Spencer's Pathology of the Lung

Fifth Edition

EDITOR

P. S. Hasleton, M.D.

Consultant Histopathologist
Wythenshawe Hospital
Honorary Reader in Histopathology
University of Manchester
Manchester, United Kingdom

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Chapter 15

Occupational Lung Disease

A. R. Gibbs

Zenker first coined the term *pneumoconiosis* for lung disease caused by inhalation of dust. Today many different forms of pneumoconioses are known, each caused by different dusts, fumes, smokes, vapors, or gases. The definition of pneumoconiosis varies; some authors restricting it to the nonneoplastic reaction of the lungs to inhaled minerals or organic dusts excluding asthma, bronchitis, and emphysema,[1] whereas others, including myself, use the term more widely to encompass any pulmonary reaction to inhaled particles from an industrial source. The exposure may not necessarily be by direct exposure to a particular mineral within an industry but can be from neighborhood or domestic (paraoccupational) exposures.

The damage caused by inhalation of different types of mineral particles varies according to the cumulative exposure, size, shape, surface properties, and durability of the particles. It should be realized that minerals given the same name but originating from different locations and processes may vary in physicochemical properties and thus biologic activity. This is particularly important with regard to asbestos and talc.

Immunologic processes are also involved to a variable extent in the response of the lungs to mineral exposures. They are important, for example, in chronic berylliosis and extrinsic allergic alveolitis. Also individual variability exists in deposition and retention of particles and the presence of other diseases (e.g., rheumatoid disease) can modify the response to the deposited particles.

Clearance mechanisms are important. It has been estimated that a nonsmoking city dweller inhales about 1 g of particulate matter each year, about half of which is deposited in the respiratory tract. Without efficient clearance mechanisms the lungs of an individual would "silt up" at a young age. Smokers inhale even greater quantities of particulate material—about 150 g/y from 20 cigarettes per day.[2]

DEPOSITION AND CLEARANCE OF PARTICLES

Airborne particles possess a range of shapes and may exist individually or as aggregates and this will affect their deposition in the human respiratory tract. Particles that are near to a sphere are designated compact and those that have a length-to-breadth ratio of 3:1 or greater as fibers. Some authorities require a minimum length of 5μm to designate a particle fibrous. Particles are deposited in the respiratory tract according to their size, density, shape and aerodynamic properties and by the volume of each inspiration.[3–5] Those in the size range of 1 to 5μm aerodynamic equivalent diameter (AED) are the most likely to deposit in the lung parenchyma. Particles of extreme shape such as fibers and plates and particles of very low density show a greater tendency to deposit in the airway walls. The likelihood of fiber deposition within the lung depends mainly on the diameter because those with diameters below 3μm align axially within the air stream.[6] The majority of fibers that deposit in the lung have diameters less than 3μm but may exceed 200μm in length. Short fibers (<5μm in length) reach the lung parenchyma more readily than long fibers (>5μm in length) because the latter exhibit greater aerodynamic drag, which increases impaction and sedimentation in the larger airways. Aggregation of particles effectively increases their AED, which will reduce deposition within the respiratory tract. Particle size also influences the toxicity of a mineral.

The pattern and rate of breathing also influence particle deposition. Because the internal volume of the airways increases with successive generations, the net effect of normal breathing at the level of the respiratory bronchioles is that the forward air flow virtually ceases. However, with heavy exertion the flow velocity increases and this increases the deposition of particles—in the upper airways by impaction and within the smaller airways by sedimentation and

diffusion.[7] The nose is more efficient than the mouth at removing particles from the air. All particles greater than 5μm in diameter are removed from the air by impaction in the nose. Mouth breathing increases the number of particles that can reach the lower respiratory tract.

Clearance of particles from the lung depends on a number of factors including the anatomic site of deposition, particle solubility, particle size and shape, the efficiency of the phagocytic system, the presence of fibrosis, and cigarette smoking. Soluble particles dissolve in the lung secretions, but insoluble particles within the acinus either lie free or within macrophages and may then move to the ciliated epithelium whereby they can be cleared by the mucociliary apparatus. Some particles within the acinus, however, may penetrate epithelial membranes and enter the interstitum,[8–10] which is more likely to lead to fibrosis. This is particularly likely to happen when the macrophage system becomes overloaded by heavy dust burdens. The particles located within the interstitium may gain access to the vascular and lymphatic systems and may then be carried to other organs, the visceral pleura, or regional lymph nodes.[11] This is reflected in the black outlining of subpleural lymphatic pathways observed in the lungs of urban dwellers and coal workers. There is a greater retention of large compared to small compact and fibrous particles within the lungs. Also the presence of fibrosis within a lung interferes with compact and fibrous particle clearance. Tobacco smoking impedes particle clearance by interfering with the mucociliary action and possibly macrophage function.[12,13] Substantial evidence indicates that for many lung diseases caused by mineral particle exposure, it is the retained mineral particle burden that is important in pathogenesis.

IN VITRO AND IN VIVO STUDIES

Experimental studies provide useful information concerning the effects of mineral exposures on the lung and pleura.[14] However, when considering the value of in vitro and in vivo experiments with mineral particles in relation to the likelihood of developing human disease, certain limitations and criticisms should be kept in mind.[15] Experimental procedures use artificial "pure" and heavy exposures to a particular mineral, often causing overload of the macrophage system in animals. It should be realized that in such heavy doses even relatively inert dusts can cause pulmonary changes. Also the experiments often utilize relatively short high exposures that do not reflect the lower long-term exposures that occur in human beings.

Intratracheal exposures result in a very uneven deposition of mineral particles quite unlike that occurring in the normal state. Intrapleural and intraperitoneal procedures bypass the normal defense mechanisms and deliver considerably higher doses of a mineral to the mesothelium than would occur in life. Mesotheliomas might occur in serosal membranes when a fibrous particle is directly implanted, but this is irrelevant if the particle cannot normally penetrate the membrane.

Inhalation studies are the most appropriate, but great care has to be taken in conducting these; the mineral used should be well characterized and sized, dosage should be appropriate and simulate long-term human exposures, and appropriate controls should be used. Unfortunately, well-conducted inhalation studies are extremely expensive and technically demanding.

Interpretation of in vitro and in vivo data on the pathogenicity of a specific mineral should be done in conjunction with the human epidemiologic, pathologic, and pulmonary mineral burden evidence. It is important that unjustified conclusions should not be made about human consequences of exposure to a mineral only from in vitro and in vivo studies. They should be regarded as screening procedures.

PATTERNS OF DISEASE

Mineral exposures can produce almost the whole gamut of pulmonary pathology. Table 15-1 gives examples.[16] A pathologist confronted by almost any form of pulmonary disease should consider mineral exposures in the list of etiologies. Of course, some types of pulmonary pathology are more closely associated with mineral exposures than others. When a subject develops a pulmonary disease a good and complete occupational history from commencement of work is essential because the pathologic sequelae may not develop until several decades after exposure (latency). The occupational histories of relatives may also need to be ascertained because some diseases (e.g., berylliosis and mesothelioma) may result from indirect paraoccupational exposures. Also it may be necessary to ask about hobbies and pastimes because these can result sometimes in exposure to hazardous minerals.

TABLE 15-1
Types of Pathologic Reaction That May Occur with Various Minerals

Compartment	Type of Reaction	Examples
Airways	Asthma	Isocyanates, metals
	Bronchiolitis	nitrogen dioxide
Airways—parenchyma	Centrilobular dust accumulations	
	Slight fibrosis	Coal, kaolin, talc, mica
	Moderate stellate fibrosis	Silica plus silicates or iron
	Marked circumscribed fibrosis	Silica
	Diffuse interstitial fibrosis	Asbestos, kaolin, talc
	Extrinsic allergic alveolitis	Farmer's lung
	Sarcoid-like	Beryllium
Parenchyma	Diffuse alveolar damage	Toxic fumes
	DIP	Asbestos, silica, silicates
	GIP	Hard metal
	Pulmonary alveolar proteinosis	Silica
	Emphysema	Coal, cadmium
Diffuse—random	PMF	Coal, kaolin, talc
	Carcinoma	Asbestos, nickel, arsenic
	Infection	Tubercle in silicosis
Pleura	Benign effusion	Asbestos
	Plaques	Asbestos, talc, wollastonite
	Diffuse fibrosis	Asbestos
	Mesothelioma	Asbestos

DIP = desquamative interstitial pneumonia; GIP = giant cell interstitial pneumonia; PMF = progressive massive fibrosis

GENERAL APPROACH TO INTERPRETATION OF PATHOLOGIC SPECIMENS

Pneumoconioses have important connotations medicolegally and a careful macroscopic examination and recording of lesions from specimens of lung and pleura is essential if the pathologist wishes to avoid considerable difficulties and potential embarassments later on. Often correlations between pathology and radiology and lung function tests will be necessary to correctly diagnose and attribute disability or death to a mineral exposure. It is wise to retain lung tissue from such cases for a considerable period of time, *if possible*, because sometimes issues are raised that were not initially considered.

Adequate sampling for histologic examination should be performed. It is important to take samples from many areas of the lung and to include background lung as well as tumor when considering an occupational cause for tumors. It is necessary to sample from areas away from the tumor and preferably from the other lung to evaluate fibrosis, when tumor is present. At least one block should be taken from each lobe to include the most abnormal, normal, and intermediate areas and at least one block from the major airways, pleura, and lymph nodes. Table 15-2 is a suggested schema for evaluating and recording macroscopic findings of the lungs and pleura.[17]

The microscopic assessment follows the usual procedure for any pulmonary disease, namely, first of all a low-power examination to decide which anatomic compartment the disease is in followed by higher-power examination to characterize the nature of the cellular and any particulate component.

TABLE 15-2
Macroscopic Recording of Lung Diseases Associated with Occupational Exposures

Primary dust foci
Average size (grade 0–3)
1 = 1–3 mm; 2 = 4–5 mm; 3 = > 5 mm
Profusion (grade 0–3)
Proportion of lobules involved:
1 = <33%; 2 = 33–66%; 3 = >66%
Secondary dust foci
Number of stellate foci according to size
Number of round foci according to size
Size of PMF lesion(s)
Emphysema
Type
Centriacinar, panacinar, irregular
Severity (grade 0–3)
1 = 1–3 mm; 2 = 4–5 mm; 3 = >5 mm
Profusion (grade 0–3
Proportion of lobules involved (similar to dust foci)
Interstitial fibrosis
Severity (grade 0–4)—microscopic
Extent (grade 0–3)
1 = up to 10% of the lung involved
2 = involvement of 10–25%
3 = involvement of >25%

PMF = progressive massive fibrosis

SOURCE: Modified from Gibbs and Seal,[17] courtesy of the editor of *Journal of Clinical Pathology.*

In some cases the pathologic examination will not provide the complete answer to diagnosis and attribution and mineralogic examination of lung tissue will be advantageous.[18] This has been used most extensively in asbestos-related diseases but it can also provide useful information in assessing silicate- and metal-induced diseases.

SILICA

The word silica is derived from the Latin noun *silex*, a flint, a stone that contains silica (silicon dioxide). Pneumoconiosis caused by the inhalation of dusts containing a large proportion of silica is called silicosis and it is a disease as old as the history of man himself. Until the discovery of the tubercle bacillus by Koch in 1882, silicosis was confused with tuberculosis, a disease to which it predisposes and with which it is often associated. Because silica and silicates are the most common constituents of the earth's crust, dusts containing them constitute an important occupational hazard in mining and innumerable industrial processes. Historical evidence of pneumoconiosis, including silicosis, has been described in Egyptian mummies,[19] Bohemian miners in the sixteenth century,[20] and stone cutters in the eighteenth century.[21] With the coming of the Industrial Revolution many new trades developed in the United Kingdom; the danger of occupational dust inhalation was not appreciated and the incidence of silicosis rose. It was during this period that occupational diseases first began to be studied seriously. In 1831, Thackrah began a study of longevity of British workmen in dusty trades and found that sandstone workers died on average before the age of 40 years.[22] The first use of the term *silicosis* has been credited to Visconti in 1870.[23] The South African authorities and investigators provided several important reports on the prevalence of disease in gold miners and inaugurated compensation schemes and improved ventilation systems at the mines in the first 20 years of the twentieth century.[24] Just after the commencement of the twentieth century sandblasting with silica was introduced, which resulted in many cases of a particularly fulminating form of silicosis.[25] In the United States at Gauley Bridge, in the early 1930s, silicosis affected a large number of tunnelers.[26] These cases led to the establishment of occupational dust standards. Regulations have become increasingly tighter in developed countries over the past 50 years. Cases of silicosis are still observed although they are uncommon. In underdeveloped countries the disease is still a significant problem.

The effect of silica inhalation on the lung depends on the dose and duration of exposure, the size of the particles, the mineral form (polymorph), the presence of associated minerals, individual variability, and presence of mycobacterial infection. Relatively high exposures to finely particulate silica dust, such as has occurred in sandblasters and silica flour workers, can lead to the acute form of silicosis (silicoproteinosis), whereas prolonged exposure to lower doses can lead to the typical chronic form of silicosis. Silica exists naturally in crystalline and amorphous forms. Amorphous forms include opal and flint, the former hydrated form being found in diatomaceous earth (kieselguhr). These are relatively nonfibrogenic unless heated to high temperatures when the crystalline forms, cristobalite and tridymite, are produced. There are several natural crystalline forms, which include *α* quartz, the most common form and which is usually meant by the terms silica and quartz. The others are tridymite, cristobalite, stishovite, and coesite. The latter two forms are very rare. Tridymite and cristobalite are formed when quartz is subjected to high temperatures, for example, in refractories; experimentally it

appears to be more fibrogenic than quartz. Virtually all human exposures to silica are associated with varying amounts of other minerals, particularly silicates, and these will modify the response to silica depending on their concentration and their own mineralogic properties. When the effects of silica and other minerals are considered to be roughly in balance, the response is referred to as *mixed dust fibrosis*. When the effect of silica is predominant, the response is referred to as *silicosis*. There is also individual variation in response to these exposures, most noticeable in those with the rheumatoid diathesis (Caplan's syndrome). Each form of silicosis predisposes to mycobacterial infection and the risk is increased also in workers exposed to silica but without radiographic abnormalities. In vitro and in vivo studies have shown that the presence of silica enhances the growth and virulence of mycobacteria.[27,28]

Sources of Exposure

There are many potential occupational sources of exposure to dusts containing a high proportion of silica and those that are given in Table 15-3 are by no means comprehensive.

Clinical Features

Generally chronic (classical or nodular) silicosis develops after more than 20 years of exposure; uncommonly cases develop within 5 to 10 years of exposure when the term *accelerated silicosis* is used. The pathology is similar in both forms. Symptoms or signs are not usually present in the simple form but dyspnea may occur in the complicated form, which progresses with the extent of the radiologic opacities. Radiographic and functional abnormalities correlate with cumulative exposure to respirable silica.[29,30] Lesions may progress after cessation of exposure and the subject may present clinically several years after exposure has ceased. *Acute silicosis* (silico lipoproteinosis) develops within 3 years of heavy exposure, is usually rapidly fatal, and shows a different pathology to the other forms.

TABLE 15-3
Industries with Possible Silica Exposure

Mining and milling of nearly all metals and nonmetals
Quarrying of granite, sandstone, and slate
Granite and stone industries
Iron and steel foundries
Manufacture of glass, pottery, and ceramics
Manufacture of refractories
Manufacture of abrasive powders
Enameling
Boiler scaling
Steel manufacture
Rubber industry
Processing of diatomaceous earth

Chronic (Nodular, Classical) Silicosis

Macroscopically, the lungs in chronic silicosis reveal firm, grayish black, sometimes calcified, well-circumscribed, whorled nodules that are most prevalent in the upper zones. They vary from a few millimeters in diameter to large massive [progressive massive fibrosis (PMF)] lesions that can occupy large areas of the lung and can extend across fissures into the adjacent lobe (Fig. 15-1). The PMF lesions are most frequently observed in the upper lobes and when present are usually bilateral. The centers of the smaller nodules and the massive lesions can cavitate and may contain grayish black fluid. This cavitation has usually resulted from ischemic necrosis but sometimes it has been caused by mycobacterial infection. In the latter case, the cavities often contain gray friable material. If the massive lesions are carefully examined, they are made up of apparently fused, individual hard nodules, so-called conglomeration. This contrasts with the massive lesions seen in the majority of cases of coal worker's pneumoconiosis and silicatoses, which are diffuse and soft. In contrast to coal worker's pneumoconiosis, focal emphysema is not a feature of silicosis. The pleural surfaces frequently show firm fibrous adhesions to the chest wall and there may be areas of pleural thickening. In the earliest stages of the disease the nodules will be observed in the subpleural tissues and as the disease progresses they will be seen in the remainder of the parenchyma. The hilar lymph nodes typically are enlarged and contain whorled, hard, often calcified nodules (Fig. 15-2) which is responsible for the "eggshell" calcification often present in chest radiographs. The changes in the lymph nodes develop before those in the lung and if nodules are absent from the lung the diagnosis of silicosis should not be made.

Microscopically, the well-developed silicotic nodule, which is the hallmark of exposure to dusts with a high percentage of silica, consists of concentric layers of hyaline fibrous tissue at its center with a peripheral zone of dust-laden macrophages, fibroblasts, and chronic inflammatory cells of variable width, which extends out irregularly into the adjacent interstitial tissues[31] (Figs. 15-3 and 15-4). The center of the nodule can exhibit necrosis and calcifi-

FIGURE 15-1
Gough-Wentworth whole lung section from a North Wales slate worker shows numerous silicotic nodules with an area of progressive massive fibrosis formed by conglomeration of nodules in the upper lobe.

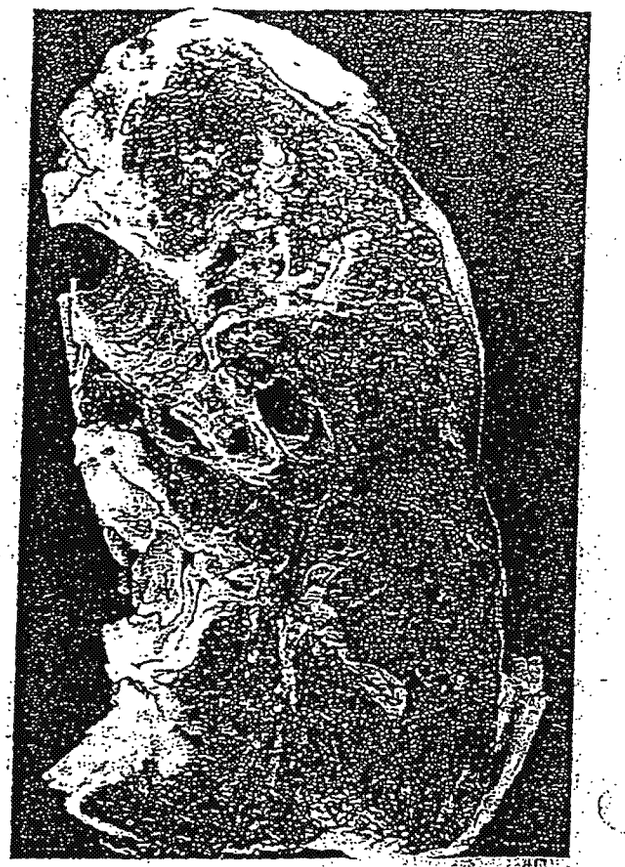

FIGURE 15-2
The lung of a stonemason shows enlarged hilar nodes with gray whorled nodules.

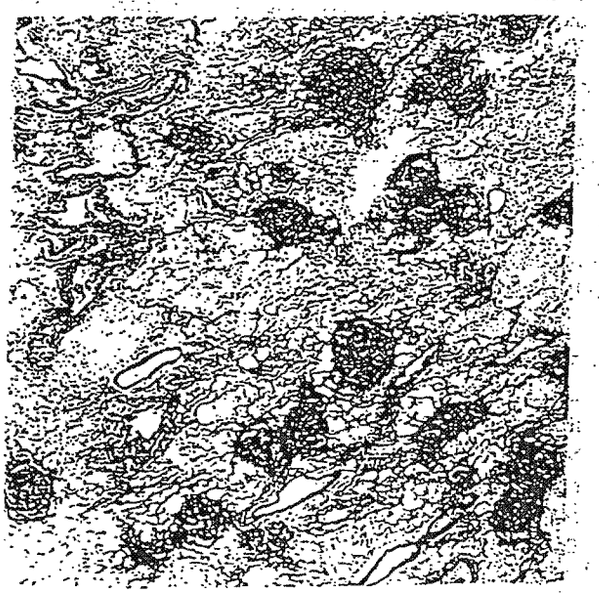

FIGURE 15-3
Numerous rounded, well-demarcated nodules in the lung of a North Wales slate worker. (Low power.)

cation. The necrosis is usually a consequence of ischemia from the formation of nodules obliterating pulmonary arterioles and perivascular lymphatics. Even so, whenever conspicuous necrosis is seen, even in the absence of granulomas, direct staining and culture for acid-fast bacilli should be performed to exclude mycobacterial infection.

The evolution of these silicotic nodules has been traced in animals and man. The earliest lesion consists of collections of free dust particles and dust-containing macrophages situated in the alveoli and interstitial tissues around the respiratory bronchioles, alveolar ducts, septa, and beneath the pleura. This is followed by the development of reticulin and collagen fibers, at first irregularly, and then at the

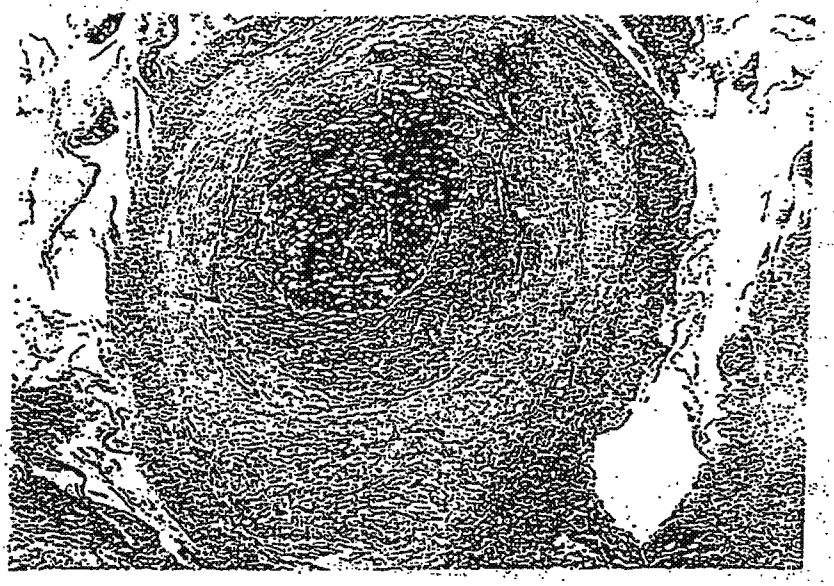

FIGURE 15-4
A silicotic nodule shows central necrosis with calcification, an intermediate zone of circumferentially arranged collagen, and a peripheral zone of dust-laden macrophages intermingled with inflammatory cells. (Low power.)

center of the lesions (Fig. 15-5). With progression the central zone takes on a concentric laminar arrangement and the dust-containing macrophages orient peripherally. This leads to obliteration of the bronchiolar and vascular architecture. Often nodules at different stages can be visualized in the same lung. Under polarized light the mineral particles at the centers of the nodules exhibit dull birefringence (quartz), whereas those in the peripheral zone exhibit strong birefringence (silicates and quartz). From the above description it will be appreciated that silicotic lesions are much more fibrous than those seen in coal worker's pneumoconiosis.

INTERSTITIAL FIBROSIS

On microscopic examination of lungs of subjects exposed to silica and silicates it is not uncommon to find foci of interstitial fibrosis in addition to the typical silicotic nodules. Occasionally the interstitial fibrosis is sufficiently severe to be associated with honeycombing. The precise contributions of silica and silicates to these lesions have not been clarified.

Rheumatoid Pneumoconiosis

In subjects with the rheumatoid diathesis the nodules may develop more quickly and become large and

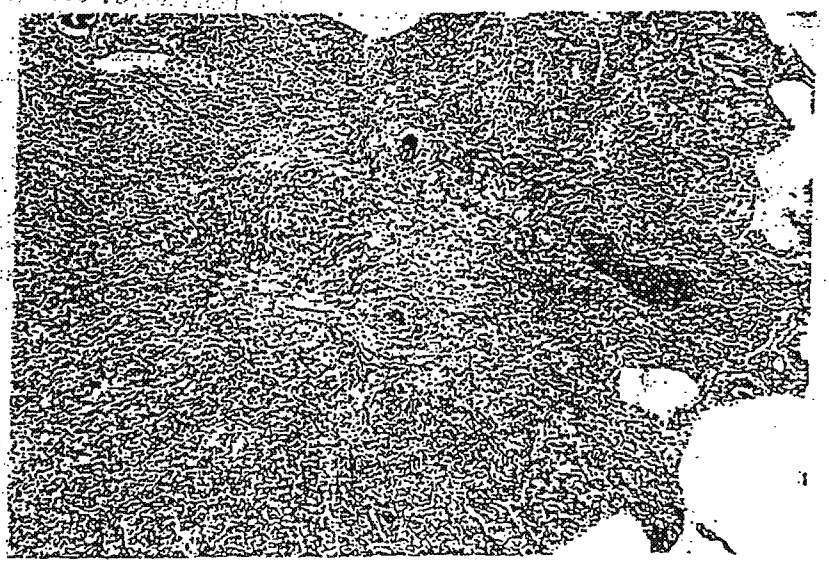

FIGURE 15-5
An "early" silicotic nodule in a North Wales slate worker shows a large collection of dust-laden macrophages and inflammatory cells with fibrosis at the center. (Low power.)

set within a background of relatively sparse small nodules, as they do in the Caplan form of coal worker's pneumoconiosis.[32] This has been described in association with silica exposures on rare occasions.

Interestingly, it has been claimed that there is an increased incidence and prevalence of rheumatoid arthritis, systemic lupus erythematosus, and scleroderma among workers exposed to silica, but not necessarily in the presence of silicosis, possibly due to the immunologic abnormalities set off by the exposure.[33,34] Others have not found this to be so.

Pathogenesis

In vitro and in vivo studies have shown that the toxicity of silica and its polymorphs depends on particle size and surface properties.[35] As the particle size distribution diminishes the cytotoxicity increases. The crystallinity of the particle's surface reflects the silanol and ionized silanol groups; the former determine mineral–cell attachment and the latter determines the interaction. The presence of trace metals, such as iron and aluminium, within the silica particle can modify the surface interaction by blocking the ionized silanol groups, which results in a lower fibrotic response. A key event is the uptake and interaction between the silica particles and macrophages, which causes damage to lysosomal membranes. This causes release of chemical attractants, which increase macrophage production and release. Death of some of the macrophages causes release of the silica particles that are then rephagocytosed by more macrophages. Some of the macrophages, however, will survive and carry the particles to other parts of the lung. There is evidence that polymorph neutrophils are also involved in the inflammatory process and that there is direct damage to type 1 pneumocytes in the centrilobular location in the early phase.[36] Macrophages containing quartz are found in the bronchoalveolar lavage fluids of silicotics and the percentage increases with duration of exposure.[37] Macrophages and neutrophils damaged by silica can release oxidants, which can result in degradation of connective tissue components of the lung and epithelial damage.[38] The macrophages can release factors, such as interleukin-1, which stimulates helper thymus-derived lymphocytes and fibroblast growth factors, which may lead to fibrosis.[39] The specific roles of these various factors and how they interact are still being elucidated.

SILICOSIS AND LUNG CANCER

There has been considerable debate for several years about the carcinogenic potential of crystalline silica.[40,41] Experimental studies have shown carcinogenicity in the rat but not the hamster or mouse[42] and this has been linked to fibrogenesis. Human studies have provided conflicting results and have been difficult to interpret because of confounding factors such as tobacco usage, radon exposure, and other industrial carcinogens that have not been adequately considered. A recent review of the subject concluded that lung cancer should not be classified as an occupational disease linked to silica exposure.[43]

Acute Silicosis (Silicoproteinosis)

This pattern of reaction occurs in association with high-dose exposures to finely particulate crystalline silica and has been described in sandblasters, tunnelers, and silica flour workers. In contrast to the other forms of silica reaction it can develop relatively rapidly over a few years. Clinically there is breathlessness and the chest radiograph resembles that of edema.

It is characterized by filling of the alveolar spaces with granular, eosinophilic material that stains positively with the periodic acid–Schiff (PAS) reaction and is also rich in lipid (Fig. 15-6). There is hyperplasia and metaplasia of the type II pneumocytes and an excess of these cells has been found on bronchoalveolar lavage.[44] It is similar to idiopathic lipoproteinosis but tends to show more interstitial inflammation and fibrosis, which is said to be a useful differential diagnostic feature. Well-developed silicotic nodules are usually absent although there may be focal collections of dust-laden macrophages with slight amounts of central fibrosis present. Polarization often, but not always, shows large numbers of birefringent particles. Mineral analysis of the lung tissue can be helpful in determining the etiology of this type of pathologic reaction.[45]

A similar condition has been produced in animals by inhalation of large amounts of quartz, tridymite, and cristobalite particles over short periods of time,[46,47] which damages and activates the type II pneumocytes causing an excess release of laminated bodies containing phospholipid, which accumulates in the alveolar spaces. This is followed by type II pneumocyte hyperplasia and further release of phospholipid. There is also evidence of impaired phagocytosis and clearance of the lipid material and particulate matter.[48]

Mixed Dust Fibrosis

This term was coined to imply concomitant exposur to silica in combination with less fibrogenic dusts such as iron oxides, carbon, kaolin, and mica.[49,50]

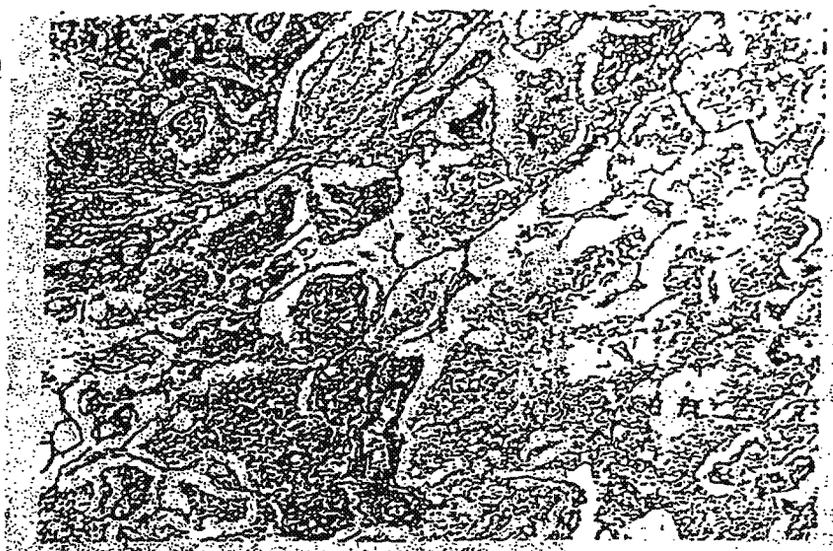

FIGURE 15-6
Acute silicoproteinosis shows a granular acellular intraalveolar exudate. (Low power.)

Pathologic descriptions have emphasized the presence of the stellate nodule with a "medusa head" configuration and on chest radiographs typically there are irregular opacities. These lesions usually predominate when the silica content is less than 10 percent. In some ways it is an artificial distinction because these lesions are frequently found alongside typical silicotic nodules and virtually all exposures to silica are associated with exposures to other minerals. Typical occupations where these lesions have been described include hematite workers, foundry workers, arc welders, china stone workers, and a small proportion of coal workers.

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Microscopically the lesions are typically stellate, firm, and their color varies according to the dusts present—reddish black in hematite miners, grayish white in china stone workers, and grayish black in coal workers. The lesions are most prevalent in the upper zones. Microscopically the typical mixed dust fibrotic nodule contains a central hyalinized collagen zone with a peripheral zone composed of radially and linearly arranged collagen and reticulin fibers intermingled with dust-laden macrophages (Fig. 15-7).

SILICATES

The nonfibrous silicates are a large group of minerals that are widespread and have an extensive range of industrial uses. Pulmonary disease has been associated with exposure to these minerals in a number of different industries.[50] They are less fibrogenic than silica and asbestos and pulmonary disease has been observed only after heavy prolonged exposures. The clinicopathologic features of these pneumoconioses show many similarities.

Kaolin Pneumoconiosis

Kaolin or china clay was discovered in a hill of extruded granite in Cornwall in Great Britain in 1750 by William Cuckworthy. It has been used in the United Kingdom and abroad for the manufacture of porcelain, as a filler and coating for paper, and in the rubber, plastics, paint, and fertilizer industries. It has also been exploited from deposits in Devon and from sedimentary deposits in Georgia and South Carolina

FIGURE 15-7
Mixed dust fibrotic nodules with stellate margins and central collagenization superimposed on simple macular lesions of coal worker's pneumoconiosis associated with emphysema. (Low power.)

in the United States. To a lesser extent it has also been produced in Australia, Brazil, France, Spain, and Germany.

During the commercial preparation and purification of china clay the granite, mica, and quartz are allowed to sediment out, the lighter kaolin particles being carried away in suspension. Nowadays, the kaolin is then allowed to settle and dry out using filter presses and mechanized drying plants. Formerly open kilns and the transfer of the dry material into storage linhays, wagons, or bags was accomplished by hand. After drying, the process was dusty but since 1970 the dust levels have been dramatically reduced.[51] After refining, the main constituent of the material is kaolinite and there may be up to 10 percent mica but quartz is less than 1 percent.

Several radiologic surveys of workers from this industry in Cornwall[52–54] and Georgia[55,56] have shown a pneumoconiosis generally characterized by small rounded opacities but occasionally PMF. Pneumoconiosis is generally seen in the millers, baggers, and loaders, where the dust is dry. Exposures after 1971 are not considered likely to lead to pneumoconiosis.

In some of the previously reported cases of kaolin pneumoconiosis it has been suggested that quartz was responsible. In the past some of the china clay workers had also worked with china stone and in these subjects pathologic examination of the lungs revealed silicotic and mixed dust fibrotic nodules. However, there are cases of pneumoconiosis that develop from exposure to kaolin without quartz—the typical china clay workers' exposure—and in these the pathology shows differences.

PATHOLOGY

On gross examination the lungs show gray, soft stellate lesions between 2 and 7 mm in diameter. Rarely massive lesions may be seen and these are diffuse soft and easily cut (Fig. 15-8). These massive lesions may cavitate. Sometimes fine honeycombing impregnated by gray dust is observed.[57] Microscopically, masses of dust-laden particles are first observed around the respiratory bronchioles but with increasing size they extend along the alveolar ducts and the interstitium of the adjacent alveoli (Figs. 15-9 and 15-10). Lesions from adjacent lobules may link up to give diffuse interstitial collections and fine fibrosis. The particles are strongly birefringent on polarization. Ferruginous bodies, formed on the platy particles, may be present but usually are not conspicuous. The massive lesions consist of masses of dust-laden particles mixed with randomly arranged collagen fibers. Mineral analysis of the lung tissue from sub-

FIGURE 15-8
The lung of a Cornish china clay worker shows a cavitated grayish white progressive massive fibrosis lesion in the upper part of the lower lobe and background stellate simple lesions.

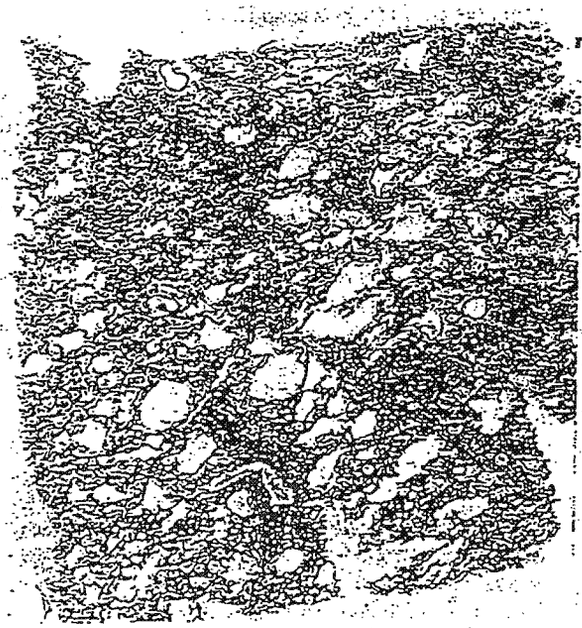

FIGURE 15-9
Extensive interstitial collections of dust-laden macrophages in the lung of a Cornish china clay worker. (Low power.)

FIGURE 15-10
Interstitial collections of dust-laden macrophages associated with slight fibrosis in the lung of a Cornish china clay worker. (Low power.)

jects exposed to china clay show a similar composition to the original dust[58]: >90 percent kaolinite, < 1 percent quartz, < 1 percent feldspar, 1 to 10 percent mica.

In summary, it is possible to develop a pneumoconiosis from exposure to kaolin in the absence of quartz when exposures are heavy. However, with the improvement in the hygiene conditions of the industry since the early 1970s this problem is likely to disappear.

Talc Pneumoconiosis

Talc or hydrated magnesium silicate ($Mg_3Si_4O_{10}(OH)_2$) is formed during the breakdown and weathering of serpentine, tremolite, anthophyllite, and rocks of similar nature. It is found in and has been exploited from the United States, Canada, France, Norway, India, Australia, Italy, Spain, and Austria. Commercial talcs can contain a number of impurities that will depend on the geologic source of the material. In some products the percentage of nontalc mineral will be greater than that of the talc; for example, the "talc" from New York State contains approximately 30 to 55 percent tremolite and 12 to 50 percent talc. Approximately 50 percent of the world's tonnage of talc contains predominantly talc (95 percent or more); in the other 50 percent talc is associated with variable percentages (10 to 50 percent) of carbonates or chlorites.[59] A further complication is that some products sold as "talcs" may not even contain the mineral talc. Therefore, one should be cautious in interpreting studies of pulmonary disease in one cohort of talc workers and extrapolating them to other cohorts exposed to different varieties of talcs. Particular care has to be taken in attributing pulmonary disease to talc exposure in workers employed in secondary industries because the mineral to which they were exposed may not be talc; for example, in the tire plants, mica and kaolin were often used instead of talc for various applications.

Talc has been used in many industries (Table 15-4). Pulmonary fibrosis has been associated with talc exposure in secondary industries and also in the mining and milling of talc. Rare cases of fibrosis have been described with tertiary exposure to cosmetic talc. The question arises as to whether the lung changes were caused by the talc or nontalc components or whether the exposure was to a different mineral completely. Often the only way to settle this question in an individual case is by mineral analysis of the lung tissues, which is difficult and requires a range of sophisticated techniques. A recent study of a series of purported cases of talc pneumoconiosis, in which these techniques were performed, showed in several of them significant quantities of minerals such as kaolin and mica, in addition to talc.[60] In one case the predominant mineral was mica. Nevertheless there appear to be genuine cases of pulmonary fibrosis that have followed heavy exposures to talc uncontaminated by significant amounts of other minerals.[60–63] Deaths shortly after extremely

TABLE 15-4
Industries with Possible Talc Exposure

Ceramics	Tires
Paper	Rubber
Plastics	Cosmetics and pharmaceuticals
Building materials	Animal feeds
Paints	Fertilizers

high exposures to talc have been reported rarely, but these have been due to suffocation rather than the toxic effects on the lung. A range of radiographic lesions has been reported in association with talc, uncontaminated by amphiboles, including fine reticular infiltrates, honeycombing, PMF, and pleural thickening.

PATHOLOGY

On gross examination of the cut surfaces of the lungs there are stellate gray macules, which in severe cases link up and are associated with honeycombing (Fig. 15-11). Less commonly present are palpable gray nodules. PMF lesions characterized by a diffuse soft gray appearance, which may occupy most of an upper lobe, sometimes cavitated, have been described occasionally.[60,63,64] Microscopically, the most common lesions are stellate interstitial collections of dust-laden macrophages associated with mild fibrosis situated around the respiratory bronchioles (Figs. 15-12 and 15-13). Progression of these lesions results in linking up of adjacent lesions that if widespread will lead to greater fibrosis and honeycombing. Severe pathologic changes are usually associated with very high mineral burdens. Less constantly present are rounded and irregular nodules composed of dust-laden macrophages with a greater amount of collagen. Mixed dust fibrotic nodules may be present when there is associated quartz exposure. PMF lesions are characterized by large collections of dust and dust-laden macrophages mixed with irregularly arranged collagen. Other features include ferruginous bodies formed on talc plates, which can be mistaken for asbestos bodies, foreign body granulomas containing large numbers of mineral particles (Fig. 15-14), and rarely sarcoid-like granulomas. It is uncertain at the present time whether the latter are a genuine feature of talcosis or a coincidental finding in a few subjects with undiagnosed sarcoidosis. Polarized light will reveal large numbers of strongly birefringent platy and acicular crystals (Fig. 15-15).

CARCINOMA OF THE LUNG

Some reports have claimed an increased risk of malignancy when exposure occurs to talcs contaminated by amphibole minerals. This has mainly centred around the New York State talc workers who were exposed to a high proportion of amphibole minerals in addition to talc. Several investigators have argued that the amphibole component is not asbestiform and therefore not hazardous.[65–69] Early cohort studies of this group found an excess mortality from lung cancer, but this was in short-term workers with less than a year's work; there was no relation to duration of exposure and the effect of smoking was not evaluated. More recent studies of the New York State talc workers and comparisons with the Vermont talc workers, who were exposed to talc free of amphiboles, indicated that there was no causal connection between lung cancer and amphiboles in the New York State workers.[70,71]

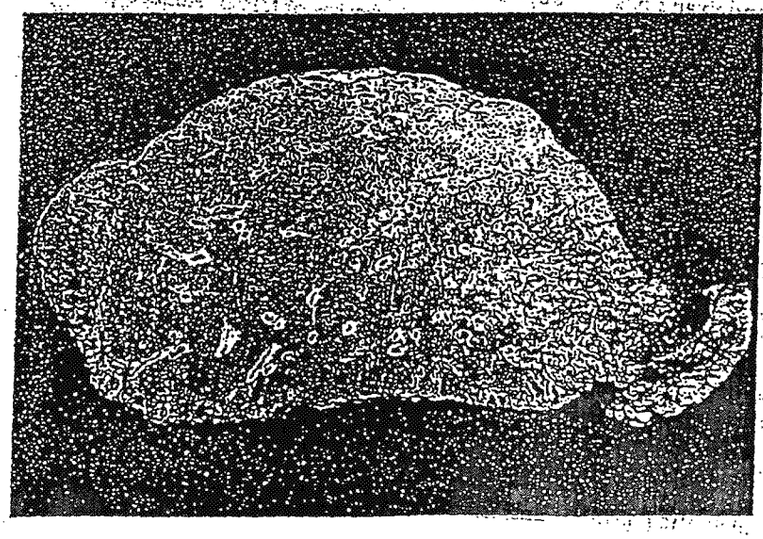

FIGURE 15-11
Lung from a worker in the rubber industry showing interstitial fibrosis with fine honeycombing. Analysis of the lung tissue shows significant quantities of talc, kaolin, and mica. *(Courtesy of the editor of Human Pathology.[60])*

FIGURE 15-12
Lung from a talc worker shows interstitial collections of dust-laden cells associated with a mild degree of fibrosis. (Low power.)

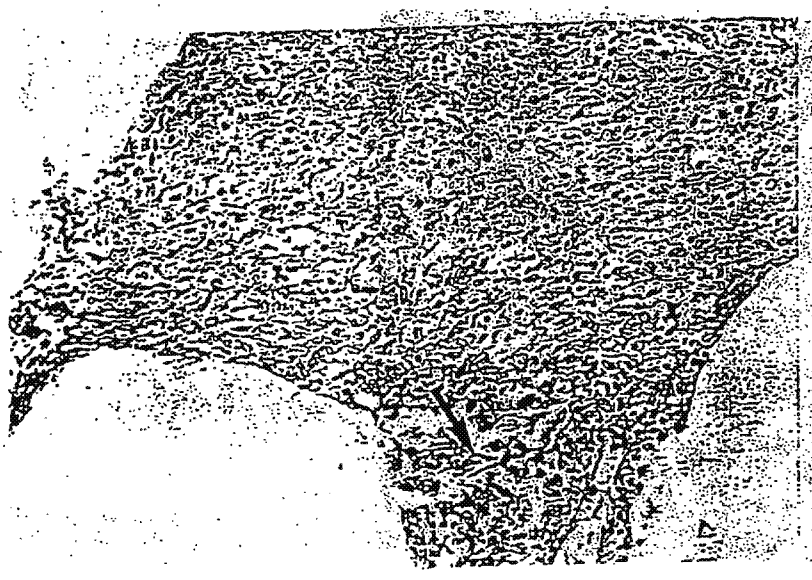

FIGURE 15-13
Lung from a talc worker shows accumulation of fine particulate material and inflammatory cells and a ferruginous body (*arrow*). (Medium power.)

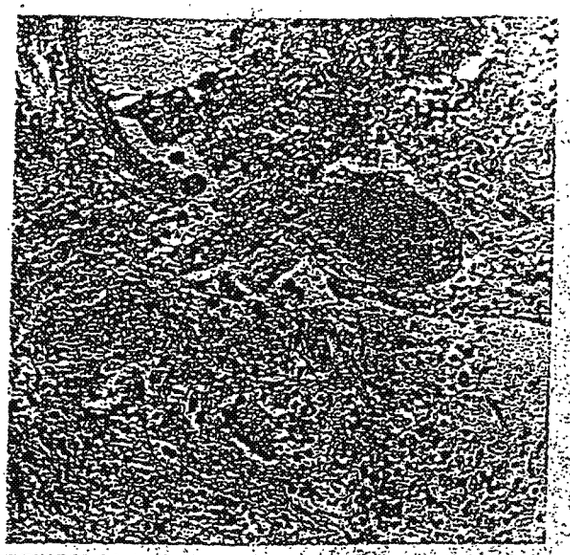

FIGURE 15-14
Particulate material composed predominantly of talc present in macrophages and foreign body giant cells. *(Courtesy of the editor of Human Pathology.[80])*

Mica Pneumoconiosis

The term mica, for practical purposes, encompasses the minerals muscovite, phlogopite, and vermiculite. Micas are produced in India, Brazil, Madagascar, the United States, France, Spain, Finland, and China. These minerals have been used in paints, plastics, fire protection boards, pigments, oilwell drilling muds, the electrical industry, and textured coatings. Exposures to relatively pure micas have occurred mainly in the grinding and packing of the minerals.

Occasional cases of pneumoconiosis and pleural thickening have been described in association with prolonged exposures.[72,73]

PATHOLOGY

On gross examination the lung shows gray, soft stellate lesions that measure a few millimeters in diameter. Rarely massive lesions have been reported (Fig. 15-16). The small lesions may link up to give a fine interstitial pattern. Microscopic examination shows initially dust-laden macrophages situated around respiratory bronchioles, which later extend out into the walls of the adjacent alveoli and alveolar ducts. In severe cases there is a diffuse interstitial collection of dust-laden macrophages associated with fine fibrosis. The dust particles show strong birefringence under polarized light. Ferruginous bodies formed on the yellowish brown mica plates and foreign body giant cells may be observed[57,74] (Fig. 15-17).

Fuller's Earth Pneumoconiosis

There is some confusion as to what is understood by the term fuller's earth because it does not mean the same mineral(s) in every country. In the United States it includes an attapulgite/calcium range of products, whereas in the United Kingdom it refers to calcium montmorillonite only. It has strong absorptive properties and is used in animal feeds, pet litter, pharmaceuticals, herbicides, and the processing of woolen garments. Some fuller's earths contain significant quantities of quartz, but there have been rare cases of pneumoconiosis described in association

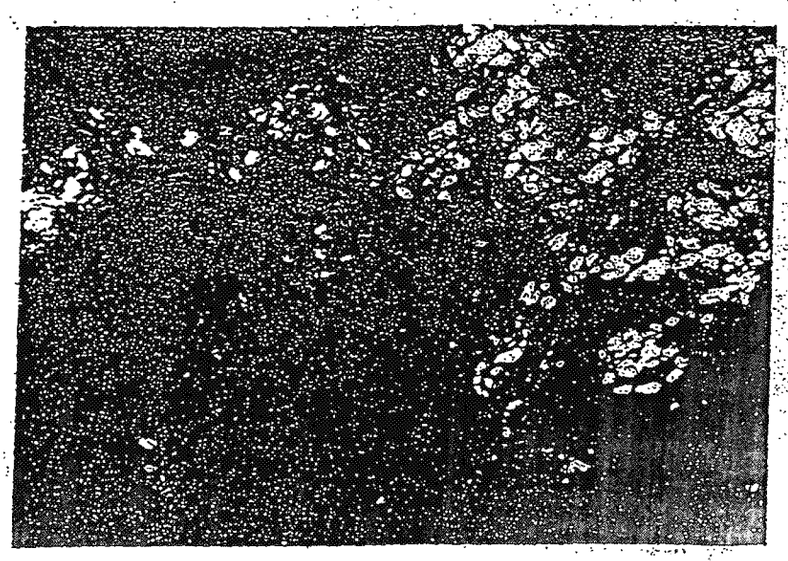

FIGURE 15-15
Strongly birefringent platy crystalline particulates—talc. (Medium power.)

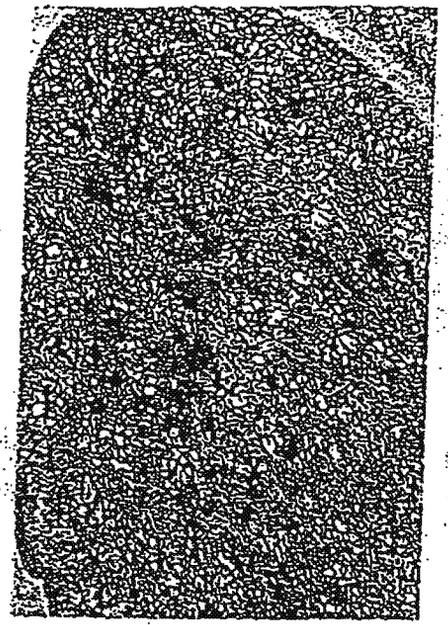

FIGURE 15-16
Mica grinder—numerous stellate gray lesions.

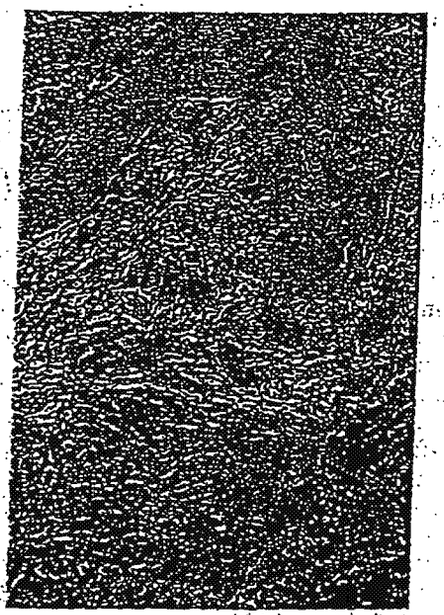

FIGURE 15-17
Mica bagger. The lung shows finely particulate gray-brown material in macrophages and foreign body giant cells in association with ferruginous bodies.

with heavy prolonged exposures to fuller's earth uncontaminated by quartz, for example, in workers at the Redhill and Combe Down deposits in the United Kingdom.[75,76] It has resulted in little clinical disability and the radiologic changes have usually taken several decades to develop.

PATHOLOGY

In those exposed to fuller's earth without quartz the macroscopic changes have consisted of gray-black stellate nodular lesions measuring a few millimeters in diameter. Microscopic examination shows peribronchiolar and interstitial collections of dust-laden macrophages associated with a slight degree of fibrosis (Fig. 15-18). The particles are strongly birefringent under polarized light.

COAL

Coal has been mined for over a thousand years in Great Britain, being first mentioned in the Saxon Chronicle of Peterborough in 852. Laennec described coal worker's pneumoconiosis in 1819.[77] With the coming of the Industrial Revolution in the first half of the nineteenth century the coal mining industry assumed major importance and it was not long before the many occupational hazards of coal mining became recognized in Scotland.[78] In 1838, a young Scots doctor (Stratton) coined the term anthracosis to describe the black discolored lungs of Fifeshire miners.[79]

In 1936, a Medical Research Council (MRC) survey was set up of coal miner's pneumoconiosis in South Wales because the incidence was higher in this than in any other British coal field. This survey contributed to much of the knowledge of this form of pneumoconiosis with regard to the clinical, radiologic, histopathologic, and experimental aspects. The survey also included an extensive geologic and petrologic study of the mines and identification of the different aspects of mine dust. The reader seeking detailed information on this subject is referred to the Medical Research Special Reports of 1942, 1943, and 1945.

The term coal worker's pneumoconiosis (CWP) is now used to cover a variety of pulmonary radiologic and pathologic changes resulting from the inhalation of coal dust and its impurities. In addition to causing pneumoconiotic changes in various categories of underground workers, Gough[80] showed that coal trimmers employed in loading coal into ships' holds might also develop similar pneumoconiotic lesions. This and the previous MRC studies settled

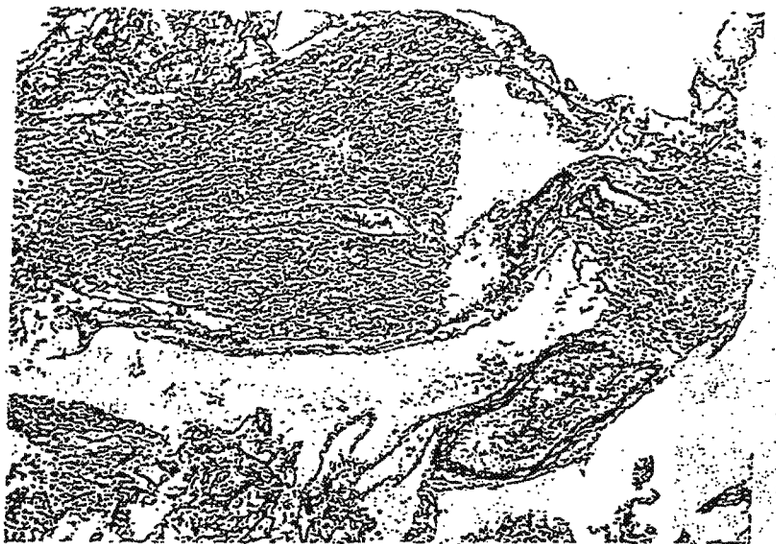

FIGURE 15-18
Fuller's earth pneumoconiosis shows interstitial accumulation of dust-laden macrophages associated with slight fibrosis. (Low power.)

the dispute as to whether CWP was caused by coal or silica exposure, showing that it could occur without significant silica exposure. In Great Britain CWP has been recognized as a disease separate from silicosis for the purposes of industrial benefits since 1943.

Further studies by the MRC in South Wales and the National Coal Board longitudinal study of 30,000 miners from 25 British collieries has taken the research further and allowed realistic standards of respirable dust exposure to be formulated.[61,62] The reduction in dust levels in the mines, decline in numbers of the workforce, early retirement, and the gradual closure of uneconomic mines has led to a decline in incidence of CWP in Great Britain, Europe, and the United States. CWP rarely develops in coal workers before the age of 50 years.

The prevalence and types of pathologic lesions observed in CWP depend on several factors (Table 15-5), which may explain the varying incidence in different coal fields and even between mines in the same coal fields. For example, in Great Britain it has occurred most frequently among miners in the South Wales coal field and especially in the miners employed in the deep anthracite mines in West Glamorgan. It is also more common among miners working in pits with small, deeply situated coal seams.

Coals are rich in carbon and are complex mineralogically, the composition varying from mine to mine. Coals are ranked according to calorific value into low, medium, and high. The higher ranked coals are the oldest and contain the least amounts of volatile matter, whereas the younger, lower ranked coals contain greater amounts of volatile matter. Inorganic material is present in coals, for the most part clays—muscovite, illite, and kaolin—which constitutes a higher proportion of lower than higher ranked coals. Coal may also contain a number of trace elements including arsenic, lead, manganese, titanium, and beryllium. Uranium is present in certain low ranked coals and lignites (up to 0.1 percent). Exposure to respirable particles will depend on the type of coal being mined and adjacent rock strata. Therefore, the job of the underground worker plays a very important part in determining the amount and composition of the respirable dust to which the worker is exposed and consequently the type and severity of pulmonary lesions the worker may develop. Miners employed as hard headers and rock workers in the construction of communicating shafts

TABLE 15-5
Determining Factors in Coal Worker's Pneumoconiosis

Cumulative exposure—dose and duration
Particle size distribution
Coal rank
Concentration and nature of silica
Associate minerals—muscovite, illite, and kaolin
Individual responses
Infection

between adjacent seams or bridging geologic faults work almost entirely in hard siliceous rocks and are exposed to high silica concentrations, which may result in silicosis rather than CWP. Other groups of coal workers exposed to high concentrations of silica include firemen and screen workers.

The incidence and progression of CWP, as one would expect, is related to cumulative exposure to respirable dust,[81] but this is not the whole story. There is also a relationship to coal rank. Several studies have shown that for equivalent exposures the incidence and severity of CWP increases as the rank increases.[81–83] For unknown reasons miners of high ranked coals show significantly more retention of dust in the lungs than those exposed to low rank coals. The histologic appearances of the pneumoconiotic lesions also varies with coal rank.[84,85] Another variable factor is quartz content, which affects the prevalence of CWP unpredictably for several reasons. Associated clay minerals may inhibit the toxic effects of quartz on the lung and this has also been demonstrated experimentally.[86–89] This inhibition may not be permanent and may vary with geologic source.[90] There is evidence that cytotoxicity of coal mine dusts increases as particle size decreases which in turn correlates with high mineral and quartz content.[91] Some miners exposed to dust with a high quartz content have exhibited unusually rapid radiologic changes of pneumoconiosis.[92]

In life the diagnosis and assessment of severity of CWP depends on the prevalence and size of opacities observed on chest radiographs. It is customarily divided into two forms—simple and complicated. The criterion for separation is size of the dust foci and this has varied with time and organization. In the International Labor Organization system of radiographic assessment of pneumoconiotic lesions, if an opacity is present which is greater than 1 cm in diameter then the condition is regarded as complicated CWP or PMF. Generally, simple CWP is not associated with symptoms or clinical signs, significant reduction in lung function or reduction in longevity.[88] Complicated CWP, particularly when lesions are very large, is associated with productive cough, breathlessness, and significant impairment of lung function and it can result in premature death. Complicated CWP is more likely to develop on a background of higher grades of simple CWP.[83] It can develop several years after leaving the industry and in my experience of South Wales coal miners over the last decade it has affected elderly retired miners who had sustained exposures several decades ago.

Pathology[93,94]

The pathology of CWP is most appropriately considered under five subdivisions: (1) simple CWP, (2) complicated CWP, (3) Caplan lesions, (4) emphysema, and (5) interstitial fibrosis.

SIMPLE CWP

Macroscopically, this is characterized by multiple bilateral, soft, stellate, impalpable, black (macular) lesions scattered through the lungs but which are most prevalent in the upper two-thirds (Fig. 15-19). At the earliest stage the lesions are only slightly larger than the soft dust foci associated with urban living. The lesions vary from about 1 mm to several millimeters in size but by definition do not exceed 10

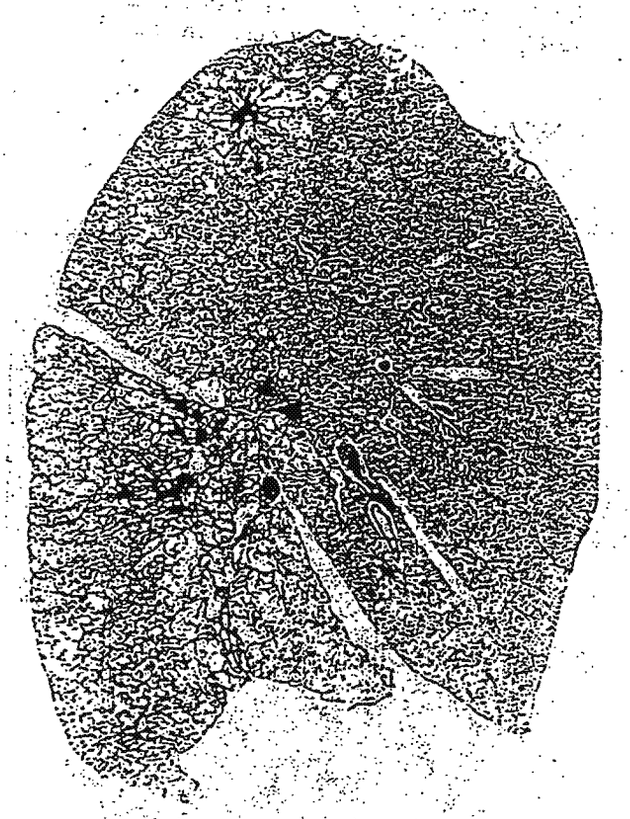

FIGURE 15-19
Gough-Wentworth whole lung section from a coal worker of many years shows numerous black macules affecting most of the lung lobules, a small number of larger stellate black lesions, and centrilobular emphysema affecting about two-thirds of the lung lobules.

mm. With progression they may come to occupy the majority of the lung lobules. This pathologic picture can be seen without there necessarily being any radiologically detectable pneumoconiosis. The number of lesions seen radiologically always appears to be less than is actually demonstrated pathologically.[95] Associated with these macular lesions are frequently variable degrees of emphysema situated at the centers of the acini (focal emphysema). Therefore, the black lesions appear to be highlighted by the surrounding pale emphysematous areas. The radiologic changes of simple CWP are due to the dust and the small amount of collagen present and do not reflect the emphysema.[96] In addition to these impalpable macular lesions there may be firm, palpable, black lesions that may be stellate or rounded in shape (fibrotic nodules). These nodules are usually much less in number and often larger than the macules (Fig. 15-20). Uncommonly they occur on their own but usually they are superimposed on a background of macules. Other features include dust impregnation of interlobular septa and the pleura; the latter is usually focal but occasionally may be diffuse. The peribronchial, hilar, and mediastinal lymph nodes are often enlarged, densely black and may be soft or firm. Sometimes they contain whorled silicotic-like nodules, usually in the absence of similar lesions in the lung. They are caused by the preferential clearance of silica from the lung to the lymph nodes.[97]

Microscopically the earliest change consists of the accumulation of dust-laden macrophages around the respiratory bronchioles and adjacent alveoli, blood vessels, septa, and beneath the pleura. Free dust particles may also be seen. The macules consist of uniformly distributed dust particles free or within macrophages intermingled with reticulin and small amounts of collagen, which contrasts with the considerable formation of collagen in silicotic nodules (Figs. 15-21 to 15-23). The dust packing of these lesions increases with decreasing ash content and increasing coal rank.[84] The nodules show much more collagen than the macules and it is arranged in bundles that radiate in all directions. Nodules are associated with the mining of lower ranked coals and increasing ash content. Nodules may show cavitation, calcification, and cholesterol clefts. If the coal worker has been exposed to a high silica concentration, mixed dust fibrotic or silicotic-type nodules may be observed, in which case the collagen fibers will either be arranged in a linear or circumferential pattern. Examination of macules or nodules under polarized light may reveal small doubly refractile

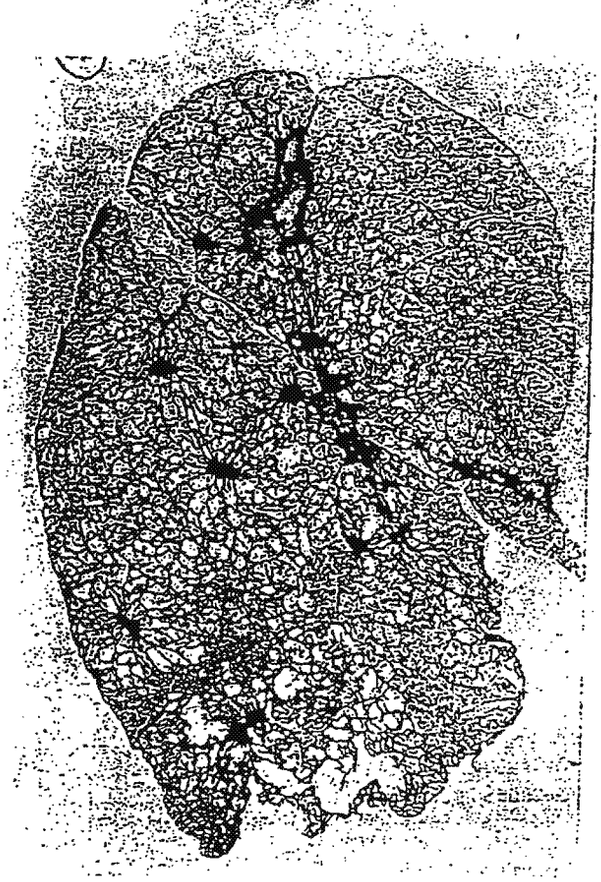

FIGURE 15-20
Gough-Wentworth whole lung section from a coal worker shows several stellate black lesions, which were palpable, and centrilobular emphysema.

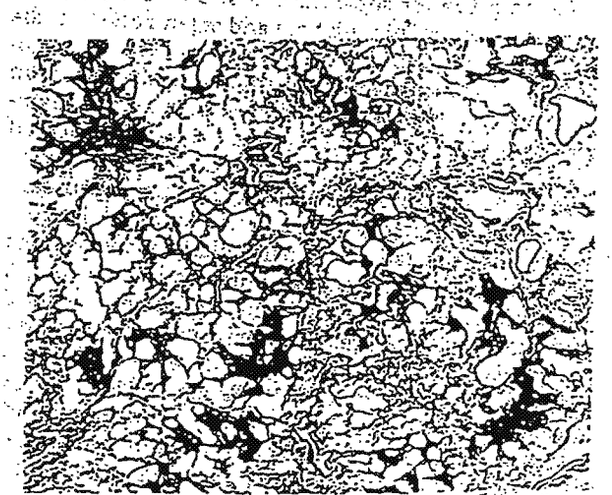

FIGURE 15-21
Simple coal worker's pneumoconiosis shows numerous stellate macular lesions associated with emphysema. (Low power.)

FIGURE 15-22
Simple lesion in a coal worker showing dust packing and relatively mild fibrosis. (Low power.)

particles, which are the silicates present within the coal dust.

COMPLICATED CWP OR PMF

The PMF lesions, which by definition are greater than 1 cm in diameter, nearly always occur on the background of severe simple pneumoconiosis. The PMF lesions most commonly occur in one or both upper lobes but can occur in any lobe. They may reach several centimeters in size and can destroy the whole of a lobe or sometimes several lobes. The lesion is typically soft, jet black, homogeneous, and well delineated and may show varying degrees of cavitation (Fig. 15-24). The cavities may contain fluid resembling India ink. The affected lobes may be adherent to the chest wall. Microscopically, the lesions are composed of dust particles, both free and within macrophages mixed with randomly arranged collagen and reticulin fibers (Fig. 15-25). The centers of the lesions may evince necrosis and cholesterol clefts. There are frequently ghost outlines of vessels and airways within the centers and at the periphery small vessels cuffed by lymphocytes and plasma cells. Necrosis within PMF lesions is usually a result of ischemia rather than infection. Often severe emphysema surrounds PMF lesions.

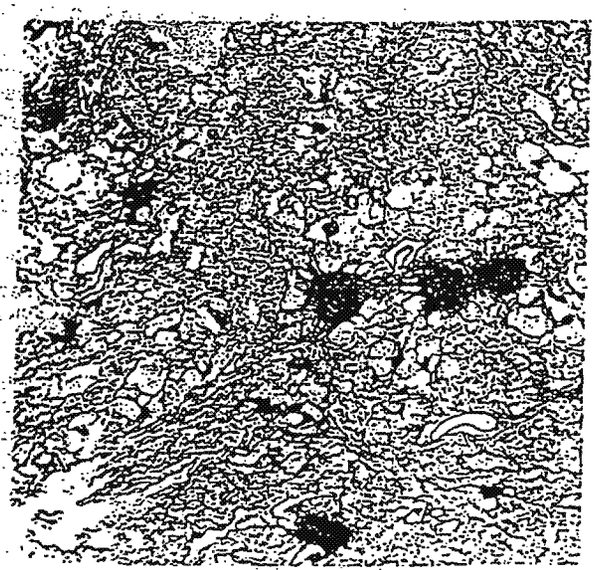

FIGURE 15-23
Coal worker. In addition to stellate macular lesions, some nodules show central collagenization. (Low power.)

A second type of PMF lesion may occur. This is characterized by hardness and a conglomerate pattern of nodules (Fig. 15-26). Mineralogic studies of lung mineral content have indicated that the first type of PMF is associated with exposure to high rank coals and the second type to lower ranked coals.[84] Obviously these PMF lesions represent ends of a spectrum and one often encounters some with intermediate features that are difficult to classify (Fig. 15-27).

CAPLAN'S SYNDROME (RHEUMATOID PNEUMOCONIOSIS)

In 1953, Caplan[98] described unusual radiologic changes in coal miners suffering from rheumatoid arthritis, and subsequently radiologists in Germany, France, Belgium, and Holland reported similar findings. The chest radiographs showed large, rounded, and well-defined shadows mainly in the peripheral

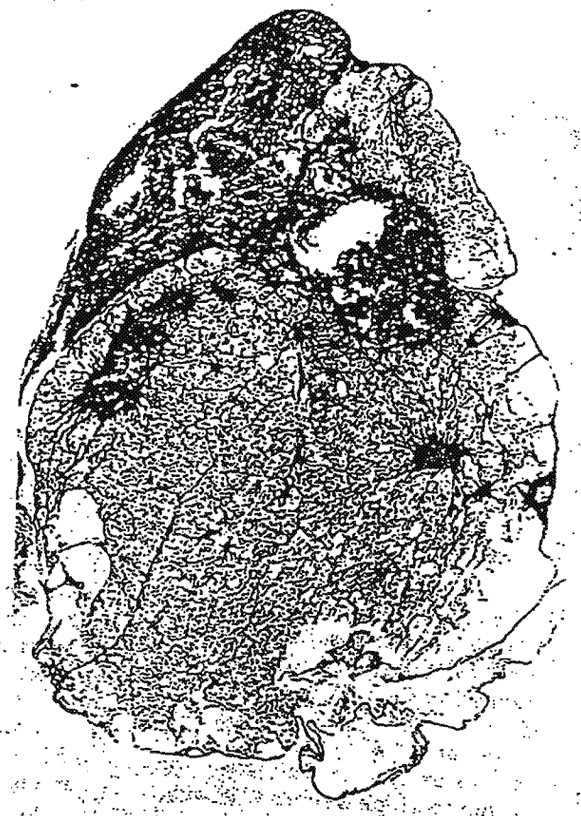

FIGURE 15-24
Gough-Wentworth whole lung section from a coal worker shows diffusely black progressive massive fibrosis mainly in the upper lobe.

FIGURE 15-26
Coal worker. An area of progressive massive fibrosis shows conglomeration of nodules and an area of cavitation.

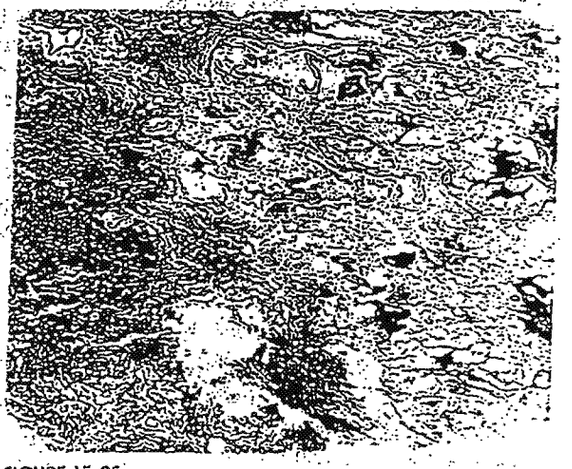

FIGURE 15-25
Coal worker. Part of a progressive massive fibrosis lesion shows diffuse black area with adjacent multiple black macules. (Low power.)

parts of the lung fields, but unlike the shadows caused by PMF they were not restricted to the upper lobes and tended to enlarge more rapidly. The appearance of the pulmonary lesions sometimes preceded the onset of arthritic lesions, as can ordinary pulmonary rheumatoid nodules. In 1962, Caplan and coworkers[99] found that 65 percent of such patients showed positive serologic tests for rheumatoid disease.

In 1955, Gough and colleagues[100] described the pathologic appearances of these lesions. They are rounded or oval, well-demarcated firm nodules that may be discrete or confluent (Fig. 15-28). They exhibit a laminated appearance with light and dark layers. They vary from a few millimeters to several centimeters in size and often are superimposed on a background of relatively slight pneumoconiosis. The nodules may show areas of liquefaction, cavitation, and calcification.

Microscopically, the central zone of the nodule consists of necrotic collagen, coal dust, and debris. Dust often lies in rings. At the edge of the necrotic

FIGURE 15-27.
Progressive massive fibrosis lesion from a coal worker shows an intermediate pattern between the diffuse black form and the conglomerate form of the condition. (Low power.)

zone a cleft separates it from the adjacent layer of spindle-shaped fibroblasts, which show variable degrees of pallisading. Between the cellular and necrotic zones is a narrow belt of neutrophils and nuclear debris (Figs. 15-29 and 15-30). Outside the fibroblastic zone there is circumferentially arranged collagen and numerous lymphocytes and plasma cells, which sometimes form germinal centers. The small vessels around the periphery of the nodule frequently show endarteritis with infiltrates of the walls composed of lymphocytes and plasma cells.

The major differential diagnosis includes tuberculous and silicotic nodules. The clue to the rheumatoid nature of these lesions is the zone of neutrophils and pallisaded fibroblasts. Direct staining for acid-fast bacilli (Ziehl-Nielsen) will be negative in Caplan lesions. In some instances, however, the external capsule may be entirely collagenous—so-called burnt out lesions—which may be extremely difficult to distinguish from encapsulated tuberculous lesions.

In subjects with rheumatoid arthritis, Caplan-like lesions also have been associated with exposure to other dusts including silica[101] and asbestos.[102,103] In those associated with asbestosis concentric dust rings are not observed but instead asbestos bodies are seen.

EMPHYSEMA AND CWP

The issue of coal dust exposure and the development of emphysema has been controversial.[104] It is important because the degree of functional disability in CWP correlates better with the degree of emphysema

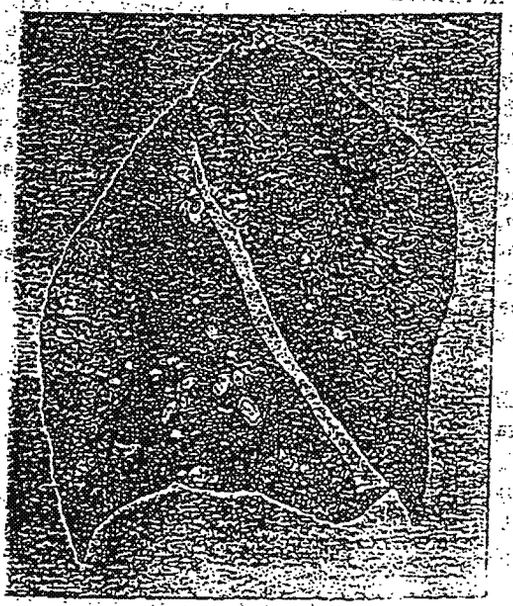

FIGURE 15-28
Caplan's syndrome. Well-demarcated whorled nodules superimposed on a background of very slight pneumoconiosis.

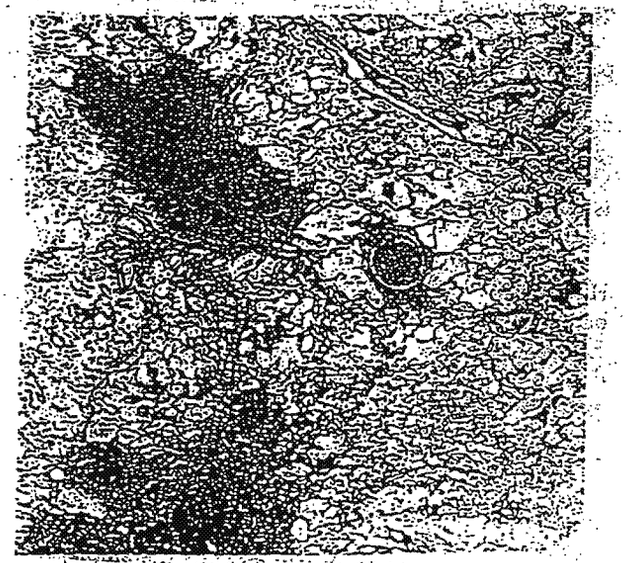

FIGURE 15-29.
Rounded, well-demarcated confluent nodules in a coal worker with rheumatoid arthritis—Caplan's syndrome. (Low power.)

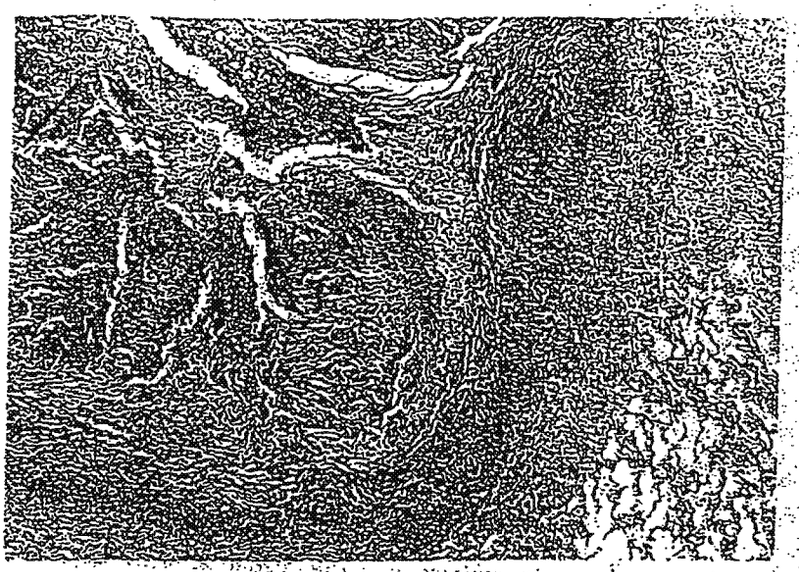

FIGURE 15-30
Caplan lesion shows central necrosis and a peripheral zone of inflammatory cells with pallisading. (Low power.)

present than with the size and number of simple dust foci.[105,106] The major confounding factor is cigarette smoking. A considerable body of evidence indicates that chronic bronchitis and emphysema in coal workers is directly related to tobacco usage and cumulative exposure to respirable dust during life.[107,108] Postmortem studies have also shown that there is a significant excess of emphysema in coal workers with pneumoconiosis when compared to a nonmining control population.[108–110] This is specific to centriacinar emphysema and unrelated to panacinar emphysema. Its occurrence is associated with increasing amounts of dust retained in the lungs and palpable lesions.[107]

When considering emphysema in relation to coal dust exposure two forms should be distinguished: focal and centriacinar. In many studies this has not been done and it has to be admitted that there is no sharp boundary where one ceases and the other begins.

Focal emphysema was the term coined by Heppleston[111] for the dilatation of the respiratory bronchioles that clustered around the stellate dust foci and that was associated with little architectural destruction. It is mild, the air spaces not usually exceeding 2 mm in diameter, and not associated with any functional abnormality (see Figs. 15-19 and 15-23). Duguid and Lambert[112] thought that it was a form of compensatory emphysema caused by increasing fibrosis and contraction of the dust focus over many years. This implies that the contracted dust focus becomes relatively less and the emphysematous part more conspicuous over time. The emphysematous changes are located at the center of the acinus and secondary lobule because of the location of the dust focus. This is where the changes of centriacinar emphysema are also located. It should be noted that similar lesions may be observed around the carbonaceous dust foci of town dwellers.

Centriacinar emphysema, in contrast to focal emphysema, was considered to be accompanied by architectural destruction of the acinus from its earliest stage and inflammation within bronchi and bronchioles.[113] Apart from the presence of the dust foci the pathologic appearances are identical to those seen in noncoal workers with centriacinar emphysema (see Figs. 15-19 to 15-21). If extensive it is likely to be accompanied by impairment of lung function of an obstructive type. It has a strong association with tobacco usage but as stated above it is related also to cumulative respirable coal dust exposure.

In the United Kingdom, the government has accepted the report of the Industrial Injuries Advisory Council's recommendation that chronic bronchitis and emphysema in *underground* coal workers should be added to the present prescribed diseases for Industrial Injury Disablement benefit. The conditions for compensation were:

1. Underground coal mining for a minimum aggregate of 20 years
2. A reduction of lung capacity at least 1 liter below expected level
3. A radiologic pneumoconiosis category of 1/1 or greater

On occasion at autopsy a pathologist will be faced with the problem of determining in a coal miner, who has died from obstructive airways disease and who

has centriacinar emphysema, whether coal dust exposure was contributory. If the subject has not had lung function tests and a chest radiograph in the last few years, this might be difficult. In this situation the pathologist will need to make a judgment of the likely appearances of the chest x-ray based on the appearance of the dust foci and emphysema at autopsy. In practice for category 1/1 there would be extensive simple coal dust lesions present.

INTERSTITIAL FIBROSIS AND CWP

There appears to be an increased prevalence of interstitial fibrosis in the lungs of coal workers. This has been observed in both South Wales and U.S. coal miners and is approximately 16 percent.[114,115] Sometimes this can be observed macroscopically but in many cases it is only seen by microscopy (Fig. 15-31). A radiologic-pathologic study of irregular opacities in CWP has indicated that they represent a combination of emphysema and interstitial fibrosis; the interstitial fibrosis can show various degrees of dust deposition.[116] The precise connection between the interstitial fibrosis and coal dust or work underground remains to be determined. The disease appears to run a slower course than cryptogenic fibrosing alveolitis.[114]

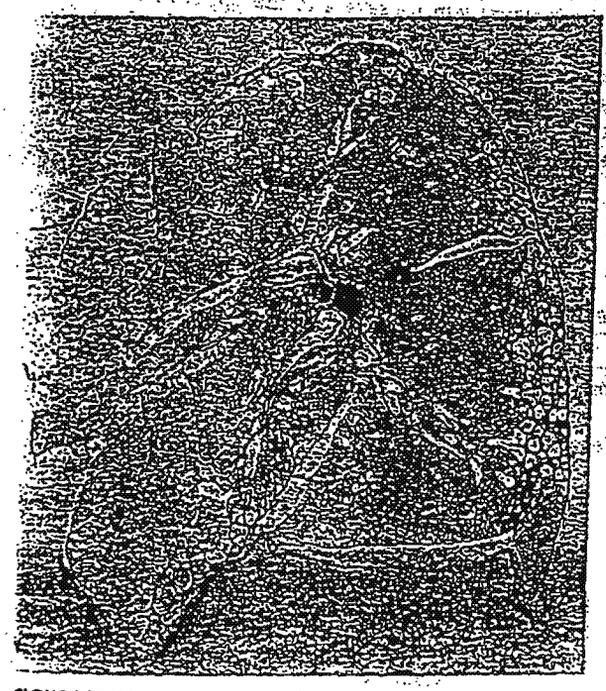

FIGURE 15-31
Gough-Wentworth whole lung section from a coal worker shows dust-impregnated honeycombing in the posterior and inferior zones.

GRAPHITE

This is a natural or synthetic crystalline form of carbon. Many commercial forms of natural graphite (plumbago) contain other minerals such as silica and various clays. It is used in refractory ceramics and crucibles, foundry facings, steel and iron manufacture, pencils, lubricants, and brake linings. Synthetic graphite is used in graphite electrodes, atomic reactors, and lubricants.[1] A number of cases of graphite pneumoconiosis have been described but in many exposure to silica or silicates may have played a part in their causation.[117]

METALS

Pulmonary responses to metals have been inadequately studied because they tend to occur in small industries with poorly characterized exposures. There have been several epidemiologic studies of various industries but there have been few systematic pathology studies. Most of the pathologic information comes from isolated case reports, with poorly characterized exposures, no mineralogic analysis of the lung tissues, and no proper controls for comparison. This account is highly selective and discusses only those metals with fairly well-documented effects on the lung. Agents that will not be considered are those that predominantly cause responses in organs outside the respiratory system even though they are inhaled.

It is rare for human exposures to occur to the pure metallic forms but it is usually to the oxides or other compounds. Not all compounds of a toxic metal are necessarily harmful to the lung. A wide variety of pulmonary responses can result from exposure to metals, which can be in the form of fumes or dusts. These responses can be acute, chronic, or neoplastic. The acute response may not develop immediately after exposure but may be delayed for some hours. Death or complete recovery may follow the acute response and rarely chronic sequelae such as fibrosis. Table 15-6 gives a broad classification of the pathologic reactions associated with exposures to metals together with examples. As with exposure to other minerals, the responses will vary with dose, physicochemical forms, associated minerals, and host factors.[118,119]

TABLE 15-6
Pulmonary Reactions Associated with Exposures to Metals

Reaction	Examples
Diffuse alveolar damage or acute bronchitis	Beryllium, cadmium, cobalt, manganese, mercury, nickel
Industrial asthma	Chromium, cobalt, nickel, platinum
Emphysema	Cadmium
Centrilobular dust accumulation with minimal fibrosis	Barium, iron, tin
Interstitial fibrosis	Aluminum, cobalt
Desquamative interstitial pneumonia	Aluminum
Giant cell interstitial pneumonia	Cobalt (hard metal)
Alveolar proteinosis	Aluminum
Granulomatous disease	Aluminum, beryllium, titanium
Carcinoma of lung	Arsenic, chromium, nickel, uranium

Aluminum

There are numerous uses for aluminum metal and its compounds and a considerable number of workers have been exposed to them. Sources of exposure include the mining and crushing of bauxite ore, smelting of bauxite (potroom workers), the manufacture of abrasives or explosives containing aluminum, and the grinding, polishing, and welding of aluminum. Various forms of lung disease, the earliest being fibrosis, have been linked to exposure to aluminum in manufacturing or processing factories but they have been rare considering the large numbers of workers potentially at risk. Some reports have been difficult to assess because of concomitant exposures to other minerals. For example, aluminum potroom workers are exposed to carbon monoxide, coal tar pitch volatiles, fluorides, sulfur dioxide, and alumina.[120] Bauxite lung (also known as Shaver's disease, corundum smelter's lung) was first recognized during World War II among a small group of workers engaged in the manufacture of aluminum abrasives (corundum; Al_2O_3) by Shaver[121] and, then by Riddell.[122] Reports from Germany during the same period described severe lung damage occurring in association with aluminum metal powder. In 1959, Mitchell[123] and McClaughlin and coworkers[124] in 1962 described further cases in Britain.

Several forms of nonmalignant lung disease have been associated with exposure to aluminum and its compounds.[125–133] These are listed together with the associated exposures in Table 15-7. None of these reactions are specific to aluminum and the association cannot be made on the histopathologic appearances alone (Fig. 15-32). However, the aluminum-associated diffuse interstitial fibrosis pattern is usually more severe in the upper zones of the lung, whereas the cryptogenic form and asbestosis are usually more severe in the lower zones. Mineral analysis of the lung tissue is essential in identifying the aluminum and excluding other mineral exposures.

TABLE 15-7
Aluminum-Associated Pulmonary Reactions

Reaction	Exposure	References
Diffuse interstitial fibrosis	Bauxite smelting	Abramson et al.[120]; Gilks and Churg[126]
	Fireworks and explosives	Mitchell[123]
	Abrasives	Shaver[121]; Riddell[122]; Jederlinic et al.[125]
	Welding	Vallyathan et al.[131]
	Polishing	DeVuyst et al.[132]
DIP	Welding	Herbert et al.[130]
GIP	Grinding	Ferryman et al.[133]
Alveolar proteinosis	Grinding	Miller et al.[127]
Granulomatous disease	Welding	Chen et al.[129]
	Chemist	DeVuyst et al.[128]

DIP = desquamative interstitial pneumonia; GIP = giant cell interstitial pneumonia

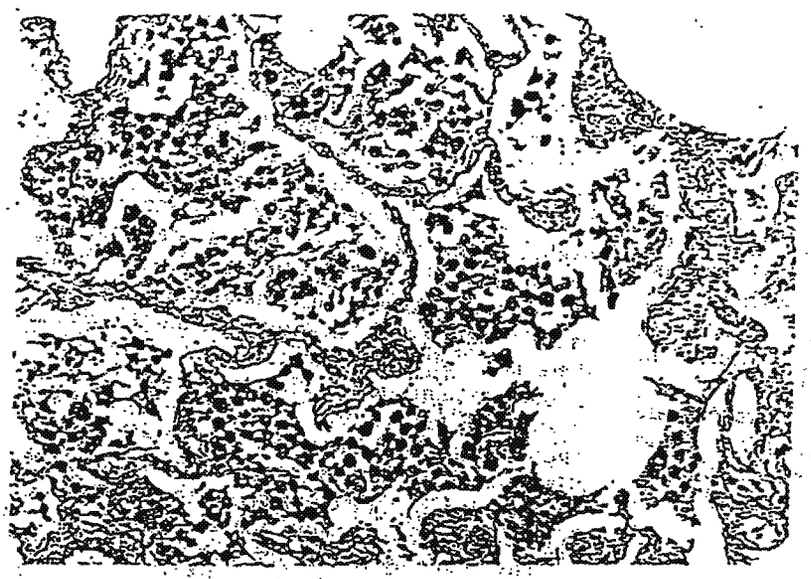

FIGURE 15-32
Diffuse interstitial fibrosis-like reaction characterized by intraalveolar collections of macrophages. (Medium power.)

Asthma-like symptoms have been reported in several groups of workers exposed to aluminum compounds,[120,134] but it is not certain whether the exposure initiates asthma or exacerbates symptoms in subjects with subclinical asthma.

An excess of lung cancer has been described in aluminum production workers but it is probably linked to coal tar pitch volatiles.[135]

Barium

Barium lung (baritosis) can follow the inhalation of dust particles from inspired air or by aspiration of barium suspensions during radiographic procedures. In the former circumstance, such as in barytes miners and grinders, the particles will tend to be uniformly and bilaterally distributed, whereas in the latter circumstance the particles will accumulate in localized areas. The radiologic changes are dense but there is usually little functional disability because there is little associated fibrosis. Microscopically, the lungs show alveolar collections of particle-laden macrophages with few other inflammatory cells. The particles are refractile and strongly birefringent on polarization.

Beryllium

Berylliosis is a disease caused by exposure to beryllium metal or its salts. The term was first used in 1935 by Fabroni[136] with reference to the experimentally produced acute form of beryllium poisoning, although an acute disease following beryllium exposure was described in Germany in 1933.[137] Hardy and Tabershaw were the first to draw attention to a chronic form of berylliosis.[138] Beryllium most frequently enters the body through the respiratory tract and most conspicuously affects the lungs. However, it is a multisystem disorder[139] and changes may occur in the skin, liver, kidney, spleen, and lymph nodes.[140] Dermatitis or chronic skin ulcers may occur as a local disease or in conjunction with systemic disease.

Acute berylliosis follows relatively high exposures to dusts, fumes, or mists, whereas the chronic form may follow limited or prolonged exposure to low doses. Individual hypersensitivity appears to be involved, which is mediated by a specific delayed-type hypersensitivity reaction to beyllium in which there is proliferation and accumulation of CD4+ (helper/inducer) T cells in the lungs.[141] The disease is uncommon even though the use of beryllium in industry has increased over the last few decades. Exposure may occur in those engaged in the extraction of the metal from its ores, most commonly beryl, and in those who handle beryllium compounds. The latter are used in refractory ceramics, the electronics industry, space and atomic engineering, laboratories, and beryllium metal and alloy production. Exposure may also occur during the reclamation of scrap metals.[139] The use of beryllium in flourescent light tubes ceased in the late 1940s and early 1950s; this industry was the cause of 46 percent of the chronic berylliosis cases listed in the U.S. Berylliosis Case Registry up to 1966.[142] Cases of berylliosis claimed to have been caused by paraoccupational and neighborhood exposure have been reported.[142–145]

Some studies have claimed that exposure to beryllium compounds causes an increased risk of lung cancer; however, the evidence for this is unconvincing.

ACUTE BERYLLIOSIS

This condition is rare nowadays with modern industrial conditions. Respiratory symptoms of breathlessness, cyanosis, productive cough, and nasal discharge manifest within 72 h following a severe exposure, but if exposure is lower the onset may take several weeks. The majority resolve without long-term sequelae, but approximately one-sixth have progressed to chronic disease. Death has occurred in about 10 percent of the cases reported.[139]

The gross and microscopic appearances are those of diffuse alveolar damage (see Chap. 11) and granulomas are absent. Diagnosis rests on a history of exposure and demonstration of beryllium within the lung tissues.

CHRONIC BERYLLIOSIS

This is an insidious disease that can follow the last exposure to beryllium with a latent period varying from 1 month to more than 40 years. It closely resembles sarcoidosis and can lead to death from pulmonary fibrosis.

Macroscopically, the lungs appear contracted and have bosselated pleural surfaces, sometimes with thickening and adhesions. The cut surface shows variable degrees of honeycombing, which tends to be more conspicuous in the upper zones.

Microscopically, the hallmark of the disease is the presence of numerous noncaseating compact epithelioid sarcoid-like granulomas located in the interstitium, septa, bronchovascular bundles, and subpleural areas. Occasionally there is necrosis within the centers of the granulomas.[146] Fusion of granulomas may occur to give rise to nodules that are 2 to 3 cm in diameter. These may show marked hyalinization. Schaumann bodies are frequently present; in the chronic fibrotic stage the granulomas may disappear leaving only the Schaumann bodies as their "calling card." In addition to the granulomas there is usually a pronounced diffuse interstitial chronic inflammatory infiltrate, which is much greater than that usually observed in cases of sarcoidosis (Fig. 15-33). There is a variable degree of diffuse interstitial fibrosis present, which may be accompanied by bronchiolectasis (honeycombing) and bronchiolоalveolar epithelial metaplasia.

The following criteria for diagnosis of chronic berylliosis have been put forward.[146,147]

1. History of beryllium exposure
2. Consistent clinico/physiologic/pathologic features
3. Presence of granulomas in tissue
4. Detection of beryllium in tissues
5. Evidence of beryllium hypersensitivity
6. Exclusion of other granulomatous diseases

Occupational histories are often difficult to assess because exposure frequently occurred several years previously, it is often mixed, and other granu-

FIGURE 15-33
Diffuse interstitial chronic inflammation with a granuloma in a worker exposed to beryllium. (Low power.)

lomatous diseases can occur in workers with claimed exposure to beryllium. The detection of beryllium in the granulomas is particularly valuable but unfortunately, because of its low atomic weight, it is one of the more problematic minerals to detect. The laser microprobe mass spectometry technique can be applied to conventional tissue sections and can detect elements in low concentrations. A recent study using the technique demonstrated beryllium in the granulomas of all 33 cases of chronic beryllium disease and in none of 30 cases of sarcoidosis.[148] It should be noted that it demonstrated beryllium in the dust lesions of coal workers. Its disadvantages are that the technique is available in few centers and it provides qualitative and not quantitative data. Other techniques for the detection of beryllium in tissues have used electron microscopy and have included ion microprobe mass spectometry and electron energy mass spectometry.

It has been postulated that chronic berylliosis is caused by immunopathologic mechanisms because of an absence of a dose–response relationship and the presence of manifestations of delayed (type 4) hypersensitivity. The latter can be useful in diagnosis. Beryllium patch testing on the skin of subjects with suspected berylliosis has been discontinued because of its unreliability and possible exacerbation of the disease. However, in vitro transformation tests to beryllium on peripheral blood and bronchoalveolar lavage lymphocytes has been positive in nearly all subjects with chronic berylliosis tested.[149–151] It can also be used for screening of workers but there is still debate as to whether a positive beryllium lymphocyte test in an asymptomatic worker represents latent disease.

The major conditions from which chronic berylliosis needs to be distinguished include sarcoidosis, chronic extrinsic allergic alveolitis, and cryptogenic fibrosing alveolitis. Table 15-8 gives helpful features in differential diagnosis.

Cadmium

Cadmium is used in the manufacture of alloys, nickel–cadmium batteries, and in electroplating and plating of automobile parts and musical instruments. Additional sources of exposure include various welding processes and the smelting of zinc, lead, and copper ores that contain cadmium. Cigarettes may contain appreciable quantities of cadmium. Three forms of lung disease have been associated with cadmium exposure: diffuse alveolar damage (acute cadmium pneumonitis), emphysema, and cancer.

Inhalation of large amounts of cadmium fume (usually the oxide) can cause diffuse alveolar damage, sometimes with death of the subject.[152] The histopathologic features are similar to diffuse alveolar damage caused by other agents. Diagnosis depends on the history of exposure and mineral analysis of the lung tissues.

The link between chronic cadmium exposure and the development of centrilobular emphysema was first noted in the 1950s, but the results of subsequent epidemiologic surveys have been controversial. This is because the majority did not consider various confounding factors particularly cigarette smoking. However, a recent well-conducted study of a cohort of workers from a copper–cadmium alloy factory reported decrements of lung function and radiologic changes consistent with emphysema.[153]

TABLE 15-8
Comparison of Chronic Berylliosis (CB) with Sarcoidosis (SAR), Chronic Extrinsic Allergic Alveolitis (EAA), and Cryptogenic Fibrosing Alveolitis (CFA)

Feature	CB	SAR	EAA	CFA
Exposure to beryllium	Yes	No	No	No
Kveim test	Neg	Pos	Neg	Neg
Serum precipitins	Neg	Neg	Pos	Neg
Predominant distribution of fibrosis	Upper	Upper	Upper	Lower
Compact granulomas	++	++	+	0
Interstitial inflammation	++	+	++	+
Hilar lymphadenopathy	Rare	+-+	0	0

Note: +, mild/moderate; ++, prominent.

Furthermore, the decrements of lung function increased with cumulative exposure to cadmium. Inhalation of cadmium chloride by rats has led to emphysema.[154]

Several epidemiologic studies of cadmium-exposed workers have reported increased numbers of lung cancers. However, recent information has cast doubt on its role in causing lung cancer because two major confounders—smoking and arsenic exposure—were not controlled for.[119]

Chromium

Alloys and compounds of chromium have been in commercial use for over a century. Chromium is a gray metal that can combine with other elements in a number of different ratios, which are termed valencies. There are divalent (e.g., chromous chloride $CrCl_2$), trivalent (e.g., chromic chloride $CrCl_3$), and hexavalent compounds (e.g., potassium chromate K_2CrO_4) compounds. Experimental and human studies indicate that the hexavalent compounds are pathogenic, particularly the relatively insoluble forms such as calcium, lead, strontium, and zinc chromates, but also soluble forms.

Occupational exposure to chromium compounds can occur in a number of situations (Table 15-9) and can cause perforation of the nasal septum and an increased risk of nasal and lung cancer.[155] These have been observed in chromium plating, chromate production, and chromate pigment production and the risk increases with duration and severity of exposure.[156–158] The occurrence of nasal perforation in a cohort of workers does not necessarily indicate that they have been exposed to types and amounts of chromium compounds capable of producing lung cancers.

Cobalt—Hard Metal

Hard metal (tungsten carbide) is a synthetic tungsten alloy used in machine tools. Pneumoconiosis has been associated with the manufacture and grinding of tungsten carbide.[159–161] The finished product contains between 5 and 25 percent of cobalt, which is thought to be the agent responsible for the disease.

Machine tools requiring very hard textured metal are made by blending tungsten and carbon and heating them to form tungsten carbide. Cobalt and other metals, such as titanium, tantalum, chromium, molybdenum, vanadium, niobium, and nickel, are then added, according to the desired properties, and then sintered into the hard metal.

Exposure to hard metal has been associated with diffuse interstitial fibrosis, desquamative interstitial pneumonia (DIP), giant cell interstitial pneumonia (GIP), hypersensitivity pneumonitis, and industrial asthma.[159–164] GIP is a rare disease and when it is encountered it is nearly always caused by exposure to hard metal (Fig. 15-34). In this disorder the giant cells may be found in the bronchoalveolar lavage fluid.[163] When an interstitial disorder is caused by hard metal exposure, analysis of the lung tissues consistently reveals tungsten but not always cobalt, because of its solubility. Experimental studies have indicated that cobalt is responsible for the interstitial diseases. A similar disease has been reported in diamond polishers exposed to cobalt but not to hard metal.[165] In hard metal asthma evidence indicates that sensitivity to both cobalt and nickel may be involved.[164]

TABLE 15-9
Exposures to Chromium Compounds

Production of chromates and pigments
Chromium plating
Production, welding, cutting, and grinding of chromium alloys
Leather tanning
Spray painting
Steel smelting and welding

Iron

Exposure to dusts or fumes composed predominantly of iron oxide causes little damage to the lung because the particles are weakly fibrogenic. The chest radiographs may show opacities but there is usually little functional impairment. In cases where exposure has been heavy and deposits of iron particles marked, the lung will appear reddish brown or brick red on gross examination (Fig. 15-35). Ferruginous bodies containing black cores are frequently present, which should not be mistaken for asbestos bodies. Microscopically, there will be collections of dark brown, dust-laden macrophages with relatively slight fibrosis (siderosis). This may occur in silver polishers, ocher workers, and arc welders. The latter may experience exposure to a variety of other mineral particles and may show a variety of pathologies (vide infra).

In some situations exposure to significant amounts of silica also will occur,[166] for example, in hematite miners, foundry workers, and boiler scalers. The lung will reflect the effects of both silica and iron—so-called silicosiderosis. Simple and complicated pneumoconiosis can develop in these workers.

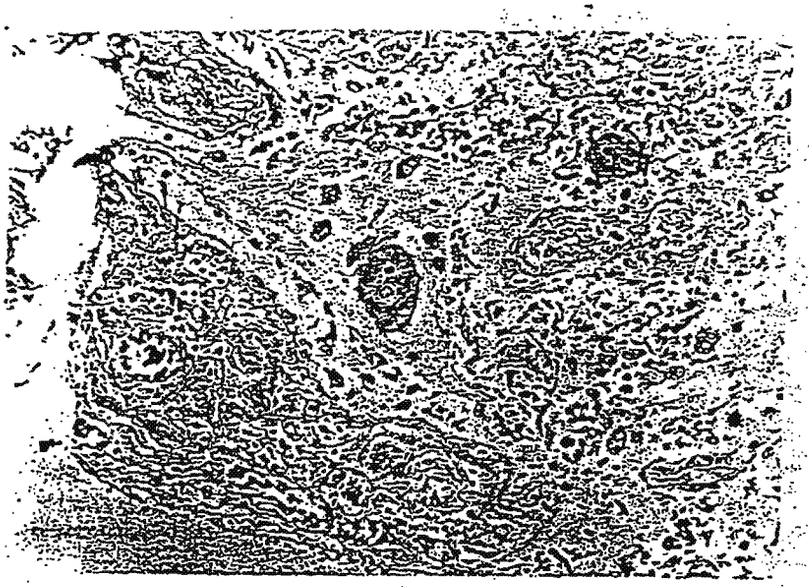

FIGURE 15-34
Chronic interstitial fibrosis with giant cells in a worker exposed to hard metal. (*Low power.*)

which will be similar to silicosis or mixed dust fibrosis depending on the amount of silica present.[167]

A high prevalence of lung cancer has been reported in the hematite miners from Cumberland, which is probably due to high levels of radon in the mines.

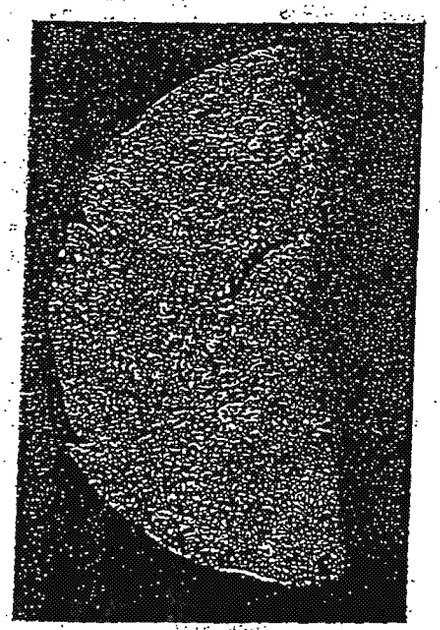

FIGURE 15-35
The lung from a subject who had been exposed to ochers for many years showing a diffuse reddish brown appearance and multiple stellate gray-brown lesions. (*See also Color Plate 4.*)

Welding is the process of joining two materials by fusion or coalescence under conditions of pressure and temperature. There are many different types of welding processes and workers will be exposed to a wide variety of airborne particulates depending on the process and other operations in the facility. The welding fumes will be contributed to by: (1) vaporization of the wire, rod, or metallic/alloying coatings; (2) decomposition and vaporization of the flux materials; (3) spatter from the arc region and weld pool and fumes therefrom; and (4) vaporization of the molten weld metal.[158] Welding fumes can comprise metal oxides such as iron, titanium, chromium, nickel, manganese, copper, zinc, and aluminum, organic materials, and crystalline materials such as silica and silicates. Welders can be exposed to asbestos. The lung's reaction to welding will therefore depend on the composition of the fumes and the cumulative exposure. Welders' lungs typically show large collections of dark brown spherical particles (iron oxide) and ferruginous bodies but little fibrosis (Figs. 15-36 and 15-37). However, a variety of pathologic responses have been described in the lungs of welders depending on the type of exposure and it should be realized that there is no such entity as welder's lung.

Nickel

Alloys and compounds of nickel have been in commercial use for over a century. Exposure to metallic nickel compounds in the forms of fumes and dusts can occur in nickel mining, refining, calcining, smelting, and electrolysis and in the production of nickel alloys. It has been known for a long time that a

FIGURE 15-36
Lung from an arc welder shows collections of dust-laden macrophages with little fibrosis. (Low power.)

high incidence of nasal and lung cancer has been associated with exposures to nickel during refining and these have become prescribed diseases. Workers involved in nickel mining and smelting have not exhibited the same levels of lung and nasal cancer risk as those in refineries. No excess risk of these cancers has been found among men working in nickel alloy production. However, because the majority of epidemiologic studies have lacked details of amounts and types of nickel compounds to which the workers have been exposed, it is not known precisely which nickel forms are carcinogenic.[166] No particular histologic type is specific to nickel exposure although squamous are the most frequent lung carcinomas.

Acute heavy exposures to nickel have caused diffuse alveolar damage. Exposure to nickel may cause occupational asthma.

Tin

A pneumoconiosis can result from the inhalation of tin dioxide (stannosis). This occurs principally among those who bag and sample the cassiterite or who smelt and refine the ores and metal. Tin dioxide ores (cassiterite) are mined in Cornwall, Great

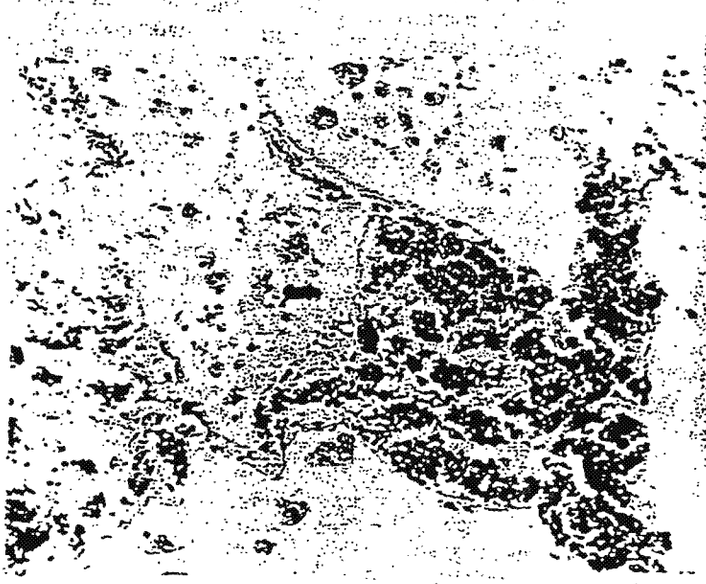

FIGURE 15-37
The same case as Fig. 15-36 shows the dust-laden macrophages. (Medium power.)

Britain, and Bolivia and those who mine the ore are also exposed to substantial amounts of silica. Therefore, in tin miners the major problem is silicosis and silicotuberculosis although in Cornwall the incidence has declined considerably since 1950.[169]

Stannosis, which is caused by exposure to tin per se, is characterized by striking radiologic opacities because tin has a high atomic number. However, the subject is usually well and shows little impairment in lung function.

Macroscopically, the lungs contain numerous gray-black macules up to about 5 mm in diameter.

Microscopically, the macules are characterized by numerous dust-laden macrophages associated with little if any fibrosis.[170] PMF does not occur. The particles are strongly birefringent. The dust content of individual lungs can reach 3 g tin dioxide. Microprobe analysis of the tissues will reveal the tin.

An inreased risk of lung cancer has been reported in Cornish tin miners but this was probably due to radon exposure.[171]

Titanium

Titanium dioxide is a white powder used in the dye industry. During the grinding of titanium dioxide, dust particles within the range 0.5 to 1.0 μm are released and can be inhaled into the lung. It is a very inert dust and in animals it is sometimes used as a negative control for inhalation studies. Elo and associates[171] studied the lung tissues from three factory workers employed in processing titanium dioxide pigments and found collections of macrophages containing black particles. These were situated around the bronchovascular bundles and in subpleural areas. The particles were birefringent when viewed with polarized light. There was little fibrosis.

A granulomatous pneumonitis has been described rarely in association with titanium exposure.[172]

ASBESTOS

Asbestos minerals are a group of naturally occurring fibrous silicates that possess good thermal, acoustic, and electrical insulating properties; they have flexibility and high tensile strength and are stable in alkaline and acid environments. Their use has been widespread and they have been incorporated into several thousand different products, including textiles, insulation products, cement, reinforced plastics, friction materials, filters, floor tiles, and paints. In fact, their use goes back several thousand years. They were used in the manufacture of Finnish pottery in 2500 B.C. The Romans knew of its fire-resistant properties. Asbestos has been referred to by Marco Polo in the thirteenth century and by Benjamin Franklin in the early eighteenth century.[173] It has been present ubiquitously in the environment for greater than 10,000 years since it has been demonstrated in Antarctic ice samples.[174] However, the major industrial exploitation of asbestos began in the 1870s when large deposits were found in Quebec (chrysotile) followed by Russia (chrysotile) and South Africa (crocidolite and amosite). The production and uses of asbestos throughout the world have increased from about 50 tons year in 1877 to a peak of nearly 6 million tons in the mid-1970s followed by a reduction to about 4 million tons in the 1980s. It should be realized that everyone is exposed to a low background level of asbestos and the normal lung contains a low level of asbestos fibers.

Asbestos minerals comprise two separate mineralogic groups: serpentine, the only member of which is chrysotile (white) asbestos, and the amphiboles, which comprise amosite, crocidolite, anthophyllite, tremolite, and actinolite. The major commercial forms have been chrysotile (90 to 95 percent) and crocidolite and amosite (5 percent).

Individual chrysotile fibers are pliable and curly with diameters averaging 0.06 μm.[175] Amphibole fibers, on the other hand, are straight, rigid and more brittle structures. The finest diameter amphibole fibers on average are crocidolite followed by amosite and the thickest are anthophyllite. Tremolite shows the greatest variation being relatively thick in some locations (e.g., California and Greenland) and thin in others (e.g., South Korea).[176] The physical forms of the fibers are important in their relative pathogenicity. The difference in chemistries between the fibers allows them to be readily identified in airborne and tissue samples by modern analytical transmission electron microscopy.

Exposure to asbestos can occur in a variety of ways, broadly classified by Zielhuis[177] into direct, indirect (bystander), paraoccupational (e.g., housewives washing their husbands' contaminated work clothes), neighborhood (living in the vicinity of asbestos mines, dumps, or factories), and ambient (in buildings where there are asbestos-containing materials). Table 15-10 gives a list of sources of exposure.

The level and size distribution of airborne fibers at these industrial sites will vary according to the amount of asbestos used, the manipulation processes (e.g., sawing, grinding, milling), and fiber type and this will determine the risk of disease. It is generally accepted that exposure to amphiboles is far more dangerous than chrysotile. This is because there is a

TABLE 15-10
Exposures to Asbestos Materials

Mining and milling of asbestos
Insulation work
Production of cement and cement products
Friction products
Shipbuilding
Textiles
Filters
Electrical work
Construction work
Railway work
Power stations
Iron and steel industry
Gas mask production
Paraoccupational (family) exposure
Neighborhood exposure—living near asbestos factories or dumps

differential rate of clearance from the lungs between chrysotile and amphiboles and it appears that it is the retained fiber burden within the lungs that is an important determinant of disease. Rapid clearance of chrysotile from the lung has been shown both in animals and human beings.[178–182] Even with continuing high exposure to chrysotile a steady state is reached after about 3 months and the level within the lung remains constant, whereas amphiboles are less rapidly removed and tend to accumulate over time if there is continuing exposure and this increased level persists after cessation. The half-life of amphiboles in the human lung is measured in decades. The clearance rate of fibers is also influenced by their length; short fibers are cleared efficiently whereas long fibers (> 10 μm) are not. Therefore, with increasing time following cessation of exposure the relative proportion of long fibers retained increases.[183,184] Animal inhalation studies using short-fiber preparations of asbestos and erionite produced little or no disease, whereas long-fiber preparations produced fibrosis and tumors.[185,186] Fiber clearance may also be inhibited by the concomitant exposure to other dusts such as quartz and titanium[187] and cigarette smoke.[188] No studies of exposure to asbestos in human beings have examined the possible potentiating role of other dusts in the disease-causing potential.

Exposure to asbestos may cause lung fibrosis (asbestosis), lung cancer, rounded atelectasis, parietal pleural plaques, diffuse pleural fibrosis, benign pleural effusion, and mesothelioma. The pleural lesions will be described in Chap. 34. However, it is worth making one very important point—exposures necessary to produce the pleural complications are far less than those required to produce asbestosis and lung cancer, probably one to two orders of magnitude difference.

Asbestosis (Including Airways Disease)

Asbestosis is defined as diffuse interstitial pulmonary fibrosis caused by asbestos exposure and the term should never be used for any pleural changes. The first histologically confirmed case was described in Great Britain by Murray in 1907 but it was not until 1924 that Cooke proposed the term "asbestosis" and published a detailed description of the disease. Following the report by Merewether and Price in 1930[189] asbestosis was officially recognized in the United Kingdom and included within the provisions of the Workmen's Compensation Acts and the Asbestos Industry Regulations were formulated. Over the decades these regulations have become progressively more stringent so that exposures to asbestos have decreased from well in excess of 100 f/mL before the 1930s to about 1 f/mL in 1980.[173]

The Merewether and Price study was of heavily exposed asbestos textile workers who showed a very high incidence of lung fibrosis with symptoms developing as early as 7 years after starting work and death occurring within 12 years. With reduction in airborne fiber levels in the workplace the disease has become less frequent and less severe. Asbestosis is usually seen after prolonged substantial direct exposure and the latency from first exposure to clinical pneumoconiosis usually exceeds 20 years. The prevalence of asbestosis is associated with age, cumulative exposure, fiber type, and smoking.[190–192] Clinically asbestosis may be associated with dyspnea, nonproductive cough, and basal crackles on auscultation. In advanced disease finger clubbing, cyanosis, and tachypnea may be present. However, many patients are asymptomatic.

Small irregular opacities are the radiologic hallmark of asbestosis although they are not specific. In particular the milder grades can be caused by smoking per se.[193,194] Pathologic examination of the lungs may reveal asbestosis when it is radiologically undetectable. Severe degrees of asbestosis may result in a honeycomb appearance although nowadays this is uncommon. Pleural abnormalities such as plaques or diffuse thickening may also be present. It has been claimed that computed tomography is more sensitive and specific for the recognition of asbestosis,[195] but this has not been validated by histopathologic studies of large series of cases.

The alterations in lung function in asbestosis are those found in restrictive forms of lung disease—a reduced vital capacity and reduced diffusion capacity for carbon dioxide. With progression the total lung capacity decreases.

MACROSCOPIC

When asbestosis is present there is frequently fibrotic thickening of the parietal and visceral pleura. In severe cases the lungs may be encased in a thick and often calcified covering of dense hyaline fibrous tissue. Parietal pleural plaques may be present. However, there is no correlation between the presence or extent of pleural change and the presence or extent of parenchymal abnormalities. In severe cases of asbestosis, if there is little or no pleural thickening, the pleural surfaces will appear bosselated. The lungs are reduced in size and show honeycomb changes, which are most marked in the lower and subpleural bases. In lesser degrees of asbestosis the lungs may just feel indurated or normal, but on microscopic examinations considerable fibrosis will be observed. At the earliest stage the fibrosis is observed as fine gray irregular streaks but with progression they become thicker and are associated with fibrocystic spaces (Fig. 15-38). Typically the changes are greatest in the lower zones but occasionally this is reversed. Because many of these subjects smoke, emphysema may also be present. This disease will counteract the tendency for shrinkage of the lungs and will be associated with an obstructive profile on lung function. It may be extremely difficult to assess the precise implications of asbestosis and emphysema to impairment of lung function and clinical disability and will require extensive sampling of the lung for microscopic evaluation.

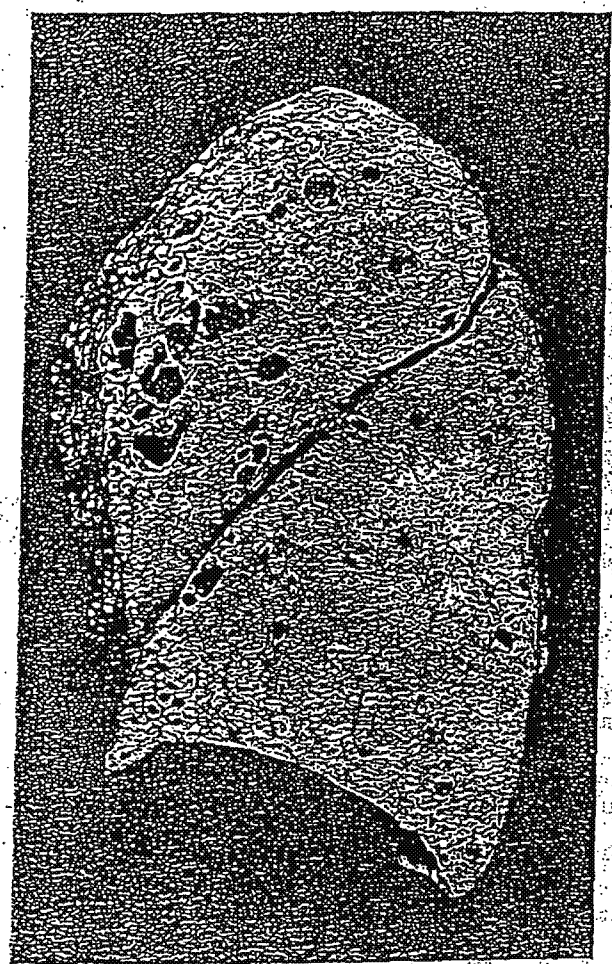

FIGURE 15-38
Lung shows extensive honeycomb change with a peripheral carcinoma in the upper part of the lower lobe.

MICROSCOPIC

Careful sampling of the lungs is necessary to diagnose and assess the severity of asbestosis. If a tumor is present the assessment should be on tissue away from the tumor and preferably on the contralateral side because tumors can result in local fibrosis. Tissue samples should be taken from the apex of the upper lobe, apex of lower lobe, and basal segments and major bronchus to include nodes,[17] but some authors have recommended as many as 15 blocks from each lung in cases suspected of asbestos-related disease.[196] The earliest changes are seen in and around the respiratory bronchioles with fibrosis of their walls. The next stage is extension proximally in the walls of the terminal bronchioles and distally in the walls of the alveolar ducts and adjacent alveolar septa. With further progression there is linking up by fibrosis of alveolar walls of adjacent respiratory bronchioles (Figs. 15-39 to 15-42). Obliteration of alveoli, alveolar ducts, and respiratory bronchioles by fibrosis then occurs, which leads to dilatation of the residual structures—so-called honeycomb change. The residual cystic spaces, which may measure up to 1.5 cm, may become lined on their internal surfaces by hyperplastic, cuboidal, or columnar epithelium, sometimes containing mucous cells. Squamous metaplasia may also occur. Cytoplasmic eosinophilic hyaline bodies, similar to the Mallory's hyaline observed in liver cells, has been observed in approximately 7 percent of cases of asbestosis.[197] The fibrosis is not uniformly distributed through the lung, the most extensive changes being seen in the lower lobes and subpleural area. However, with progression the microscopic changes will also be observed in the

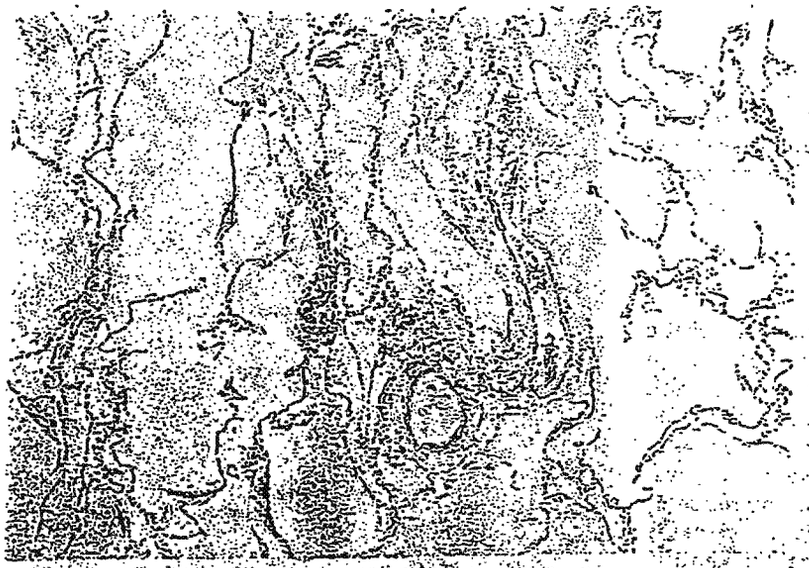

FIGURE 15-39
Slight fibrosis and dust accumulation around a respiratory bronchiole—grade 1. (Low power.)

upper lobes. The fibrosis will be accompanied by variable numbers of chronic inflammatory cells.

Several grading systems have been applied to these stages of asbestosis.[17,196,198] The following is a simple scheme based on microscopic examination.

Grade 1 Slight increase of reticulin and collagen around the respiratory bronchioles

Grade 2 Fibrosis around respiratory bronchioles, which extends into adjacent alveolar ducts, atria, and alveoli but does not join up with fibrosis extending from other respiratory bronchioles

Grade 3 Fibrosis that links up adjacent respiratory bronchioles and with little architectural distortion

Grade 4 Widespread fibrosis with or without honeycombing

Asbestos bodies are the hallmark of pulmonary fibrosis due to asbestos exposure. Because they form on asbestos fibers—nearly always amphiboles—they

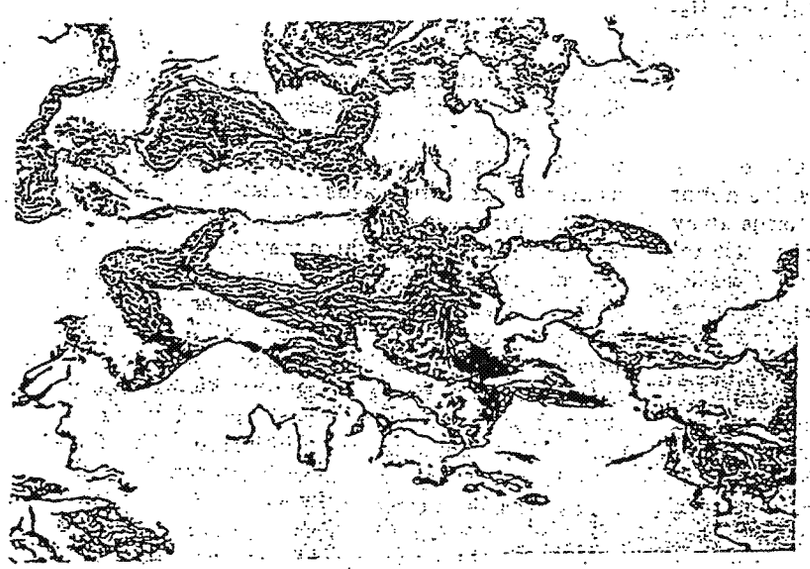

FIGURE 15-40
Slight fibrosis around a respiratory bronchiole with extension into adjacent alveolar walls—grade 2. (Low power.)

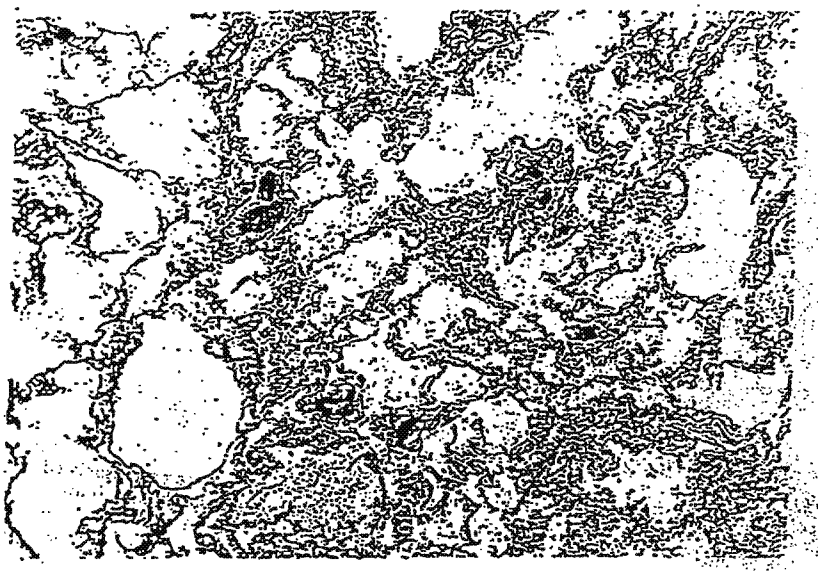

FIGURE 15-41
Interstitial fibrosis linking up adjacent lobules but with little architectural distortion—grade 3. (Low power.)

possess a clear fibrous core. They are coated with an iron–protein–mucopolysaccharide substance and appear as golden brown, beaded, dumbbell or drumstick structures (Figs. 15-43 to 15-45). They show positivity with Prussian blue stain because of the iron present. This can be used as a screening procedure for histologic sections. Asbestos bodies average 2 to 5 μm in diameter and usually exceed 20 μm in length. Great care needs to be taken in identifying them; it is the core that is important and it is characterized by a transparent fibrous appearance. There are other forms of ferruginous bodies that can be mistaken for them,[199,200] but their cores appear different. They can be located within the alveolar spaces or interstitium and in cases of moderate to severe asbestosis are usually easily found. When they are not easily found it is usual that the fibrosis has not been caused by asbestos exposure; it is uncommon in my experience to demonstrate a very high asbestos fiber lung burden by mineral analysis in such cases.

In the majority of instances only a minority of fibers become coated to form bodies (Fig. 15-46) and this depends on fiber length, fiber width, fiber type, and the presence of the dusts in the lungs.[201,202] In general, longer thicker fibers tend to become more easily coated than shorter thinner ones and amphi-

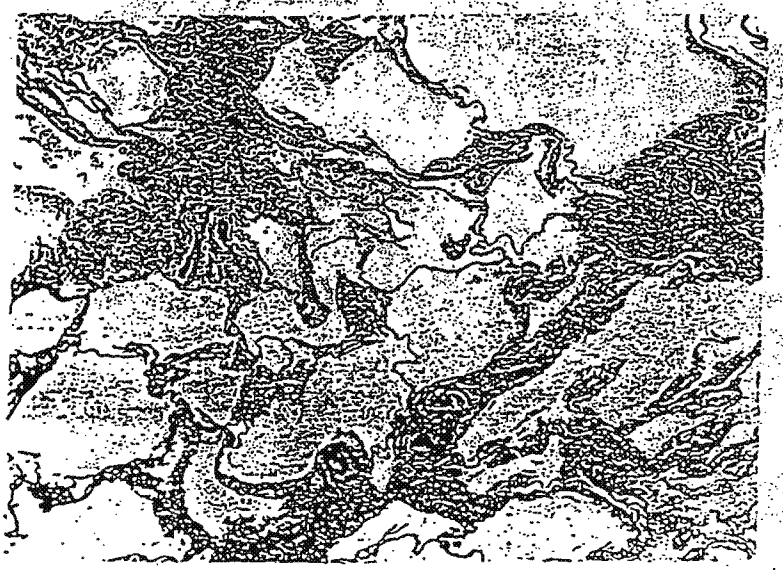

FIGURE 15-42
Severe interstitial fibrosis with architectural distortion—grade 4 lesion. (Low power.)

FIGURE 15-43
Grade 3/4 interstitial fibrosis associated with numerous asbestos bodies. (Low power.)

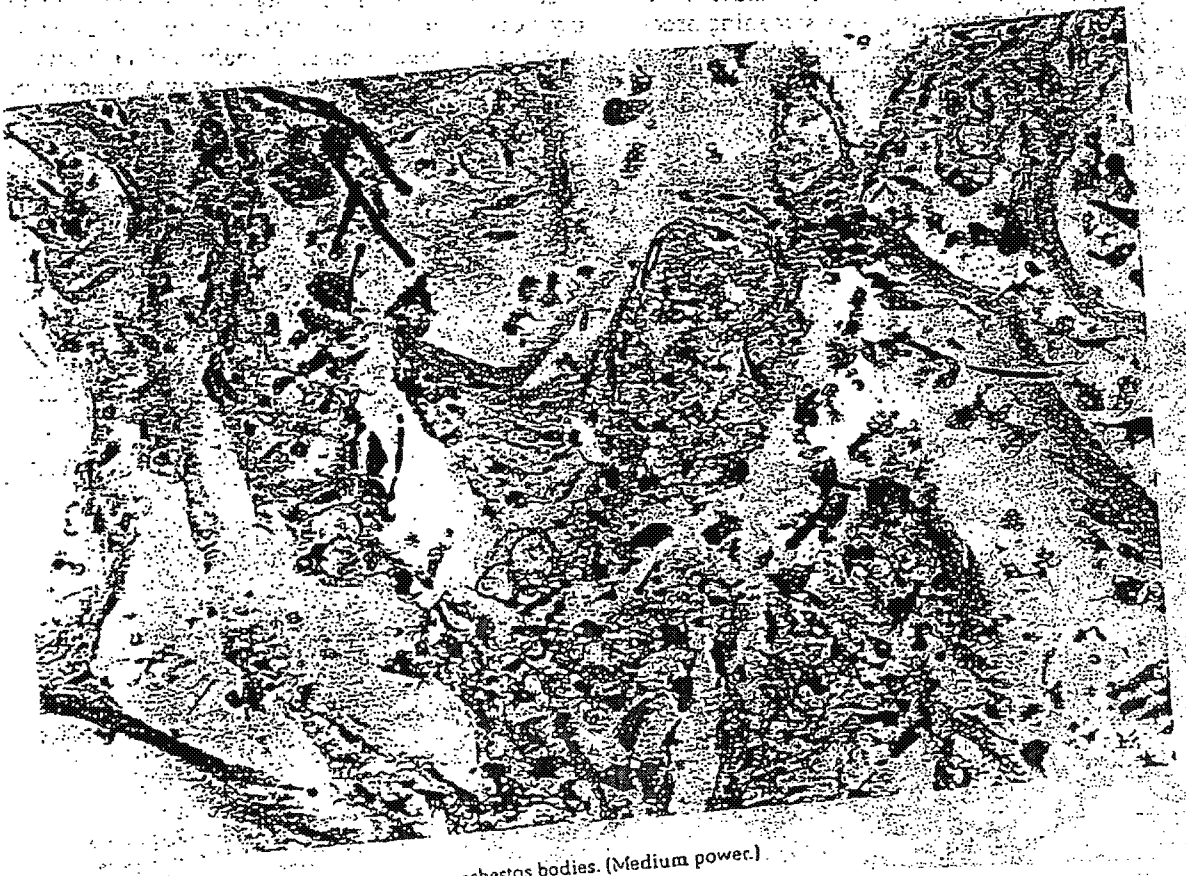

FIGURE 15-44
Same case as in Fig. 15-43 showing numerous asbestos bodies. (Medium power.)

FIGURE 15-45
Asbestos bodies with clear fibrous cores. (High power.)

boles more easily than chrysotile. Subjects with a high iron oxide content in their lungs, for example, welders and steel workers, tend to form ferruginous bodies more easily both on asbestos fibers and other mineral particles.[199] In these subjects great care has to be taken in evaluating lung fibrosis in relation to ferruginous body content because many of the ferruginous bodies will not be formed on asbestos. One can also use a grading scheme for asbestos bodies.[203] This shows a good correlation with asbestos fiber level determined microanalytically and extent of fibrosis. Other features that may be seen in cases of asbestosis are foreign body giant cells, often located around the asbestos bodies, osseous metaplasia within the fibrous tissue[204] and pulmonary blue bodies.

Some authors have agreed that peribronchiolar fibrosis associated with asbestos bodies (i.e., grade 1 asbestos) should not be called asbestosis but "mineral dust mining disease."[203] This is largely a matter of semantics. However, it should be realized that peribronchiolar fibrosis is frequent in the lungs of routinely autopsied subjects in whom no exposure to asbestos has occurred and in most cases is related to cigarette smoking. Secondly, a variety of other mixed dusts including silica, coal dust, iron oxide, and aluminum oxide can be associated with similar changes. Mineral analysis is required in this situation to assess the relationship to asbestos. However, these changes on their own are unlikely to be of great functional significance. Also they are unlikely to be progressive unless the asbestos fiber load within the lung is great enough to cause such changes.

FIGURE 15-46
Electron microscopic appearance of naked amphibole fibers and asbestos bodies.

DIFFERENTIAL DIAGNOSIS

The macroscopic and microscopic changes within the lungs are similar in both idiopathic pulmonary fibrosis and asbestosis except for the presence of numerous asbestos bodies indicating a heavy asbestos fiber load. Pleural thickening and plaques are more common in cases of asbestosis. However, pleural changes result from much lower levels of exposure than asbestosis. Cases of idiopathic pulmonary fibrosis can occur in subjects with asbestos exposure,[208] and they may also show pleural changes but examination of the lung tissues will reveal scant or absent asbestos bodies. Mineralogic analysis of these cases is useful in demonstrating a relatively low fiber level.

The diagnosis of asbestosis should not be made on small biopsies because they are frequently unrepresentative. Also if a tumor is present in the lung, fibrotic changes in the vicinity should not be overinterpreted because tumors frequently result in fibrotic changes per se. If one is dealing with a postmortem case the assessment of fibrosis is best performed on tissue specimens obtained from the nontumorous lung.

Sarcoidosis, extrinsic allergic alveolitis, and histiocytosis X also have to be distinguished from asbestosis. They tend to show a greater upper zonal distribution of fibrosis although there are exceptions to this. The demonstration of granulomas or foci of histiocytosis X will exclude asbestosis. If there are any doubts mineralogic analysis will be helpful.

Other mineral dusts including talc, mica, kaolin, and hard metals can result in interstitial fibrosis. Lung fibrosis induced by nonfibrous silicates is associated with extremely heavy mineral burdens,[203] and there should be a good history of exposure and numerous easily identified mineral particles within the lung. Mineral analysis can be helpful in this situation.

Hammar has reported focal ossification in about one-third of cases of grade 4 (severe) asbestosis[207] and has implied that it is helpful in distinguishing asbestosis from interstitial pulmonary fibrosis (Fig. 15-47). However, this feature may be seen in interstitial pulmonary fibrosis and the most reliable diagnostic indicator is a high level of asbestos within the lungs whether determined by asbestos body content or mineralogically.

Asbestos-Related Lung Cancer

The link between lung cancer and asbestos exposure was first established by the systematic epidemiologic studies of Doll[208] and Breslow[209] published in 1955. In 1979, Hammond and colleagues published a study examining the effects of smoking and asbestos exposure and the risk of the development of lung cancer.[210] They found that the effect of smoking and asbestos exposure on the risk of lung cancer was multiplicative. It should be realized, however, that this risk was applicable to a heavily exposed group of insulation workers, nearly all of whom had asbestosis[211] and should not be applied to all other groups of asbestos-exposed workers. The excess lung cancer risk was much less in other cohorts and varied with industrial process, being relatively high in textile workers and very low in friction products and asbestos cement manufacturing.[212] In some groups the risk was between additive and multiplicative.[213] It is rare to observe a lung cancer in a nonsmoking individual exposed to asbestos.

The risk of lung cancer also varies with fiber type; consistently lower rates occur in occupational cohorts exposed to chrysotile relative to similar cohorts exposed to amphiboles. For example, the standard mortality rate for lung cancer for chrysotile mining and milling is 125 whereas for amphibole mining and milling it is 264.[213]

FIGURE 15-47
Severe interstitial fibrosis with an area of ossification. (Low power.)

The latent period from the first exposure to asbestos and the development of an asbestos-related lung cancer is usually in excess of 20 years and usually requires prolonged heavy direct exposure. Churg reviewed the literature pertaining to lung cancer type and asbestos exposure and found that all the major histologic types occurred.[215] However, there are several limitations to this kind of analysis. In many studies there has been no attempt to separate within the cohorts those tumors that are related to asbestos exposure and those that are not. Similarly little attempt was made to control for confounders such as sex and year of diagnosis. A study by Johansson and associates,[216] which controlled for these factors, found that there was an association between adenocarcinoma of the lung and a peripheral localization with asbestos exposure. However, the data are still not sufficient to use the histologic type of carcinoma in an asbestos-exposed worker for ascription or not of lung cancer to asbestos exposure.

There is now reasonable evidence to use the presence or absence of asbestosis as the criterion for ascribing a lung cancer to asbestos (see Fig. 15-38). Epidemiologic and histopathologic studies have indicated that lung cancer risk from asbestos exposure is increased in those industries where asbestosis occurs but not in those where it does not and that it increases with severity of asbestosis.[217,218] Furthermore, the increase appears to develop when there is radiologic evidence of fibrosis,[219] and this corresponds to histopathologic grades of 2 or 3 or greater. Animal studies have shown a strong link between the development of lung fibrosis and tumor formation.[220]

Nonasbestos Fibers

These include natural and synthetic fibers (Table 15-11), a proportion of which are respirable and therefore potentially pathogenic. Information concerning their health effects is limited but continued vigilance for possible health effects from exposure to these fibers should be maintained because of the long latent periods between first exposure to a fiber and the development of pleural and pulmonary disease. Their use as asbestos substitutes, particularly the synthetic fibers, has been increasing over recent years.

The natural group includes sepiolite, attapulgite (palygorskite), wollastonite, and zeolite. The information on these fibers is very limited. Attapulgite exposure has been linked to lung cancer[221] and wollastonite has been associated with pleural plaques and lung fibrosis.[222] Further studies of these fibers are needed. Environmental exposures to erionite (a fibrous zeolite) have been associated with very high rates of mesothelioma and lung cancer in three villages in Turkey.[223] In animal inhalation studies erionite has produced the highest rate of mesothelioma from any known fiber.

TABLE 15-11
Commonly Used Inorganic Nonasbestos Mineral Fibers

Natural	Synthetic
Sepiolite	Mullite
Attapulgite/palygorskite	Glass
Wollastonite	Wool
Zeolite	Fiber
	Continuous filament
	Mineral wools
	Rock
	Slag
	Ceramic

The synthetic group includes a variety of different fibers and both workers and the general public have been exposed to them. Mullite fibers are frequently found in the lungs of normal individuals because the fibers are formed from combustion of fossil fuels; increased numbers are found in the lungs of coal-fired power station workers but they do not appear to have any pathogenetic significance.

The other fibers are rarely encountered on mineral analysis of human lungs. This is probably because the majority are not durable in lung tissues. The majority of epidemiologic studies of glass wool, rock/slag wool, and continuous filament production workers have not shown an increased risk of lung cancer or mesothelioma. A few studies have shown an excess of lung cancer in rockwool and slagwool production workers but this has been in the workers in the early production phase and the studies have not been well controlled for confounders such as smoking and asbestos. In summary, the excess lung cancer mortality found in some production workers may not necessarily be caused by exposure to airborne manmade mineral fibers.[224,225]

There is some concern about refractory ceramic fibers because these are durable in lung tissues. Animal inhalation studies with these fibers have produced lung cancers and mesotheliomas.[226] They have been produced in limited quantities and only represent approximately 1 to 2 percent of world production. They have been used in paper, boards, blan-

kets, and heat-resistant linings of furnaces. No mesotheliomas or lung cancers in humans have been linked to refractory ceramic fiber exposure so far.

ORGANIC DUST DISEASE

A simple classification of organic dust diseases is shown in Table 15-12.

Occupational Asthma

"Occupational asthma is asthma which is due, in whole or part, to agents encountered at work."[227] Largely due to better recognition, but also due to an increased number of chemicals in the workplace, the prevalence of occupational asthma has increased over the last two decades. More than 200 chemical agents have been implicated in its causation. Some of the most frequent are isocyanates, anhydrides, colophony, metals, animal proteins, wood dusts, and grain and flour dusts. Occupational asthma is now the most prevalent occupational lung disease in developed countries.[228]

There is a lag period varying from months to years after starting a job before symptoms commence. Initially, symptoms occur at work and improve when the subject is away from the workplace but as the condition progresses the symptoms may become persistent and the typical work related pattern lost.

Agents can cause occupational asthma by several mechanisms.[229]

1. *Immunologic*—through an immunoglobulin (IgE)-dependent mechanism where specific IgE antibodies can be identified in the subject. Positive skin tests to the antigen may be present, although these do not always coincide with symptoms and may therefore be a marker of exposure rather than disease. This is usually induced by high molecular weight compounds such as animal and plant proteins.

Through non–IgE-dependent mechanisms but probably involving cell-mediated immunity. Specific IgE antibodies to offending agents are not usually identified in the subjects. The majority of low molecular weight compounds that cause occupational asthma act through this pathway, for example, isocyanates, colophony, and wood dusts.

2. *Nonimmunologic*—In this type reexposure to small amounts of the offending agent does not cause the symptoms. Some may be due to direct irritant or pharmacologic reactions.

The pathologic changes for each type of occupational asthma have not been well studied but appear to be similar to those of nonoccupational asthma.

TABLE 15-12
Classification of Organic Dust Diseases

Allergic	Occupational asthma
	Humidifier fever
	Byssinosis
	Hypersensitivity pneumonitis
Toxic	Acute organic dust toxic syndrome (mycotoxicosis)

Byssinosis

Byssinosis, derived from the Greek work meaning flax, is the term applied to respiratory disease caused by the inhalation of cotton dust and now also caused by flax and hemp.

For over a hundred years it had been recognized that some of the workers engaged in the Lancashire cotton mills developed a chest disease similar to chronic bronchitis. It has also been reported among cotton mill operatives in North and South Carolina. A similar illness has been described among flax workers in Northern Ireland,[230] and hemp workers in Italy and France.[231] In the cotton industry it occurs particularly among those employed in blowing and carding the raw cotton, formerly a very dusty process and the prevalence is increased in cigarette smokers.[232]

Clinically, the condition presents as a tightness of the chest, cough, and asthmatic wheezing, which is most noticeable when the operative returns to work on Monday after being away from the mill for the weekend. It does not usually develop with less than 20 years of exposure. Roach and Schilling[233] divided the severity of byssinosis into several grades.

Grade 0	Symptomless on Mondays
Grade 1/2	Occasional chest tightness on the first working day of the week or mild symptoms such as irritation of the respiratory tract
Grade 1	Chest tightness or breathlessness on the first day of the working week only
Grade 2	Chest tightness or breathlessness on the first and other days
Grade 3	Chest tightness or breathlessness accompanied by permanent respiratory incapacity from reduced ventilatory capacity

Edwards and coworkers[234] studied the lungs from 43 byssinotics and found that the proportions of

mucous gland, muscle, and cartilage were increased in the named bronchi. Emphysema does not appear to be increased.[235] So-called byssinosis bodies have been described but these are probably ferruginous bodies formed on carbonaceous material and are neither specific for nor found in every case of byssinosis. It will be realized from this description that the pathologic changes are nonspecific and the diagnosis has to be made on clinical grounds.

Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)

See Chap. 13.

Humidifier Fever

Subjects exposed to "conditioned" air contaminated by microorganisms such as bacteria and fungi can develop a condition called humidifier fever, characterized by mild malaise, fever, sweats, cough, breathlessness, and generalized aches. It usually develops on the first day of work after a weekend or holiday but resolves spontaneously within a day or two even though there is continued exposure. The pathology and pathogenesis of the condition are unknown. The clinical and laboratory changes are similar to those of acute extrinsic allergic alveolitis except radiologic changes are absent and it does not progress to lung fibrosis.

Acute Organic Dust Toxic Syndrome (Mycotoxicosis)

This syndrome follows exposure to very high levels of organic dust containing fungal spores and hyphae and it is thought to act through a toxic rather than a hypersensitivity mechanism.[238,237] It has been described in farm workers who have unloaded storage silos, cotton workers ("mill fever"), and storage elevator workers ("grain fever"). After exposure the subject develops an acute influenza-like illness and crackles are frequently heard on auscultation. Chest radiographs show diffuse infiltrates. The disease is usually self-limiting although it may persist for several days. It shares many features with acute farmer's lung and silo-filler's disease, which is due to nitrogen dioxide toxicity.

Few cases have been studied pathologically. A neutrophilic infiltrate affects bronchioles, alveoli, and interstitium and fungal spores may be present. Granulomas are not seen (cf extrinsic allergic alveolitis). Bronchoalveolar lavage fluid taken within a few days of the onset shows an increased number of neutrophils and frequently fungal spores.[238]

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