Key points

- There is a considerable overlap between occupational and environmental respiratory disease, allowing them to be dealt with together.
- The commonest work-related respiratory disease is occupational asthma, which can be caused by a range of agents.
- Asbestos is responsible for a large spectrum of respiratory disease, from asymptomatic to serious. These may be difficult to diagnose and the involvement of asbestos may not be clear.

The following two articles have been modified from an ERS School Course held in London in 2007 on the subject of clinical applications of pathology and imaging in respiratory disease. Original slides, webcast and material can be found at www.ers-education.org. Parts of the first text have been reproduced from [1], with permission from the publisher.

Environmental and occupational pulmonary diseases: pathology

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Educational aims

- To update and enhance understanding of occupational and environmental lung disease.
- To impart practical information about diagnosing these conditions.
- To help refine diagnostic accuracy and thus improve patient care.

Summary

Human lungs are exposed to an enormous range of environmental insults, many of which are work-related. Over 250 agents have been identified in the aetiology of occupational asthma, the most common work-related pulmonary ailment. Conversely, a single agent – asbestos – is responsible for a huge range of lung diseases, and is the only known cause of some diseases. Other common environmental lung diseases include pneumoconiosis and extrinsic allergic alveolitis. The pathogenesis of some of these diseases remains obscure and diagnosis may be difficult.

Occupational and environmental lung disease are discussed together because many respiratory hazards encountered in the workplace are also met by the general public. Thus, as well as direct exposure to asbestos at work, exposure may also be:

- indirect, as experienced by the families of asbestos workers
- paraoccupational, as experienced by those working alongside asbestos workers
- 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.

Pattern of work-related lung disease

The pattern of work-related respiratory disease in the UK as shown in table 1 is probably representative of that encountered in most industrialised countries.

Occupational asthma

Occupational asthma is the commonest cause of work-related respiratory disease in the UK (table 1). It occurs in many industries (table 2) and occupational factors have been identified

as contributing to asthma in ~2% of adult cases. Over 250 aetiological agents have been identified. In the UK, one-third are organic, one-third are chemical, 6% metallic and the rest miscellaneous. The commonest agents, in descending order, are isocyanates, flour and grain, laboratory animals, glutaraldehyde, solder or colophony (pine resin) and hardening agents.

Atopy appears to predispose to occupational asthma when the allergen is of high, but not 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 diisocyanate, which is a serious health problem in the manufacture of polyurethane. Similarly, platinum salts are such potent sensitising agents that nearly all those who work with them develop asthma. Asthma-provoking metals other than platinum include chromium, cobalt, nickel and vanadium, all of which are used in steel alloys. Other asthma-inducing factors encountered in industry include grain and flour dust, certain wood dusts, soldering fluxes containing colophony, epoxy resin hardeners such as phthalic anhydride, isocyanate-containing foams and paints, formaldehyde and the excreta of laboratory animals. Periodic outbreaks of asthma in Barcelona provide an example of environmental asthma, with the cause eventually attributed to the unloading of soya flour. Contaminated humidifiers may cause occupational asthma as well as humidifier fever and extrinsic allergic alveolitis [4]. Occupational asthma is pathologically identical to nonoccupational asthma.

Table 1 *Work-related respiratory disease in the UK*

Disease	Estimated annual number of cases
Occupational asthma	941
Nonmalignant 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	3267

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Table 2 *Agents that cause occupational asthma and examples of the occupations involved*

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 manufacture
Seafoods	Food processing
Gums	Carpet and drug manufacture
Low molecular weight agents (patients are not necessarily atopic)	
Isocyanates	Foam, plastic
Anhydrides	Plastic and epoxy resins
Wood dusts	Forestry, carpentry
Soldering fluxes	Electronics
Formaldehyde, glutaraldehyde	Histopathology, nursing
Amines	Shellac, lacquers
Dyes	Textiles
Acrylates	Adhesive application
Metals	Solderers, refiners
Drugs	Pharmaceutical work

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Byssinosis

Byssinosis is a further form of occupational asthma, 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. 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 being spun. Affected workers suffer more 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.

Asbestos-induced pleuropulmonary disease

Respiratory disease attributable to the inhalation of asbestos includes pleurisy (generally accompanied by an effusion), pleural fibrosis, pleural mesothelioma, asbestosis and pulmonary carcinoma (figure 1).

In contrast to asbestosis and asbestos-induced lung cancer, both of which generally require relatively high exposure levels, all pleural diseases attributable to asbestos are associated with relatively low asbestos burdens in the lung. Furthermore, it is very difficult to identify asbestos in pleural lesions themselves, despite these being attributable to asbestos inhalation.

Benign asbestos pleurisy and pleural effusion

An exudative pleurisy may develop within 10 years of first contact with asbestos and, therefore, is found in people currently working in the industry. The effusion may be asymptomatic or the patient may complain of pleuritic pain, sometimes accompanied by fever, leukocytosis and an elevated blood sedimentation rate. The effusion is usually small and blood-stained, giving rise to a suspicion of malignancy. It often resolves spontaneously, only to recur, perhaps on the other side. It may progress to diffuse pleural fibrosis requiring decortication. Asbestos-induced pleurisy is not thought to play a part in the development of pleural mesothelioma.

Asbestos-induced pleural fibrosis

Bilateral obliteration of the costophrenic angles is a common radiographic finding in healthy asbestos workers. It presumably reflects the organisation of previous asymptomatic effusions. Pleural fibrosis of nonspecific character is common in such workers, and in those suffering from asbestosis a diffuse but thin fibrous thickening of the visceral pleura is almost invariably present. Indeed, apart from the presence of asbestos in the lungs, this is one of the few pathological features that distinguishes asbestosis from idiopathic pulmonary fibrosis.

This thin fibrous thickening of the visceral pleura is of no clinical consequence but occasionally asbestos-exposed individuals develop extensive, thick fibrosis of the pleura in the absence of asbestosis and this may severely compromise expansion of the chest (figure 2). It may be bi- or unilateral. If bilateral, the resultant restrictive defect in lung function is responsible for incapacitating breathlessness. Mesothelioma may develop in patients with such restrictive pleural fibrosis but the tumour is thought to arise independently. Diffuse pleural fibrosis is diagnosed when the thickening is bilateral, >5 mm thick and affects >25% of the pleura. Although generally limited to the pleura, it occasionally extends into the chest wall and mediastinum.

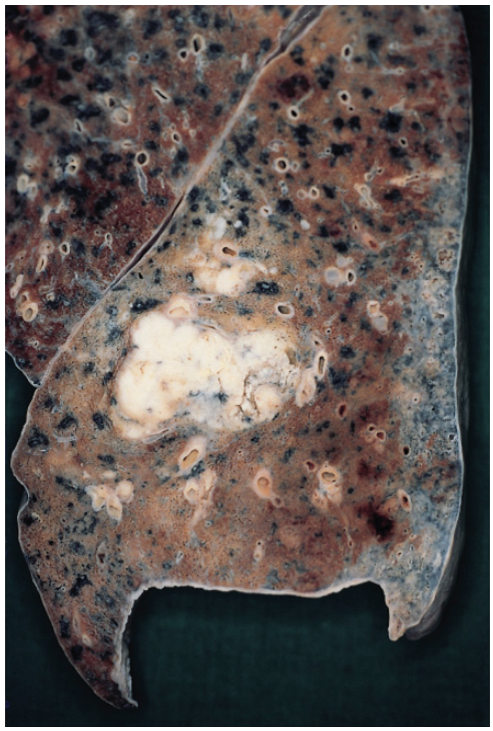

Figure 1
Asbestosis associated with carcinoma of the lung. The asbestosis has been highlighted by barium sulphate impregnation and is seen as a grey subpleural band to the right of the picture. Although the carcinoma has arisen in the same lobe as the asbestosis it has not obviously arisen in an area affected by asbestosis. Reproduced from [1], with permission from the publisher.

Blesovsky's disease (folded lung, rounded atelectasis)

Localised patches of pleural fibrosis may be important clinically, not for their functional effects, but because they may mimic a peripheral lung tumour radiographically. The contracture of the pleural scar draws the adjacent lung tissue to it, causing a localised area of collapse (figure 2). The bases of the lungs are particularly affected. The collapsed lung often appears to be folded upon itself and the resultant radiographic opacity has a comet's tail appearance. The condition is variously known as Blesovsky's disease, folded lung or rounded atelectasis. In 25% of cases the lesion is bilateral. There is often a history of asbestos exposure, but like the other forms of asbestos-induced pleural fibrosis, the condition is thought to play no part in the pathogenesis of mesothelioma.

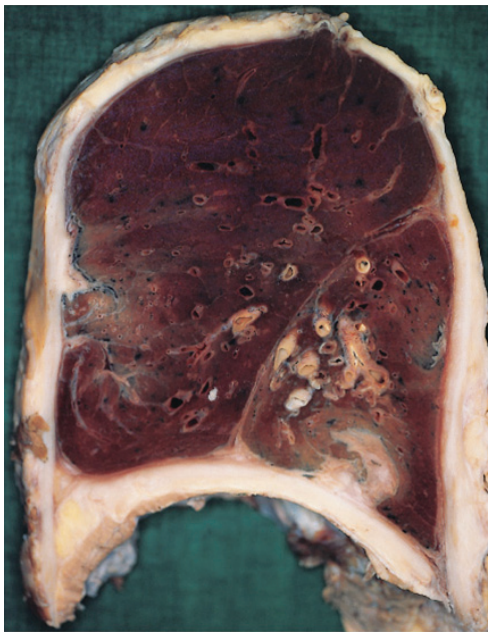

Figure 2
Thick fibrous thickening of the pleura in an asbestos worker. At the base of the lower lobe there is also a localised area of pleural thickening (Blesovsky's disease). Reproduced from [1], with permission from the publisher.

Pleural plaques

Pleural plaques are a further form of asbestos-induced pleural fibrosis, described separately because of their distinctive pathological appearance. Although they are occasionally found in people with no history of asbestos exposure, the association with asbestos is strong, based on both epidemiological evidence and the identification of asbestos in the underlying lung. Pleural plaques, therefore, provide strong evidence of asbestos exposure, which may be occupational or environmental. They occur after exposure to all types of asbestos, but anthophyllite is particularly potent. Plaques are common in areas where the soil is contaminated with asbestiform minerals, for example parts of Finland and Greece. The longer and heavier the exposure, the more extensive the plaques, but even slight exposure can be sufficient for plaque formation. Very few develop within 15 years of first exposure and most appear after 30 years. Post-mortem studies show that plaques are more common than can be appreciated from radiological examination in life. Pleural plaques are harmless and have no relationship to mesothelioma, or lung cancer, other than their association with asbestos.

Pathologically, plaques are localised raised areas that are generally multifocal and bilateral (figure 3a). They may occur on the visceral pleura or even the peritoneum but usually affect the parietal pleura, particularly in relation to the ribs and the central tendon of the diaphragm. They have an irregular outline, a smooth shiny pearly-grey surface and a low profile, typically about 5 mm in height: their other dimensions are very variable. Microscopically, plaques are hyaline, avascular and almost acellular (figure 3b). In a pleural biopsy, even a small number of spindle cells in a hyaline lesion should suggest the possibility of paucicellular hyaline mesothelioma rather than plaque. The hyaline collagen bundles have a characteristic pattern that is often likened to basket weave. Calcification is common. Inflammation is not found, except to a mild degree at the periphery.

Although the connection between asbestos and plaques is firmly established, the pathogenetic mechanism is obscure. Organisation of exudates probably underlies the other less distinctive forms of pleural fibrosis found in asbestos workers but it is difficult to envisage a special type of exudate that may give rise to plaques. Furthermore, the plaques are covered by an intact mesothelium and are not usually attended by adhesions. It has been suggested that the parietal pleura is particularly affected because it is abraded by asbestos fibres projecting through the visceral pleura, but no such projections have been identified. A further possibility derives from consideration of the lymphatic drainage of the pleural cavity, which is largely through the parietal pleura. Short asbestos fibres have been identified in the visceral pleura and it is likely that some reach the pleural cavity, whence their disposal would be by the stomata and lymphatics of the parietal pleura. Any fibres arrested by the ribs or the tendinous portion of the diaphragm would elicit submesothelial fibrosis at these sites. Ferruginous bodies are not usually seen in the plaques but they have been recorded there.

Mesothelioma

Mesotheliomas are malignant neoplasms that most commonly arise in the pleura but also develop in the peritoneum and occasionally in the pericardium or tunica vaginalis of the testis. The disease was very rare in the 19th and early 20th centuries but its incidence has been rising steadily and in industrialised countries mesothelioma now accounts for ~1% of all cancer deaths. Measures to curtail exposure to its principal cause, asbestos, were introduced and progressively strengthened in many countries in the latter half of the 20th century but such is the long latent interval between exposure and disease that these do not have an effect for several decades. The durability of asbestos is another factor hampering efforts to reduce the incidence of mesothelioma. It is calculated that numbers in the UK will triple between 1991 and 2020 and

only then decline. In contrast, there is already a decline in the incidence of mesothelioma in the USA where the use of amphibole asbestos was restricted as early as the 1960s.

1. Aetiology

Asbestos and similar fibrous substances are virtually the only recognised causes of mesothelioma. Smoking does not increase the risk of mesothelioma. Cases that can be attributed to causes such as radiation, chronic inflammation and scarring are exceptionally rare. However, there is evidence suggesting that simian virus 40 (SV40) promotes the development of mesothelioma, acting either independently or synergistically with asbestos. This virus contaminated monkey kidney cells used in the manufacture of early batches of poliomyelitis vaccine and may have reached man in this way. SV40 sequences are selectively expressed in many mesotheliomas, the development of which has been attributed to the ability of the sequences to inactivate the p53 and Rb tumour suppressor genes and promote the secretion of various growth factors. However, subsequent investigations have resulted in both supportive and contrary findings and the relationship of SV40 infection to the development of mesotheliomas remains uncertain.

Even after an exhaustive occupational history and the most detailed analysis, some mesotheliomas provide no evidence of asbestos exposure or other cause whatsoever. The proportion of such cases varies considerably, probably depending upon the degree of industrialisation, so that in a nonindustrialised country the low background incidence becomes important. In the UK and the USA, 10–20% of mesotheliomas appear to be unrelated to asbestos exposure. One group reported that asbestos bodies were identified in histological sections in 57% of mesothelioma cases, that the figure reached 83% when asbestos bodies were sought in lung digests by light microscopy and 89% when electron microscopy was used to identify coated and uncoated fibres in lung digests [5, 6].

Evidence that there is a low background of mesothelioma unrelated to asbestos derives from several sources:

- mortality trends in industrialised countries record an equal sex incidence in the early 20th century
- the subsequent increase in mesothelioma is largely confined to men
- mesothelioma in childhood is rare, but well established

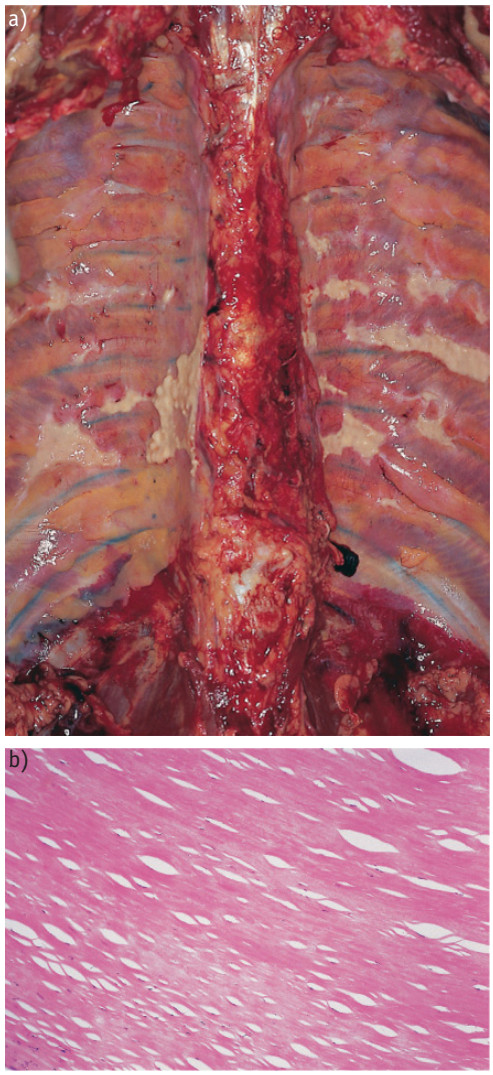

Figure 3

Pleural plaques. a) The eviscerated thoracic cavity showing pearly white and irregular plaques on the inner side of the chest wall. b) Microscopically, the plaques are practically acellular, consisting of hyaline collagen that has a 'basket-weave' pattern. They provide strong evidence of asbestos exposure. Reproduced from [1], with permission from the publisher.

- although rare, associations with possible causes such as radiotherapy and chronic infection are recorded.

2. Macroscopic features

Pleural mesothelioma is more common on the right than the left, with a ratio of 3:2. The reason for this is poorly understood but may depend upon differences in fibre burden, pleural area and chest wall movement on the two sides.

Asbestos fibres reaching the pleural cavity are concentrated in Kampmeier's foci and thoracoscopy has shown that mesothelioma first involves the parietal pleura where these foci are found, appearing there as multiple small grape-like nodules: involvement of the visceral pleura follows [7]. Progression of the tumour results in coalescence of the nodules to form plaques and, ultimately, a continuous sheet of tumour fusing the visceral and parietal pleura and obliterating the pleural space, except for occasional residual loculi

containing glairy fluid or blood. Areas of necrosis or haemorrhage and softer areas of mucoid consistency may be seen and occasionally the whole tumour appears gelatinous. In the late stage, tumour encases the lung as a layer of dense white tissue up to several cm thick, which extends into fissures and infiltrates the peripheral lung parenchyma so that at autopsy the lung has to be forcibly dissected from the chest wall. It is very rare for a mesothelioma to remain localised and form a solitary mass. A feature of mesothelioma that is often stressed is a supposed predeliction to infiltrate along biopsy tracks or surgical incisions, but this is a feature of all malignant tumours. Metastasis is late but at death may be widespread.

3. Microscopic features

Needle biopsy of the pleura is often disappointing and a firm diagnosis of mesothelioma is sometimes not possible until thoracoscopic or open biopsy, or even autopsy, is undertaken. Despite their epithelioid appearance, mesothelial cells are of mesodermal origin and their malignant counterparts display a wide diversity of differentiation. This diversity is reflected in the traditional histological classification of mesotheliomas as epithelioid, sarcomatoid (or fibrous) and biphasic (or mixed).

4. Differential histological diagnosis

The classic gross appearance of a pleural mesothelioma, that of a firm pale tumour encasing the lung, may be mimicked by extensive pleural fibrosis or by a peripheral carcinoma of the lung growing along the pleura: so-called pseudomesotheliomatous carcinoma of the lung. Each of the histological types of mesothelioma presents its own diagnostic problems. Distinctions must be drawn between:

- Biphasic mesothelioma and other biphasic tumours
- Epithelioid mesothelioma and adenocarcinoma
- Poorly differentiated epithelioid mesothelioma and poorly differentiated squamous cell carcinoma
- Epithelioid mesothelioma and reactive mesothelial hyperplasia
- Sarcomatoid mesothelioma and other spindle cell tumours
- Sarcomatoid mesothelioma and fibrosis.

Pneumoconiosis

The term pneumoconiosis 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 medico-legal 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 has 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" [8]. PARKES [9] recommends that cancer and asthma caused by mineral dust should also be excluded from the definition. Several morphological forms are described (table 3).

Extrinsic allergic alveolitis

Extrinsic allergic alveolitis is a chronic granulomatous disease of the lungs that results from the inhalation of any of a wide variety of organic substances capable of acting as a foreign antigen and triggering a local hypersensitivity reaction. Atopy is not a prerequisite. Anyone may develop this disease but certain alleles of the major histocompatibility complex appear to increase genetic susceptibility. Conversely,

Table 3 *Pulmonary reactions to mineral dust*

Pulmonary reaction	*Examples*
Macrophage accumulation with a little reticulin deposition	*Anthracosis* *Siderosis* *Stannosis* *Baritosis* *Coal macules*
Nodular or massive fibrosis	*Silicosis* *Mixed dust* *Coal nodules*
Diffuse fibrosis	*Asbestosis* *Hard-metal disease*
Epithelioid and giant cell granulomas	*Berylliosis*
Alveolar lipoproteinosis *COPD*	*'Acute' silicosis* *Various dusts*

smoking appears to confer protection as the disease is unusual in smokers. Farmers' lung is the archetypal example but there are numerous different circumstances and allergens, frequently designated by exotic names, all with identical pathology. A more meaningful division is into those of sudden or gradual onset. Thus, the pigeon fancier with a large flock is likely to relate the onset of his symptoms to mucking out his loft a few hours previously, whereas the owner of a single budgerigar will probably not suspect that her gradually increasing breathlessness is attributable to the pet she has succoured without ill effect for many years. In each case the allergen consists of avian protein in the birds' droppings.

Histological appearances

Lung biopsies taken during the first few months of extrinsic allergic alveolitis show poorly formed non-necrotising granulomas. These are generally smaller and less frequent than those seen in sarcoidosis, and are accompanied by widespread thickening of the alveolar walls by a diffuse lymphocytic infiltrate (figure 4). No fungal elements are found, but small fragments of foreign material may be present. Schaumann bodies may also be observed. Isolated giant cells with cytoplasmic clefts are frequently observed: these are suggestive of the diagnosis but not specific. In contrast to sarcoidosis, the hilar lymph nodes are unaffected. The diffuse background interstitial inflammation is another feature distinguishing the condition from sarcoidosis as it is only seen in the latter if biopsy is undertaken very early in the course of the disease. A further difference is the presence of knots of granulation tissue within alveoli and respiratory bronchioles, which is evidence of organisation of luminal exudates and is responsible for the accumulation of lipid-laden macrophages which may also be evident.

Granulomas tend to resolve with time but the diagnosis may still be suggested by the inflammatory process being peribronchiolar; these airways being the portal of entry of the aetiological agent (figure 5). The peribronchiolar distribution of the inflammation also helps to distinguish extrinsic allergic alveolitis from non-specific interstitial pneumonia and lymphoid interstitial pneumonia. The latter is a condition that may also show poorly formed granulomas but it is characterised by a more diffuse, intense infiltrate that is seldom accompanied by any appreciable degree of fibrosis.

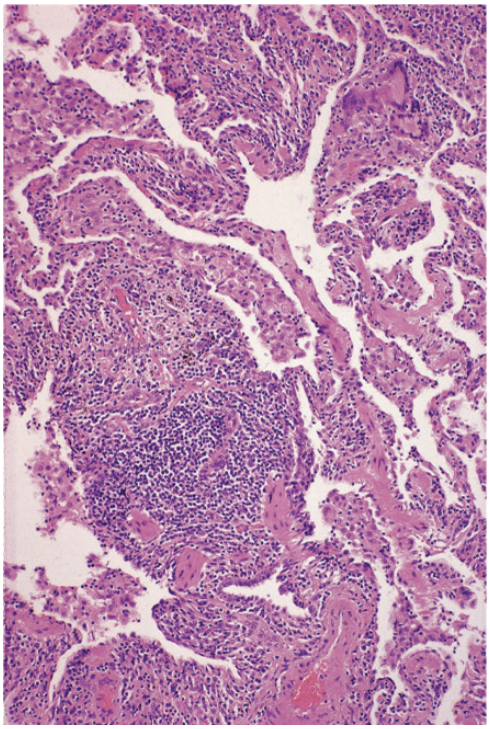

Figure 4
Extrinsic allergic alveolitis. A poorly formed non-necrotising giant cell granuloma (top right) is associated with widespread interstitial pneumonitis. Reproduced from [1], with permission from the publisher.

Although the histological appearances are characteristic and permit a confident pathological diagnosis, exhaustive environmental and serological investigations quite commonly fail to identify the cause.

Granulomas resolve within about 6 months, unless there is further exposure, but the inflammation frequently progresses to irreversible scarring. In advanced cases, the lungs show end-stage features such as honeycombing. The upper lobes are affected more than the bases, although in acute cases chest radiographs show a basal preponderance. The fibrosis is bronchiolocentric in distribution, rather than subpleural and paraseptal as in usual interstitial pneumonia.

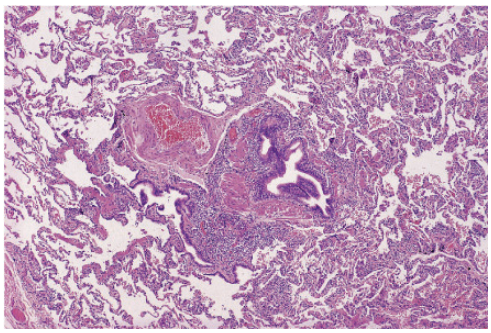

Figure 5
In extrinsic allergic alveolitis the inlammatory infiltrate is maximal around bronchioles. Reproduced from [1], with permission from the publisher.

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