in many applications. It is more rigid than steel, has a high melting point and is an excellent conductor of heat and elecricity. Unfortunately, the inhalation of beryllium dust or fume is exceedingly dangerous.[321,322] Those who worked with beryllium compounds before precautionary measures were taken suffered a high morbidity and mortality. Sometimes, the escape of dangerous fumes from the factories was on such a scale that people living in nearby houses, downwind from the places in which these materials were being worked, contracted and occasionally died from berylliosis ('neighbourhood cases').[323] Alternatively, contamination of a beryllium worker's clothes might lead to berylliosis in a
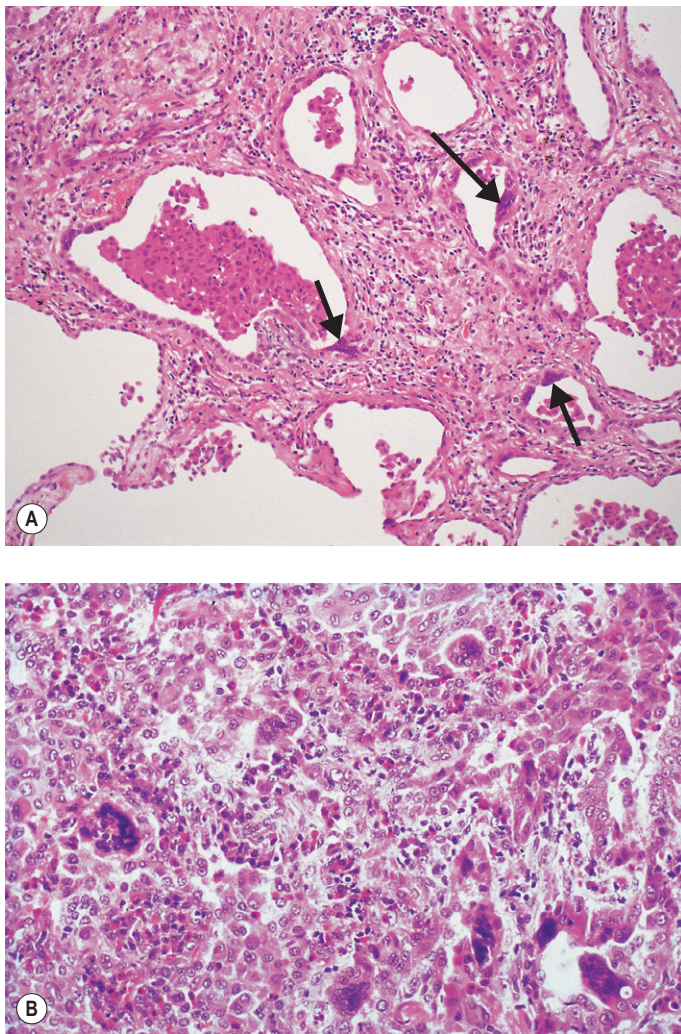
Figure 7.1.29 Giant cell interstitial pneumonia in hard-metal workers. (A) There is interstitial pneumonia and fibrosis and several alveolar epithelial cells are multinucleate (arrows). (B) Higher magnification shows a light lymphocytic infiltrate, numerous alveolar macrophages and several multinucleate giant cells.

relative.[324] Beryllium compounds may also cause contact dermatitis and conjunctivitis.[325] Beryllium is also classified as a probable pulmonary carcinogen,[326] but this is controversial.

Two forms of berylliosis are recognised, acute and chronic. Acute berylliosis was first reported in Germany in 1933[327] and is now largely of historical interest, being only encountered as a result of rare accidental or unexpected exposure. It follows the inhalation of a soluble beryllium salt and represents chemical injury, the pathology being that of diffuse alveolar damage (see p. 136). Further consideration will be confined to chronic berylliosis, which is allergic in nature.

Uses of beryllium and occupations at risk

Chronic berylliosis was first reported in 1946 in the fluorescent lamp industry.[328] Beryllium has now been replaced in this application but it has since proved to be of great value in the nuclear, electronic, computer and aerospace industries and the production of refractory materials and crucibles that are to be subjected to particularly high temperatures. The alloys of beryllium are also now widely used, especially those with copper, on which it confers elasticity and resistance to fatigue. Alloy manufacture and the machining of beryllium alloys are therefore further activities that entail a risk of berylliosis, as is the recovery of the metal in the recycling of scrapped electronic and computer parts. Seemingly innocuous occupations such as dental laboratory technician are not without risk of chronic berylliosis.[329]

Pathogenesis

There are good grounds for regarding chronic berylliosis as being an allergic condition. Many of those affected react strongly to skin tests with dilute solutions of beryllium salts, although these must be undertaken with care: occasionally in a highly sensitised person even so small an exposure may evoke a systemic reaction. The skin reaction is of the delayed type, occurs in only 5% of exposed individuals, is not associated with a clear-cut dose–response curve and represents a granulomatous response. Further evidence for the disease having an allergic basis derives from bronchoalveolar lavage, which demonstrates an excess of T-helper lymphocytes that proliferate in vitro on exposure to beryllium salts.[330] A positive transformation test given by these lymphocytes is a more reliable indicator of disease than in vitro blood lymphocyte transformation testing,[52] which is safe but not wholly reliable and indicates only sensitization, rather than berylliosis.

Susceptibility to berylliosis varies widely from person to person and it is notable that chronic pulmonary disease is strongly associated with the HLA antigen DPβ1 and the *Glu69* gene.[331,332] The importance of genetic factors is supported by a report of the disease in identical twins.[333]

Chronic berylliosis is thought to be initiated by the metal binding to tissue proteins and acting as a hapten to initiate a delayed hypersensitivity response characterised by a proliferation of T-helper lymphocytes. These sensitised cells in turn secrete a variety of cytokines (e.g. interleukin-2, tumour necrosis factor-α and interferon-γ) that recruit and activate macrophages, which mature into epithelioid cells. The resultant epithelioid cell granulomas destroy the lung tissue and lead to pulmonary fibrosis.

Pathological changes

If beryllium enters the subcutaneous tissues through a cut or abrasion, as often happened in the earlier days of fluorescent lamp manufacture, a sarcoid-like granuloma soon appears at the site; in time, the overlying epidermis may break down to form an ulcer.

Even more serious are the lesions produced by the inhalation of beryllium. Chronic pulmonary berylliosis takes the form of a widespread granulomatous pneumonia with a histological picture identical to that of sarcoidosis (Fig. 7.1.30A). Both berylliosis and sarcoidosis affect the upper lobes more than the lower (Fig. 7.1.30B) and in both diseases the granulomas are preferentially distributed along lymphatics and may involve adjacent blood vessels. In neither condition is there widespread necrosis but in both diseases the granulomas occasionally display a little central necrosis or hyalinisation. As in sarcoidosis, the hilar lymph nodes may be involved but, unlike sarcoidosis, not in isolation.

Over a period of many years, the sarcoid-like granulomas gradually undergo progressive fibrosis, with consequent impairment of pulmonary function. In the later stages, when the disease has become chronic, dispersal of beryllium from its site of initial absorption may lead to generalisation of the disease and to the appearance of similar granulomas elsewhere, particularly in the liver, kidneys, spleen and skin, but this is unusual.
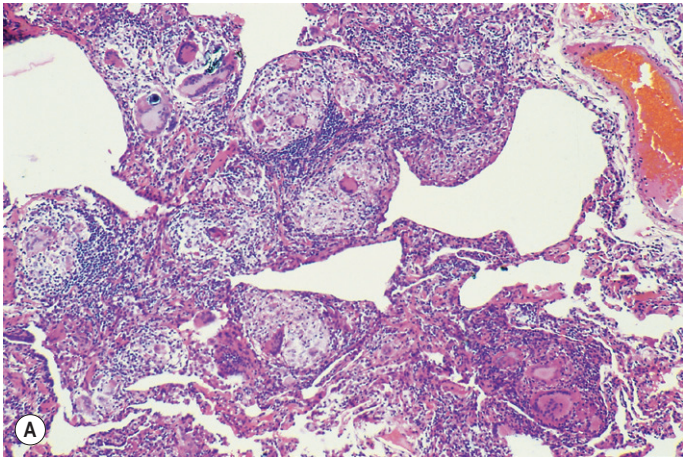
Figure 7.1.30 Chronic berylliosis. (A) Numerous non-necrotising epithelioid and giant cell granulomas are seen in the lungs. (B) The upper and middle lobes and the apex of the lower lobe are contracted by extensive fibrosis. Paper mounted whole lung section.

Clinical features

Chronic berylliosis is characterised by the gradual onset of cough, shortness of breath, chest pain, night sweats and fatigue. These symptoms may develop within a few weeks of exposure or many years later. Once the worker is exposed, the beryllium is retained in the tissues

and there is a lifelong risk of disease. Progression often entails alternating exacerbations and remissions, long after exposure has ceased.

Analysis

In keeping with the view that berylliosis is a hypersensitivity reaction, very little beryllium is necessary to cause the disease. Particulate beryllium is so scanty in the affected tissues and the atomic number of beryllium so low that electron microprobe analysis is generally unsuitable for its detection. Furthermore conventional detectors are protected by a beryllium window. However, the substitution of a polymeric window has enabled beryllium to be detected by electron microprobe analysis, presumably in a patient with fairly heavy exposure.[334] Ion or laser microprobe mass spectroscopy can also detect very small amounts of beryllium in tissue sections but these techniques are not widely available.

Differential diagnosis

The differential diagnosis of chronic berylliosis is from sarcoidosis, to which it is identical morphologically.[335–337] However, as noted above, it is unusual for berylliosis to cause significant hilar lymphadenopathy in the absence of pulmonary disease, which is a common feature of sarcoidosis. Extrathoracic granulomas, erythema nodosum and uveitis, which are all common in sarcoidosis, are unusual in berylliosis. However, one group found that 6% of patients initially diagnosed as having sarcoidosis actually had chronic berylliosis.[338] Similar findings have been reported by others.[324,339] Any patient thought to have sarcoidosis who has worked with or near metals should be offered a beryllium lymphocyte transformation test. A list of laboratories performing this test can be found at www.dimensional. com/~mhj/medical_testing.html.

POLYVINYL CHLORIDE PNEUMOCONIOSIS

Although polyvinyl is not a mineral and the reaction of the lungs to its presence is therefore not a true pneumoconiosis, it is generally so termed and is dealt with here for convenience. Workers are exposed to polyvinyl chloride dust in the milling and bagging of this plastic and micronodular opacities may be detected in their lungs radiologically. However, the material is non-fibrogenic and histology merely shows a foreign-body reaction to the dust particles.[340] The radiological opacities may abate when exposure ceases.[341] Nevertheless, one polyvinyl chloride worker developed systemic sclerosis,[342] which is a recognised complication of silicosis (see p. 335). Polyvinyl chloride is produced from vinyl chloride monomer, which has a causal association with angiosarcoma of the liver and probably other forms of cancer, including carcinoma of the lung (see p. 534).

FLOCK WORKER'S LUNG

In the late 1990s a characteristic lung disease was identified in workers at several factories producing plush material by spraying nylon flock on to an adhesive backing material.[343–346] The flock fibres are too large to be inspired but may be mixed with smaller nylon shards of respirable size. The workers complained of cough and breathlessness and were found to have a restrictive ventilatory defect with interstitial markings on radiography. Their symptoms improved on removal from the workplace but relapsed on return to work. Pathologically, there was lymphocytic bronchiolitis and peribronchiolitis with widespread lymphoid hyperplasia represented by lymphoid aggregates.

Granulomas were not identified. The histological appearances suggest a severe immunological reaction and raise possibilities such as rheumatoid disease and Sjögren's syndrome but consideration of the clinical and serological setting and the occupation should permit recognition of the cause.

POPCORN WORKER'S LUNG

The industrial production of popcorn and other foodstuffs appears to carry a risk of obstructive airway disease.[347–350] Biopsy of affected workers has shown peribronchiolar fibrosis and granulomas and air sampling has identified many volatile organic compounds, of which the flavouring agent diacetyl (2,3-butanedione) is suspected of being responsible for the bronchiolitis.

PAINT SPRAYING

It is difficult to continue paint spraying (air brushing, aerographics) without adequate respiratory protection but in the early 1990s several small aerographic factories operated in the neighbourhood of Alicante, southeastern Spain without any concern for the workers' health. The workers were required to paint patterns on textiles using a hand-held spray gun. The atmospheric pollution was intense but complaints of respiratory difficulties were met with reassurances and the workers urged to continue. This they did because of the otherwise poor economy, often returning to work when disabling breathlessness had settled down. A change of paint (to Acramin F) may have contributed because the worst-affected workers were employed at two plants that had made this switch. Their illness has been described as the 'Ardystil syndrome' after the name of one of these factories. Some workers were left with permanent respiratory disability. One required a lung transplant and 6 others died.[351–354] Transbronchial biopsy showed organising pneumonia, which in the fatal cases had progressed to irreversible interstitial fibrosis. A similar outbreak of respiratory disease was subsequently reported in Algerian textile factories where Acromin F was applied by the same technique.[355,356] Acromin F is marketed as a paste and used as such without ill-effect. Its use in heavy spray form appears to be responsible for the 'Ardystil syndrome'.

MINERAL OILS AND PETROLEUM

Workers in engineering workshops may be exposed to the prolonged inhalation of fine sprays or mists of the longer-chain hydrocarbons that constitute many mineral oils. This may result in exogenous lipid pneumonia,[357] which is described on page 314, or extrinsic allergic alveolitis.[358–360] The vapour of shorter-chain hydrocarbons such as paraffin oil (kerosene: $C_{10–16}$) and petrol (gasoline: $C_{4–12}$) and gaseous hydrocarbons such as propane may act as acute asphyxiants or central nervous system depressants but have negligible pulmonary toxicity. However, if they are ingested or aspirated in their liquid form they are acutely toxic to the lungs, producing a chemical pneumonitis with the features of diffuse alveolar damage. Ingestion may be accidental or deliberate (see Fig. 4.19, p. 142) whereas aspiration is generally inadvertent, occurring in siphoning accidents, such as those experienced by fairground operatives who 'breath or eat fire' ('fire-eater's lung').[361,362] Animal experiments involving the intratracheal injection of kerosene resulted in acute pulmonary exudates, which cleared except for residual bronchiolitis.[363]

Table 7.1.9 Principal respiratory risks of welding

Source	Derivative	Effect
Metals being welded	Iron	Siderosis
	Zinc	Metal fume fever
	Beryllium	Berylliosis (acute or chronic)
	Chrome, nickel	Asthma
	Cadmium, manganese	Diffuse alveolar damage
	Chrome, nickel, arsenic	Lung cancer
Burning of adjacent surfaces	Isocyanates	Asthma
	Phosgene	Bronchitis, bronchiolitis
	Tetrafluoroethylene	Polymer fume fever
	Oxides of nitrogen	Bronchitis
Electrode insulation Protective clothes	Asbestos	Mesothelioma
Gas used to prevent oxidation	Carbon dioxide	Asphyxia
Combustive gas	Carbon monoxide	Carbon monoxide poisoning
Ultraviolet light	Ozone	Bronchitis
Various	Silica, silicates	Silicosis, mixed-dust pneumoconiosis

WELDING

Welder's pneumoconiosis, first recognised in 1936,[364] essentially represents the fairly harmless deposition of iron in the lungs (siderosis – see p. 337). However, welders may suffer various ill-effects from the inhalation of substances other than iron (Table 7.1.9). Some of these are para-occupational risks, that is, encountered by welders because they work near another process and are inadvertently exposed: thus, shipyard welders may be exposed to asbestos,[365] and those in foundries to silica. Welders may therefore develop a mixed-dust pneumoconiosis (see p. 337), rather than just siderosis. However, one analytical investigation identified excess amounts of iron alone in association with pulmonary fibrosis; the silicon content did not differ from that in controls.[366]

More directly, welders may be exposed to asbestos insulation that they themselves use, while welders of special steel alloys run the risk of metal-induced asthma, metal fume fever, polymer fume fever and the consequences of toxic metal fume inhalation,[367] all of which are described separately in this chapter, as is lung disease in aluminium welders. Chronic bronchitis has been attributed to the inhalation of low concentrations of irritants such as ozone and nitrogen dioxide by welders but this risk is unproven and the subject of much controversy. Welders may also inhale carcinogenic hexavalent chromium compounds in the course of their work and therefore develop lung cancer. The term 'welder's lung' is often applied indiscriminately to any of these diseases and, as it has no specific meaning, is best avoided.

TOXIC FUMES AND GASES

Dust, fume and gas are some of the terms used to describe different physical forms of respirable agents. They are defined in Table 7.2.1 on

page 372. The parts of the respiratory tract at which they exert their maximal effect are influenced by particle size and solubility (see Table 7.2.2 and Fig. 7.2.2, p. 372).

Toxic metal fume[368]

The finely divided fume of several metals is highly toxic to the lungs and capable of producing severe acute and chronic damage to both the conductive airways and the alveoli, resulting in acute tracheobronchitis and bronchiolitis, diffuse alveolar damage, obliterative bronchiolitis and pulmonary fibrosis. Important metal fumes in this respect include aluminium, which is released together with silica fume in bauxite smelting (see Shaver's disease,[369] above), cadmium from welding or cutting special steels, chromium from cutting its alloys or in the manufacture of chromates, cobalt released in the production and use of its alloys (see hard-metal disease, above), mercury released in various industries and in the home,[370] nickel carbonyl released during the purification of metallic nickel or the manufacture of nickel alloys[371] and beryllium (see above).

Toxic gases

Many irritant gases cause severe acute and chronic damage to both the conductive airways and alveoli. The changes are non-specific and similar to those wrought by toxic metal fumes (see above) and viruses amongst other agents. They consist of acute tracheobronchitis and bronchiolitis, obliterative bronchiolitis, diffuse alveolar damage and pulmonary fibrosis.

The gases liable to produce such damage include oxides of nitrogen, sulphur dioxide, ozone, phosgene, chlorine, ammonia and various constituents of smoke, notably acrolein. Some of these are also touched upon in Chapter 7.2 because they are of general as well as occupational importance, although there is no rigid difference between general and occupational pollution.

Ozone, sulphur dioxide and nitrogen dioxide are oxidising gases that may be found together as industrial atmospheric pollutants. Each is capable of producing diffuse alveolar damage by means of its oxidising properties and the release of free active radicals. In addition, they cause damage to distal airways, particularly terminal and respiratory bronchioles, with resulting bronchiolitis.

Oxides of nitrogen may be encountered with fatal consequences by farmhands seeking to free a blockage in a silo when they encounter pockets of this gas that have accumulated on top of the fermenting silage: the term 'silo-filler's disease' is generally applied to the initial haemorrhagic oedema or the obliterative bronchiolitis that develops in those who survive the initial chemical injury.[372–375] Asphyxia due to the farmhand encountering pockets of carbon dioxide is a further hazard within agricultural silos. Other farmhands have suffered from the inhalation of toxic gases or bacteria when handling liquid manure.[376–379] Welding, which is considered below, may also involve exposure to toxic gases such as oxides of nitrogen.

Ozone, the principal oxidant gas of photochemical smog, produces pulmonary changes at relatively low levels and may be encountered at higher concentrations in various industries. Potentially dangerous levels of ozone are produced from atmospheric oxygen by ultraviolet radiation given off in welding while ozone is used in industry to sterilise water, bleach paper, flour and oils, and mask the odour of organic effluents. The damage wrought by ozone is predominantly centriacinar in distribution, affecting terminal and respiratory bronchiolar epithelium and proximal alveolar epithelium.[380–382] There is loss of cilia and necrosis of centriacinar alveolar type I epithelial cells. The changes are dose-dependent and, in one study, the youngest animals were most sensitive.[383] In long-term experiments, hyperplastic bronchiolar Clara and ciliated cells extended peripherally to line alveolar ducts.[384] The role of granulocytes is stressed in some experimental studies[385] and it is notable that neutrophil migration is prominent when the human lungs are damaged by ozone.[386]

Aldehydes such as acetaldehyde, formaldehyde and acrylic aldehyde (acrolein) are widely used in the plastics and chemical industries. The first is a liquid and the others are water-soluble gases. Pathologists are of course familiar with formaldehyde solution from its use as a disinfectant and histological fixative. All these aldehydes are intensely irritant and their acute effects generally prevent prolonged exposure to high concentrations. Chronic effects include skin sensitivity and asthma, and in rats nasal carcinoma. However, the doses to which these experimental animals were exposed far exceed any that are likely to be encountered by humans, in whom there is no convincing evidence of aldehyde-induced cancer.[387]

Ammonia gas is extensively used in industry as a raw material, notably in the manufacture of nitrogenous products such as fertilisers and plastics. It is highly soluble and its acute irritative effects are mainly felt in the eyes, nose and throat, but high levels affect the major airways, possibly leading to them being blocked by exudates. Survival usually brings full recovery but bronchiectasis and obliterative bronchiolitis have been described.

Chlorine gas is widely used in the chemical industry. It is transported and stored under pressure in liquid form. Heavy exposure through its accidental release or use as a war gas has proved fatal through its acute toxicity causing exudative airway occlusion and pulmonary oedema. Survivors usually recover completely but, as with nitrogen dioxide and ammonia, there is a risk of obliterative bronchiolitis.

Phosgene (carbonyl chloride, $COCl_2$) is a poisonous, colourless gas that was responsible for thousands of deaths during World War I, when it was used in chemical warfare. It is used industrially in the preparation of some organic chemical compounds and is formed, perhaps inadvertently,[388] by the combustion of methylene chloride in products such as paint strippers. Phosgene causes injury to terminal bronchioles and alveoli, with resulting oedema and hyaline membrane formation. The mechanism of cell damage is uncertain but it may depend on inactivation of intracellular enzymes by the gas. Long-term problems are rare but chronic bronchitis and emphysema have been described in survivors.

Mustard gas (bichloroethyl sulphide, $C_4H_8Cl_2S$) is a further agent that has been used in chemical warfare. It is primarily a skin vesicant but when inhaled it results in widespread epithelial destruction and pulmonary oedema. Survivors may be left with irritant-induced asthma (reactive airways dysfunction), chronic bronchitis, tracheobronchomalacia, bronchiectasis and bronchiolitis obliterans.[389–391]

Thionyl chloride is used in the manufacture of lithium batteries where it is liable to result in the release of sulphur dioxide and hydrochloric acid fumes. Workers in such factories have developed lung injury varying from mild, reversible interstitial disease to severe obliterative bronchiolitis.[392]

Hydrogen sulphide is the principal chemical hazard of natural gas production. High levels of the gas also buid up in sheds housing large numbers of pigs, the source here being the pig manure. Once inhaled the gas is rapidly absorbed into the blood stream. The effects are therefore widespread but include the usual respiratory effects of irritant gases, varying from sneezing to pulmonary oedema and acute respiratory distress, depending upon the exposure. In Alberta 221 cases were identified over a 5-year period. The overall mortality was 6%; 5% of victims were dead on arrival at hospital. Most required admission to hospital but the survivors experienced no long-term adverse effects.[392a]

Table 7.1.10 Work-related respiratory disease in the UK[394]

Disease	Estimated annual number of cases
Occupational asthma	941
Non-malignant pleural disease	730
Mesothelioma	644
Pneumoconiosis	341
Inhalation accidents	280
Lung cancer	70
Infectious disease	59
Extrinsic allergic alveolitis	46
Bronchitis	38
Byssinosis	1
Other diagnoses	117
Total	3207

Table 7.1.11 Agents that cause occupational asthma and examples of the occupations involved[397]

Causative agent	Occupations involved
High-molecular-weight agents (patients are usually atopic)	
Laboratory animals	Laboratory animal handling
Flour and grain	Baking, milling, farming
Enzymes	Detergent and drug manufacture, baking
Seafoods	Food processing
Gums	Carpet and drug manufacture
Low-molecular-weight agents (patients are not necessarily atopic)	
Isocyanates	Foam and plastic manufacture, spray painting, insulation
Anhydrides	Plastic and epoxy resin handling
Wood dusts	Forestry, carpentry
Soldering fluxes	Electronics
Formaldehyde, glutaraldehyde	Histopathology, nursing, radiography
Amines	Shellac and lacquer handling, soldering
Chloramine	Cleaning
Dyes	Textiles
Acrylates	Adhesive application
Metals	Solderers, refiners
Drugs	Pharmaceutical work

ANOXIC ASPHYXIA

The danger of asphyxia from the inhalation of gases devoid of oxygen is fairly widespread in industry.[393] It generally arises from the use of inert gases, which, being non-toxic, give a false sense of security. Pockets of these gases tend to form in confined spaces. Anoxic death from the accumulation of methane is well known in mines and has also occurred in slurry pits and sewers. Anoxic asphyxia in diving (and anaesthesia) has resulted from the incorrect connection of gas cylinders or failure to notice that a mixed gas contains insufficient oxygen. Deaths have occurred in welding when argon or carbon dioxide has been used to shield the weld and prevent oxidation of the metals at the high temperatures employed. Deaths have also resulted from inadvertent entry to discharged oil tanks filled with nitrogen to reduce the risk of explosions, or from the formation of pockets of nitrogen gas applied in liquid form to freeze the contents of damaged pipes so that they can be repaired without the necessity to drain down.

The respiration of a gas devoid of oxygen causes loss of consciousness within seconds because it not only fails to provide oxygen but removes that present in the pulmonary arterial blood. The changes at autopsy are those common to cellular hypoxia. They include cerebral and serosal petechiae and pulmonary congestion and haemorrhage but these features are not specific and are not always present. The cause of death can generally only be surmised from the circumstances surrounding the death.

OCCUPATIONAL ASTHMA

Occupational asthma is the commonest cause of work-related respiratory disease in many western countries (Table 7.1.10).[394–396] The reported incidence ranges from 13 per million workers in South Africa to 174 per million workers in Finland.[395,396] It occurs in many industries (Table 7.1.11)[397] and occupational factors can be identified as contributing to asthma in about 15% of adult cases.[398] Over 250 aetio-

logical agents have been identified.[399] In the UK a third are organic, a third chemical, 6% metallic and the rest miscellaneous. The commonest, in descending order, are isocyanates, flour and grain, laboratory animals, glutaraldehyde, solder or colophony and hardening agents.[400]

Atopy appears to predispose to occupational asthma when the allergen is of high molecular weight but not when it is of low molecular weight. For example, atopic individuals are particularly prone to develop asthma if employed in the manufacture of biological detergents, whereas atopy does not increase the risk of asthma from sensitisation to toluene di-isocyanate, which is a serious health problem in the manufacture of polyurethane. Similarly, platinum salts are such potent sensitising agents that nearly all those exposed to them develop asthma. Asthma-provoking metals other than platinum include chromium, cobalt, nickel and vanadium, all of which are used in steel alloys, and possibly aluminium (see pot-room asthma, p. 357). Other asthma-inducing factors encountered in industry include grain and flour dust, certain wood dusts, soldering fluxes containing colophony (pine resin), epoxy resin hardeners such as phthallic anhydride, isocyanate-containing foams and paints, formaldehyde and the excreta of laboratory animals. Contaminated humidifiers may cause occupational asthma as well as humidifier fever and extrinsic allergic alveolitis.[401] Pathologically, occupational asthma is identical to non-occupational asthma (see p. 109).

Byssinosis

Byssinosis is a further form of occupational asthma,[402] one encountered in the cotton industry. The sensitising agent is a component of the cotton bract, which is the part of the cotton harvest other than the cotton fibre. Bract consists of dried leaf, other plant debris and soil particles and contains a variety of fungal and bacterial residues, including lipopolysaccharide endotoxin, but the exact nature of the sensitising agent remains unknown.[403] The endotoxin is unlikely to be responsible for byssinosis but may be the cause of so-called mill fever, a self-limiting illness characterised by malaise, fever and leukocytosis that is experienced by many people on first visiting a cotton mill.

Dust levels and the risk of byssinosis are particularly high in the carding rooms where the raw cotton is teased out before it is spun. Affected workers are worse when they return to work after the weekend break, a feature attributed to antibody levels having built up during this brief respite from the cotton dust. There is no link with atopy and the fluctuating antibodies are precipitins of the immunoglobulin G class. Complement activation by both arms of the complement cascade has been reported.[404,405]

When the Lancashire economy was largely cotton-based, necropsies on workers suffering from byssinosis generally showed gross emphysema, and this came to be accepted as evidence of byssinosis. However, it is now realised that in this heavily industrialised part of the UK, emphysema is as common in the general population as in cotton workers and it can no longer be considered a component of byssinosis. Other findings in byssinosis are more commensurate with asthma, namely an increase in bronchial muscle and mucous cells.[406] No granulomas or other evidence of extrinsic allergic alveolitis are found.

OCCUPATIONAL FEVERS

Fever may be the predominant feature in a variety of occupational illnesses and the unifying term 'inhalation fever' has been proposed.[407] However, the individual occupations are of interest and these conditions will therefore be considered separately. Mill fever has been mentioned above under byssinosis.

Humidifier fever[408]

Humidifier fever is an acute illness characterised by malaise, fever, myalgia, cough, tightness in the chest and breathlessness, all of which are worse on Monday mornings if the humidifier responsible is at work rather than home. The chest complaints, and their aggravation on return to work after the weekend, are features shared with byssinosis (see above) but the general complaints fit better with extrinsic allergic alveolitis (see p. 279). Humidifier fever develops in circumstances that also lead to the development of a form of extrinsic allergic alveolitis, and not surprisingly the same name has been extended to this latter condition, with inevitable confusion. Both diseases are caused by microbiological contamination of humidifiers or air conditioners so that a fine spray of microorganisms is emitted into the office, factory or home. Investigations have generally shown the baffle plates of the air conditioner to be covered with a slime of bacteria, fungi or protozoa (mainly amoeba and ciliates), and extracts of this have been used to identify precipitins in the patient's sera, as in extrinsic allergic alveolitis. However, unlike extrinsic allergic alveolitis, humidifier fever resolves within a day and leaves no permanent injury. For this reason there is seldom the opportunity to study the tissue changes, and partly for this reason it remains unclear whether the disease is mediated by immune complexes, as in extrinsic allergic alveolitis, or by endotoxins derived from the contaminants.

Pulmonary mycotoxicosis

A febrile illness occurring in precipitin-negative farm-workers after heavy exposure to fungi in their silos was attributed to inhaled fungal toxins and named pulmonary mycotoxicosis.[409] It is also known as precipitin test-negative farmer's lung and organic dust toxic syndrome.[410] The condition is generally self-limiting and is seldom biopsied but desquamative interstitial pneumonia and diffuse alveolar damage have been reported.[411,412]

Metal fume fever

This is a self-limiting acute illness characterised by fever, sweating, myalgia, chest pain, headache and nausea, that comes on Monday mornings when occupational exposure is experienced after a weekend's respite, as with bysinnosis and humidifier fever; during the week tolerance develops.[368,413] The disease involves the release of cytokines such as tumour necrosis factor and is presumed to have an allergic basis.[414] The metals involved are chiefly zinc, copper and magnesium, and, to a lesser extent, aluminium, antimony, iron, manganese and nickel. Occupations at risk include any that generate such metal fumes, but particularly welding. It is most commonly associated with welding zinc-coated surfaces. If the symptoms persist, alternative diagnoses, such as acute cadmium poisoning and other specific toxic metal fume diseases, should be suspected: these are not self-limiting and may cause severe bronchiolitis or diffuse alveolar damage (see above).

Polymer fume fever

This illness resembles metal fume fever except that it occurs without regard to previous exposure: no tolerance develops and there is therefore no particular susceptibility on Mondays. The polymers concerned are quite inert, except when heated to produce fume: polytetrafluorethylene (PTFE, Teflon, Fluon, Halon) is a notable example. As with other self-limiting diseases, little is known of the tissue changes.

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Chapter | **7** |

7.2   Environmental lung disease

ENVIRONMENTAL IRRADIATION

Environmental irradiation chiefly affects the skin but in some parts of the world rocks near the surface release significant amounts of radon gas. This carcinogen is liable to accumulate in buildings and be inhaled, so subjecting the occupants to an increased risk of lung cancer. The installation of underfloor ventilation is therefore advocated in such areas. This subject is explored more fully on page 533.

ATMOSPHERIC PRESSURE CHANGES

The body is vulnerable to both increases and decreases in pressure and it is the lungs that often bear the brunt of the damage. Increased pressure may result in blast injury or crushing of the chest while decreased pressure may result in the lungs literally bursting or dissolved gases being released within the blood (caisson disease), or the vascular alterations that underlie mountain sickness developing. Some of these pressure changes entail a risk of pneumothorax and it is essential that this is properly investigated postmortem by the chest being opened under a water seal. Loud music has been incriminated as a specific form of air pressure change causing pneumothorax and metereologists have shown that 'spontaneous' pneumothoraces tend to occur in clusters associated with natural drops in atmospheric pressure.[1,2]

Blast injury

Explosions may cause injury by the body being violently thrown against a less moveable object, by objects being thrown against the body or by the blast wave hitting the body. These mechanisms often act together but sometimes there is only blast injury, to which the lungs are particularly vulnerable. For a time it was considered that the damage was direct, the blast wave travelling down the airways to injure the lungs. However, at the start of the Second World War, experiments conducted in the UK showed that the lungs were injured indirectly, the blast wave being transmitted to them through the chest wall: pulmonary blast injury is worst on the side of the body towards the explosion, and can be reduced by protective clothing.[3] Underwater explosions are particularly dangerous because water is incompressible. There may be severe internal injury but no external evidence of damage other than a trickle of blood from the mouth or nose. This is because the injury is rate-dependent. Quite small thoracic deform-

ation may produce severe pulmonary damage if peak compression is attained very quickly, typically in less than 5 ms. Conversely, severe chest wall distortion may produce only minor pulmonary contusion if this time is extended beyond 20 ms.[4]

At necropsy, the lungs are contused, with blood evident in the airways and parenchyma. Depending on the force of the blast, the haemorrhage may be pinpoint, patchy or confluent. It tends to follow the lines of the ribs and may be accompanied by pleuropulmonary lacerations having the same distribution. In this case there will also be haemothorax, pneumothorax and possibly air embolism. Patchy pulmonary haemorrhages cuff the blood vessels.[5,6] In patients who survive for a few days, the lungs resemble the liver macroscopically and histologically show chronic interstitial inflammation and fibrosis as well as haemorrhage.[7] Other injuries are often present and fat embolism, aspiration pneumonia, fluid overload and infection may all be added to the effects of the blast wave.

Chest squeeze

'Chest squeeze' is another form of barotrauma caused by high pressure but here the body is compressed rather than subject to a sudden wave of pressure as in blast injury. It is experienced by divers who descend very deeply, thereby subjecting their bodies to such high pressure that their chest walls are literally crushed, so that their ribs break and their lungs are severely compressed. More common mishaps experienced by divers include drowning and decompression sickness, both of which are dealt with below, and neurological syndromes such as nitrogen narcosis, which will not be considered further.[8]

Burst lung

'Burst lung' is the most acute form of decompression sickness.[9] It is experienced by divers and submariners making rapid ascents from depth and by aviators who ascend too rapidly in unpressurised aeroplanes, experience failure of a plane's pressure system or have to eject at high altitudes. Injury to the lung is caused by trapped alveolar gas expanding so rapidly that it exceeds total lung capacity before it can escape through the trachea. The lungs literally burst: the alveolar walls rupture and blood mixes directly with alveolar air. The victim experiences chest pain and there may be blood-stained froth at the mouth or frank haemoptysis. Air may enter the alveolar walls to cause interstitial emphysema or air embolism. Asthmatics may be at particular risk because of regional air-trapping.[10] Diving mammals such as porpoises and whales are protected from such dangers of peripheral air-trapping by cartilage extending far out into the finest conductive airways so that these passages never close, even at the end of full expiration (Fig. 7.2.1).[11,12]

Patients requiring positive-pressure artificial respiration are also at risk of burst lung, but the complications of the resultant interstitial emphysema differ from those experienced by divers. In divers, the chest wall is buttressed by the surrounding water and air in the interstitium is liable to track towards the hilum of the lungs and enter pulmonary veins, with resultant cerebral and coronary air embolism, either of which may prove fatal.[13] Iatrogenic burst lung, on the other hand, takes place in patients whose chest wall is not so buttressed, and then outward rupture of the interstitial air is more likely, resulting in pneumothorax. Extension of the interstitial emphysema to the mediastinum, neck and chest wall is also more likely in such patients, resulting in surgical emphysema at these sites. However, there are exceptional cases marked by both cerebral embolism and extensive air tracking.[14]
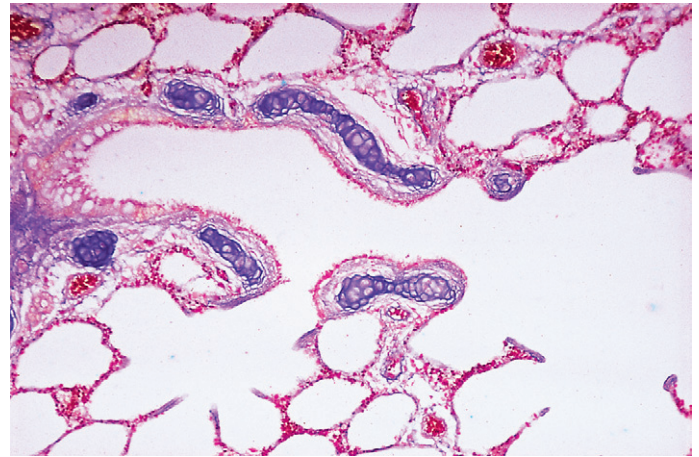
Figure 7.2.1 Sea lion lung. The smallest airways of deep-diving mammals such as the sea lion are buttressed by cartilage to ensure that all air is evacuated from the lungs when the animal is at depth to prevent the lungs bursting on rapid ascent. In humans there are several generations of airways that lack cartilage (the bronchioles) and consequently close before exhalation is complete. The trapped gas (the residual volume) is normally of no consequence but it poses a danger that the lungs may burst or of decompression sickness if ascent is rapid, whether in the sea or by air. *(Courtesy of Professor D Denison, Brompton, UK.)*

Decompression sickness (caisson disease)

The same circumstances that lead to burst lung may also cause decompression sickness, which is also known as caisson disease.[9] In this condition there is a sudden release of nitrogen gas that has gone into solution in the lipids of adipose tissue and of myelinated nervous tissue at the higher pressure: the released nitrogen gains access to the blood stream in which it forms bubbles.[15] Doppler ultrasound techniques show that this is quite customary when divers ascend from depth,[16] but the lungs generally provide an effective filter so that there are no untoward systemic effects, although there may be sudden chest pain on deep inspiration ('the chokes'). Gradual decompression permits the nitrogen to diffuse across the alveolar membranes and be exhaled. If, however, substantial amounts of nitrogen are released from solution, sufficient pulmonary arteries may be blocked to cause pulmonary hypertension, with resultant opening of arteriovenous communications or a patent foramen ovale, so permitting the gas to enter the systemic circulation. This is often followed by limb pains ('the bends') and perhaps cerebral symptoms ('the staggers'). Fatal cases are characterised by gas bubbles within blood vessels throughout the body and froth in the heart chambers. Delayed effects include ischaemic necrosis of bones and other tissues.[17]

Deep-diving mammals are protected by the same mechanism that prevents them suffering from burst lung. They exhale before diving and during the dive the chest is compressed to the extent that virtually all the gas in the lungs passes into the cartilage-buttressed nonrespiratory airways (see Fig. 7.2.1), resulting in very little to be absorbed by the blood. The pulmonary collapse also serves to reduce buoyancy. The distribution of the little gas that is absorbed is minimised by bradycardia.[18] Many viscera experience anaerobic respiration but hypoxia is minimised in the heart and musculature by high levels of haemoglobin and myoglobin. The brain is further protected by the supplying arteries drawing on oxygen stored in an unusual sponge-like cervical organ known as the rete mirabilis.

Mountain sickness

Mountain sickness is due to reduced atmospheric pressure brought about more slowly than that responsible for decompression sickness.[19,20] It may be acute or chronic.

Acute mountain sickness

Acute mountain sickness is likely to be experienced by anyone who ascends above 3000–4000 m without a period of acclimatisation at intermediate levels. Symptoms are as liable to occur in people born at high altitude who return after a few weeks spent at sea level as in those who go to the mountains for the first time: acclimatisation is obviously short-lived and is therefore necessary whenever an ascent is to be made. The ill-effects are commonly precipitated by exercise. In the susceptible, acute mountain sickness commonly appears within 3 days of ascent.

The basis of acute mountain sickness is tissue hypoxia. It results in deteriorating intellectual and psychological function, headache, nausea, vomiting, and more rarely pulmonary and cerebral oedema. High-altitude pulmonary oedema is characterised by increasing dyspnoea, cyanosis and a dry cough, and later the production of copious, frothy sputum, which sometimes becomes blood-stained.[21] The pulmonary artery pressure is markedly raised but wedge pressures are normal, indicating that the left side of the heart is unaffected and that pulmonary venous constriction is unlikely to be an important contributory factor.

The pulmonary oedema fluid has a high protein content[22] and the condition has been characterised as a non-cardiogenic high-permeability oedema associated with excessive pulmonary hypertension.[23,24] Hypoxia is a well-known cause of pulmonary arteriolar constriction but in acute mountain sickness the vascular response appears to be exaggerated for the pulmonary artery pressure is considerably higher than is usual for the altitude. An association with certain HLA complexes (HLA-DR6 and HLA-DQ4) suggests that this has a genetic basis.[25] Although arteriolar constriction only tends to protect the pulmonary capillaries, it could explain the oedema if the process was patchy – as is the resultant oedema – for patchy arteriolar constriction would subject the rest of the lung to abnormally high pressures and lead to capillary stress failure in these areas (see pp. 402 and 448).[26,27] Measurements of capillary pressure suggest that this is indeed the case.[28] Furthermore, vasodilators such as calcium channel blocking agents and inhaled nitric oxide gas[23,29,30] have been used with success to counter acute mountain sickness, supporting the idea that hypoxic vasoconstriction plays a central role.

Autopsy shows the lungs to be heavy and firm. The cut surface weeps oedema fluid, which is often blood-stained, but a striking feature is the patchy distribution of the changes. Areas of haemorrhagic oedema alternate with others that contain clear oedema fluid and others that are normal apart from overinflation. Pulmonary arterial thrombi are commonly found. Microscopy confirms the presence of haemorrhagic oedema and may show neutrophils and hyaline membranes in the alveoli. The alveolar capillaries are congested and may contain thrombi. There may also be an increase in mast cells and rarely pulmonary infarction. The right ventricle is commonly dilated whereas the left ventricle is normal. Highlanders generally show right ventricular hypertrophy and increased muscle in their pulmonary arteriesm, changes that are not apparent in lowlanders.[31,32]

Chronic mountain sickness

Prolonged residence at high altitude leads to hypoxic pulmonary hypertension (see p. 424), an increase in red cell mass and cor pulmonale. Livestock taken from lowland plains to high-altitude pastures suffer similarly but the natural stock of the Himalayas and Ethiopian highlands are apparently immune. So too are other species long established at high altitude such as the llama and yak. These species are said to have adapted to their climate, that is, the forces of natural selection have bred out the pulmonary vasoconstrictive response to hypoxia. Cattle of European origin and humans acclimatise to high altitude by processes such as increasing their red cell mass but generally they are not adapted like native species and suffer hypoxic pulmonary hypertension at altitudes in excess of 3000 m. Certain Himalayan highlanders may be an exception to this in that their small pulmonary arteries are reported not to show the muscularisation that characterises hypoxic pulmonary hypertension.[33]

In cattle of European origin, the dependent oedema of right-sided cardiac failure caused by hypoxic pulmonary hypertension affects the breast (brisket) particularly and in the Rocky Mountains of North America such cattle are said to have 'brisket disease'.[34] A human counterpart of this has been described in children of Chinese ancestry who have been taken to reside in Tibet and who have developed a fatal form of subacute infantile mountain sickness.[35]

A small minority of permanent residents in the Andes develop the changes of chronic mountain sickness to a marked degree and are said to suffer from Monge's disease.[36] The basis of this is alveolar hypoventilation, which leads to a progressive fall in systemic arterial oxygen saturation and elevation of haemoglobin concentration to an unusually severe degree. The latter averages about 25 g/dl, which exceeds even the 20 g/dl found in healthy high-altitude residents. Patients with Monge's disease are so deeply cyanosed that their lips are virtually black. Their pulmonary artery resistance is also markedly raised. The cause of the alveolar hypoventilation is uncertain but the only cases of Monge's disease that have come to necropsy had conditions such as kyphoscoliosis that predispose to alveolar hypoxia.

DROWNING

Drowning is defined as suffocation by submersion, and usually occurs in water. It is the commonest cause of accidental death among divers but 96% of drowning accidents do not involve deep descents. Falling into quite shallow water is a particularly common cause of drowning in young children. In adults, men outnumber women by 4 to 1. More die in fresh water than the sea, not because it is more hazardous to the lungs than sea water, but because unguarded inland waters and swimming pools are visited more frequently. Alcohol consumption contributes to many deaths by drowning.

Drowning is not simply a matter of being unable to keep one's head above water. This may be merely a secondary event. For example, the entry dive may result in underwater head injury, or the exertion of swimming may precipitate a heart attack. Furthermore, the struggling swimmer going down for the third time ('drowning not waving') is the exception: most drowning is characterised by the swimmer failing to surface or quietly dropping beneath the surface without anyone noticing.

Swimming underwater can be extremely hazardous if it is preceded by hyperventilation, a danger that needs to be more widely appreciated. Hyperventilation results in undue loss of carbon dioxide so that instead of hypercapnia forcing the swimmer to surface to breathe, progress under water may be continued until hypoxia causes sudden loss of consciousness.

Panic contributes to many swimming accidents and is often precipitated by the inadvertent aspiration of just a little water. Most people are naturally buoyant, but only slightly so. With the lungs fully expanded the average adult has a positive buoyancy of about 2.5 kg, which is sufficient to keep the head out of the water if the rest of the body is submerged. If an arm (weight about 3 kg) is raised to wave for help, the head will go down. If the swimmer shouts, exhalation reduces buoyancy to neutral at normal end-expiration and to negative at residual volume. Buoyancy cannot be regained when the head is submerged and unless able to swim to the surface, the person will continue to sink.

Autopsy generally shows that the lungs are full of water, but some victims die of 'dry drowning' due to laryngospasm. Events may also be modified by the temperature of the water. Sudden immersion in cold water may result in tachycardia, hypertension and hyperventilation, making it difficult for the victim to keep the airways free of water. It may also result in sudden death due to ventricular fibrillation. Even a good swimmer loses consciousness within an hour of immersion in very cold water. Drowning is then inevitable unless a correctly fitted life jacket is worn, in which case there is a danger of death from hypothermia. However, as in open heart surgery, cold prolongs the interval before there is irreversible brain damage.

If the person is rescued, water in the lungs is quickly absorbed, even if it is saline, and therefore hyperosmolar:aspirated sea water is quickly equilibrated by pure water joining it from the blood but the alveolar epithelial barrier remains impermeable to protein and once osmotic equilibrium is reached, all is quickly reabsorbed.[37–39] Fresh water is absorbed even more quickly. It is unnecessary to tip the patient to hasten this process. Any water recovered in this way comes from the stomach and time that should be devoted to mouth-to-mouth breathing and cardiac massage is lost. These resuscitative efforts may need to be prolonged as fresh water in particular inactivates alveolar surfactant, leading to alveolar collapse which persists until the surfactant is replenished. Very few victims who are resuscitated on site fail to survive, and very few who cannot be resuscitated on site recover later.

Interchange of fluid between the blood and air spaces may cause major fluctuations in plasma volume with consequent changes in ionic concentrations and haemolysis. Hypervolaemia may cause circulatory problems but hyperkalaemia consequent upon the haemolysis is not thought to be as important as was formerly believed: ventricular fibrillation following submersion is more likely to be a complication of hypothermia than of electrolyte imbalance.

Circulatory collapse may ensue shortly after rescue. This is due to loss of the circulatory support provided by the pressure the water exerts on the body, which results in a considerable increase in cardiac output while the body is immersed. On leaving the water the loss of this support results in a tendency to venous pooling. Although this is countered by baroreceptor responses, these are reduced by prolonged immersion in cold water. Circulatory collapse is believed to be the cause of death in many persons who perish within minutes of rescue. To counter this effect, patients should be lifted out of the water in the prone position.

It can be seen that, in fatal cases, the pathologist is faced with several possibilities. Thus, death may have been due to:

- natural causes before the body entered the water
- unnatural causes before entry, the body merely being disposed of in the water
- natural causes in the water
- injuries received in the water from impact with rocks, a boat or a ship's propeller, or in tropical waters from predators such as a crocodile or a shark (any of which may also be incurred after death, as may disfigurement by fish and rats)

- 'dry drowning'
- true drowning
- hypothermia
- circulatory failure after rescue.

True drowning is indicated by froth in the airways and heavy water-filled lungs. Both fresh and salt water contain numerous microscopic algae known as diatoms and those representative of the water in which the drowning occurred are found in the lungs. Unless death occurred before submersion, diatoms are also found in other viscera because these tiny life forms easily enter the circulation. Thus, the presence of diatoms in digests of organs such as the kidneys, liver, brain and bone marrow suggests that death was due to drowning. Because they have a siliceous capsule, diatoms are resistant to putrefaction as well as digestion and can be identified in the body long after death. However, a positive test is not always accepted as proof of drowning and a negative test does not exclude drowning.

INHALED TOXIC AGENTS

The various physical forms in which respirable environmental agents may be encountered are defined in Table 7.2.1. Some effects of inhalant lung injury are recognised as distinct disease entities and are dealt with elsewhere: for example, the pneumoconioses on page 327, extrinsic allergic alveolitis on page 279, chronic bronchitis on page 98 and lung cancer on page 532. Other respirable agents, such as lead fume and carbon monoxide gas, exert their harmful effects elsewhere in the body and will not be considered further. This section is concerned with toxic substances that may be inhaled by the general public. Those that are more likely to be encountered in the workplace or in war zones are considered on page 355.

The lungs have a rather stereotyped pattern of response to inhaled toxins, displaying degenerative changes and inflammation of varying degree, the former sometimes amounting to necrosis. In general, the site of maximal absorption or injury is related to solubility (for gases and vapours) and particle size (for aerosols such as dusts, fog, fumes, mists, smog and smoke): the less water-soluble and the smaller the particle size, the further down the respiratory tract the agent will penetrate (Fig. 7.2.2 and Table 7.2.2).[40–42] Thus, ammonia produces intense congestion of the upper respiratory passages and laryngeal oedema whereas phosgene has little effect on these sites but causes pulmonary oedema.[40]

Air pollution[43–47]

The toxic (as opposed to allergenic) air pollutants thought to pose the greatest threat to the lungs comprise smoke particles, sulphur dioxide, oxides of nitrogen, various aldehydes and ozone. Smoke and sulphur dioxide derive particularly from the combustion of fossil fuels in domestic fires and power stations, nitrogen dioxide is an important car exhaust and domestic gas appliance pollutant and ozone is the principal photochemical product of smog. Aldehydes such as formaldehyde and acrylic aldehyde (acrolein) also contribute to general air pollution because they are released in the combustion of diesel oil and petrol. Collectively, these pollutants have been incriminated in the exacerbation (rather than causation) of asthma. They also predispose to respiratory infection and result in airway inflammation and hypersecretion.[48,49] Their effect on children is of particular concern because development of the lungs is known to continue well into childhood and damage to the lungs before their growth is complete

Table 7.2.1 Definitions of respirable agents by physical form

Gas	A formless compressible fluid in which all molecules of the agent move freely at room temperature (25°C) and standard pressure (760 mmHg) to fill the space available
Vapour	Gaseous state of an agent which is normally liquid or solid at room temperature and standard pressure
Aerosol	Dispersion of solid or liquid particles of microscopic size in a gaseous medium. The following are all examples:
Dust	Dispersion of solid particles. Those of respirable size are not readily seen with the naked eye unless they are bathed in bright light
Fog	Dispersion of liquid particles generated by condensation from the vapour state
Fume	Dispersion of solid particles generated by condensation from the vapour state
Mist	Dispersion of liquid particles generated by condensation or mechanical means (e.g. nebulisation). The droplets are generally larger than those of a fog and may be visible individually to the naked eye
Smog	Mixture of smoke and fog, the former being the result of industrial pollution, the latter of natural climatic factors
Smoke	Dispersion of small particles (usually less than 0.1 μm diameter) resulting from incomplete combustion of organic substances

Table 7.2.2 Relation of solubility of an inhaled gas to its major site of absorption or toxicity[41]

Gas	Henry's constant at 37°C	Major site of absorption or toxicity
Ammonia	0.0011	Upper respiratory tract
Sulphur dioxide	0.05	Upper respiratory tract and trachea
Formaldehyde	0.56	Upper respiratory tract and trachea
Ozone	6.4	Tracheobronchial
Nitrogen dioxide	8.8	Tracheobronchial and pulmonary
Oxygen	42	Pulmonary
Nitrogen	77	Pulmonary

Henry's constant: moles/l(air)/moles/l(water).

Figure 7.2.2 The site of maximum uptake of an inhaled gas is dependent upon its solubility. Thus, ammonia, sulphur dioxide and formaldehyde, which are highly soluble, have their major impact on the upper respiratory tract and trachea whereas oxygen, phosgene ($COCl_2$) and nickel carbonyl ($Ni(CO)_4$), which are less soluble, are taken up in the alveoli, where their toxicity is mainly experienced.

is likely to be irreparable. At the other extreme of life episodes of severe air pollution are known to hasten the deaths of many patients with chronic airway disease. Particularly high concentrations of the agents responsible for air pollution may be encountered in industry and their effects are therefore also considered in Chapter 7.1, on occupational diseases of the lung. Many of the polycyclic hydrocarbons found in polluted air are carcinogenic (see p. 532) and it is therefore not surprising that urban air pollution has been found to be associated with excess mortality from lung cancer.[50]

Domestic air pollution is rife in many of the poorer parts of the world due to the burning of biomass (wood, dried cow dung, bagasse, straw) in unventilated living rooms for heating and cooking. The women are particularly at risk of developing chronic bronchitis while their children have an increased incidence of acute respiratory infections.[51,52,52a]

Volcanic ash (tephra) irritates the eyes, skin and respiratory tract and in some eruptions may contain much free silica (e.g. Montserrat in 1995 and Mount St Helens, Washington state, USA in 1980) or be associated with the release of radon gas (e.g. the Azores in 1957).[53] The destruction of the World Trade Center in 2001 caused massive air pollution of New York city that had lasting respiratory effects on survivors, rescue workers and local residents.[54–56] At the time of the disaster there was much smoke from combustion of aeroplane fuel and flammable materials in the building while the collapse of the twin towers released dust from cement and dry-wall partitions that was highly alkaline.[57–59] This caused considerable irritation of the eyes and the conductive airways. A year later many victims were still suffering from bronchial hyperreactivity and poor ventilatory function, in a so-called reactive airways dysfunction syndrome[54,55] and there was continuing spirometric decline 5 years later.[60] The respirable portion of the dust formed only a small fraction of the whole but given the level of exposure its future effects cannot be discounted, particularly as it contained substances such as asbestos. Unusual effects attributed to the disaster include acute eosinophilic pneumonia and granulomatous pneumonitis.[61,62]

Allergenic air pollutants are dealt with in detail in the sections on asthma (see p. 109) and extrinsic allergic alveolitis (see p. 279). Allergenic air pollution is generally occupational or domestic but periodic widespread air pollution was responsible for the epidemics

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Box 7.2.1 Diseases related to smoking

Respiratory diseases caused by smoking
Carcinoma
Chronic obstructive lung disease
Chronic bronchitis
'Small-airways disease'
Emphysema
Respiratory bronchiolitis
Desquamative interstitial pneumonia

Respiratory diseases that are commoner or worse in smokers
Adult respiratory distress syndrome
Respiratory infections
Common cold
Influenza
Varicella pneumonia
Bacterial pneumonia
Tuberculosis
Pneumothorax
Cryptogenic fibrosing alveolitis
Langerhans cell histiocytosis
Asbestosis
Goodpasture's disease

Respiratory diseases that are less common or less severe in smokers
Extrinsic allergic alveolitis
Sarcoidosis

Quite advanced interstitial fibrosis has been reported in smokers with no clinical evidence of interstitial lung disease.[69b] Early changes detectable in smokers include chronic bronchiolitis, fibrosis of the bronchiolar wall and mild peribronchiolar interstitial fibrosis.[70,71] Even earlier changes are detectable at the molecular level: as many as 152 smoking-responsive genes that are significantly up-regulated or down-regulated have been identified in normal cigarette smokers.[72] There is marked individual variation, which may explain why many lifelong heavy smokers experience no respiratory problems.

Histological evidence that a patient smokes is provided by an increase in the number of alveolar macrophages and a characteristic brown discoloration of cytoplasm due to the phagocytosis of tar and other particulate matter derived from tobacco smoke (Fig. 7.2.3).

Cigarette smokers are at greater risk of lung disease than cigar and pipe smokers, probably because they inhale more deeply. They do this because cigarette smoke is more acid than cigar and pipe smoke and its nicotine content is therefore absorbed more easily through the lungs than the buccal mucosa. Smokers obviously put their own health at greatest risk but the lesser hazards of passive smoking are now well recognized (see p. 532). Passive smoking involves both the smoke exhaled by others and that coming from smouldering tobacco between puffs, the latter being known as sidestream smoke. The harmful effects of maternal smoking on the unborn child also come in this category. They include increased airway responsiveness and reduced lung function during the neonatal period and an increased risk of sudden infant death syndrome. Reduced numbers of alveolar attachments to the bronchioles have been demonstrated in such infants.[73] Smoking is also associated with disease of other organs (e.g. carcinoma of the oesophagus and bladder) but these are outwith the remit of this text.
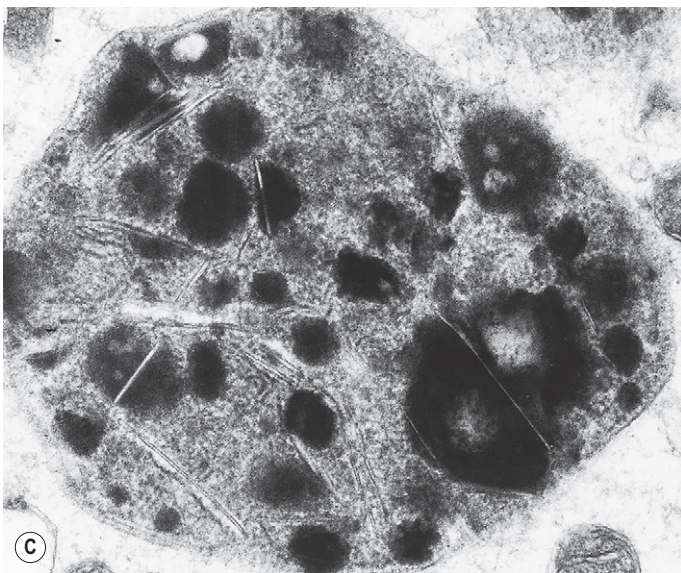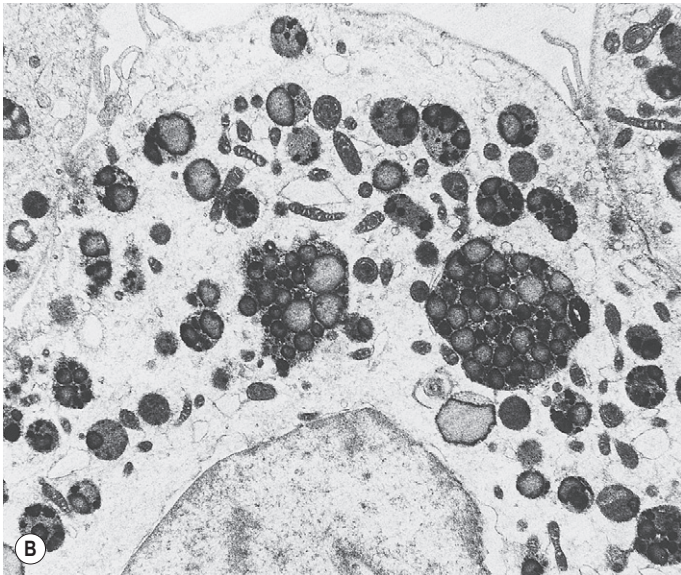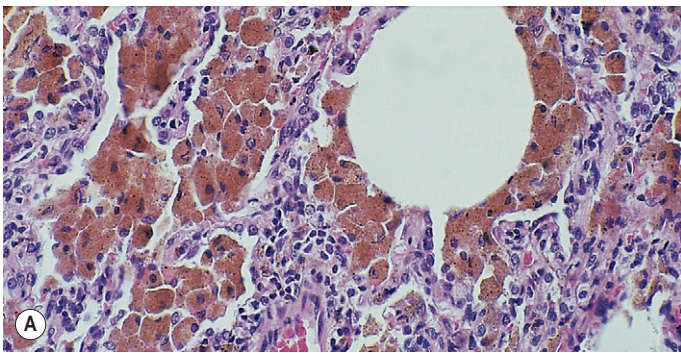
Tobacco smoking by waterpipe (shisha, hubble-bubble) is enjoying a rise in popularity, both in its heartland, the Middle East, and western countries, and wherever it is practised it is widely perceived as being less dangerous than smoking cigarettes.[74] This is probably a misconception. What evidence there is suggests that waterpipe tobacco smoking is just as harmful as cigarette smoking, if not more so.[75]

of asthma seen in Barcelona in the 1980s, which were eventually traced to ships discharging cargoes of soya flour (see p. 114).

Tobacco smoke

Smoking-related diseases figure large throughout this book and in this section they are merely summarised collectively. Of the greatest importance, both in the number of patients they affect and in their clinical effects on the individual, are the various forms of chronic obstructive lung disease and lung cancer, but there are many other respiratory diseases associated with smoking, and a few that are less common in smokers (Box 7.2.1).[63] Not surprisingly, these diseases are often encountered in combination and sometimes one may obscure another. For example, a cigarette smoker may have emphysema in the upper lobes and idiopathic pulmonary fibrosis in the lower lobes.[64,65] Alternatively, Langerhans cell histiocytosis and desquamative interstitial pneumonia may affect the same parts of the lungs, in which case the focal lesions of the former may be masked by the latter condition.[63]

The term 'smoking-related interstitial lung disease' has been introduced to cover a spectrum of interstitial diseases related to smoking[63,66,67] as well as being used in a more restricted sense to describe a combination of air space enlargement and interstitial fibrosis predominantly affecting the lower lobes.[68,69,69a]

Burns and smoke inhalation

The lungs may be injured in burned patients in many ways (Box 7.2.2)[76,77] but an important consideration when a body is recovered from a fire is whether death was due to the fire or took place beforehand, the latter raising the possibility of foul play. A vital reaction to the skin burns and the presence of soot in the lower airways provide evidence that death occurred in the fire but an absence of soot from the airways may be due to death occurring rapidly, from asphyxia or poisoning by gases released in the conflagration. Soot is cleared rapidly and if the patient survives a few days an absence of soot from the airways is to be expected.[76]

Lung injury may result directly from heat and smoke inhalation or indirectly from the release of mediators associated with blast injury or shock. Although air temperature in a fire may reach very high temperatures thermal injury seldom extends beyond the carina but more extensive injury from heat alone was seen in men exposed to steam escaping from a fractured boiler pipe.[78] Those dying immediately showed coagulative necrosis of the respiratory mucosa down to the level of the alveolar ducts and alveolar congestion and oedema, while those surviving a little longer exhibited diffuse alveolar damage. The diffuse alveolar damage probably represented a manifestation of shock from their extensive cutaneous scalding whereas the mucosal necrosis is directly attributable to heat. Diffuse alveolar damage is

Box 7.2.2 **Possible pulmonary insults in burned patients, arranged in approximate sequential order**

Blast injury
Asphyxia
Poisoning by combustion products (e.g. carbon monoxide, cyanide)
Direct thermal injury (largely limited to the trachea)
Irritant smoke, fume and gas (e.g. oxides of nitrogen, ammonia,
   acrolein, sulphur dioxide)
Hypovolaemic shock secondary to skin loss
Septicaemic shock from:
   Infected skin burns
   Infected central lines
Secondary viral and bacterial pneumonia
Fluid overload
Tracheostomy complications, including tracheobronchitis, pneumonia
   and barotrauma
Oxygen toxicity
Absorption of toxic topical disinfectants
Thromboembolism
Uraemia

Figure 7.2.3 Macrophages of a heavy cigarette smoker. (A) Numerous brown macrophages fill the alveoli. Electron microscopy shows that the lysosomal dense bodies are increased in number and contain lipidic 'tar bodies' (B) or the needle-shaped crystals of kaolinite (C). *(Transmission electron micrographs, courtesy of Miss A Dewar, Brompton, UK.)*

usually part of systemic multiorgan failure in these patients, and is the leading cause of death in burns.[79]

The ubiquity of plastics today means that smoke contains numerous irritants, including isocyanates, aldehydes and fluorinated organic chemicals. Irritant smoke products have two principal effects. Firstly, they cause an immediate painful stimulation of the eyes and respiratory tract which at low concentrations may prevent escape and at high concentrations may cause laryngeal spasm and death. Secondly, they cause bronchopulmonary injury some hours after exposure. Burned patients dying within 4–12 days often show tracheobronchial necrosis and diffuse alveolar damage with prominent hyaline membranes.[76,77,80] Secondary herpesvirus infection is often present.[81,82]

The respiratory changes caused by heat and smoke are non-specific and careful consideration of the many causes of lung injury in burned patients listed in Box 7.2.2 and of the clinical circumstances and management is generally required. Often it will be concluded that the cause of the lung injury is multifactorial. Long-term consequences of smoke inhalation include bronchiectasis and obliterative bronchiolitis.[83]

Methyl isocyanate, the chemical released at Bhopal

The Bhopal catastrophe of 1984 was caused by the accidental release of 30 tons of methyl isocyanate gas (CH_3–N=C=O) from a pesticide plant.[84] Over 200 000 people were exposed, of whom 2500 died, mostly within hours of exposure, and 60 000 were seriously injured. The victims complained of intense ocular and respiratory irritation. Some survivors were left with persistent respiratory impairment, which was thought to be due to obliterative bronchiolitis.[85,86]

Methyl isocyanate is an extremely potent respiratory irritant, destroying the epithelium throughout the conducting airways, with comparatively less parenchymal injury. In survivors, epithelial regeneration, often involving squamous metaplasia, quickly commences, but not before endobronchial granulation tissue projections have developed, resulting in obliterative bronchiolitis.

Tear gas

Tear gases are chemical irritants delivered as an aerosol for the purpose of riot control. They react with mucocutaneous sensory nerve receptors causing intense irritation of the eyes, mucous membranes and skin. The respiratory effects are mainly concentrated on the upper tract so that there is violent sneezing, severe rhinorrhoea and cough but there may also be tracheobronchitis and rarely pulmonary oedema.[87] Patients with pre-existent asthma or chronic obstructive pulmonary disease are most severely affected while others may be left with reactive airways dysfunction.

INGESTED TOXIC AGENTS

Toxins reaching the lungs via the blood stream may be drugs, food contaminants, metabolites produced elsewhere in the body, or chemicals ingested intentionally or accidentally, either in the home or the workplace.

The lungs are selectively damaged by certain blood-borne toxins for a variety of reasons. For example, the herbicide paraquat is preferentially taken up by the lungs because of its molecular homology with certain endogenous substances. As detailed below, the type I alveolar epithelial cells are the cells that bear the brunt of the damage in paraquat poisoning. On the other hand, the alveolar capillary endothelium has its own selective uptake mechanisms (see Metabolic functions of the pulmonary endothelium, p. 23) which may be responsible for it being selectively damaged by other chemicals.

The bronchiolar Clara cells are selectively injured by some ingested chemicals because they are equipped to deal with inhaled xenobiotics, but occasionally this activity results in metabolites that are extremely toxic. An example of this from veterinary medicine is provided by the furan-derivative 4-ipomeanol, which is found in mouldy sweet potatoes and results in acute pulmonary oedema in cattle fed such a diet. When this chemical is injected into mice, the bronchioles are denuded of Clara cells whereas the intervening ciliated cells are completely unaffected. The selective damage to the bronchiolar Clara cells appears to stem from the oxidative efficiency of their P-450 cytochromes,[88] which is much higher than those of the liver. Chemicals having a similarly selective effect on bronchiolar Clara cells include 3-methylfuran, carbon tetrachloride, naphthalene and 1,1-dichloroethylene, the last of which is a volatile compound that is widely used in the plastics industry. Procarcinogens may be activated in the airways by similar mechanisms.

Paraquat

Paraquat is a dipyridylium compound that is widely used in agriculture as a herbicide. It kills all green plants but is inactivated on contact with the soil. It is applied as a spray and if the manufacturer's instructions are followed there is no danger to health. Most fatal cases of paraquat poisoning, both accidental and suicidal, have been due to ingestion of the 20% aqueous solution Gramoxone. The less concentrated granular form Weedol is unlikely to be ingested accidentally but may be taken suicidally.[89] Paraquat is not absorbed by the intact skin but repeated or prolonged application damages the epidermis so that absorption into the blood stream with consequent systemic effects is possible, but rare.[90]

Although paraquat has toxic effects on the liver, kidneys and myocardium, these are transient and attention has centred on the pulmonary changes, which are usually fatal. Following suicidal ingestion of large amounts of paraquat, death from multiorgan failure and pulmonary haemorrhage occurs within a few days, whereas most
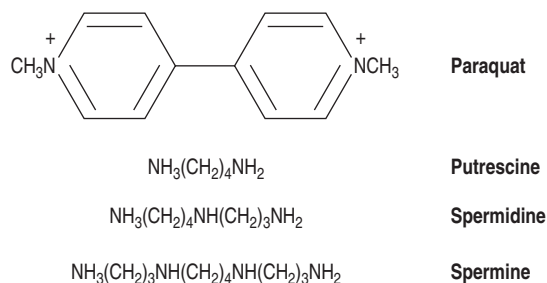
Figure 7.2.4 Formulae of paraquat and the endogenous oligoamines putrescine, spermine and spermidine showing the molecular similarities. The name paraquat derives from the chemical's *para*-methyl groups and its *quat*ernary nitrogen atoms.

victims of accidental paraquat poisoning die from progressive pulmonary fibrosis between 10 and 14 days after ingestion. In those who survive longer, a honeycomb pattern of pulmonary fibrosis may be apparent.[91]

Paraquat is a powerful oxidant and owes its toxicity to the production of active oxygen radicals. The lungs are particularly susceptible because paraquat is concentrated there by an active uptake mechanism in the alveolar epithelium. The inadvertent uptake of paraquat probably stems from a similarity between the molecular arrangement of its quaternary nitrogen atoms and the amine groups of endogenous oligoamines such as putrescine, spermidine and spermine, which are concerned in alveolar epithelial cell division and differentiation (Fig. 7.2.4).[92] This results in paraquat levels being 6–10 times higher in the lung than in the plasma. Once taken up by the lung, paraquat is not metabolised but participates in redox cycling so that superoxide radicals are constantly produced. Epithelial injury is proportional to the concentration of paraquat, while it is lessened by hypoxia and antioxidants such as superoxide dismutase, and potentiated by increased concentrations of oxygen.[93–96] The high concentration of oxygen in the alveoli is a further reason why the lungs are particularly vulnerable to paraquat.

Knowledge of the toxic effects of paraquat comes from observations on autopsy series[89,97,98] and from experimental studies that have enabled the sequence of pulmonary changes to be observed.[99–102] In accordance with paraquat being taken up by the alveolar epithelium, electron microscopy shows that these cells suffer more profound damage than the endothelium.[99] Type I epithelial cells swell and undergo necrosis (Fig. 7.2.5),[103] whilst type II cells, although remaining capable of proliferation, show ultrastructural evidence of damage with derangement of cell organelles.[99,100] Histological changes in the lungs follow the pattern of diffuse alveolar damage, with a characteristic feature of the early exudative phase being intense vascular congestion and alveolar haemorrhage.[89,97,104] Hyaline membranes are most clearly seen by about 5 days (Fig. 7.2.6) and epithelial proliferation and fibrosis are conspicuous by about 14 days.

The pattern of pulmonary fibrosis in paraquat poisoning has been disputed. Some authors have stressed its interstitial position, whereas others have clearly demonstrated that it is intra-alveolar.[98,102,104–107] However, as described on page 148, it generally assumes an obliterative pattern of intra-alveolar fibrosis in which the lumina of several adjacent alveoli are totally effaced, rendering them completely airless (see Fig. 4.24, p. 148).

Toxic oil syndrome

A new multisystem disease appeared abruptly in the environs of Madrid in 1981.[108–110] Over 20 000 people were affected and about 1
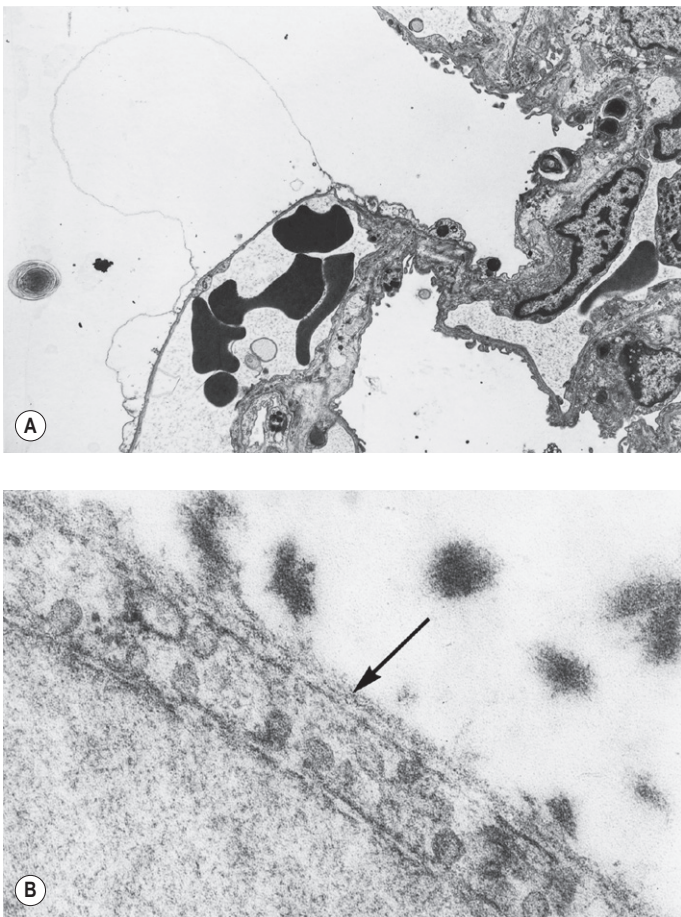
Figure 7.2.5 Paraquat poisoning. After initial swelling of the cytoplasm (A) the type I alveolar epithelial cells proceed to complete necrosis (B), exposing the basement membrane (arrow) they share with the alveolar capillary endothelium to alveolar air. Flecks of fibrin are seen in the alveolus. Intact endothelium and part of an erythrocyte are seen beneath the denuded basement membrane. *(Reproduced by permission of the editors of the* Journal of Pathology[99] *and* Progress in Respiratory Research.[103])
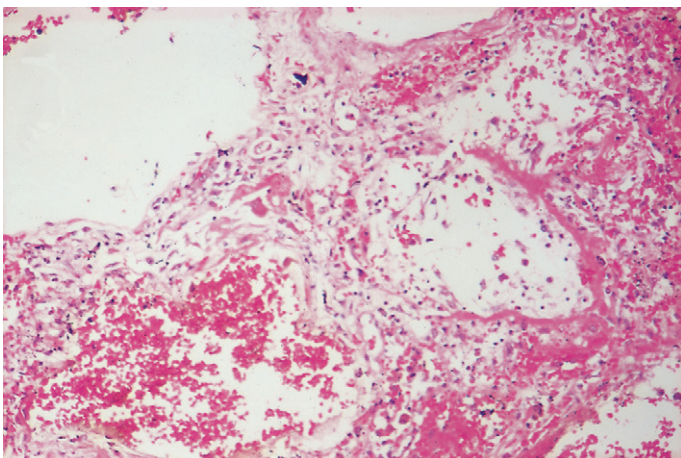
Figure 7.2.6 Suicidal paraquat poisoning. The ingestion of large amounts of the chemical has led to death from pulmonary haemorrhage and diffuse alveolar damage within 3 days. Note the hyaline membrane formation and early interstitial fibrosis. *(Courtesy of Dr D Melcher, Brighton, UK.)*

in 60 died. The disease was initially thought to be *Mycoplasma* pneumonia but was soon found to be associated with the use of adulterated oil sold illicitly by door-to-door salesmen. Although it was sold for culinary purposes the oil had been produced for industrial use in steel manufacture. It consisted of rapeseed and olive oil mixed with liquified animal fat, aniline and other organic chemicals. It has not been possible to identify the exact chemical responsible for the disease or to reproduce the changes in other species but the later induction of similar pathological changes by another substance contaminated with an aniline derivative is possibly relevant (see L-tryptophan-induced eosinophilia–myalgia syndrome, p. 389).[111] Some clinical and pathological features of the disease suggest that immune mechanisms may also be involved.

The initial clinical features included fever, respiratory distress, cough, haemoptysis, skin eruptions and marked eosinophilia. Radiographs suggested pulmonary oedema and sometimes showed pleural effusion. About 5% of patients died at this stage but most recovered quickly. However, within a few weeks many were readmitted to hospital with nausea, vomiting, diarrhoea and abdominal pain. About a quarter then proceeded to develop weakness, myalgia, weight loss, scleroderma-like skin signs and pulmonary hypertension.[112,113] Many of these patients died after a long, wasting illness or are permanently disabled with neurological and hepatic disorders.

In the early phase the lungs showed the most severe changes, which consisted of a combination of diffuse alveolar damage, eosinophilic infiltrates and arterial luminal narrowing by endothelial swelling and vacuolation, intimal foam cell infiltration and a non-necrotising vasculitis.[109,112,114] There was also capillary thrombosis, which later extended into arteries and veins, culminating in fibrosing obliteration of these blood vessels. In some patients dying of haemoptysis, dilated thin-walled blood vessels were identified in the mucosa of major blood-filled airways. Late features in the lungs included plexogenic arteriopathy (see p. 420), possibly secondary to changes in the liver. Similar inflammatory and vascular changes were seen in many other tissues. Notable extrapulmonary features included fasciitis, vasculitis, neuronal degeneration, perineuritis, hepatic injury and tissue eosinophilia.

Sauropus androgynus

Sauropus androgynus is a vegetable that is widely cultivated for the table in many south-eastern Asian countries. It is apparently harmless when cooked but recently there has been a vogue in Taiwan for consuming large amounts of its unprocessed juice, blended with that of guavas or pineapple, because of its supposed efficacy as a slimming aid and in blood pressure control. Coincident with this fad there has been an upsurge in patients with symptoms of obstructive lung disease. Within a 4-month period more than 60 such patients were seen at one hospital.[115–117] They had four features in common: recent consumption of uncooked *S. androgynus* juice, fixed ventilatory obstruction, radiological evidence of bilateral bronchiectasis and an absence of any previous chronic respiratory disease. Four patients agreed to undergo open-lung biopsy. This showed chronic bronchiolitis or obliterative bronchiolitis of constrictive pattern. The lymphocytes were mainly T cells but immunofluorescent and electron microscopy showed no evidence of an immune process. Four patients underwent single-lung transplantation. The excised lungs showed sclerotic obliteration of bronchial arteries in the walls of bronchi 4–5 mm in diameter with segmental necrosis of bronchi 2–4 mm in diameter. The changes were considered to fit best with segmental ischaemic necrosis of bronchi at the watershed zone of the bronchial and pulmonary vasculature.[118] Further patients have required lung transplantation but public education of the dangers of this herbal medicine now appears to have been successful.[119]

RECREATIONAL DRUGS

Alcohol and nicotine outstrip all other recreational drugs in popularity and their effects are of course well known. Those of tobacco smoking are summarised above and dealt with in detail in the chapters on obstructive lung disease (Chapter 3) and carcinoma of the lung (Chapter 12.1). Less well known is the lung disease that results from smoking Blackfat tobacco, a practice popular with Guyanese Indians. Blackfat is the trade name of a type of tobacco that is flavoured with mineral oil, some of which vaporises and is inhaled when the tobacco is smoked, to cause exogenous lipid pneumonia (see p. 314 [Ch8]).[120] In recent years the smoking of two other substances, marijuana and cocaine, has gained in popularity. It would not be surprising if the long-term effects of smoking these substances were similar to those of cigarette smoking but as yet it is too early to judge. However, the short-term effects are similar to those of tobacco smoking and this bodes badly for their ultimate effects.
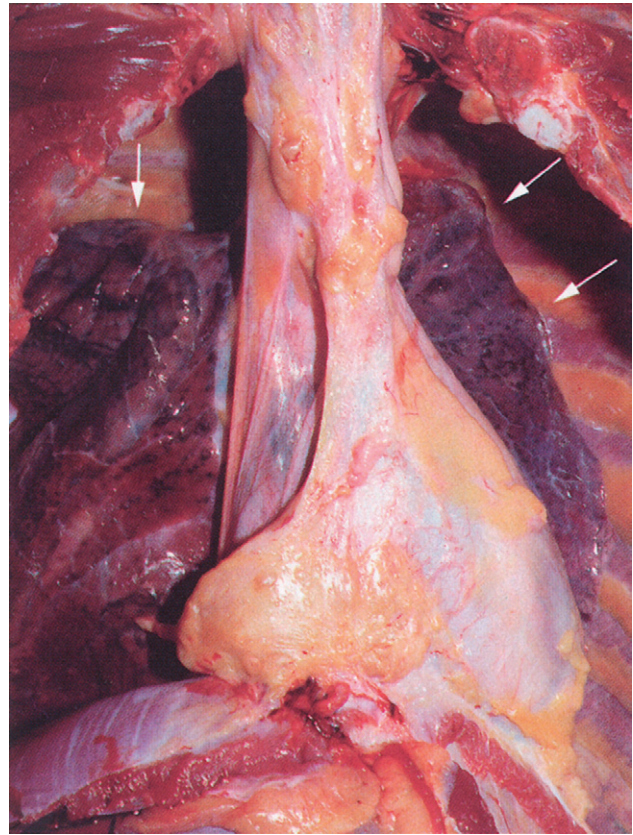
Marijuana

Marijuana consists of the dried leaves of the cannabis plant, also known as hemp, as opposed to hashish, which is the plant's resin, and a further extract known as 'weed oil'. All these substances are smoked because they contain cannabis alkaloids which have psychoactive effects. However, this habit also exposes the lungs to many of the same respiratory irritants that are found in tobacco smoke. Initial exposure to marijuana smoke often results in coughing while habitual smokers produce black sputum. Bronchial biopsy shows inflammation and squamous metaplasia and bronchoalveolar lavage demonstrates increased numbers of cells, which are predominantly macrophages but also include neutrophils.[121–125] These changes are virtually identical to the short-term effects of tobacco smoke and are therefore likely to be similarly followed by the development of chronic obstructive lung disease and lung cancer. Indeed, the dangers of smoking marijuana are probably greater than those of smoking tobacco as compared with tobacco smoking it is associated with a fivefold greater increase in blood carboxyhaemoglobin and a threefold increase in the amount of tar inhaled.[126] It is estimated that three cannabis cigarettes result in the same degree of bronchial damage as 20 tobacco cigarettes.[127] There is also evidence that the effects of smoking marijuana and tobacco are additive.[128]

Not surprisingly therefore, epidemiological studies report a dose-related impairment of large-airway function in marijuana smokers.[129] There are also several reports attributing pneumothorax to marijuana smoking (Fig. 7.2.7).[130,131] The pneumothorax may be spontaneous or develop during the deep, sustained inspiratory effort involved in smoking marijuana (or cocaine), which may be enhanced by a partner applying positive ventilatory pressure by mouth-to-mouth contact. Thoracoscopy in such cases has shown predominantly apical, irregular bullous emphysema, while lung biopsy has demonstrated widespread alveolar filling by heavily pigmented macrophages.[131,132] Evidence is also beginning to accumulate that long-term cannabis use increases the risk of lung cancer.[133] Smoking cannabis in the form of weed oil is also reported to result in exogenous lipid pneumonia.[134]

Cocaine

Cocaine hydrochloride is a fine white powder derived from the leaves of the plant *Erythroxolon coca* by a complex chemical process. It is heat-labile and therefore cannot be smoked. Users inject it intravenously or inhale it unheated through the nose, the latter practice

Figure 7.2.7 Bilateral pneumothoraces in a 23-year-old man who died suddenly while smoking marijuana. The collapsed lungs (arrows) have retracted towards the mediastinum. *(Courtesy of Dr JF Tomashefski Junior, Cleveland, USA.[131])*

being known as 'snorting'. However, a heat-stable free-base form that can be smoked is easily prepared from the hydrochloride with baking powder and a solvent such as ether. This process results in a crystalline deposit that is known as 'rock' because of its appearance or 'crack' because of the crackling sound it emits when heated. When smoked, the cocaine is readily absorbed and an intense surge of euphoria is experienced within 8 seconds. The intravenous route takes twice as long and 'snorting' several minutes. The hard addict therefore prefers to smoke 'crack'.

A variety of pulmonary complications of smoking free-base cocaine has been reported.[128,135–144] Acute effects include cough, shortness of breath, chest pain and haemoptysis. Asthma may be aggravated, black sputum is produced, and pneumothorax and interstitial emphysema have resulted from Valsalva manoeuvres undertaken in the belief that they promote even more rapid absorption. Biopsy has shown pulmonary congestion and oedema, organising pneumonia, haemorrhage, haemosiderosis, diffuse alveolar damage and interstitial pneumonia or fibrosis. Less common effects include eosinophilic pneumonia, extrapulmonary eosinophilic angiitis, medial thickening of pulmonary arteries and the barotrauma described above (see Fig. 7.2.7). Severe burning of the airways has also been seen due to 'crack' being smoked before all the ether used in its preparation has evaporated.

'Snorting' unheated cocaine has its own complications: substances such as cellulose or talc with which the drug is 'cut' (mixed as a
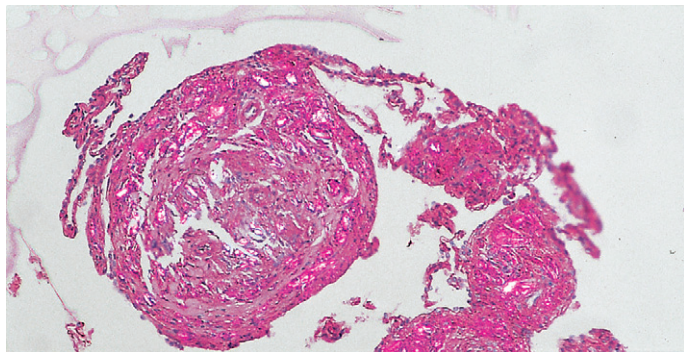
diluent) are liable to provoke a foreign-body giant cell reaction in the lungs (Fig. 7.2.8).[145] However, particles of foreign material larger than those in the usual respirable range (allowing for the fibrous shape of substances such as cellulose) should suggest intravenous use (see 'Filler embolism', below).

Heroin

Heroin is usually injected, but it may be smoked, when, as with marijuana, it is liable to lead to a very pronounced macrophage response. Intravenous heroin abuse sometimes causes the sudden onset of a potentially fatal high-permeability pulmonary oedema (Fig. 7.2.9). Intravenous abuse of heroin and other drugs is also liable to cause 'filler embolism', which will now be considered.

'Filler embolism'

'Filler embolism' is the result of illicit drug usage in which compounds designed for oral use are injected intravenously to heighten their effects. Oral preparations consist largely of fillers such as talc or starch and this insoluble particulate matter accumulates in the pulmonary capillaries. It provokes a foreign-body giant cell reaction, thrombosis and fibrosis and may cause pulmonary hypertension (Fig. 7.2.10 and see Fig. 8.1.13, p. 412).[146–153] The various materials may be distinguished by their morphology, staining characteristics (see Fig. 7.2.10 and Table 7.2.3) and elemental composition, as studied by X-ray spectroscopy (see p. 330).

4-methyl-aminorex

This 'designer' drug, taken for its central stimulant activity (street names 'ice' or 'U-4-E-uh', pronounced euphoria), is related to the appetite suppressor aminorex, discussed on page 424, and has similarly been associated with pulmonary hypertension.[154]

Figure 7.2.9 Frothy oedema fluid protrudes from the nostrils of a person who died while injecting heroin intravenously. Similar froth filled the whole respiratory tract. *(Courtesy of Dr JF Tomashefski Junior, Cleveland, USA.[131])*

Figure 7.2.8 A foreign-body granulomatous response in the lungs to cellulose filler inhaled by a cocaine sniffer. Section viewed by partially polarised light microscopy.

Table 7.2.3 Tablet filler materials				
Filler	**Shape**	**Size**	**Polarisation**	**Histochemistry**
Starch	Round	8–12 μm	Maltese cross	d-PAS
Talc	Platy but seen edge-on as needles	5–15 μm	Strong	None
Cellulose	Fibrous	25–200 μm	Strong	PAS, Congo red
Crosprovidone	Globular or coral-like	100 μm	Negative	Mucicarmine, Congo red
Magnesium stearate	Irregular	5–10 μm	Positive	None
Silica	Irregular	10–20 μm	Positive	None
d-PAS, diastase-controlled periodic acid–Schiff.				
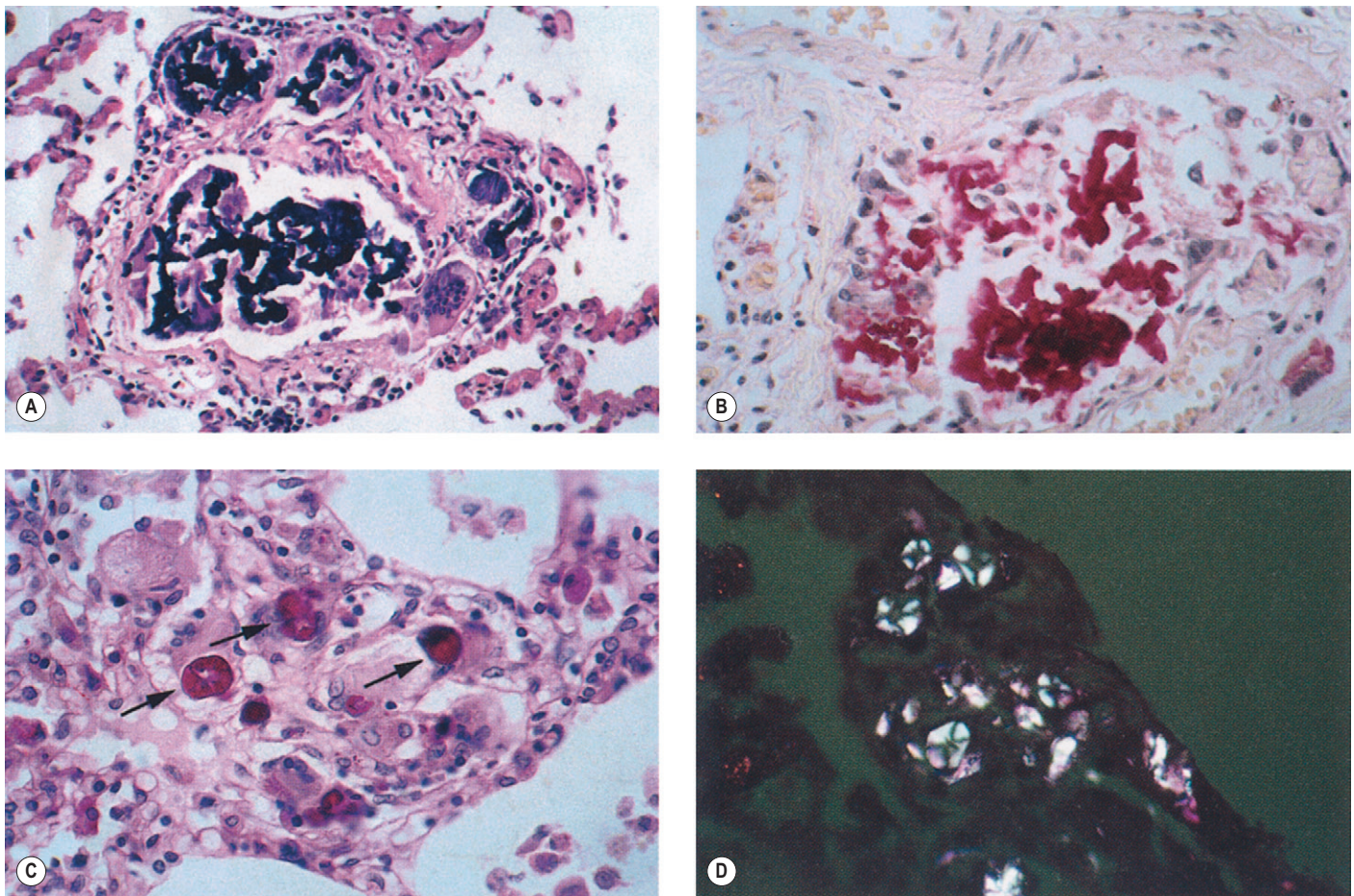
Figure 7.2.10 Tablet filler materials in the lungs. (a) Intravascular and perivascular deposits of the tablet dispersant crospovidone eliciting a foreign-body giant cell reaction. (b) A crosprovidone granuloma stained with mucicarmine. (c) A starch granuloma stained with periodic acid–Schiff reagents. (d) The Maltese cross birefringence of starch viewed by polarized light. *(Courtesy of Dr JF Tomashefski Junior, Cleveland, USA.[131])*

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Chapter | 7 |

7.3   Iatrogenic lung disease

ADVERSE DRUG REACTIONS

It is estimated that 5% of all hospital admissions are due to effects of therapeutic drugs, that 10–18% of inpatients experience a drug reaction and that 3% of deaths in hospital may be related to drug therapy.[1–4] The lungs are often involved in these adverse reactions.

Mechanisms of adverse drug reactions[5]

The mechanism of an adverse drug reaction may be based on:
- overdosage: toxicity linked to excess dose, or impaired excretion, or both
- side-effect: undesirable pharmacological effect at recommended dose
- interaction with other drugs

and in susceptible individuals only:
- intolerance (representing a low threshold to the normal action of the drug)
- idiosyncrasy (an abnormal reaction based on a genetically determined metabolic or enzymic deficiency)
- allergy in the form of any of the four main hypersensitivity reactions:
  1. immediate IgE-mediated hypersensitivity
  2. IgG- or IgM-mediated cytotoxicity
  3. IgG- or IgM-mediated immune complex disease
  4. T-cell-mediated cellular hypersensitivity
- pseudoallergic reaction: A reaction with the same clinical manifestations as an allergic reaction (e.g. as a result of histamine release) but lacking immunological specificity.

Classification of adverse drug reactions

One classification of adverse drug reactions is that based upon the type of drug (Box 7.3.1).[6] This is not adopted here but in passing it is worth noting that pharmacists are generally very helpful in supplying details of adverse reactions to specific drugs. Alternatively, information on the long list of potentially pneumotoxic drugs may be obtained at http://www.pneumotox.com. A useful scheme for

Box 7.3.1 Principal therapeutic agents known to cause pulmonary disease[6]

Chemotherapeutic drugs

Azathioprine
Bleomycin
Busulphan
Chlorambucil
Cyclophosphamide
Etoposide
Ifosfamide
Melphalan
Mitomycin
Nitrosoureas
Procarbazine
Vinblastine
Cytosine arabinoside
Methotrexate

Antibiotics

Amphotericin B
Nitrofurantoin
Sulphasalazine
Sulphonamides
Pentamidine

Anti-inflammatory drugs

Acetylsalicylic acid
 (aspirin)
Gold
Methotrexate
Non-steroidal anti-
 inflammatory agents
Penicillamine

Immunosuppressive drugs

Ciclosporin
Interleukin-2

Analgesics

Diamorphine (heroin)
Ethchlorvynol
Methadone
Naloxone
Propoxyphene
Salicylates

Cardiovascular drugs

Amiodarone
Angiotensin-converting enzyme
 inhibitors
Anticoagulants
β-antagonists

Fibrinolytic agents

Protamine
Tocainide

Inhalants

Aspirated mineral oil
Oxygen

Intravenous agents

Ethanolamine oleate (sodium morrhuate)
Iodised oil (lymphangiography)
Fat emulsion

Miscellaneous

Bromocriptine
Dantrolene
Hydrochlorothiazide
Methysergide
Oral contraceptives
Tocolytic agents
Tricyclics
L-Tryptophan
X-irradiation

Particularly common agents are italicized.

Table 7.3.1 Pathological patterns of drug-induced lung disease

Pathological pattern	Prototypic drug(s)
Cytotoxicity 　Diffuse alveolar damage 　Interstitial fibrosis (NSIP, UIP, mixed) 　Organising pneumonia	Chemotherapy
Phospholipidosis	Amiodarone
Alveolar proteinosis	Chemotherapy
Eosinophilic pneumonia	Nitrofurantoin
Eosinophilia–myalgia syndrome	L-tryptophan
Granulomatous alveolitis	Methotrexate
Aspiration lesions	Liquid paraffin
Pulmonary vascular disease 　Hypertension 　Thromboembolism 　Haemorrhage	 Aminorex Oestrogen Anticoagulants
Opportunistic infection	Immunosuppressive agents
Metastatic calcification	Vitamin D
Carcinoma of the lung	Arsenicals
Pleural disease	Practolol

NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

assessing whether a particular clinical manifestation represents an adverse drug reaction considers previous experience with the drug, alternative aetiological agents, the timing of events, drug levels, and the effect of withdrawing the drug and rechallenge with the drug.[7] It is worth bearing in mind that:

- One drug may cause several patterns of disease.
- One pattern of disease may be produced by a variety of drugs.
- A drug reaction may develop long after the drug has been withdrawn.
- A drug reaction may develop suddenly even though the dose of the drug has not been altered.
- Drug effects may be augmented by factors such as age, previous radiotherapy and elevated oxygen levels.
- Drug reactions may be localised.
- Many drugs cross the placenta to affect the fetus.

An alternative classification of adverse drug reactions, which is more appropriate to pathology practice and which will be followed here, is one based on the pattern of disease. Some pathological patterns of drug-induced lung disease are shown in Table 7.3.1.

Reduced respiratory drive

Central depression of respiration occurs as a side-effect of barbiturates, morphine and its derivatives, and even mild sedatives, and may be particularly troublesome in patients suffering from chronic obstructive lung disease. Ventilation in such patients may be largely dependent on hypoxic respiratory drive and treatment with oxygen may therefore also have an adverse effect on respiration by lowering the degree of hypoxia and so diminishing the stimulation of the respiratory centre. Peripheral impairment of the respiratory drive may be brought about by aminosides and other antibiotics, while corticosteroids may result in a myopathy affecting the respiratory muscles. Other iatrogenic hazards affecting the peripheral nerves controlling respiration include nerve root disease complicating immunisation and surgical damage to the spinal and phrenic nerves.

Drug-induced bronchospasm

Asthmatic patients are particularly susceptible to exacerbations of their disease by drugs (Box 7.3.2). This effect may occur either as a predictable pharmacological side-effect of the drug or as an idiosyncratic response. Examples of the former include β-adrenergicic antagonists and cholinergic agents while examples of the latter include sensitivity to the colouring agent tartrazine, for which reason many manufacturers have eliminated tartrazine from their red, orange and yellow tablets. Allergic bronchoconstriction also forms part of generalised anaphylactic reactions induced by vaccines and antisera and occurs as a localised response to penicillin, iodine-containing contrast media, iron dextran and other medicaments. Bronchospasm may also be initiated by the non-specific irritant effect of inhaling nebulised drugs if they are prepared as a hypotonic solution, a side-effect that is prevented by using isotonic solutions.

> **Box 7.3.2 Drugs known to cause or aggravate bronchoconstriction**
>
> **Non-specific**
> Hypotonic nebulised preparations
>
> **Pharmacological**
> β-sympathetic antagonists
> Cholinergic agents, e.g. pilocarpine
>
> **Idiosyncratic**
> Penicillin
> Iodine-containing contrast media
> Iron dextran
> Tartrazine
>
> **Prostaglandin potentiation**
> Aspirin and other non-steroidal anti-inflammatory agents
>
> **Occupational allergy**
> Penicillin
> Cephalosporin

Aspirin-induced asthma has been recognised for many years and more recently several of the newer anti-inflammatory drugs have been found to exacerbate asthma in certain sensitive individuals. The basis for this is uncertain but the likelihood of an individual anti-inflammatory drug provoking an asthmatic response is related to its potency as an inhibitor of prostaglandin cyclooxygenase pathway, resulting in the production of leukotrienes.[8–10]

As well as asthma being exacerbated by drugs, the disease has been caused by occupational exposure in the pharmaceutical industry to certain drugs which can be inhaled during manufacture, notably penicillin, cephalosporin, methyldopa, cimetidine and piperazine.

Obliterative bronchiolitis

Obliterative bronchiolitis of the constrictive type has been reported with penicillamine[11,12] and gold[13,14] but in many cases it is possibly the underlying condition rather than the drug that is responsible (see p. 123). This is often rheumatoid disease, which is sometimes complicated by bronchiolitis obliterans whether the patient is under treatment or not.[15]

Organising pneumonia extending into peripheral bronchioles (see p. 120) may be seen with a variety of drugs but results in a restrictive rather than obstructive lung defect and is to be regarded as a cytotoxic effect of the drug acting primarily at the alveolar level (see below).

Raw *Sancropus androgyns* taken as a slimming aid causes severe obliterative bronchiolitis (see p. 376).

Cytotoxic effects of drugs

The cytotoxic effects of drugs may be acute or chronic, leading to changes as varied as pulmonary oedema, diffuse alveolar damage, pulmonary haemorrhage and haemosiderosis, organising pneumonia, interstitial pneumonitis and interstitial fibrosis.[16,17] Some of the most severe acute effects are seen with the chemotherapeutic agents used in malignant disease[18] but they are also recorded with drugs that are not traditionally thought to be cytotoxic, e.g. desferrioxamine administered as a prolonged intravenous infusion in acute iron poisoning.[19]

Pulmonary toxicity due to busulphan was first described in 1961,[20] and has been the subject of several subsequent studies.[21–24] It remains the mainstay of treatment for chronic myeloid leukaemia. Like other alkylating agents, it acts by cross-linking DNA strands. Clinical estimates of the incidence of pulmonary toxicity vary around 4% but subclinical damage is thought to be much more common. Although not strictly dose-dependent, toxicity is rarely seen with a total cumulative dose of less than 500 mg. Synergy with radiation and other cytotoxic drugs occurs.[25] Similar effects have been reported for most cytotoxic agents, particularly bleomycin.[26] Pulmonary toxicity is seen less commonly with other alkylating agents, such as cyclophosphamide and melphalan.[27–30]

Bleomycin is a cytotoxic antibiotic derived from *Streptomyces* species. It is widely used in the treatment of neoplasms such as lymphomas and germ cell tumours, and is thought to produce its therapeutic and toxic effects by altering the normal balance between oxidants (active oxygen radicals) and antioxidant systems.[26] Bleomycin produces superoxide radicals when incubated with oxygen and iron in vitro. Oxygen enhances its effects,[31] a fact well known to anaesthetists who accordingly take care to limit concentrations of inspired oxygen to 30% in patients on bleomycin who are undergoing surgery.[32–34] Radiotherapy and cytotoxic agents such as bleomycin are also synergistic. Bleomycin is preferentially concentrated in the lungs and pulmonary fibrosis can be produced in animals when it is administered intravenously, intraperitoneally or by intratracheal instillation. Electron microscopy shows that the early changes consist of swelling and vesiculation of endothelial cells, interstitial oedema and type I epithelial cell necrosis.[35,36] The reported incidence of bleomycin toxicity varies from 2 to 40% depending on the type of patient being treated and on dosage. In general, toxic effects increase with age and cumulative dose: above a total dose of about 500 units they rise significantly.

The acute morphological changes attributable to drugs include pulmonary oedema and diffuse alveolar damage. Acute pulmonary oedema is seen in heroin addicts who die while injecting themselves intravenously but it is also seen in patients administered a variety of drugs therapeutically, for example hydrochlorothiazide, salicylate, opiates, vinorelbine,and desferrioxamine. The oedema is of the high permeability type (see p. 402), rich in protein, and is occasionally haemorrhagic or accompanied by the hyaline membranes of diffuse alveolar damage.

Diffuse alveolar damage has alveolar epithelial necrosis as its basis (Figs 7.3.1 and 7.3.2). However, the continuing action of many cytotoxic drugs affects the regeneration process so that atypical type II epithelial cells develop, a characteristic feature that was first described with busulphan and subsequently with bleomycin.[21,37] These two drugs differ chemically but both act (by different mechanisms) on DNA. The atypical cells have abundant deeply eosinophilic or amphophilic cytoplasm and large nuclei, which may be multiple but are usually single. The nuclei measure up to 12 μm and are densely stained throughout or contain either large homogeneous deeply eosinophilic inclusions or clear vacuoles (Fig. 7.3.3). Electron microscopy distinguishes the inclusions from nucleoli and shows them to consist of tubular aggregates derived from the internal nuclear membrane.[37] Airway epithelium shows similar nuclear changes and often undergoes squamous metaplasia. The presence of such cells in sputum specimens submitted for cytology can lead to a misdiagnosis of malignancy.

Fibrosis may follow diffuse alveolar damage or develop insidiously, perhaps many years after drug therapy ceased (Fig. 7.3.4).[38] It may be both interstitial and intra-alveolar. The interstitial component is often accompanied by a non-specific chronic inflammatory infiltrate. The proportions of inflammation, which is potentially reversible, and fibrosis, which when collagenous is irreversible, obviously bear on the prognosis. However, most case reports antedate the recent
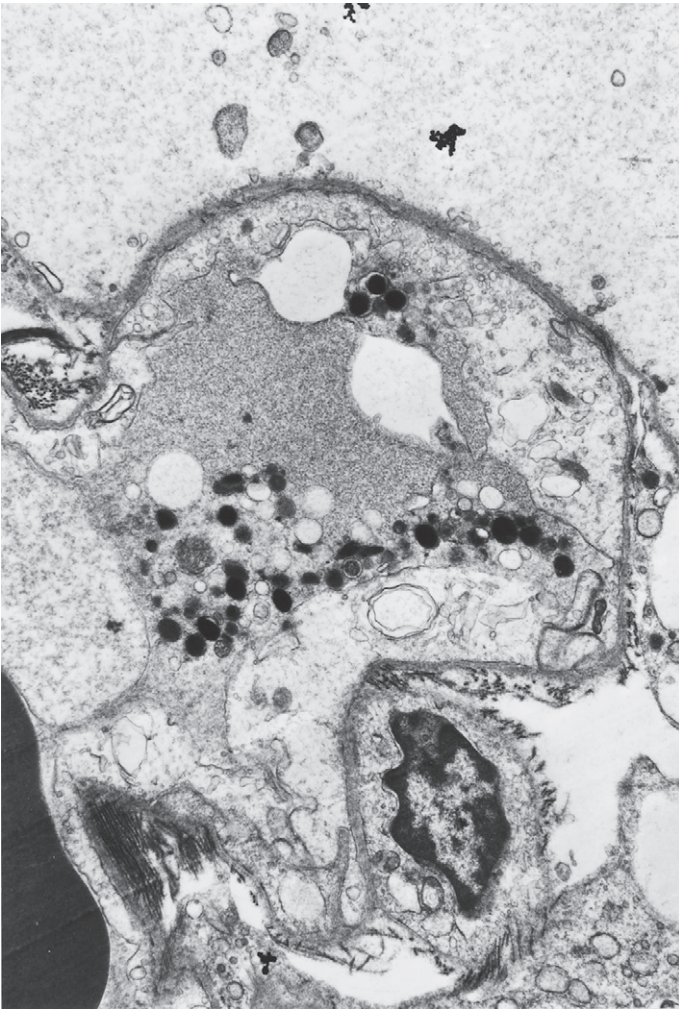
Figure 7.3.1 Drug toxicity. A cancer patient administered a cocktail of cytotoxic drugs developed acute respiratory distress and biopsy showed loss of the type I alveolar epithelial cells when examined by electron microscopy. The alveolar basement membrane is bare on its alveolar aspect (above). Capillary endothelial cells show cytoplasmic swelling. *(Courtesy of Miss A Dewar, Brompton, UK.)*
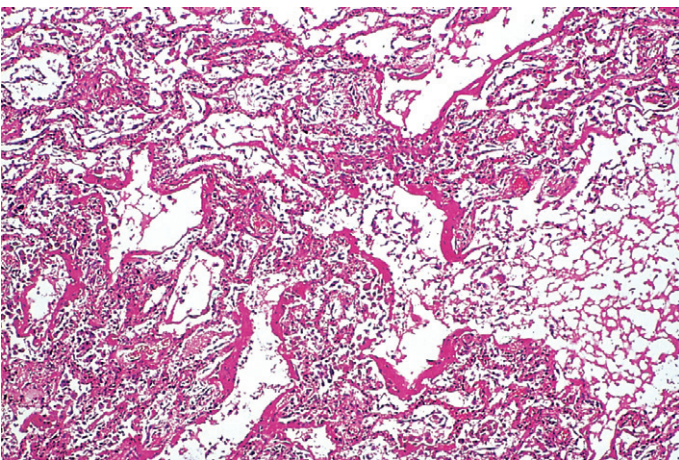
Figure 7.3.2 Amiodarone toxicity resulting in diffuse alveolar damage characterised by hyaline membrane formation.
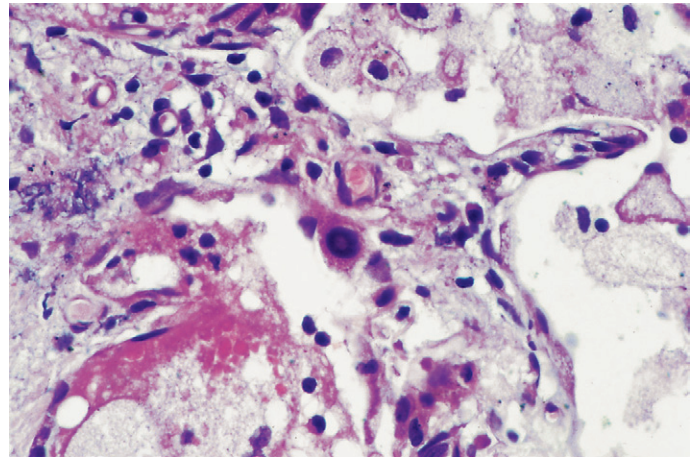
Figure 7.3.3 Busulphan toxicity. The alveoli are lined by regenerating epithelial cells and the central cell has a very prominent nucleus.

Figure 7.3.4 Fatal pulmonary fibrosis resulting from busulphan therapy, which had been administered for 2 years several years previously.

classification of interstitial pneumonia described in Chapter 6 and it is uncertain how their pathological appearances would now be classified. The majority lack the classic features of usual interstitial pneumonia and fibrotic non-specific interstitial pneumonia. Many show overlapping patterns of intersitital pneumonia and this alone should arouse suspicion that a drug may have been responsible. However,
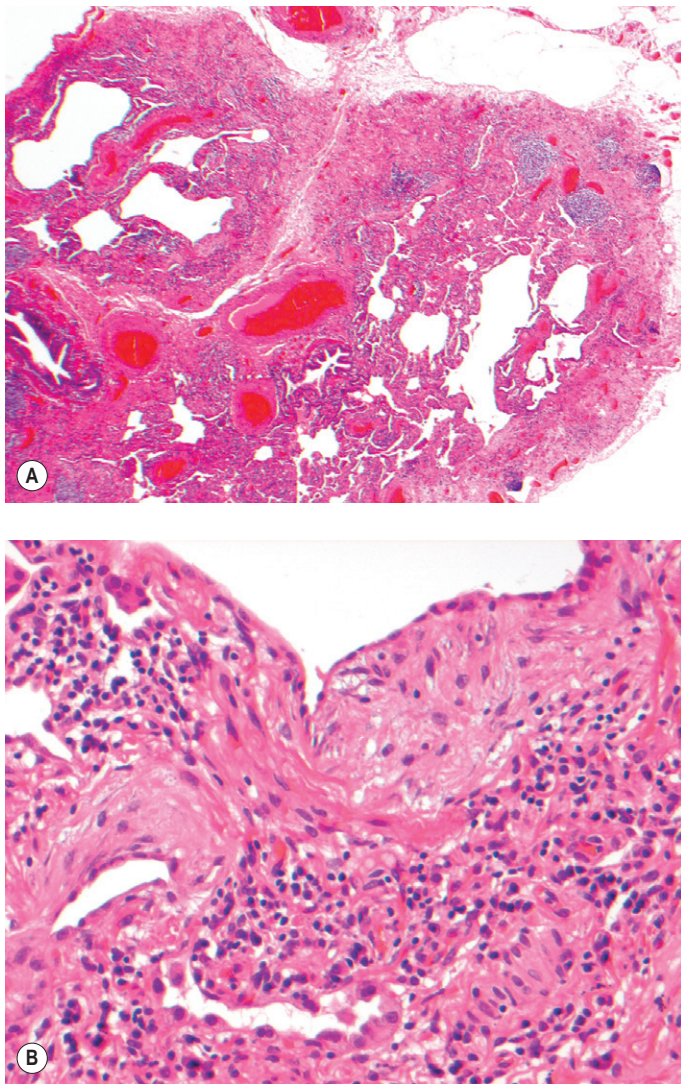
Figure 7.3.5 Nitrofurantoin toxicity. The lung shows patchy subpleural fibrosis (A) with fibroblastic foci (B). These are the classic features of usual interstitial pneumonia but lung function improved after withdrawal of the drug.

there are drugs that undoubtedly cause a usual interstitial pneumonia pattern, for example the chemotherapeutic agents and nitrofurantoin (Fig. 7.3.5), while others, for example the statins, are recorded as having induced a non-specific interstitial pneumonia pattern.[39] A drug history is therefore imperative when assessing any patient with diffuse parenchymal lung disease.

Organising pneumonia similar to the cryptogenic condition described on page 308, and probably similarly reversible with steroids, has been encountered with a variety of drugs, including amiodarone, sulphasalazine and pencillamine.[40] Penicillamine has also been incriminated in the development of both diffuse alveolitis and bronchiolitis obliterans, but both these changes could well be due to the underlying rheumatoid disease for which the pencillamine is administered.[15] In busulphan lung there may be an organising intra-alveolar fibrinous exudate,[21] which at its most extreme results in irreversible effacement of the alveolar architecture by sheets of loose connective tissue (see p. 148).

Some cytotoxic drugs result in pulmonary changes by more than one mechanism: for example, methotrexate may produce hypersensitivity reactions with granuloma formation[41–44] or pulmonary eosinophilia[45] as well as diffuse alveolar damage. Pulmonary toxicity is also occasionally seen in patients undergoing treatment with gold salts for rheumatoid disease: in addition to diffuse alveolar damage, there may be eosinophilia and dermatitis in these cases, again indicating possible hypersensitivity.[46] Nitrofurantoin is another example of a drug resulting in a variety of patterns of alveolar injury: diffuse alveolar damage, desquamative interstitial pneumonia, giant cell interstitial pneumonia, organising pneumonia and eosinophilic pneumonia have all been recorded in association with this drug.[47–49]

It should also be noted that in patients with neoplastic disease, clinical features suggestive of a pulmonary drug reaction may be due to factors other than drugs. In leukaemic patients, for example, these include direct infiltration of the lungs by leukaemic cells, opportunist infection and, if bone marrow transplantation has been undertaken, the effects of irradiation and possibly graft-versus-host disease.
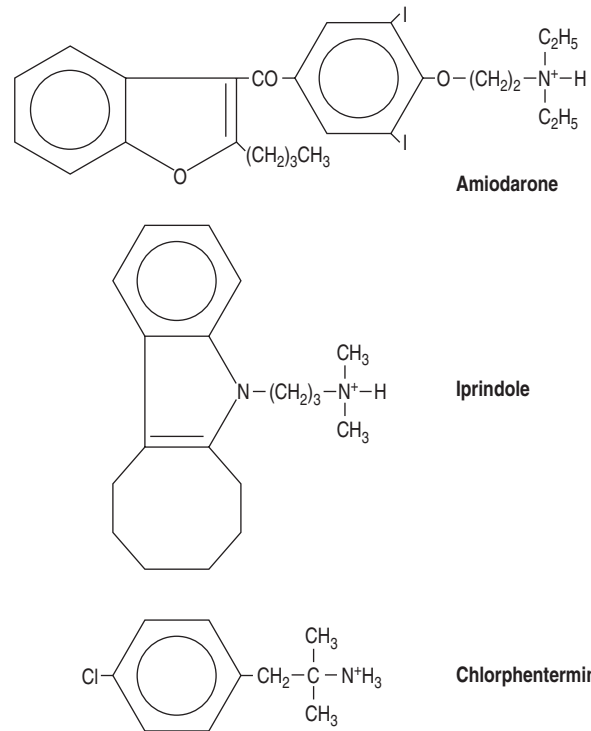
Phospholipidosis

Phospholipidosis is encountered with drugs such as the antidysrhythmic agent amiodarone,[50] which block lysosomal enzymes involved in the breakdown of complex lipids. This leads to their accumulation throughout the body but the effect is most marked in tissues that take up the drug and contain cells rich in lysosomes. The lung fulfils both these requirements through its rich complement of alveolar macrophages. These cells accumulate the enzyme substrate (phospholipid) in their cytoplasm with the result that large foam cells fill the alveoli (Fig. 7.3.6). The appearances are those of endogenous lipid pneumonia, similar to that seen in obstructive pneumonitis. However, with amiodarone cytoplasmic vacuolation is also seen in epithelial and interstitial cells. The phospholipid inclusions contained within the vacuoles are particularly well seen in unstained frozen sections viewed by polarised light.[51] Identical changes to those induced by amiodarone were seen in the lungs of rats exposed to very high levels of the antidepressant drug iprindole[52] and the anorectic drug chlorphentermine.[53] These three compounds, iprindole, chlorphentermine and amiodarone, all belong to the amphiphilic group of drugs which block lysosomal phospholipase and sphingomyelinase. Although their pharmacological actions are very different, a molecular homology is apparent (Fig. 7.3.7).

It is likely that all patients receiving substantial amounts of amiodarone develop phospholipidosis throughout the body, but this is generally well tolerated. Only a minority experience respiratory impairment and in these there is also evidence of pulmonary inflammation and fibrosis, which is possibly mediated immunologically.[54] These patients generally have a restrictive lung deficit, the onset of which may be acute or chronic. Bronchoalveolar lavage shows foamy macrophages but these cells indicate exposure to the drug rather than drug toxicity; nor are they specific to amiodarone, being observed on occasion with other drugs. Lymphocytes of suppressor type may also be detected on lavage.[54] Histologically, amiodarone toxicity is diagnosed on a combination of phospholipidosis and interstitial pneumonia and fibrosis. Occasionally the hyaline membranes of diffuse alveolar damage are superimposed on the interstitial changes (see Fig. 7.3.2).[55–57] In some patients the fibrosis is intra-alveolar rather than interstitial and the appearances are those of organising pneumonia.[58] The process may be localised and mimic a neoplasm radiologically.[59,60]

Amiodarone toxicity is probably dose-dependent but there is considerable individual variation in the amount required,[61,62] which appears to be under genetic control.[63] Amiodarone toxicity is uncommon in patients taking daily doses of 200 mg or less whereas the
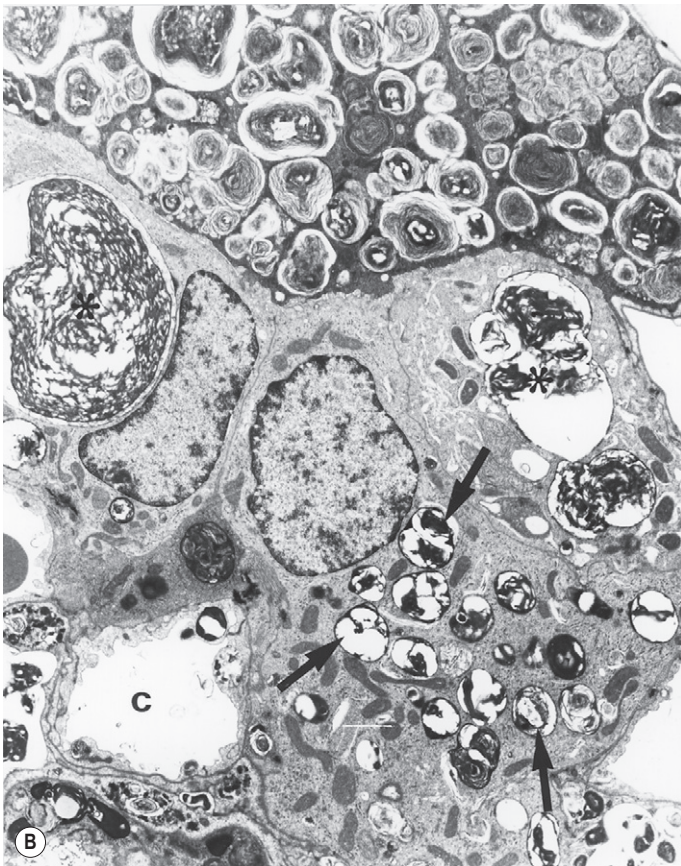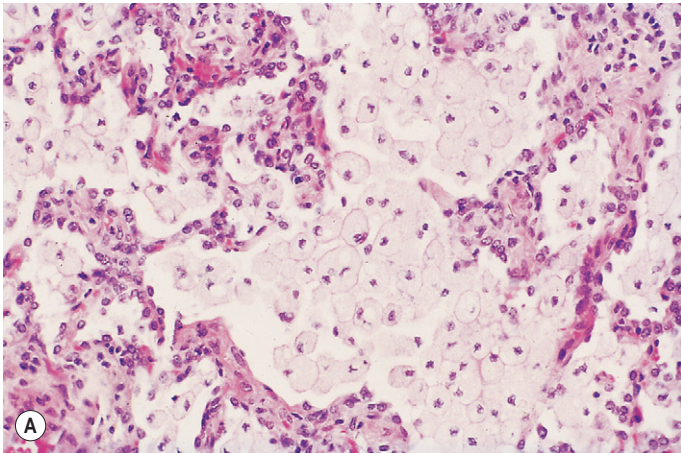
Figure 7.3.6 Phospholipidosis due to prolonged amiodarone administration. Amiodarone blocks lysosomal phospholipases, leading to the accumulation of phospholipids in many organs. In the lung this is manifest as endogenous lipid pneumonia. (A) By light microscopy the alveoli are filled with foamy macrophages. (B) Electron micrograph showing an alveolar macrophage (top) packed with osmiophilic lamellar bodies. The macrophage covers several type II pneumocytes that, in addition to their normal surfactant inclusions (arrows), contain large lamellated drug-induced inclusions (asterisks), which are also seen in capillary endothelial cells. C, capillary. *(Reproduced with permission from Costa-Jussa et al. (1984).[50])*

Figure 7.3.7 Formulae of several amphiphilic drugs, all of which block lysosomal phospholipases and cause endogenous lipid pneumonia. The pharmacological actions of these drugs differ but a molecular homology is evident.

prevalence of the disease exceeds 50% in patients treated with doses of 1200 mg/day. Duration is also important: it may require 2–3 years for a patient on 200 mg/day to develop symptoms but only 10 months for one on 400 mg/day. The drug has a long half-life and may take weeks to clear the body completely. Previous pulmonary injury renders the lung unduly sensitive to amiodarone. Acute toxicity has been encountered in patients on moderate doses who have experienced recent or even concomitant pulmonary procedures such as intubation, lobectomy or ventilation with high concentrations of oxygen.[64]

Alveolar proteinosis

With continued experimental administration of the drug iprindole mentioned above, the phospholipidosis it produced gradually evolved into alveolar proteinosis (more properly called lipoproteinosis; see p. 316),[65] but this has not been reported as a drug effect in humans. Alveolar proteinosis has however been recognised in a number of patients receiving chemotherapy for conditions such as leukaemia. The mechanism here is probably based on the cytotoxic action of the drug and the material filling the alveoli may represent the detritus of degenerate alveolar cells rather than excess pulmonary surfactant, as in the primary auto-immune form of alveolar proteinosis.

Eosinophilic pneumonia

Eosinophilic pneumonia, the pathology of which is described on page 461, may be caused by several drugs, including nitrofurantoin, *para*-aminosalicylic acid, sulphasalazine, phenylbutazone, gold compounds, aspirin and penicillin (see Box 9.3, p. 460).[66,67] It may also follow radiation to the chest.[68] The tissue eosinophilia is generally accompanied by a rise in the number of eosinophils in the blood. The

clinical picture varies from transient asymptomatic opacities on a chest radiograph to a life-threatening illness with severe respiratory distress and hypoxaemia, so-called acute eosinophilic pneumonia (see p. 462). The reaction is often associated with a florid rash. Withdrawal of the drug may be all that is required to effect resolution but corticosteroids are usually given as they produce a marked improvement.

Churg–Strauss syndrome

This syndrome of necrotising granulomatosis, vasculitis and eosinophilia in asthmatic patients, which is described more fully on page 465, has been reported when leukotriene receptor antagonists have been used to treat asthma. However, it is likely that the syndrome has been merely unmasked by the antileukotriene permitting a reduction in corticosteroid dose rather than representing a direct effect of the antileukotriene.[69,70] Mesalazine has also been implicated in inducing a vasculitis during treatment for inflammatory bowel disease.[71]

Eosinophilia–myalgia syndrome

The eosinophilia–myalgia syndrome was identified in the USA in 1989 and quickly identified as being due to the ingestion of L-tryptophan from one particular Japanese supplier. Withdrawal of this substance led to the virtual elimination of the disease, but not before 2000 patients had been affected, 1 in 60 fatally.[72–76] Cases were subsequently described in Europe where there were further fatalities.

L-tryptophan is an essential amino acid that is freely available to the public: its purchase does not require a medical prescription. It has been promoted as a dietary supplement and as an agent against insomnia and premenstrual tension. Women in the reproductive years preponderated in the patients affected by the resultant eosinophilia–myalgia. The clinicopathological features of the syndrome are similar to those of the Spanish toxic oil syndrome (see p. 375) and differ more in degree than type. The discovery of an aniline-derived contaminant in the tryptophan-induced condition is a further link connecting these two syndromes.[77] An immune basis is suggested by the identification of T lymphocytes activated against fibroblasts in the eosinophilia–myalgia syndrome.[78]

The illness is a multisystem disorder and besides blood eosinophilia and myalgia there may be arthralgia, fever, rash and involvement of the lungs, liver and central nervous system. As in the toxic oil syndrome, there is fasciitis, wasting and muscle pain associated with blood and tissue eosinophilia. The lungs are affected in 60% of cases. Pulmonary symptoms have included cough, dyspnoea and chest pain. Radiographs have shown diffuse bilateral infiltrates and pulmonary hypertension has been documented in a few cases.[79]

Histology of the lungs shows an oedematous myxoid intimal thickening affecting small pulmonary blood vessels and a diffuse interstitial lymphocytic and eosinophilic infiltrate.[72,73,75,76,80] These cells may also be seen within the walls of the thickened blood vessels (Fig. 7.3.8).[72,76] Massive ingestion of L-tryptophan has resulted in the appearances of an organising pneumonia.[81]

Granulomatous alveolitis

As an adverse drug reaction, granulomatous alveolitis is best exemplified by the extrinsic allergic alveolitis of pituitary snuff-takers, but it is also encountered on rare occasions with cytotoxic and other drugs, including methotrexate, bacille Calmette–Guérin (BCG) immunisation, interferons, ciprofloxacin, antiviral therapy and tumour necrosis factor antagonists.[42–44,48,82–90] The histological appearances may suggest extrinsic allergic alveolitis or sarcoidosis but the centri-
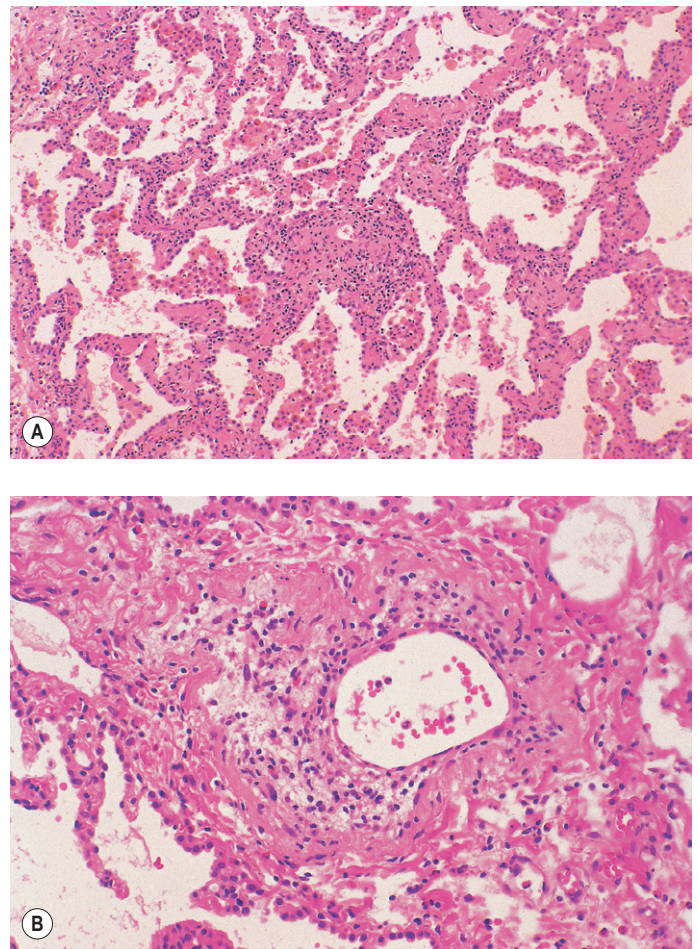
Figure 7.3.8 L-tryptophan toxicity. (A) There is a diffuse interstitial infiltrate of lymphocytes with smaller numbers of eosinophils. (B) The same infiltrate involves pulmonary blood vessels. *(Courtesy of Dr TV Colby, Scottsdale, USA.)*

acinar or lymphangitic concentration of these conditions is usually lacking. However, unless an infective agent can be demonstrated the diagnosis generally requires consideration of the clinical and environmental details, including any drug regimen.

Aspiration lesions

Exogenous lipid pneumonia may result from the unintentional aspiration of various fat-based medicaments such as liquid paraffin, oily nose drops and petroleum jelly or of fat-rich dietary supplements in the form of ghee.[91–97] The consumption of liquid paraffin as an aperient is common in some countries and may be taking place without the knowledge of the patient's medical practitioner. Regurgitation and aspiration of ingested oil are especially likely to happen during sleep in the presence of a hiatus hernia or when the oesophagus fails to empty completely into the stomach because of achalasia of the cardia. The aspiration of vegetable oil occurred in the past from the use of menthol in olive oil for the treatment of tuberculous laryngitis, and occasionally from the use of iodinated vegetable oils for bronchography.[98–101] More recently exogenous lipid pneumonia has developed from the constant sucking of lollipops formulated for the administration of the analgesic fentanyl but also containing a stearate component.[102] The treatment of epistaxis by nasal packing

with paraffin gauze has also led to exogenous lipid pneumonia. The pathology of exogenous lipid pneumonia is described on page 314. Other medicines may also be aspirated unwittingly, for example a ferrous sulphate tablet may cause brown iron staining and necrosis of the bronchus at the point of impact, progressing to bronchial stenosis.[103–105] Distal infection is then likely, as with any foreign body. Barium sulphate aspiration may complicate gastrointestinal radiography.[106] Large amounts may impair ventilation but being inert there is no permanent injury to the lungs, although the striking changes are evident on the chest radiograph.

Pulmonary hypertension

An outbreak of pulmonary hypertension affecting many Swiss, Austrian and German patients in the period 1966–68 was probably due to the anorectic drug aminorex,[107] which was accordingly withdrawn with regression in the number of new cases. The pathology in these patients was identical to that of primary pulmonary hypertension (see p. 420) and it proved impossible to reproduce the condition in laboratory animals but the epidemiological evidence that aminorex was to blame is very strong. Fenfluramine and phentermine, further anorectic drugs that are chemically similar to aminorex, have also been associated with such plexogenic pulmonary hypertension,[108–112] and with fibroproliferative plaque on the tricuspid valve and pulmonary arteries.[113]

Pulmonary hypertension due to pulmonary veno-occlusive disease has sometimes complicated the use of cytotoxic chemotherapeutic agents[114] or followed bone marrow transplantation.[115]

Non-steroidal anti-inflammatory agents such as indomethacin and diclofenac cross the placenta and, if given in late pregnancy, may cause premature closure of the ductus arteriosus, resulting in severe neonatal pulmonary hypertension.[116,117]

Pulmonary hypertension is a well-recognised association of human immunodeficiency virus (HIV) infection but until recently has been unexplained. Now, however, evidence is emerging that the highly active antiretroviral therapy administered to HIV-positive patients might be responsible for the pulmonary hypertension.[118]

Pulmonary embolism

The older high-oestrogen contraceptive drugs carried a slight risk of thromboembolism but this is not seen with the newer preparations. Pulmonary thromboembolism has also occurred with a drug-induced lupus syndrome associated with anticardiolipin antibodies. Chemotherapeutic drugs such as mitomycin may cause widespread small-vessel thrombosis resulting in the haemolytic–uraemic (thrombotic microangiopathic) syndrome. There is prominent involvement of pulmonary vessels and patients often suffer from respiratory as well as renal insufficiency, and pulmonary hypertension. The syndrome can develop during treatment or up to several months after the drug has been withdrawn. Pulmonary thromboembolism is also recorded as a complication of immunoglobulin infusion.[119]

Non-traumatic fat embolism has resulted from the agglutination or 'creaming' of fat emulsions administered intravenously as a source of calories to debilitated patients.[120–125] The agglutinated liposomes occlude fine blood vessels throughout the body, causing effects such as priapism, osteonecrosis and pancreatitis. They may be demonstrated in the pulmonary capillaries but the lungs have considerable vascular reserve and it is uncertain what effect the vascular occlusion has on pulmonary function. Agglutination of these fat emulsions is particularly common in severely ill patients and this has been attributed to the elevated blood levels of acute-phase proteins, especially C-reactive protein, that are found in the very ill. The agglutination is also induced by calcium and may be brought about by
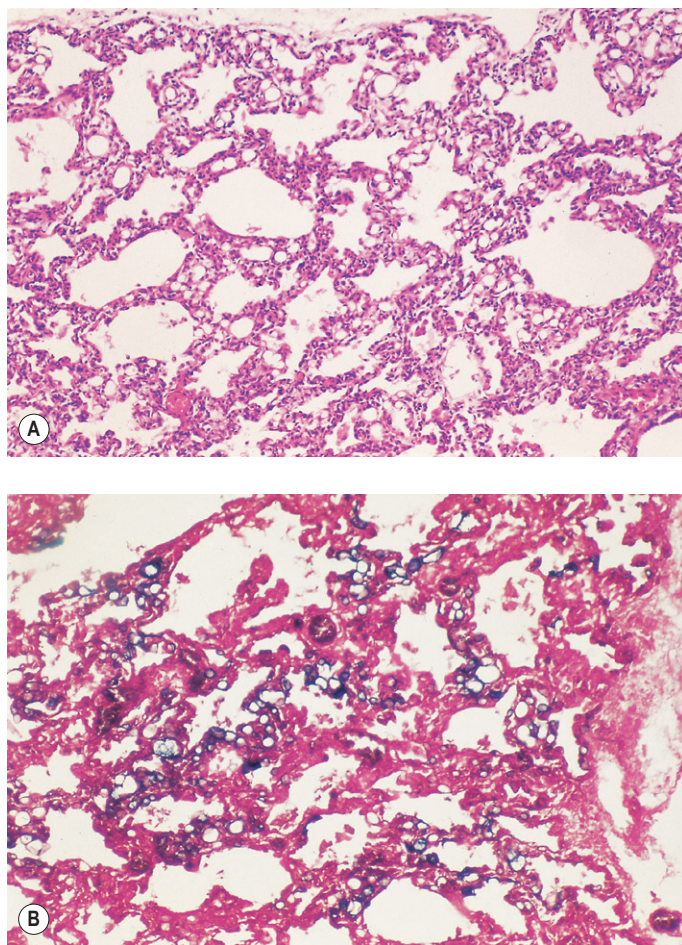
Figure 7.3.9 Agglutination of emulsified fat administered intravenously. (A) With haematoxylin and eosin staining, seemingly empty vacuoles appear to occupy the alveolar capillaries. (B) The agglutinated fat has not been dissolved in processing and can be demonstrated by Sudan black. *(Courtesy of Dr G Hulman, Nottinghamshire, UK.)*

administering calcium and other mineral supplements through the same venous line as the fat. Once agglutinated, the fat is less soluble and may be demonstrated in paraffin sections. Sudan black is especially useful for this purpose (Fig. 7.3.9). Microvascular crystal embolism is a further risk of parenteral nutrition, the crystals representing various calcium salts that may precipitate in the circulation.[126]

Transient diffusion abnormalities attributed to oil embolism are very common in patients undergoing lymphangiography but serious respiratory impairment is limited to those patients with pre-existing lung disease or in whom substantial amounts of contrast medium are injected rapidly.[127–130]

Other emboli of an iatrogenic nature described in pulmonary arteries include the broken-off ends of intravenous catheters and cannulas, particles from dialysis tubing,[131] prosthetic implants of substances such as Teflon and silicone[88,132–135] and various materials injected to occlude abnormal blood vessels.[136,137]

Diffuse pulmonary haemorrhage

Diffuse pulmonary haemorrhage may result from interference with the clotting mechanism by anticoagulants[138] or from widespread pulmonary capillaritis, the latter reported in leukaemic patients

treated with retinoic acid.[139] Pulmonary haemorrhage has also been reported as an idiosyncratic reaction to lymphangiography media[140] and as a complication of immunoglobulin infusion,[141] while the development of anti-basement membrane antibodies resulting in Goodpasture's syndrome has been attributed to penicillamine.[141a]

Opportunistic infection

Infection is a common pulmonary hazard in any patient receiving corticosteroids, chemotherapy or any other immunosuppressant drug. Viral, bacterial, fungal and protozoal infections, often in combination, may all develop in the lungs of such patients and tissue reactions may be atypical. *Pneumocystis jiroveci,* for example, may elicit a granulomatous reaction or cause diffuse alveolar damage rather than the usual foamy alveolar exudate (see p. 226).

Metastatic calcification

Metastatic calcification, described on page 489, may result from any drug causing hypercalcaemia, e.g. high doses of vitamin D, calcium and inorganic phosphate or excessive alkali intake in the treatment of peptic ulceration.

Carcinoma of the lung

Carcinoma of the lung may be promoted by drugs. Arsenicals cause squamous metaplasia of the bronchi and occasionally squamous carcinoma, while peripheral scar cancers, usually adenocarcinomas, have developed in lungs showing fibrosis due to drugs such as busulphan.

Pleural disease

Drugs may result in a variety of pleural diseases.[142] Common examples include effusions, chronic inflammation and fibrosis. These are usually encountered in isolation but may be associated with chronic interstitial pneumonia or fibrosis. Sometimes there is also serological evidence of systemic lupus erythematosus: many drugs, including hydantoin, practolol, procainamide, hydralazine and sulphonamides, are associated with the development of a syndrome resembling systemic lupus erythematosus that includes pleural disease. Whether the drugs are directly responsible for the syndrome or merely promote the development of latent natural disease is uncertain.

Ergotamine derivatives such as methysergide and bromocriptine are notable for the production of pleural fibrosis, which is sometimes associated with mediastinal and retroperitoneal fibrosis large amounts or prolonged treatment are generally required to produce this effect.[143–145] In patients given practolol, pleural thickening has become evident several years after the drug was discontinued. This shows the need for a careful drug history in any patient with unexplained pleural fibrosis.

RADIATION INJURY

Reports of radiation-induced lung damage began to appear soon after ionising radiation became widely used in the treatment of malignant disease.[146–148] Despite refinements in radiotherapy techniques it is often impossible to avoid irradiating small areas of lung when treating cancer of the lung, breast, spine, thymus and oesophagus. Parts of the lungs are also included in 'mantle' irradiation of mediastinal lymph nodes affected by lymphoma. Occasionally, the whole of both lungs

is irradiated, as in the treatment of widespread pulmonary metastases or as part of whole-body irradiation prior to marrow transplantation for the treatment of leukaemia. Radiation pneumonitis, usually localised, is estimated to affect about 8% of patients.[149]

Therapeutic irradiation is given as divided doses over several weeks in order to minimise damage to adjacent tissue. The effects of such fractionated treatment are cumulative. In the lungs an early exudative phase soon passes and progressive damage becomes apparent only after months or even years.[150,151] The changes are generally confined to the area of lung that is irradiated but are widespread when the whole body is irradiated prior to bone marrow transplantation or there is accidental whole-body irradiation. However, localised irradiation of the lung has been followed by abnormalities in non-irradiated areas. These include bilateral alveolar exudates,[152] migratory organising pneumonia affecting both lungs[153,154] and fulminant bilateral interstitial pneumonia.[155] The likelihood of lung injury is increased by the simultaneous use of cytotoxic drugs and oxygen therapy.[156] Furthermore, chemotherapy following irradiation may result in exacerbation of the injury in areas previously irradiated, a phenomenon termed 'recall pneumonitis'.[157,158] In the long term, irradiation also results in an increased incidence of lung carcinoma. This was seen in patients given therapeutic irradiation to the spine for ankylosing spondylitis[159] and is still encountered on occasion following irradiation for breast cancer.[160] The pathogenesis of radiation injury is described on page 146.

Radiation damage to the lung is traditionally separated into fulminant acute injury coming on within days, subacute pneumonitis developing within several weeks (typically 2–3 months) and interstitial fibrosis slowly evolving from the subacute stage or making itself apparent years later. The migratory organising pneumonia referred to above is an unusual further effect, as is chronic eosinophilic pneumonia.[68] In the pleura, radiation causes fibrinous effusions and adhesions. Pleural effusion and pulmonary oedema may be augmented by the long-term effects of radiation on the heart.

Fulminant acute injury is an unusual and unexpected effect of therapeutic radiation but one that is likely to come to the attention of the pathologist as an autopsy is often requested. The clinical features are those of acute lung injury and the pathological changes are those of diffuse alveolar damage. The cause is likely to be accidental overdosage, augmentation of the radiation damage by accompanying oxygen therapy or treatment with cytotoxic drugs. Occasionally however these factors can be excluded, in which case the damage has to be ascribed to 'hypersensitivity'.

Subacute radiation pneumonitis is encountered more commonly. After an interval of about 2–3 months the patient complains of shortness of breath and a non-productive cough. The chest radiograph shows hazy opacification proceeding to more dense consolidation. Lung biopsy shows alveolar and interstitial oedema, possibly with residual hyaline membranes, proliferation of atypical alveolar epithelial cells and interstitial fibroblasts and organising thrombosis. Later, as the process advances, there is widespread fibrosis comparable to that illustrated in Figure 4.24 on page 148 and ultimately dense scarring (Fig. 7.3.10).

Tracheal and aortic injury may complicate radiation treatment of tracheal lesions, sometimes resulting in an aortotracheal fistula.[161]

RESPIRATOR LUNG AND OXYGEN TOXICITY

Patients requiring mechanical ventilation are liable to suffer lung injury in a number of ways. In addition to effects of barotrauma such as pneumothorax and surgical emphysema, they often develop diffuse alveolar damage. The high oxygen tension that is often combined with

Figure 7.3.10 Radiation damage. A dense scar is seen in an area of the lung that had been irradiated previously.

mechanical ventilation is a major factor[162–164] but mechanical forces other than the high pressures responsible for barotrauma can also contribute to this form of lung injury, notably by resulting in excessive end-expiratory stretch and repeated collapse/recruitment of the alveolar walls.[165,166] Low tidal volume ventilation is therefore a fundamental part of the management of diffuse alveolar damage.

Although oxygen is necessary to life, it is cytotoxic in high concentrations. Severe hyperoxia damages DNA, inhibits cellular proliferation and ultimately kills cells. Its toxicity is thought to be due to the intracellular production of active oxygen radicals, some of which derive from activated neutrophils attracted to the site of injury.[167–170] Under normal conditions most of the oxygen is reduced to water by cytochrome oxidase, and any active radicals produced are eliminated by superoxide dismutase, catalase and other antioxidants. However, these defence mechanisms may prove inadequate when active radicals are produced in excess.[171]

Problems are likely to arise in clinical practice when lung disease necessitates the concentration of oxygen in the inspired air being raised in order to maintain normal blood levels of oxygen and prevent cerebral hypoxia.[172–174] A 'safe' level for oxygen administration is not firmly established and, because of species differences in susceptibility to oxygen, caution is needed in extrapolating from animal studies. However, animal experiments have shown that previous damage to the lungs renders them unduly sensitive to oxygen[175,176] and conversely that prior exposure to high levels of oxygen confers some resistance to subsequent oxygen exposure.[177] Clinical studies suggest that less than 50% oxygen (at atmospheric pressure) can be tolerated for long periods without ill effect. Little, if any, serious lung damage results from administration of 100% oxygen for up to 48 hours but concentrations between 50% and 100% carry a risk of damage if this period is exceeded.[171,178] Extracorporeal oxygenation of the blood circumvents the problem but if it is to be prolonged it becomes a

major undertaking that poses its own hazards; it is therefore generally reserved for patients who remain hypoxaemic despite other measures.[179] Intravenous blood oxygenators are employed to minimise the supplementation of inspired oxygen and partial liquid ventilation utilising perfluorocarbon has also been used.[180] Experimentally, disruption of CD40 binding to reduce the release of proinflammatory cytokines has shown promising results in blunting oxygen-induced lung injury.[181]

None of the morphological changes attributable to oxygen toxicity is specific.[174] The earliest ultrastructural change in experimental oxygen poisoning is swelling of endothelial cells, the cytoplasm of which becomes grossly oedematous and vacuolated. Swelling and fragmentation of type I epithelial cells follow and these cells become separated from their basement membrane, which is then coated by thin strands of protein.[178] This coating is replaced by proliferating type II cells by the 12th day. With recovery in room air the lungs practically return to normal.[182] The full clinical picture of oxygen poisoning is the acute respiratory distress syndrome and the corresponding pathological changes are those of diffuse alveolar damage,[174] as described on page 136.

BLOOD TRANSFUSION

Patients with hypovolaemic shock or undergoing major surgery often require massive blood transfusions and this provides another possible cause of pulmonary damage. Although hypervolaemia is the commonest cause of pulmonary oedema after blood transfusion, transfusion-related acute lung injury is more often fatal. Platelet and white cell aggregates are known to develop in stored blood, but a relationship between the number of microaggregates transfused and the degree of respiratory impairment has not been convincingly demonstrated. Leukocyte antibodies are a more likely cause of lung injury in these patients. Such antibodies are often found in multiparous female donors as a result of sensitisation by fetal white cells during pregnancy. Alternatively, the recipient may have developed them during pregnancy or as a result of previous blood transfusions. The implicated antibodies are thought to initiate alveolar capillary damage within hours of transfusion by stimulating granulocyte aggregation.[183,184] Electron microscopy has shown capillary endothelial damage with activated granulocytes in contact with alveolar basement membranes.[185]

CARDIOPULMONARY BYPASS

Cardiopulmonary bypass entails oxygenation and circulation of the blood by extracorporeal devices, so permitting major heart surgery. In the early days of such surgery it was not unusual for patients to develop fatal respiratory insufficiency in the postoperative period. This led to the term 'postperfusion lung'. Electron microscopic studies showed alveolar damage with degranulation of neutrophils in pulmonary capillaries.[186,187] The syndrome is now less common but infants remain susceptible.[188]

The most likely explanation is that the synthetic materials with which blood comes into contact during the bypass procedure are able to activate complement. This is mediated by Hageman factor (factor XII) and the alternative pathway. Aggregation of neutrophils leads to their sequestration in the lungs and damage results from their release of lysosomal enzymes and active radicals.[188–190] The process is delayed by hypothermia.[189]

COMPLICATIONS OF CARDIAC INJURY

A postcardiac injury syndrome develops after a variety of myocardial or pericardial injuries: it has been described after cardiac surgery (post-pericardiotomy syndrome), myocardial infarction (Dressler's syndrome), blunt trauma to the chest, percutaneous puncture of the heart and implantation of a pacemaker.[191] There is a delay of anything between a few days and a few months between the cardiac injury and the onset of symptoms, which comprise chest pain, breathlessness, dyspnoea and fever. Examination usually reveals haemorrhagic pleural or pericardial effusions and pulmonary infiltrates. The syndrome usually resolves spontaneously and few pathological studies have therefore been conducted. However, the changes of diffuse alveolar damage have been reported, principally hyaline membrane formation and type II pneumocyte hyperplasia.[192] The pathogenesis is obscure. Antibodies reacting with myocardial antigens often develop after cardiac surgery but there is no relationship between these and the development of the syndrome.[192–194]

COMPLICATIONS OF RADIOFREQUENCY ABLATION

This minimally invasive technique is used to destroy lesions as varied as pulmonary metastases and the connection between the left atrium and ectopic foci in the muscular sleeves that surround the terminations of the pulmonary veins (see p. 76). The former may be complicated by pneumothorax and the latter by pulmonary vein stenosis.[195,196]

COMPLICATIONS OF CENTRAL VASCULAR CANNULATION

Central venous cannulation (synonym: catheterisation) is widely used in treating seriously ill patients and may give rise to serious complications. The commonest early complications related to the respiratory tract are caused by local trauma: they include pneumothorax, subcutaneous emphysema, haemothorax and air embolism. Infection occurs later, causing endocarditis, septic emboli and lung abscesses.[197] Thrombosis is another common late complication: one autopsy study of patients with central venous lines showed that 15% had major pulmonary emboli and 65% had microscopic emboli in their pulmonary arteries.[198] Pulmonary artery cannulation, for example with a Swan–Ganz catheter, may result in pulmonary infarction or any of the traumatic complications of central venous catheterisation mentioned above.

COMPLICATIONS OF TRACHEAL MANIPULATIONS[199,200]

Tracheotomy entails a small immediate risk of haemorrhage from damaged subthyroidal arteries, while an endotracheal tube predisposes to infection, as with all foreign bodies. Infection is also promoted by the filtering action of the upper respiratory air passages being bypassed. The latter factor also necessitates humidification of the inspired air and on occasion the humidifier or ventilator has become contaminated so that an aerosol of bacteria is introduced directly into the lower respiratory tract.[201] High-pressure ventilation
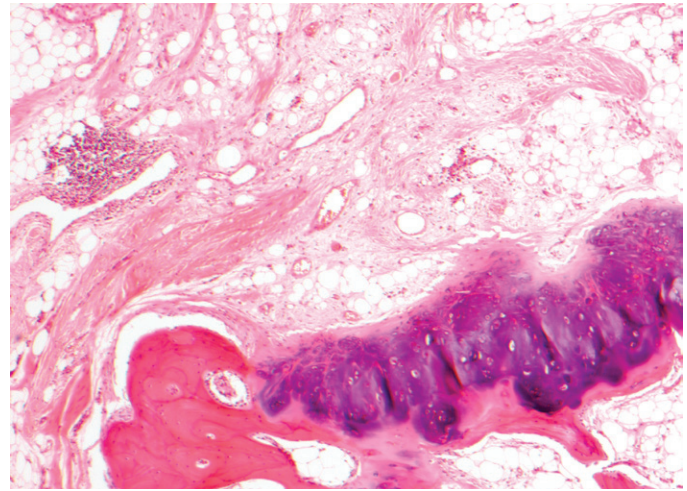
Figure 7.3.11 Tracheal stenosis following prolonged intubation. The tracheal wall shows fibrosis while the tracheal cartilage is dysplastic and shows osseous metaplasia, appearances similar to those seen in relapsing polychondritis (compare with Fig. 3.4, p. 95).

may also lead to interstitial emphysema, pneumothorax and surgical emphysema.

Asphyxia may follow an endotracheal tube becoming blocked by secretions or through it being badly positioned. Secretions need to be constantly removed yet repeated suctioning to achieve this has led to cardiac dysrrythmia and even cardiac arrest.[202]

If the balloon on the endotracheal tube is too near the tracheostomy it may act as a fulcrum, causing the tip of the tube to press into the tracheal wall. Pressure necrosis and perforation may follow, leading to mediastinitis, tracheo-oesophageal fistula or erosion of a large blood vessel. These are also complications of tracheobronchial laser therapy.

Pressure from the balloon may lead to a tracheal diverticulum and after the tube is withdrawn the trachea may become narrowed at either the site of the incision or further down where the balloon on the tracheal tube causes pressure. Small, shallow ulcers generally heal quickly but deeper ulcers cause necrosis of the tracheal cartilage, and healing is then often accompanied by fibrous stenosis (Fig. 7.3.11) or web formation. This results in wheezing and dyspnoea but not before the trachea has narrowed to 30% of its original size, which may take months. Earlier narrowing may be caused by oedema or a fibrinous pseudomembrane.[203,204] Sometimes the stenosis takes the form of a large mass of granulation tissue at the tracheostomy site, a so-called granuloma ball. In children especially, intubation may lead to tracheomalacia so that after the tube is removed the airway collapses.[205] Necrotising sialometaplasia is a further complication of prolonged intubation.[206] The incidence of such posttracheostomy complications can be minimised by careful placement of the stoma and tube, avoidance of large apertures and high cuff pressures, elimination of heavy connecting equipment and meticulous care of the tracheostomy.

Nasogastric feeding tubes may of course lead to aspiration lesions in the lungs and even fatal asphyxia if they are inadvertently allowed to enter the trachea rather than the oesophagus.

COMPLICATIONS OF BRONCHOSCOPY

Bronchoscopy is generally a safe, almost routine procedure. A review of 23 862 patients who underwent bronchoscopy identified severe

complications in 152 (0.637%), of whom three died.[207] The fatal cases comprised a 78-year-old with coronary heart disease who developed cardiac arrest and two patients who had had tracheal transplantation for oesophageal cancer and required bronchoscopic laser treatment but died of airway obstruction.

COMPLICATIONS OF THORACIC DRAINAGE TUBES

The pleural cavity is intubated in the treatment of pneumothorax and pleural effusions the tube being placed anteriorly to drain air and posteriorly to drain fluid. Complications include laceration of an intercostal artery or vein, the lung, the diaphragm and the heart.

PNEUMONECTOMY[208]

Pneumonectomy has been practised since the 1930s, since when the mortality associated with this operation has dropped from over 50% to near zero in the best hospitals. Risk factors include underlying lung disease, other medical conditions and more extensive procedures such as pleuropneumonectomy and pneumonectomy combined with chest wall resection.

The anatomical changes that take place soon after pneumonectomy have been extensively studied by radiologists who describe the air-filled postpneumonectomy space gradually filling with fluid and contracting as the mediastinum shifts and the ipsilateral dome of the diaphragm rises.[209] Much of the space is filled by fluid within 2 weeks but complete opacification may take up to 6 months. Rapid filling in the immediate postoperative period suggests haemorrhage or chylothorax. However, fluid accumulation is normally rapid after pleuro-pneumonectomy and may compromise the function of the other lung.

Pathologists conducting autopsies long after the operation may find complete fibrous obliteration of the postpneumonectomy space, coupled with mediastinal shift and elevation of the hemidiaphragm, but often there is persistent brown fluid, which may be clear, cloudy or occasionally purulent.[210] The remaining lung is generally enlarged, with its volume greater than predicted. Animal studies have shown that if one lung is excised early in life the enlargement is partly due to enhanced growth but later it represents only dilatation of existing air spaces. Hepatocyte growth factor is thought to be involved in the proliferation of residual lung cells following pneumonectomy.[211]

Pulmonary complications include those typically seen after other thoracic procedures, such as haemorrhage and infection, and those unique to the postpneumonectomy state, namely anastomotic dehiscence and postpneumonectomy pulmonary oedema. The latter presents as the acute respiratory distress syndrome and represents the early stages of diffuse alveolar damage. It follows severe shift of the heart and mediastinum, which is commoner in children and young adults, in whom the tissues are more compliant.[212–215] The condition complicates up to 4% of lung resections[216,217] and is commoner following excision of the right lung when severe herniation of the left lung into the postpneumonectomy space stretches the trachea and left main bronchus and the latter is compressed between the left pulmonary artery in front and the arch of the aorta behind. In the long term the compression can result in bronchomalacia and postobstructive bronchiectasis. If postpneumonectomy oedema develops the immediate postoperative mortality is high – 50% following pneumonectomy, 42% following lobectomy and 22% following sublobar resections.[217,218] The pathogenesis is probably multifactorial but apart from factors such as fluid overload and high inspired oxygen concentrations there is probably an element of alveolar wall injury, induced by oxidant generation secondary to lung stretching and general surgical trauma.[219,220]

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