to repeated Mantoux testing is negative.[2150] It may be extremely difficult to isolate tubercle bacilli during life in patients with progressive massive fibrosis, despite subsequent postmortem demonstration of active tuberculous infection.[2817]

## ASBESTOSIS

Asbestosis is the most important member of the group of pneumoconioses known as the *silicatoses*, in which salts of silicic acid are the exciting agents. The importance of asbestos lies not only in the hazard it presents to those involved in its mining, but also, and perhaps more importantly, because of its extensive use in a wide variety of occupations. In addition to asbestos, three other silicates can cause pneumoconiosis—talc, kaolin (china-clay), and mica.

### Epidemiology

The use of asbestos in industry has increased enormously during the past half century—world production has jumped from 500 tons in 1900 to 3 million tons in 1968.[2818]

The prevalence of the mineral throughout the world and its potentially hazardous effects on man is indicated by the large percentage of cases in which asbestos bodies are found at routine necropsy: this incidence ranges from 24.3 per cent in London[2819] to 41 per cent in Pittsburgh[2820] and 48 per cent in Montreal.[2821] As has been pointed out by Anjilvel and Thurlbeck,[2821] these reported differences in incidence probably indicate only the different pathologic techniques by different observers. However, it is noteworthy that these results were obtained on unselected routine necropsy series—not on asbestos workers; similarly, they represent the incidence of demonstrable asbestos bodies, not the morphologic state characteristic of asbestosis. It also is of some importance that proof is lacking that these "asbestos bodies" are, in fact, derived from asbestos. The finding of asbestos bodies in the lungs during routine necropsies occurs more commonly in males and in urban residents; fibrosis, usually of only minimal degree, is found in some of those with multiple asbestos bodies.[2822]

Exposure to asbestos dust in sufficient quantity and long enough to produce disease occurs most commonly in miners. Industrial occupations that may be hazardous include asbestos weaving or spinning and steam-pipe lagging. One report of the development of asbestosis in a worker engaged in automobile undercoating[2823] indicates the hazard of this occupation, although a survey of other workers in this field showed no other cases, perhaps because few remain for long in this uncomfortable occupation. A unique characteristic of asbestos is that it may produce pleuropulmonary disease in persons not directly involved in mining or processing but merely living in the *vicinity* of these activities;[807, 2825, 2826] in fact, the disease can develop in those who repeatedly handle the clothes of asbestos workers.[2819]

Asbestos exists in several forms, and the manifestations of asbestosis may vary according to the variety of asbestos to which an individual is exposed. This applies particularly in mining, since most commercial asbestos is a mixture of types. The ore leaves the mine as crushed rock containing a silicate of iron, magnesium, and aluminum which, when refined, is composed of fibers which can be spun, woven, or carded. The most common form is *chrysotile* (white asbestos), which is produced mainly in Quebec and consists of hydrated magnesium silicate extracted from serpentine rock. This fiber appears to have less malignant properties than the long blue fiber known as *crocidolite* which is found largely in South Africa and contains mostly iron rather than magnesium. The short-fibered *amosite* (brown asbestos) also is found largely in South Africa and is predominantly iron-containing. *Anthophyllite* and *tremolite* are mined principally in Finland[2827] and have a strong propensity to incite pleural reaction in the form of plaques, not only in miners but also in persons living in the vicinity of the mines.[807]

The asbestos fiber is inhaled and, despite its length (100$\mu$ or more), reaches the respiratory bronchioles and alveoli. This remarkable tendency for such a long fiber to penetrate so deeply into the lung parenchyma is probably explained by the relationship between the falling speed of a fiber and its diameter:[2828] with a diameter of about 3$\mu$, the asbestos fiber has a slow falling speed which allows it to escape deposition in the upper airways.

### Pathologic Characteristics

As with other pneumoconioses, the development of pulmonary or pleural disease in asbestosis appears to depend on a combination of the degree and the length of exposure. Characteristically, manifestations of the disease do not appear until 20 to 40 years after the beginning of exposure. The precise mechanism by which the fibers produce pulmonary and pleural disease is not known, but mechanical irritation by the fiber and the slow liberation of silicic acid as it decomposes may act individually or in combination. As with silica particles the asbestos fiber becomes coated with protein, and this gelatinous coat probably protects the pulmonary tissue to some extent. It may be that the precipitated protein and subsequent fibrosis represent antigen-antibody formation and the effect of antibody on the tissues. The fiber is relatively soluble compared with quartz dust, which may explain the diffuse nature of the fibrosis and the relative paucity of asbestos bodies in advanced asbestosis.[2801]

In experimental asbestosis, the fibers are found first in bronchioles and respiratory bronchioles and within a few hours in alveoli: peribronchiolar edema and intra-alveolar hemorrhage result. Botham and Holt[3720] have beautifully illustrated the formation of asbestos bodies: these are formed by the deposition of ferritin on the asbestos fibers within macrophages, first as a smooth coating and then in the form of beading as the macrophages shrink and rupture. Fibrosis first occurs in the peribronchiolar region and then in the interstitium. Varying degrees of fibrosis and distortion result, ranging from relative preservation of lung architecture to gross distortion with formation of microcysts and honeycombing (bronchiolectasis). Asbestos fibers lie both in the interstitium and free in air spaces. Striking pleural thickening is usually present.

The pleural changes are thought to be due to penetration of the visceral pleura by the asbestos fiber, with irritation of the parietal pleura and subsequent fibrosis of this layer. Using a technique of incineration and phase-contrast microscopy, Hourihane and colleagues[2819] detected asbestos fibers within pleural plaques, an observation which has led to the use of pleural biopsy to establish the diagnosis.

### Roentgenographic Manifestations

The roentgenographic changes in the chest in asbestosis may be both pleural and parenchymal, but only recently was it recognized that the former are far more striking than the latter.[597, 2827] The accuracy with which the commonly accepted roentgenographic signs may be recognized is rather poor; in their 1960 observer-error study, Williams and Hugh-Jones[2829] showed wide disparity in the opinions registered by 11 experienced observers in assessing the roentgenograms of patients with established asbestosis.

The roentgenographic changes in the lungs may be divided into three stages:[655] (1) a fine reticulation occupying predominantly the lower lung zones, associated with a "ground-glass" appearance which has been attributed to pleural thickening although without absolute justification;[2830] (2) a stage in which interstitial reticulation becomes more marked; a combination of parenchymal and pleural changes leads to partial obscuration of the heart border—the so-called "shaggy-heart" sign—and of the diaphragm (Figure 12-10); and (3) a late stage in which reticulation becomes visible in the mid and upper lung zones and the cardiac and diaphragmatic contours become more obscured.[655, 2808] Hilar lymph-node enlargement is seldom if ever notable.[2831]

The *pleural* manifestations dominate the picture roentgenographically:[597, 2827] of 56 cases described by Freundlich and Greening,[2827] 48 per cent showed pleural thickening alone, 41 per cent showed combined pleural and parenchymal manifestations, and only 11 per cent showed parenchymal changes alone; the shaggy-heart sign was observed in 20 per cent. A similar predominance of pleural over parenchymal changes was reported by Anton:[2830] of 40 patients with proved asbestosis, only five had parenchymal changes in the lung bases, pleural plaques being the sole manifestation of the disease in the other 35.

Pleural thickening or pleural plaques usually are bilateral (Figure 12-10), more prominent in the lower half of the thorax, and tend to follow the rib contours.[2819] The frequency of pleural calcification is variable; Anton[2830] reported finding calcified and noncalcified plaques in roughly equal numbers of his 40 cases, whereas

*Figure 12–10.* Asbestosis. This 61-year-old man had been involved in asbestos mining for many years. A posteroanterior roentgenogram (*A*) reveals severe disorganization of lung architecture, most of the lungs being the site of a very coarse reticulation which in the right base has become confluent resulting in obliteration of the right hemidiaphragm. The central lung zones appear to show considerable emphysema. Marked pleural thickening is present over both lungs particularly in the apical and axillary regions. A spontaneous pneumothorax is present on the left. Four months later, an anteroposterior roentgenogram (*B*) reveals marked deterioration in the appearance of the chest; the lungs have undergone further loss of volume, and much of the reticulation, particularly that in the lower lung zones, has become confluent resulting in obliteration of the heart borders (the "shaggy heart" appearance) and diaphragm. On neither of these roentgenograms is there evidence of hilar lymph-node enlargement or pleural calcification.

B

Freundlich and Greening observed calcification in only 21 per cent of their 56 cases.[2827] In an American survey of 261 workers exposed to asbestos in industry, calcified pleura was found in none,[2832] whereas in Finland it is common,[807] a difference in incidence which probably relates to the variety of asbestos concerned. Regardless of which figures are accepted, it is clear that noncalcified plaques occur often enough to be regarded as strongly suggestive evidence of asbestosis; in fact, Anton[2836] believes that the roentgenographic appearance of multiple pleural plaques is so specific that in the absence of an occupational history of exposure to the related minerals, talc and mica, exposure to asbestos can be concluded when the plaques are present.

In contrast to the visceral pleural involvement which characterizes previous hemothorax or empyema, the plaques of asbestosis arise from the parietal pleura, most commonly over the anterolateral chest wall and the central diaphragmatic domes.[805–807, 2833] It may be difficult to visualize uncalcified plaques, particularly *en face*, and tangential roentgenograms may be necessary. Calcified plaques vary from small linear or circular shadows commonly situated over the diaphragmatic domes to complete encirclement of the lower portions of the lungs.[2834] When calcification is minimal, a roentgenogram overexposed at maximal inspiration facilitates visibility.[2831]

## Clinical Manifestations

SYMPTOMS AND SIGNS. It is probable that the great majority of patients with pleuropulmonary asbestosis have no symptoms.[655, 807] Rarely, an acute pleural effusion is considered to be precipitated by asbestos fibers, in which circumstances the patient experiences acute pleural pain.[2835] Symptoms, which seldom develop before at least 20 to 30 years' exposure,[2836, 2837] include shortness of breath on exertion and cough, sometimes with mucopurulent sputum. Physical examination may reveal evidence of deformity of the thoracic cage, due to underlying pleural disease, even in symptom-free patients.[807] Basal crepitations may be present, and finger-clubbing occurs in many cases.[2837] Asbestos bodies are almost invariably found in the sputum of patients with roentgenographic evidence of the disease, even in the absence of symptoms.[2836]

PULMONARY FUNCTION STUDIES. Correlation is poor between the roentgenographic changes in asbestosis and the physiologic measurements of function. Function may be impaired despite a normal chest roentgenogram; on the other hand, roentgenographic changes may be extensive with little evidence of dysfunction.[2734] Function tests in patients with parenchymal involvement show a decrease in VC and sometimes in RV, with relatively well-preserved ventilatory capacity. Ventilation-perfusion inequality appears to occur early in the disease and is mirrored in a decrease in diffusing capacity and increase in alveolar-arterial oxygen difference. Exercise may provoke hypoxemia, but the $P_{CO_2}$ is normal or low; pulmonary compliance characteristically is greatly reduced.[2816, 2837, 2839, 2840]

## Relationship to Neoplasia

Of all non-neoplastic pulmonary diseases, asbestosis undoubtedly has the highest incidence of associated neoplasia, especially bronchogenic carcinoma, bronchioloalveolar carcinoma, and particularly mesothelioma.[1861, 2819, 2825–2827, 2831, 2835, 2841–2849] In fact, Doll[2846] concluded that cancer of the lung is a specific industrial hazard of certain asbestos workers and that the average risk for men thus employed for 20 years or more is ten times that for the general population. Selikoff and colleagues[1861] reported an incidence of bronchogenic carcinoma in patients with a history of long and heavy exposure to asbestos six to eight times that expected. Lung cancer is usually of oat-cell or anaplastic type, although squamous-cell carcinoma and adenocarcinoma also have been reported.[1874, 2846]

A latent period of at least 20 years' exposure is characteristic of those asbestos workers in whom pleuropulmonary malignancy develops.[2665] Even when fibrosis is of only minimal degree, asbestos bodies are present in the lung parenchyma and in some cases in the neoplasm also.[1874] Patients very heavily exposed to asbestos may die of asbestosis and cor pulmonale before sufficient time has elapsed for the development of neoplasia. In a follow-up

of 370 asbestos workers with heavy exposure, Selikoff and colleagues[3018] found the incidence of death due to bronchogenic carcinoma, mesothelioma of the pleura and peritoneum, and gastrointestinal carcinoma to be significantly higher than expected. Their results indicated a synergistic carcinogenic effect of cigarette smoking and asbestos exposure: non-cigarette smokers did not die of bronchogenic carcinoma, although three succumbed to asbestosis and one to mesothelioma.

The incidence of associated neoplasia appears to relate to the type of asbestos involved. The crocidolite variety is the most commonly implicated, particularly with mesothelioma, a relationship which was first described by Wagner and associates[2826] in crocidolite miners and in residents in the vicinity of the mines. Most authors report a similar although less-marked relationship between chrysotile exposure and mesothelioma.[2825, 2843] In their study of chrysotile miners Elwood and colleagues[2845] found no increase in incidence of mesothelioma but more deaths than expected from bronchogenic carcinoma; an extensive study by Braun and Truan[2850] of asbestos workers in Quebec, the main source of chrysotile asbestos, revealed no evidence of a greater incidence of bronchogenic carcinoma in these men than in the general population of Canada and the U.S.A.

Hourihane[2847] established criteria for differentiating mesothelioma from simple pleural fibrosis and concluded that diffuse mesothelioma could be diagnosed with reasonable accuracy from histologic examination of small pieces of tissue; consequently, he considers that needle biopsy is usually sufficient to permit this differentiation.

The incidence of peritoneal mesotheliomas also is greater in patients with asbestosis.[2841, 2842] Enticknap and Smither[2842] described 11 patients with peritoneal neoplasms, all of whom had worked in the same asbestos factory. Curiously, one group of observers[1861] found an unexpectedly large number of insulation workers exposed to asbestos who died from carcinoma of the stomach or rectum, despite a death rate for other cancers which was within the expected limit. The reason for this incidence is not known.

## Talcosis

This relatively uncommon variety of *silicatosis* results from many years' exposure to high concentrations of fibrous or tremolite talc (magnesium silicate).[2851, 2852] The disease has been described in miners, millers,[2853] rubber workers,[2854] and soap-stone workers.[2855]

### Pathologic Characteristics

In several cases necropsy has revealed diffuse and nodular fibrosis with scattered asbestos-like bodies and numerous birefringent particles, resembling short needles, within the nodules.[2854, 2856] Irregular areas of fibrosis surround bronchioles and small vessels, resulting in dilatation of the former.[2734]

### Roentgenographic Manifestations

The sheet-anchor in the roentgenologic diagnosis of talcosis is pleural plaque formation. These are often diaphragmatic in position and may be massive, often bizarre in shape and extending over much of the surface of both lungs (*see* Figure 4-166, page 368)[2852, 2857] and sometimes involving the pericardium. The incidence of pleural abnormality in talcosis is similar to that in asbestosis; in a study of 221 workers exposed to tremolite talc, Smith found pleural plaques in 14 (6.3 per cent).[2852] Parenchymal involvement is said to be similar to that in asbestosis,[2854, 2857, 2858] the roentgenographic pattern being one of general haziness, nodulation, and reticulation, with sparing of the apices and costophrenic sinuses.[2858] Some cases may show confluence of lesions, giving a tumor-like appearance (Figure 12-11).[2859]

### Clinical Manifestations

Symptoms are similar to those of any other disabling pneumoconiosis and include dyspnea and productive cough. Decreased breath sounds (presumably due to pleural thickening), rales at the lung bases, limited chest expansion, and finger clubbing are found on physical examination.[2857, 2860] In a study of 110 men employed in the mining and processing of soap stone in Sweden, Ahlmark and asso-


*Figure 12–11.* Pulmonary Talcosis. This 31-year-old woman had noted the onset of dyspnea on exertion several months previously and at the time of this roentgenographic examination could only climb ten stairs without stopping; on occasion, she awoke at night gasping for breath and had to use two pillows to sleep. There was no cough or recent hemoptysis. A posteroanterior roentgenogram (*A*) reveals extensive involvement of both lungs by a rather coarse reticular pattern. In the upper axillary zone on the right and in the left mid-lung (*B*) are two areas of homogeneous consolidation possessing poorly-defined margins. Paratracheal lymph-node enlargement is present bilaterally, more marked on the left. At thoracotomy, biopsies obtained from lung and lymph node revealed multiple fibrotic and hyalinized granulomata lying in close proximity to blood vessels and containing extremely numerous doubly-refractile crystals. In view of these findings, the patient was questioned further regarding her habits and finally admitted (somewhat reluctantly) to an extraordinary history of excessive inhalation of lavender-scented talcum powder during a three-month-period when she was pregnant two years previously; she was in the habit of spreading the talcum powder liberally over her pillow and blankets at night and actually inhaled it in large amounts from her cupped hands! Subsequent assay of the doubly-refractile particles observed histologically proved them to be talc.

ciates[2855] found five cases with at least 20 years' exposure who showed minimal roentgenographic evidence of pneumoconiosis and no restriction of work capacity. Diffusing capacity is said to correlate with the extent of parenchymal involvement seen roentgenographically. We studied one case, proved by biopsy, in which both VC and RV were moderately decreased and repeated measurement of the steady-state DLco was less than 50 per cent of predicted normal.

### Kaolin (China-Clay) Pneumoconiosis

This rare form of *silicatosis* is due to the inhalation of a mixture of sand, mica, and aluminum silicate. The initial process in the mining of china clay is wet, so that exposure to the dust does not occur until the material is dried in kilns and subsequently placed in bags. The incidence of significant chest disease varies in reported series; in one study of 5130 workers in the kaolin industry,[2861] it was concluded that their general state of health varied little from that of the regional general population of corresponding age and race. By contrast, in a study of 553 Cornish china-clay workers exposed to kaolin dust for periods exceeding five years, 48 (9 per cent) showed clinical and roentgenographic evidence of disease; findings were positive in 23 per cent of those exposed for more than 15 years.[2862]

The roentgenographic pattern varies widely: there may be no more than a general increase in lung markings; with prolonged and severe exposure, a diffuse nodular and miliary mottling is present; and a late manifestation is bilateral progressive massive fibrosis identical to that in silicosis, talcosis, and coal-worker's pneumoconiosis.[2734, 2838]

Even after many years' exposure, most of the patients have no disability and show only slight increase in lung markings roentgenographically. Disabling pneumoconiosis is believed to develop in only a small proportion of these workers.[2856b]

### Pneumoconiosis Due to Mica

Mica is a complex silicate of potassium, aluminum, magnesium, calcium, and fluorine. Pneumoconiosis is a rare complication with roentgenographic and clinical manifestations virtually indistinguishable from those of related silicatoses, asbestosis, and talcosis.[2832, 2863, 2864]

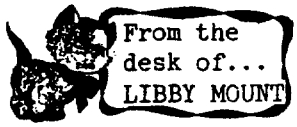
### Coal-Workers' Pneumoconiosis

Exposure to mixed dusts containing varying percentages of free silica in combination with carbon or hematite can produce several different pneumoconioses which usually are known by the occupation with which they are associated—coal-workers' pneumoconiosis (anthracosis, anthracosilicosis), graphite-workers' pneumoconiosis, foundry-workers' lung, welders' siderosis (siderosilicosis), and the pneumoconiosis of hematite miners. The content of free silica in these dusts is small, usually less than 10 per cent.

#### Epidemiology

Whereas in a small percentage of coal miners silicosis will develop as a result of high quartz content of certain coal seams, in the majority a pneumoconiosis develops which is entirely different and which is characterized by absence of symptoms in the early stages, a roentgenographic pattern which lacks the well-defined nodularity of silicosis and a morphologic picture quite distinct from that of pure silicosis. Although a small amount of free silica is present in all coal dust and can be found in the ash of coal-workers' lungs at necropsy, it seems that the morphologic changes are due chiefly to the deposition within the lungs of large quantities of carbon. The finding of pathologic changes identical to those of coal-workers' pneumoconiosis in carbon-electrode workers,[2865] in whom the inhaled dust consists of coke and anthracite and almost no quartz, supports the contention that free silica plays little part in the lung disease of coal workers.[2856c]

Although the great majority of reports on coal-workers' pneumoconiosis originate in Great Britain and continental Europe, a disease with similar clinical, roentgenographic, and pulmonary function patterns is recognized in the U.S.A. also.[2866–2869] The incidence of coal-workers' pneumoconiosis varies from colliery to colliery, probably relating to dust




B. C. file

Charlie —

Mr. Holland said that he is sorry he did not have attached copy available yesterday to share with you.

Libby

10-25-83