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The Pneumoconioses: Asbestosis

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The term asbestos refers to a group of mineral fibers with the common properties of thermal and electrical resistance, high tensile strength, and resistance to corrosion. The term originates from the Greek words meaning "unquenchable" or "indestructible." The various types of asbestos fibers occur as hydrated fibrous silicates and are mined directly from the earth. The main deposits that have been commercially exploited are found in Canada, South Africa, western Australia, and the Commonwealth of Independent States.

Asbestos is conventionally divided into serpentine and amphibole varieties (Display 36-1). Chrysotile, the only form of serpentine asbestos, is also referred to as white asbestos and accounts for 90% to 95% of the asbestos that has been used commercially. The remaining five types of asbestos belong to the amphibole group. Two of the amphiboles, crocidolite (*i.e.*, blue) asbestos and amosite (*i.e.*, brown) asbestos, are commercially valuable and have been mined almost exclusively in South Africa. The remaining three amphibole varieties—tremolite, anthophyllite, and actinolite—are primarily important as contaminants of other mineral species. For example, tremolite is a well-recognized contaminant of chrysotile asbestos and of some deposits of talc and vermiculite.

There are some important morphologic differences between the amphibole and serpentine varieties of asbestos (Fig. 36-1). Amphibole fibers consist of a backbone of silica tetrahedra linked to one another to form a chain, and these fibers tend to be straight with a rhombohedral appearance on cross section. Chrysotile fibers are formed as a sheet silicate, with a silica layer joined to a brucite layer. The layer or sheet is rolled up into a scroll so that a cross-sectional view reveals a central tubule or capillary. Chrysotile fibers tend to be curly, wavy, or curved, especially fibers exceeding 10 μm in length, and the ends of the fibers are often splayed.[1] Large numbers of either amphibole or chrysotile fibers with lengths greater than 5 μm may penetrate to the periphery of the lung in experimental animals exposed to asbestos fibers in inhalation chambers.[2,3]

Asbestos fibers can be readily identified by analytic electron microscopic techniques, which can demonstrate their characteristic morphologic features. In addition, their chemical composition can be determined by means of energy-dispersive x-ray analysis. Selected area electron diffraction can further reveal information about the crystalline structure of individual fibers. This information may be especially useful for the identification of chrysotile, which has a characteristic electron diffraction pattern (Fig. 36-2).

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO ASBESTOS

Asbestos is a naturally occurring mineral; because of its many useful properties, it has been incorporated into more than 3000 different products.[4] Therefore, virtually everyone in industrialized society has some exposure to asbestos, and small amounts of asbestos can be found in the lungs of individuals in the general population. However, excessive exposure to asbestos, over and above these background levels, occurs under certain circumstances. During the past century, there have been some remarkable changes in the patterns of exposure in both occupational and nonoccupational settings. Also, more stringent controls and regulation of exposure levels in the workplace have resulted in some modification of the patterns of associated disease.

During this century, exposure to asbestos and the consequent diseases have been categorized into three waves of exposure.[5] The first wave represents workers whose activities actually generated asbestos for commercial use. These include miners, millers, and packagers of asbestos, who transformed raw asbestos ore into an industrially useful material. Historically, observations among these workers resulted in the recognition of asbestos-related diseases.

The second wave represents workers involved with the manufacture and construction use of asbestos-containing materials.

DISPLAY 36-1. TYPES AND CHEMICAL COMPOSITIONS OF ASBESTOS MINERALS

Serpentine

Chrysotile: $Mg_3Si_2O_5(OH)_4$

Amphibole

Amosite: $(Fe–Mg)_7Si_8O_{22}(OH)_2$
Crocidolite: $Na_2Fe_3^{++}Fe_2^{+++}Si_8O_{22}(OH)_2$
Tremolite: $Ca_2Mg_5Si_8O_{22}(OH)_2$
Anthophyllite: $(Mg–Fe)_7Si_8O_{22}(OH)_2$
Actinolite: $Ca_2MgFe_5Si_8O_{22}(OH)_2$

Among these workers were asbestos insulators and shipyard workers involved with the construction and maintenance of ships during World War II and the decades that followed. These exposures are responsible for much of the asbestos-related diseases being observed currently and in the past few decades.

The third wave represents workers exposed to asbestos already in place in buildings and in homes as a result of the extensive use of asbestos in construction materials. Workers especially at risk with respect to exposure to asbestos in place include maintenance workers, construction workers, and asbestos abatement workers.

Because of the widespread use of asbestos in a variety of materials, there are a number of occupations at risk for asbestos exposure in addition to those referred to above. These include asbestos cement workers, asbestos textile manufacturers, brake-lining manufacturers and brake repair workers, and railroad workers, especially during the steam locomotive era. Substantial exposure to asbestos can also occur among household contacts of asbestos workers or among individuals living in proximity to an asbestos mine, mill, or manufacturing plant.[5]

ASBESTOS BODIES AND NONASBESTOS FERRUGINOUS BODIES

The asbestos body (AB) is the hallmark of exposure to asbestos. This structure consists of a central core fiber of asbestos that has been coated with an iron-protein-mucopolysaccharide layer, resulting in a structure with a golden brown, segmented, javelin-shaped or dumbbell appearance (Color Fig. 36-1; Fig. 36-3). ABs range in size from 20 μm to over 200 μm in length and 2 to 5 μm in diameter. The average AB is about 35 μm in length.[6]

ABs are formed when fibers 20 μm or greater in length are deposited in the lung parenchyma, and alveolar macrophages attempt to phagocytize these foreign invaders. Because of the fiber's length, the macrophage is unable to incorporate it within the cell's cytoplasm. This frustrated phagocytosis apparently trig-

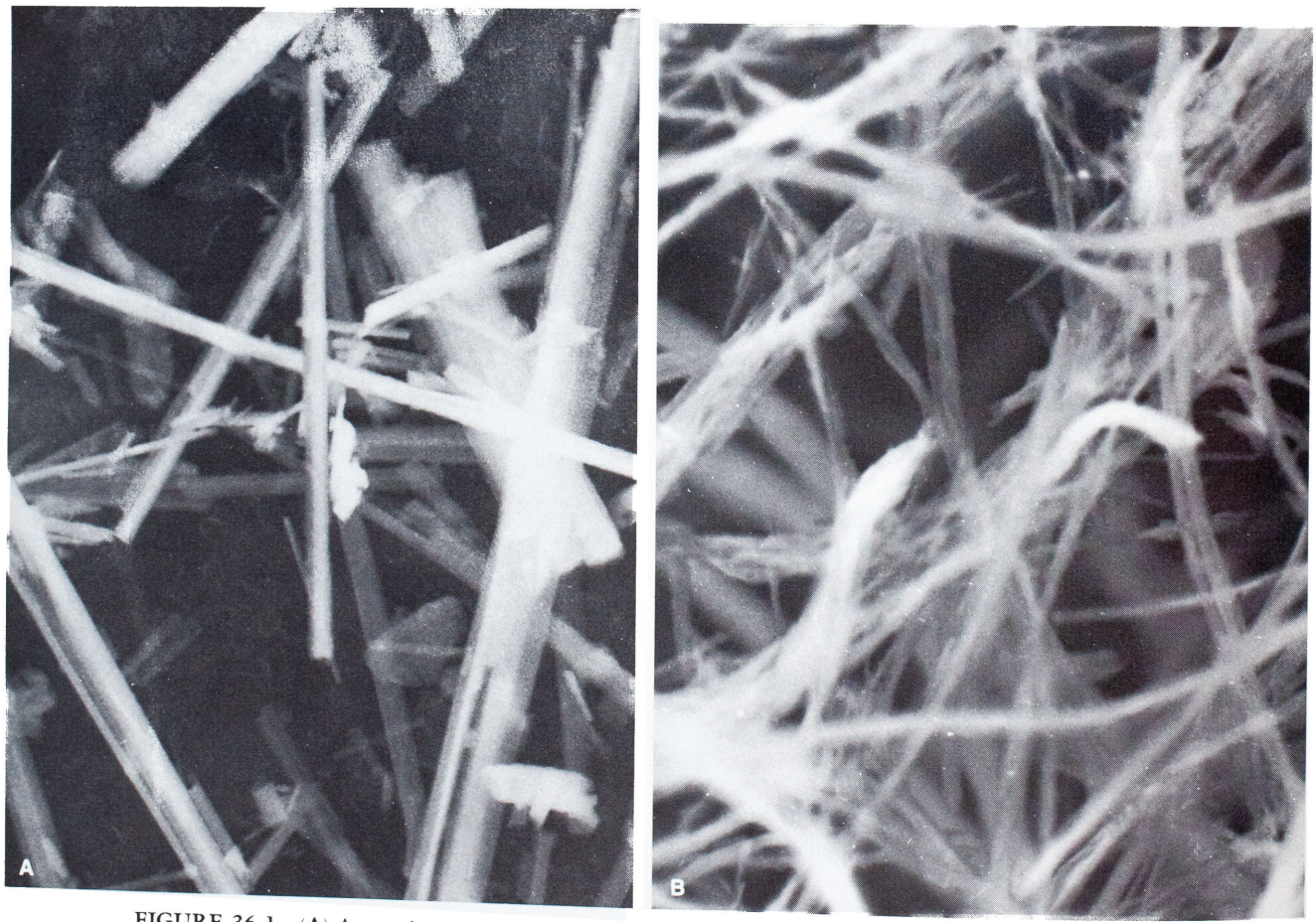

FIGURE 36-1. (**A**) A scanning electron micrograph of amosite asbestos shows long, straight fibers of varying diameter. (**B**) A scanning electron micrograph of chrysotile asbestos emphasizes its curly morphology, particularly for longer fibers. (Original magnification × 7000.)

FIGURE 36-2. Selected area electron diffraction pattern of a chrysotile asbestos fiber shows the typical 0.53-nm interlayer line spacing. The prominent streaking along the layer lines is characteristic of chrysotile asbestos. (From Roggli VL, Coin PG. Mineralogy of asbestos. In: Roggli VL, Greenberg SD, Pratt PC, eds. Pathology of asbestos-associated diseases. Boston: Little, Brown and Co, 1992.)

gers the coating process, whereby iron micelles within a protein matrix are deposited onto the surface of the fiber.[7–9] The degree of segmentation and the completeness of the coating vary from one AB to another. More heavily coated asbestos fibers are more readily identified in histologic sections. Iron stains such as Prussian blue or Perls iron assist in their identification.

A few ABs can be found in the lungs of most individuals from the general population when sensitive digestion-concentration procedures are employed.[10] However, the levels are of such magnitude that it is extremely unlikely that ABs will be identified in histologic sections from such individuals.[6] Among individuals with heavy occupational exposure, large numbers of ABs may be recovered from the lungs, and ABs are easily identified in histologic sections.

In some cases, ABs have even been isolated from extrapulmonary sites, although this finding may be due to contamination of formalin by ABs from the lung. Extrapulmonary sites at which ABs have been recovered by digestion-concentration techniques include the adrenal gland, bone marrow, brain, esophagus, heart, kidney, larynx, liver, lymph nodes, large and small intestine, stomach, spleen, pancreas, prostate, thyroid gland, and urinary bladder.[4,7,8]

Only a small proportion of asbestos fibers become coated to form ABs. Therefore, ABs serve as a marker for the much larger numbers of uncoated asbestos fibers present within the lung parenchyma. Most ABs have a core fiber of amosite or crocidolite; tremolite, anthophyllite, actinolite, and chrysotile ABs do occur but are considerably less common. The numbers of ABs in lung tissue correlate well with the number of amphibole fibers 5 μm or greater in length.[11,12] AB counts generally correlate rather poorly with the number of chrysotile fibers in the lung.[13]

Because almost any durable fiber with the appropriate dimensions can become coated by macrophages after deposition in the lung, some have suggested the use of the more noncommittal term ferruginous body when the nature of the core fiber is not known with certainty. However, ferruginous bodies with thin, translucent core fibers found in human lungs virtually always have an asbestos core and are thus appropriately referred to as ABs.[8] An exception to this rule is the zeolite body found in the lungs of individuals from certain Turkish villages exposed to the fibrous zeolite erionite, which closely resembles amphibole asbestos fibers.[14] Zeolite bodies have thus far not been reported in North American lung specimens.

Most ferruginous bodies with a nonasbestos core fiber (*i.e.*, pseudoasbestos bodies) can be recognized on the basis of their morphology by light microscopy. Bodies with black central core fibers are composed of whiskers of carbon or various metal oxides, such as iron, aluminum, chromium, or titanium. Bodies with broad, yellow, often irregularly shaped core fibers often have sheet silicate cores.[8] These are often seen in talc workers, sheet metal workers, and welders (see Color Fig. 36-1; see Fig. 36-3*B*).

ASBESTOSIS

Asbestosis is a pneumoconiosis that results from the inhalation and accumulation of asbestos fibers within the lung parenchyma. It is the prototype of diseases related to the inhalation of mineral fibers. Asbestosis generally occurs among individuals with prolonged and relatively intense exposures to asbestos. As is the case for most asbestos-associated diseases, there is a prolonged latent interval from initial exposure to asbestos to diagnosis, generally ranging from 15 years to several decades. However, increasing intensity of exposure shortens the duration of the latency period. Any of the various types of asbestos can produce asbestosis if inhaled in sufficient amounts.[15]

Clinical manifestations of asbestosis range from absence of symptoms to dyspnea at rest, and they can progress to respiratory failure and death. Progression of disease may continue even after cessation of exposure, because fibers remain entrapped within the lungs for long periods of time. Inspiratory crackles (*i.e.*, rales) at the lung bases and digital clubbing may also be present, particularly in individuals with more advanced disease.

Radiographically, the earliest findings are small irregular opacities, usually most pronounced at the lung bases. A classification scheme has been developed by the International Labor Office for the semiquantitative assessment of the severity of disease on plain chest films based on the size and profusion of small irregular opacities.[16] Other findings include honeycomb changes and reduced lung volumes. It should be pointed out that plain films may be entirely normal in 10% to 18% of patients with histologic evidence of asbestosis.[17,18] Computed tomography (CT) of the thorax, especially high-resolution CT, enhances the sensitivity for detecting earlier and milder forms of asbestosis.[19]

Pulmonary function tests in patients with asbestosis usually show a restrictive pattern, with a decrease in the forced vital

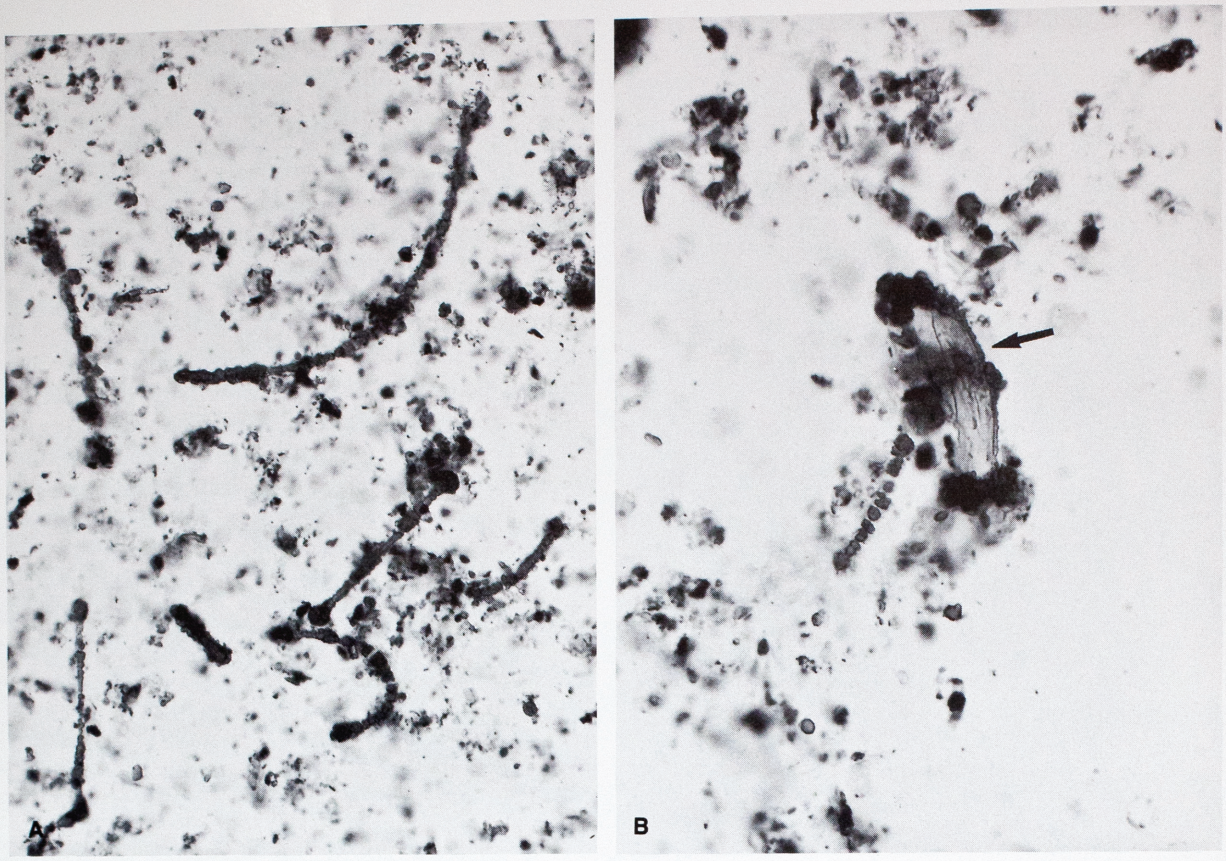

FIGURE 36-3. (**A**) Asbestos bodies on a Nuclepore filter (Nuclepore, Burlingame, CA) show the range of morphologic appearances, including dumbbell shapes, beaded structures, and lancet forms. Note the variable quantity of iron coating on the fibers. (**B**) A pseudoasbestos body of the sheet silicate type has a broad yellow core (*arrow*). (High magnifications.) See Color Figure 36-1.

capacity. Obstructive features may also be observed (*i.e.,* diminished forced expiratory volume in 1 second), especially among workers who also smoke. Total lung capacity (TLC) is more variable, because the tendency of asbestosis to decrease the TLC may be counterbalanced by the tendency for emphysema to increase TLC in smokers.[20] Finally, exercise testing may reveal subtle abnormalities in workers with mild disease and normal conventional pulmonary function tests.

Pathology

Macroscopically, the appearance of the lungs in asbestosis ranges from normal in the earliest stages to small, firm, and fibrotic in more advanced disease. Between these extremes, one may observe linear gray-white fibrotic lesions that are most readily apparent at the lung periphery and bases (Fig. 36-4). In advanced cases, honeycomb changes may be observed (Fig. 36-5). These consist of cystlike spaces up to 1 cm in maximum dimension in areas of dense fibrosis. In exceptional cases, the fibrotic changes of asbestosis are more severe in the upper lobes.[21] The tracheobronchial tree and regional lymph nodes are usually unremarkable upon gross inspection. The pathologic changes are best observed in slices prepared from lungs that have been inflated and fixed by intrabronchial instillation of fixative solution for at least 2 days.[15,22]

Histologically, asbestosis is recognized by the presence of bronchiolocentric fibrosis and ABs within paraffin sections of lung parenchyma. The earliest changes consist of fibrosis in the walls of respiratory bronchioles. Some investigators prefer the term asbestos airways disease when the scarring is confined to the walls of respiratory bronchioles.[23] In more advanced cases, the fibrosis extends proximally to involve terminal bronchioles and distally to involve the walls of alveolar ducts; septal fibrosis also develops in the walls of alveoli surrounding these structures (Color Fig. 36-2; Fig. 36-6).

Fibrosis may be observed in other portions of the interstitial compartment, including the visceral pleura, the secondary lobular septa, and the perivascular areas. In the most advanced cases, there is honeycomb formation. This consists of cystlike spaces lined by cuboidal epithelium and fibrotic walls. These spaces often contain pools of mucous secretions. Masson trichrome stain is useful for the assessment of fibrosis. ABs may be found either within the fibrotic pulmonary interstitium or within alveolar spaces. Occasionally they are observed within foreign-body giant cells (Fig. 36-7). They are often found in association with peribronchiolar or perivascular deposits of anthracotic pigment.

ABs are not necessarily distributed within histologic sections in an even manner. Nonetheless, there have been 2 AB/cm^2 of lung parenchyma in virtually all cases of asbestosis studied in my laboratory.[15] Iron stains such as Prussian blue can greatly facilitate the identification of ABs. As noted, ABs may also be found in histologic sections of hilar lymph nodes.[24]

Various grading schemes have been proposed for the assessment of the histologic severity of asbestosis. Perhaps the most widely recognized scheme is the one developed by the Pneu-

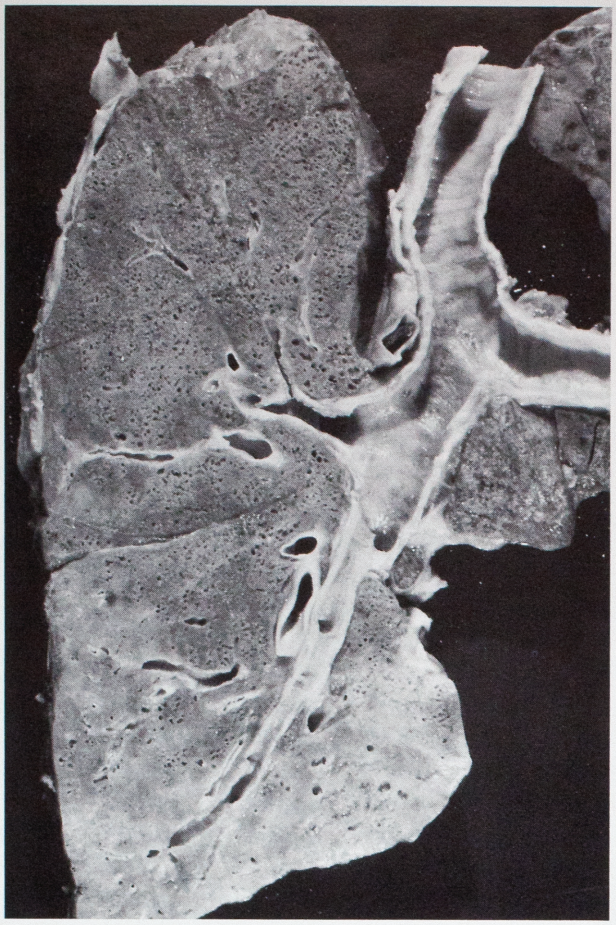

FIGURE 36-4. Whole section of the left lung in a patient with asbestosis shows extensive fibrosis, particularly at the lower lobe, with retraction and fine honeycombing. (Contributed by the editor.)

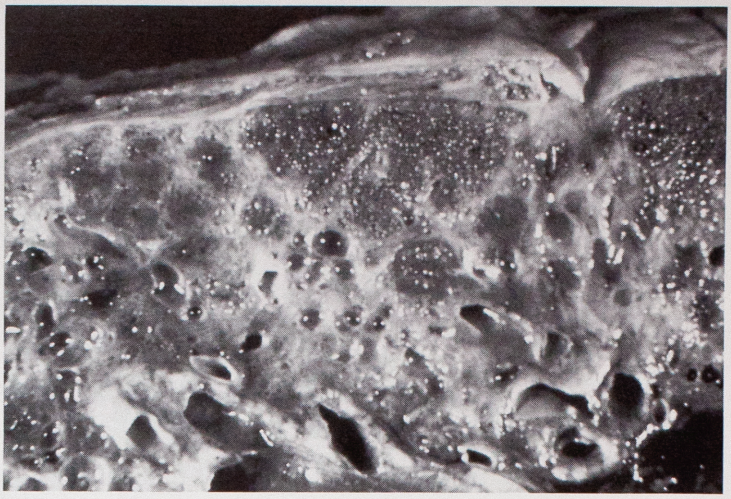

FIGURE 36-5. Asbestosis causes extensive scarring and honeycombing of lung tissue. (Courtesy of G.T. Hensley, M.D., Miami, FL.)

moconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health.[22] According to this scheme, the severity is graded on a 12-point scale, with 0 representing no detectable fibrosis and 12 representing the most advanced degree of pulmonary fibrosis. The scale includes both a severity score, based on the most advanced abnormality present in a section, and a profusion score, based on the proportion of bronchioles showing fibrotic changes. These two scores are multiplied together to give the combined score for each slide, and the grade for an individual patient is determined by averaging the scores for each slide.

The severity score ranges from 0 to 4. A score of 0 implies no detectable peribronchiolar fibrosis; a score of 1 means fibrosis is confined to the walls of respiratory bronchioles and the first tier of adjacent alveoli; a score of 2 indicates that fibrosis extends beyond the first tier of the adjacent alveoli; a score of 3 is given if fibrosis involves all alveolar septa between two adjacent bronchioles; and a score of 4 indicates the presence of honeycomb changes. The profusion score ranges from 0 to 3. A score of 0 implies no bronchioles with peribronchiolar fibrosis; a score of 1 means peribronchiolar fibrosis involves a few respiratory bronchioles; a score of 2 indicates peribronchiolar fibrosis involves many bronchioles, but less than one half of them; and a score of 3 refers to peribronchiolar fibrosis involving more than one half of all bronchioles in a particular slide. I use a somewhat simplified version of this grading scheme, which is outlined in Display 36-2.[25]

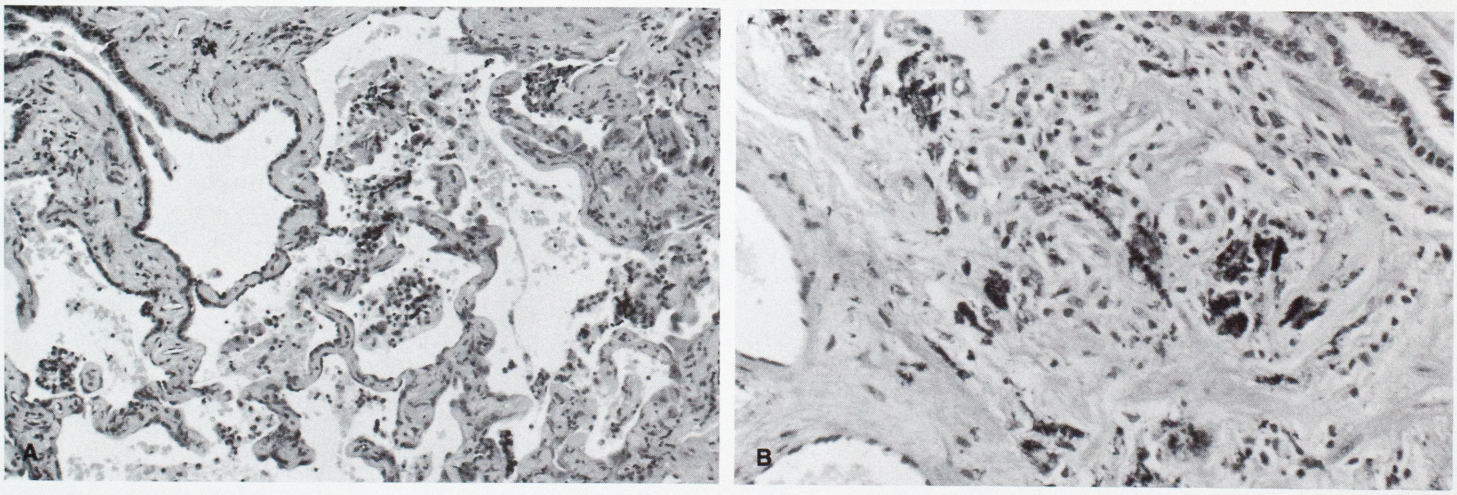

FIGURE 36-6. (**A**) Interstitial fibrosis is present in a peribronchiolar distribution. (**B**) A more advanced degree of fibrosis than in (**A**). (H & E stain; low magnifications; contributed by the editor; see Color Figure 36-2.)

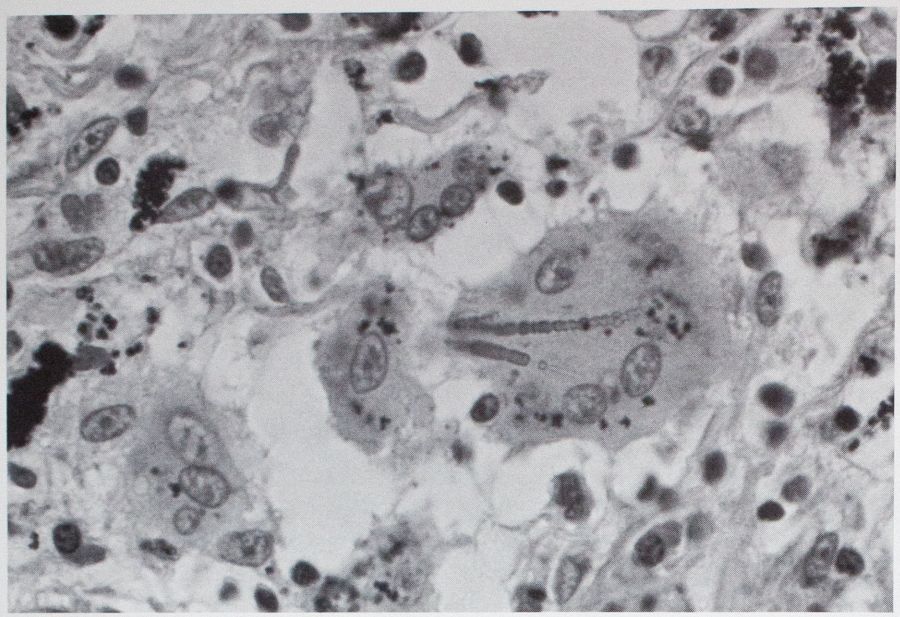

FIGURE 36-7. Alveolar tissue in a patient with asbestosis shows multiple giant cells containing asbestos bodies. (H & E stain; low magnification; contributed by the editor.)

Other histologic features are observed less commonly in patients with asbestosis. Foreign-body giant cells are observed within alveoli or the pulmonary interstitium in about 15% of patients. Proliferation of cuboidal bronchiolar epithelium lining adjacent alveoli or alveolar ducts occurs in about 10% of patients and creates a pattern sometimes referred to as pulmonary adenomatosis. Hyperplastic alveolar type II cells contain cytoplasmic hyalin in approximately 7% of patients, and this material has morphologic and tinctorial characteristics identical to those of alcoholic hyalin within hepatocytes. Alveoli are packed with macrophages in a pattern resembling desquamative interstitial pneumonitis in about 6% of patients. Dendriform pulmonary ossification[26] and pulmonary blue bodies[27] are observed in 2% and 1% of patients, respectively, in my series. In addition, pulmonary infections with *Aspergillus* species have been reported in patients with asbestosis.[15,28] These uncommon histologic findings are generally observed in the more advanced histologic stages of asbestosis.[15,22]

DISPLAY 36-2. HISTOLOGIC GRADING OF ASBESTOSIS*

Grade 0

No appreciable peribronchiolar fibrosis or less than one half of bronchioles involved

Grade 1

Fibrosis confined to the walls of respiratory bronchioles and the first tier of adjacent alveoli, with involvement of more than one half of all bronchioles on a slide

Grade 2

Extension of fibrosis to involve alveolar ducts or two or more tiers of alveoli adjacent to the respiratory bronchiole, with sparing of at least some alveoli between adjacent bronchioles

Grade 3

Fibrotic thickening of the walls of all alveoli between at least two adjacent respiratory bronchioles

Grade 4

Honeycomb changes

** An average score is obtained for an individual case by adding the scores for each slide and dividing by the number of slides examined.*

From Roggli VL, Pratt PC. Asbestosis. In: Roggli VL, Greenberg SD, Pratt PC, eds. Pathology of asbestos-associated diseases. Boston: Little, Brown & Co., 1992:77.

Asbestosis must be distinguished from pulmonary fibrosis due to exposure to other mineral dusts. Silicosis is characterized by hyalinized collagenous nodules within the lung parenchyma and hilar lymph nodes. These nodules tend to be most numerous in the upper lung zones (see Chap. 35). Peribronchiolar fibrosis may be observed in individuals exposed to silica, iron oxides, or aluminum oxides.[29,30] The distinction is based on the presence or absence of ABs in histologic sections.

Some peribronchiolar fibrosis can be seen in association with cigarette smoking as well.[23] Small airway disease due to cigarette smoking tends to involve terminal (*i.e.*, membranous) bronchioles and is associated with chronic inflammation, goblet cell metaplasia, and mucus plugging. On the other hand, asbestosis preferentially begins in respiratory bronchioles and is associated with ABs.

Asbestosis must also be differentiated from idiopathic pulmonary fibrosis (see Chap. 31), desquamative interstitial pneumonitis (see Chap. 32), and pulmonary fibrosis secondary to radiation therapy or cytotoxic drugs (see Chaps. 15 and 16). The presence of ABs in histologic sections and the tendency of the fibrosis to be centered on bronchioles permit the distinction of asbestosis from other disorders in most instances. In difficult cases, analysis of tissue mineral fiber content may be necessary to make a clear distinction.[31,32] It should be noted that transbronchial biopsies are in most instances inadequate to reveal the intricate and subtle distinctions noted above.[15,22,25]

MESOTHELIOMA

Mesothelioma is discussed in detail in Chapter 57. However, some remarks are in order regarding the context of asbestos-related diseases. Malignant or diffuse mesothelioma is a signal neoplasm

that is strongly associated with a prior history of exposure to asbestos. A substantial proportion of reported cases have occurred among the large numbers of workers exposed to asbestos in shipyards and in the insulation trades. Cases have also occurred among asbestos miners and millers, railroad workers, asbestos factory workers, and other individuals with an occupational exposure to asbestos.[33–37] In addition, mesothelioma has been reported among individuals living near an asbestos factory or mine and among household contacts of asbestos workers.[38] In general, mesotheliomas may result from exposures substantially lower than those associated with the development of asbestosis.[37–39]

The latency period for mesothelioma ranges from 15 years after the initial exposure to asbestos to as long as 70 years after exposure, with a peak occurrence at 30 to 40 years. Not all patients have a prior history of asbestos exposure; this has led some investigators to search for other causes of mesothelioma in man.[40] Likely causative factors include exposure to the fibrous zeolite known as erionite, therapeutic radiation, and chronic inflammation with scarring of the pleura.[37] Also, there appears to be a familial or hereditary predisposition in some patients.[41]

Malignant mesotheliomas occur most frequently in the pleura, followed in incidence by the peritoneum and pericardium.[42] Occasionally, the tumor may invade along needle tracks subsequent to biopsy procedures.[43] Pleural mesotheliomas are often associated with a bloody pleural effusion, peritoneal mesotheliomas with ascites, and pericardial mesotheliomas with bloody pericardial effusion.[44] Metastases are found in the majority of patients at autopsy.[45]

Histologically, mesotheliomas can occur in a variety of patterns. These are classically divided into three varieties: epithelial, approximately 50% of patients; sarcomatoid, approximately 20%; and mixed or biphasic, approximately 30%.[37,42,43] The neoplastic cells in the epithelial variant may be arranged in a tubulopapillary pattern, may appear as solid nests, may line cleftlike spaces, or may grow as solid sheets. The sarcomatoid or spindle cell pattern most often resembles fibrosarcomas of soft tissue origin, but patterns resembling osteosarcoma, chondrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, or neurogenic sarcoma may be observed as well.

Biphasic or mixed mesotheliomas display various combinations of the epithelial and sarcomatoid patterns described above. Other patterns may also be observed less commonly, such as desmoplastic mesotheliomas characterized by abundant collagen bundles in a storiform pattern with rather inconspicuous, widely separated tumor cells. This pattern is associated with frankly sarcomatous areas that can be identified by careful sampling, foci of bland necrosis, and invasion of chest wall or lung.[44]

Lymphohistiocytoid mesotheliomas contain an abundant lymphoplasmacytic infiltration, giving them a superficial resemblance to certain non-Hodgkin lymphomas.[46] The distinction is based on the finding of characteristic keratin-positive tumor cells with immunohistochemical stains.

BENIGN ASBESTOS-RELATED PLEURAL DISEASES

A variety of benign pleural diseases may occur as the result of inhalation of asbestos fibers. These include parietal pleural plaques, diffuse pleural fibrosis, rounded atelectasis, and benign asbestos effusion.[47] Benign asbestos-related pleural diseases may occur after low-level exposure to asbestos, and they have been associated with lower pulmonary asbestos burdens than are usually found in patients with asbestosis.

Injury to the pleura is thought to occur as a result of transport of asbestos fibers through the lung to the pleural surface, either directly through the alveoli or by way of the pulmonary lymphatics. Fibers reaching the pleural surface incite an inflammatory reaction that eventually leads to pleuritis and fibrosis. All forms of serpentine and amphibole asbestos fibers are capable of causing benign asbestos-related pleural diseases.

Parietal pleural plaques are the most common form of benign asbestos-related pleural disease. Autopsy surveys have shown their prevalence to range from 8% to as high as 39%.[48] Parietal pleural plaques are most often bilateral but may be unilateral as well. Bilateral plaques are almost pathognomonic of asbestos exposure. Unilateral plaques may also be caused by asbestos, but other possible causes, such as trauma with organized hemothorax, old empyema, or tuberculous pleuritis, must be considered as well. Plaques appear as localized areas of pleural thickening on chest x-ray films and are most readily seen when they are calcified. Their detection is enhanced by means of CT of the thorax.[19] There is no evidence that pleural plaques are a precursor lesion of mesothelioma. Furthermore, the term asbestosis, which refers to pulmonary interstitial fibrosis, should not be applied to parietal pleural plaques or any of the other benign asbestos-related pleural diseases.

Parietal plaques are elevated, firm, sharply circumscribed areas of pleural thickening, usually found within the costal pleura, where they lie parallel to the ribs, or on the domes of the diaphragm (Fig. 36-8*A*). They are ivory-colored and have either a smooth, shiny surface or a knobby appearance. The latter appearance has been described as analogous to candle-wax drippings.[22] They vary in size from just visible to the naked eye to 12 or more centimeters across, and from a few millimeters to a centimeter or more in thickness.

Microscopically, parietal plaques consist of dense layers of hyalinized collagen arranged in a basket-weave pattern (Fig. 36-8*B*). Foci of dystrophic calcification are commonly observed. Small clusters of lymphocytes are usually seen at the interface between the plaque and the subjacent chest wall. ABs are not observed in either hematoxylin and eosin–stained or iron-stained histologic sections.

In contrast to parietal pleural plaques, diffuse pleural fibrosis typically involves the visceral pleura. The entire lung may be surrounded by and encased within a fibrotic pleura several millimeters thick (Fig. 36-9). The process may extend into the major fissures and can be either unilateral or bilateral. Microscopically, the fibrous thickening of the visceral pleura consists of dense collagenous tissue and varying numbers of chronic inflammatory cells, including lymphocytes, macrophages, and plasma cells. A fibrinous exudate may be observed on the surface of the collagenous tissue in some cases. Diffuse pleural fibrosis may be of sufficient extent and severity to result in restrictive changes on pulmonary function tests with consequent impairment and disability.[49]

Rounded atelectasis, also known as folded lung syndrome,[50] is a peculiar disorder that is frequently associated with a history of asbestos exposure.[51] It is characterized by a rounded pleural-based mass, 2 to 7 cm in diameter, subjacent to an area of localized visceral pleural thickening. Chest roentgenograms and CT of the

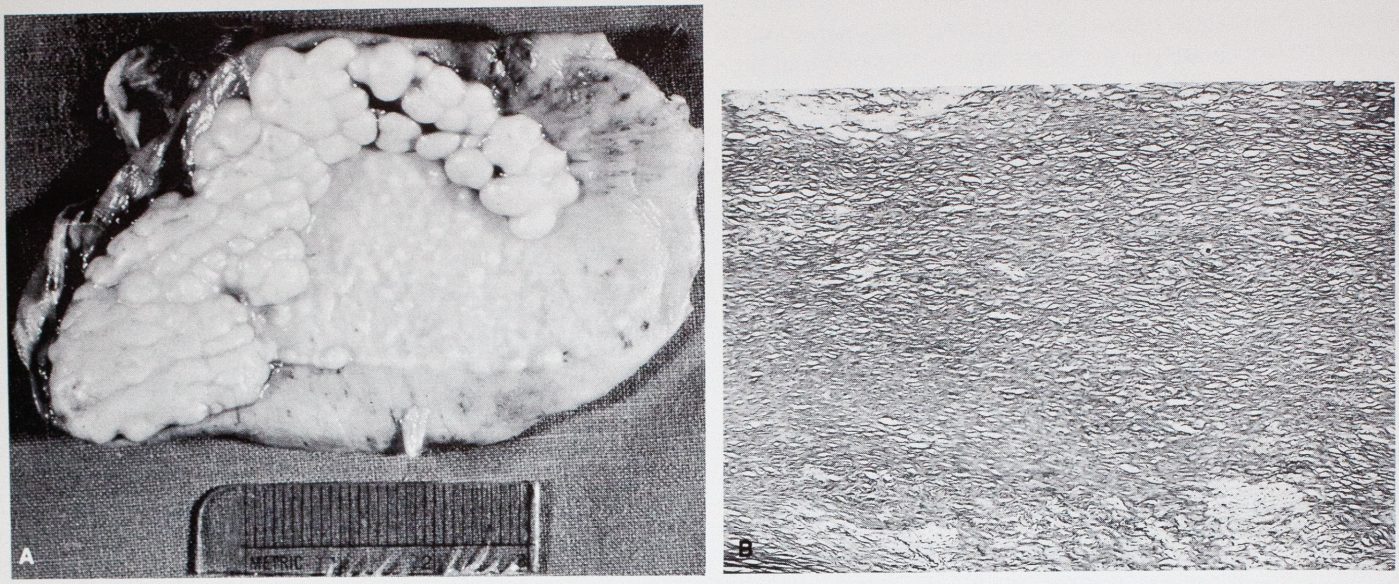

FIGURE 36-8. (**A**) Gross appearance of the diaphragm with plaque shows irregular, 12-cm pleural plaque with smooth and nodular areas, the latter resembling candle-wax drippings. (**B**) Histologic section of the parietal pleural plaque shows the typical basket-weave pattern of the collagen fibers. (H & E stain; low magnification.)

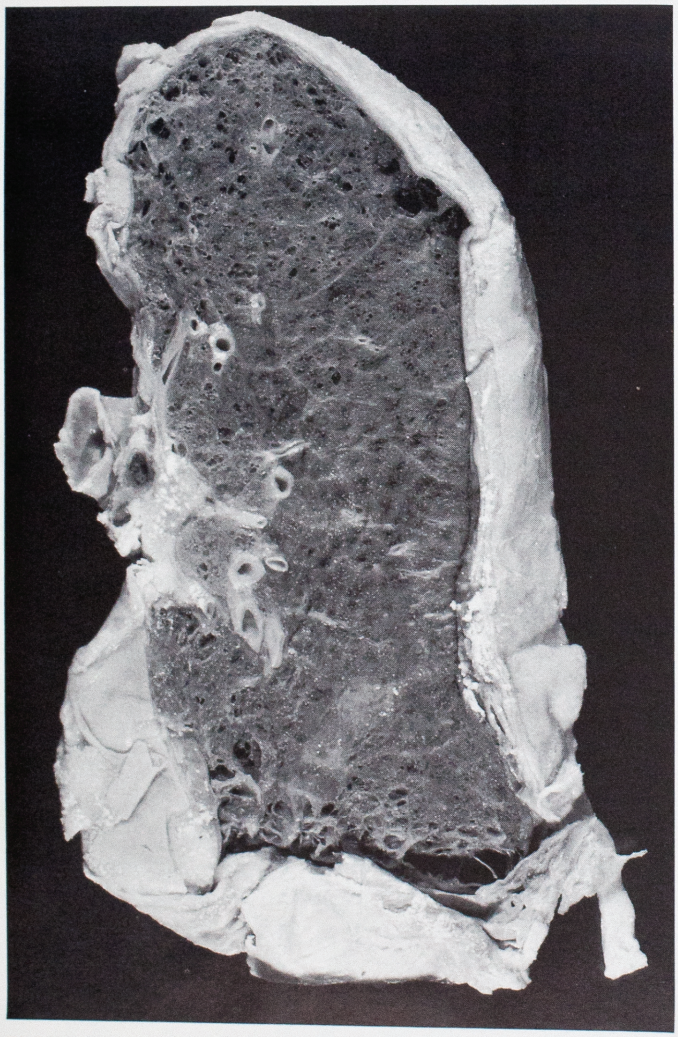

FIGURE 36-9. Diffuse pleural fibrosis with calcification was present in this 67-year-old grain mill worker. The lung is encased in a rind of visceral pleural thickening several millimeters thick. An elevated asbestos content was present in the lung parenchyma.

thorax often show curvilinear bronchovascular structures extending from the mass toward the hilum.[19]

Rounded atelectasis usually presents as a solitary mass lesion, but it may be multiple and bilateral. The pleura is densely hyalinized and markedly thickened and may be buckled or puckered and thus drawn into the underlying lung parenchyma. The entrapped lung parenchyma is atelectatic (Fig. 36-10). The mechanism of formation is believed to involve visceral pleural thickening and fibrosis in which adhesions between visceral and parietal pleura were prevented from forming because of an associated pleural effusion. Contraction and buckling of the fibrotic visceral pleura lead to atelectasis and folding of the immediately subjacent lung.[50] Radiographic recognition of this entity is important because it may spare the patient a thoracotomy.

Benign asbestos pleural effusion is the most common asbestos-related lesion occurring in the first decade after exposure.[52]

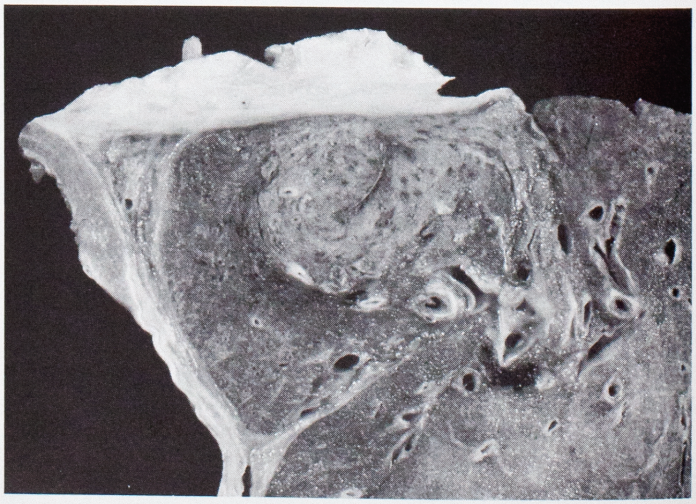

FIGURE 36-10. Gross appearance of rounded atelectasis in the lung of a man who had asbestos exposure and pleural fibrosis. (Contributed by the editor.)

However, it can also occur at a later date. Pleural effusions develop in 5% to 7% of heavily exposed individuals.[52,53] They are typically exudates of moderate volume (500–2000 mL), may be clear or hemorrhagic, and are associated with substantial numbers of eosinophils in about 25% of patients. Criteria for the diagnosis of benign asbestos effusion include the following:

- clinically documented pleural effusion
- history of asbestos exposure
- exclusion of other causes, such as infection, collagen-vascular disease, or malignancy
- follow-up of at least 2 years to ensure that the effusion is benign.

The effusions may be bilateral and frequently recur. The pathologic features of benign asbestos effusion have not been well defined. In four patients undergoing decortication, pathologic examination showed chronic nonspecific fibrotic pleurisy.[54]

ASBESTOS AND CARCINOMA OF THE LUNG

Exposure to asbestos is associated with an increased risk of carcinoma of the lung, especially among asbestos workers who also smoke. All of the commercial types of asbestos have been associated with this increased risk. Cigarette smoking and asbestos exposure appear to have a multiplicative or synergistic effect on lung cancer. This synergistic effect was well demonstrated in the study by Hammond and colleagues, in which cancer mortality among 17,800 insulators was compared with cancer death rates in the general population.[55] Cigarette-smoking asbestos insulators had a 55-fold increased risk of carcinoma of the lung in comparison to a nonsmoking, non–asbestos-exposed reference population. Other studies have confirmed this synergistic relationship between asbestos exposure and cigarette smoking.[56–58]

Studies have also demonstrated a dose-response relationship between asbestos exposure and lung cancer risk, and a long latency period of 15 or more years from initial exposure to manifestation of disease. Some investigators believe that the available data are most consistent with a linear dose-response model with no threshold, whereas others believe that there is evidence of a threshold level of exposure to asbestos below which no excess deaths from carcinoma of the lung will occur.[59] According to this latter view, only patients with asbestosis are at increased risk for carcinoma of the lung.[60] In this regard, a histopathologic study of 138 insulators with lung cancer demonstrated asbestosis to be present in 100% of patients.[18]

This controversy is of more than academic importance, because there are considerably more individuals who are asbestos-exposed than there are workers with asbestosis. My personal view is that the weight of the evidence at this time indicates that, in an asbestos worker with carcinoma of the lung who is also a cigarette smoker, asbestosis must be present clinically or histologically if one is to assign a substantial contributing role to asbestos in the causation of the cancer.

There is also evidence for an increased risk of carcinoma of the lung among nonsmoking asbestos workers. Hammond and colleagues described four patients with lung cancer among their cohort of insulation workers who had never smoked regularly.[55] This represented a fivefold increase in risk over the number of patients expected in a nonsmoking, non–asbestos-exposed control population. Berry and associates reported four additional patients with lung cancer among nonsmoking asbestos factory workers,[57] and Lemen reported another four patients among nonsmoking women in a predominantly chrysotile asbestos textile plant.[61]

I have studied four additional patients with carcinoma of the lung; these patients were nonsmoking, asbestos-exposed individuals in whom an elevated tissue asbestos burden was identified by digestion analysis. Two of the patients were women and two were men, and they ranged in age from 40 to 75 years. All four had pulmonary adenocarcinoma, two of which were of the bronchioloalveolar cell type. It is my opinion that, in patients with carcinoma of the lung who are nonsmokers and who have an elevated pulmonary asbestos burden, asbestos is a substantial contributing factor to these cancers even in the absence of asbestosis.

Carcinomas of the lung are classically divided into proximal bronchogenic carcinomas arising from a main-stem, segmental, or subsegmental bronchus and presenting as a hilar mass, and peripheral carcinomas arising from small airways and presenting as a coin lesion on chest roentgenogram. Asbestos-related lung cancers can assume either of these gross appearances. Indeed, there are no discernible differences between the macroscopic appearance of carcinomas of the lung among asbestos workers and that in individuals not exposed to asbestos.[22,60] However, carcinomas among cigarette smokers from the general population occur about twice as often in the upper as compared with the lower lobes, whereas the reverse is true for carcinomas among asbestos workers.[62]

All of the four main histologic patterns of lung cancer—squamous cell, small cell, large cell, and adenocarcinoma—may occur in asbestos workers.[12,22] I have examined the distribution of histologic types of lung cancer in 350 patients, including 73 with asbestosis, 75 with elevated lung AB burdens but without asbestosis, 27 with normal lung AB burdens, 83 with some history of asbestos exposure but with no lung parenchyma available for assessment of asbestosis or ABs, and 100 consecutive lung cancer patients with no known asbestos exposure. Although there was a slight excess of adenocarcinomas among the patients with asbestosis and those with elevated AB burdens but without asbestosis, there was no statistically significant difference in the distribution of histologic types among these five groups.[63]

Because the pathologic features of carcinoma of the lung do not differ between those exposed to asbestos and those not exposed, it is important for the pathologist, in order to establish causality, to search for other indications of asbestos-related tissue injury, such as asbestosis or parietal pleural plaques. In addition, ABs should be searched for in histologic sections, and lung parenchyma uninvolved by tumor should be saved for tissue digestion analysis in patients with a known history of exposure to asbestos.

OTHER NEOPLASIA

A variety of other neoplasms have been associated with asbestos exposure, including malignancies of the gastrointestinal tract, larynx, kidney, liver, pancreas, ovary, and hematopoietic systems.[35,64,65] The strength and consistency of such associations have varied from study to study and remain controversial or unproved. However, I feel that sufficient information is available to link asbestos exposure with carcinomas of the larynx and esophagus when there is evidence of other asbestos-related tissue injury, such as asbestosis or parietal pleural plaques.

CYTOPATHOLOGY AND ASBESTOS-ASSOCIATED DISEASES

ABs in histologic sections of lung may be found within the pulmonary interstitium or within alveolar spaces. Bodies in the latter location may be mobilized onto the mucociliary escalator to be expectorated or swallowed in the sputum. Intraalveolar ABs are accessible to bronchoalveolar lavage fluid (BALF) or fine needle aspiration (FNA). Therefore, ABs in any of these samples provide important clues regarding past occupational exposures.

Cytologic preparations of sputum specimens often demonstrate ABs in close association with alveolar macrophages (Fig. 36-11), and their detection may be enhanced in iron-stained preparations. Some studies have shown that the detection of ABs within sputum cytology specimens is a rather insensitive marker of exposure to asbestos. In a survey of 900 heavily exposed amosite asbestos workers, only 35% had detectable ABs within sputum specimens.[66] However, sputum ABs are an exquisitely specific marker of occupational exposure, with no false-positive cases identified in a survey of more than 11,000 subjects from the outpatient clinics of a large general hospital.[67] Sputum ABs are therefore an irrefutable marker of substantial asbestos exposure, with a specificity approaching 100%. Indeed, there is a good correlation between tissue AB content and the occurrence of ABs in sputum samples. ABs are unlikely to be found within sputum cytology specimens until the pulmonary burden exceeds 1000 AB/cm^3 of lung tissue[68] or 900 AB/g of wet lung tissue.[69] However, it should be pointed out that identification of ABs in cytologic specimens is a marker of exposure but not necessarily of disease.

With the advent and widespread use of fiberoptic bronchoscopy, bronchoalveolar lavage has become an effective tool for sampling secretions of the lower respiratory tract. This technique involves the instillation of 100 to 300 mL of saline solution in aliquots of equal size, followed by recovery of as much of the fluid as possible by suction through the bronchoscope. Studies have shown that ABs can frequently be recovered from BALF from workers exposed to asbestos. DeVuyst and colleagues showed that 98% of workers with asbestosis and 95% with benign asbestos-related pleural diseases had lavage fluids positive for ABs.[70] The highest counts were found in workers with asbestosis, whereas significantly lower counts were found among workers with benign pleural disease or with normal chest x-ray films.

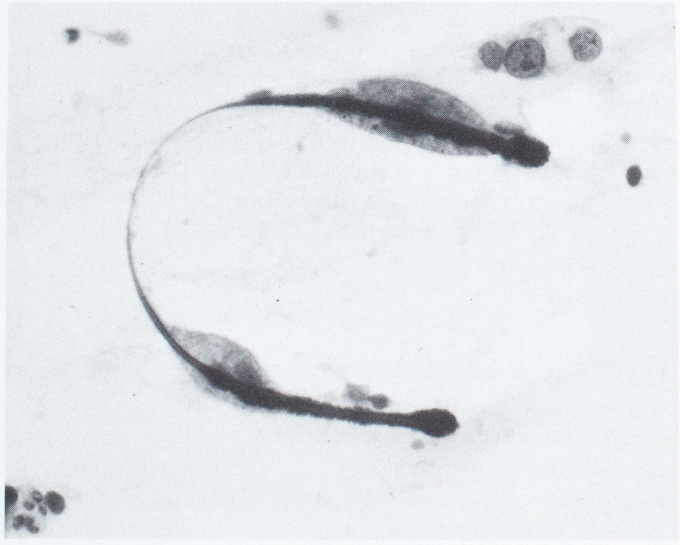

FIGURE 36-11. An asbestos body isolated from a sputum cytology specimen has a horseshoe shape. Alveolar macrophages are attached to each end of the structure. (Papanicolaou stain; intermediate magnification.)

ABs were occasionally recovered from control patients with no known exposure to asbestos, but these were almost always at concentrations of 1 AB/mL of BALF or less. Thus, the finding of ABs in BALF is a more sensitive but less specific marker for asbestos exposure than is the finding of ABs in sputum samples. AB content of BALF also differs significantly between individuals with asbestosis and individuals with other interstitial lung diseases unrelated to asbestos.[71] Finally, there is a good correlation between AB content of BALF and that of lung parenchyma.[72,73] A concentration of 1 AB/mL of BALF was found to correlate with a tissue AB concentration of 1000 AB/g of dry lung tissue or more, or approximately 100 AB/g of wet lung tissue or more.

Because of the increasing popularity of FNA cytology, ABs from lung parenchyma may also be recovered by means of this technique. Roggli and associates reported two cases in which ABs were recovered in cytologic preparations of FNA of lung masses.[74] In each patient, large numbers of ABs were recovered from samples of lung parenchyma by means of a sodium hypochlorite digestion procedure (see Analysis of Tissue Mineral Fiber Content). Leiman subsequently reported finding ABs in FNA specimens from 57 of 1256 consecutive transthoracic needle aspirates (4.5%) from a center serving a large mining population in South Africa.[75] More than one half of the masses aspirated were malignancies, whereas about one third were infectious processes. The identification of ABs in FNA specimens of the lung is indicative of considerable occupational exposure to asbestos.[74]

ANALYSIS OF TISSUE MINERAL FIBER CONTENT

A variety of techniques have been developed for the characterization and analysis of the mineral fiber content of lung tissue.[76,77] These techniques involve three basic steps: dissolution and removal of the organic matrix material of the lung in which fibers are embedded; recovery and concentration of the mineral fibers; and analysis of the fiber content by some form of microscopy. The dissolution or digestion step generally involves alkali wet chemical digestion using 5.25% sodium hypochlorite solution (*i.e.*, commercial bleach). Other investigators have employed low-temperature plasma ashing to remove the organic residues.

In the recovery step, the fibers are collected on the surface of an acetate or polycarbonate filter with a suitable pore size. ABs can then be quantified by means of brightfield light microscopy,[6,8,12,15,45] and both uncoated fibers and ABs can be counted by phase-contrast light microscopy.[78] However, because of the limited resolution of light microscopy and the inability to discriminate among the various fiber types, most investigators prefer some form of electron microscopy accompanied by energy-dispersive spectrometry (EDS).[79]

Electron microscopy permits the detection and quantification of both ABs and uncoated fibers (Fig. 36-12), including fibers beyond the resolution of light microscopic techniques. Furthermore, EDS permits discrimination among the various fiber types on the basis of their elemental composition (Fig. 36-13).

FIGURE 36-12. A scanning electron micrograph of a Nuclepore filter (Nuclepore, Burlingame, CA) preparation of lung tissue from an asbestos insulator who had malignant pleural mesothelioma and asbestosis shows numerous asbestos bodies and uncoated asbestos fibers. The patient's lung tissue contained nearly 3 million asbestos bodies and more than 9 million uncoated fibers 5 μm or greater in length per gram of wet lung. (Original magnification × 600.)

There is some site-to-site variation in mineral fiber concentration within the lung, ranging as high as tenfold.[80] Therefore, it is important to select tissue for analysis in a way to minimize such variation. Ideally, multiple sites should be analyzed from lung tissue obtained at autopsy, pneumonectomy, or lobectomy. However, open lung biopsy specimens may be analyzed as well. Formalin-fixed tissue is preferred, but paraffin blocks are also suitable for analysis.[12] Areas of tumor, consolidation, or congestion should be avoided as much as possible.

Interlaboratory comparison trials have demonstrated considerable variation in analytic results between different laboratories, even when the same sample is analyzed.[81] Therefore, it is necessary for each laboratory performing such analyses to determine its own normal range. Results may be reported in terms of ABs or fibers per gram of wet or dry lung tissue or per cubic centimeter of lung tissue. As a rule of thumb, 1 fiber/g of wet lung $\simeq$1 fiber/cm^3 $\simeq$10 fibers/g of dry lung.

Analyses of tissue mineral fiber burdens in patients with asbestosis indicate a heavy lung asbestos burden in most cases.[15,25] This observation is consistent with epidemiologic evidence that asbestosis occurs primarily in individuals with heavy and prolonged exposure to asbestos.[76] There is also a positive correlation between the pulmonary asbestos burden and the severity of interstitial fibrosis as assessed histologically.

Detailed mineralogic analysis of lung tissue from 76 patients with asbestosis has been performed in my laboratory. AB counts were determined by light microscopy, and the concentration of fibers 5 μm or greater in length was determined by scanning electron microscopy (Table 36-1).[15,25] The median AB count was 37,800 AB/g of wet lung tissue (range, 600–1,600,000 AB/g). At these concentrations, an average of five microscopic fields of histologic sections would have to be examined at a magnification of 400× to find the first AB.[82]

In contrast, the normal range of AB content is 0 to 20 AB/g, with an average of 1 AB per 100 4-cm^2 histologic sections of lung tissue for individuals with no known exposure to asbestos.[6] The median concentration of fibers 5 μm or greater in length was 330,000 fibers/g (range, 18,000–12,500,000 fibers/g). More than 90% of fibers analyzed by EDS in these cases were commercial amphiboles, amosite or crocidolite. The normal range is 400 to 16,900 fibers/g, and almost 80% of fibers analyzed by EDS are determined to be nonasbestos mineral fibers.[25]

Analyses of tissue mineral fiber burdens in patients with malignant mesothelioma indicate a level well below that associated with asbestosis in most cases that were analyzed.[82] This observation is in keeping with epidemiologic studies showing that mesothelioma may occur following brief, low-level, or indirect exposure to asbestos.[37,38,44] Detailed analysis of lung tissue from 67 patients with mesothelioma yielded a median AB count of 1390 AB/g (range, 1–1,600,000 AB/g) and a median concentration of fibers 5 μm or greater in length of 32,100 fibers/g (range, 1200–9,300,000 fibers/g; see Table 36-1). The highest levels occurred in patients who also had asbestosis; intermediate levels occurred in patients with pleural plaques; and the lowest levels occurred in patients with neither asbestosis nor plaques. ABs were observed in histologic sections of lung parenchyma in over one half of the patients.[82]

In a larger series of 143 patients with mesothelioma in which AB counts were determined by light microscopy, the median value was 380 AB/g. A histogram of the distribution of AB counts in these 143 patients shows a bimodal log normal distribution; 76% of patients have AB counts outside of the normal range (Fig. 36-14). This finding is consistent with the observation that 70% to 80% of patients with mesothelioma have an identifiable exposure to asbestos.[83]

Approximately 55% of fibers analyzed by EDS in patients with mesothelioma are commercial amphiboles. Amosite is about 20 times more common than crocidolite among mesothelioma patients in North America.[84,85]

Patients with parietal pleural plaques who do not have asbestosis have considerably smaller pulmonary asbestos burdens than do patients with asbestosis, and levels that are about the same order of magnitude as those in patients with malignant mesothelioma (see Table 36-1). Detailed analysis of lung tissue from 40 patients with pleural plaques but without asbestosis yielded a median AB count of 1450 AB/g (range, 6.8–18,900 AB/g) and a median concentration of fibers 5 μm or greater in length of 26,000 fibers/g (range, 800–243,000 fibers/g).

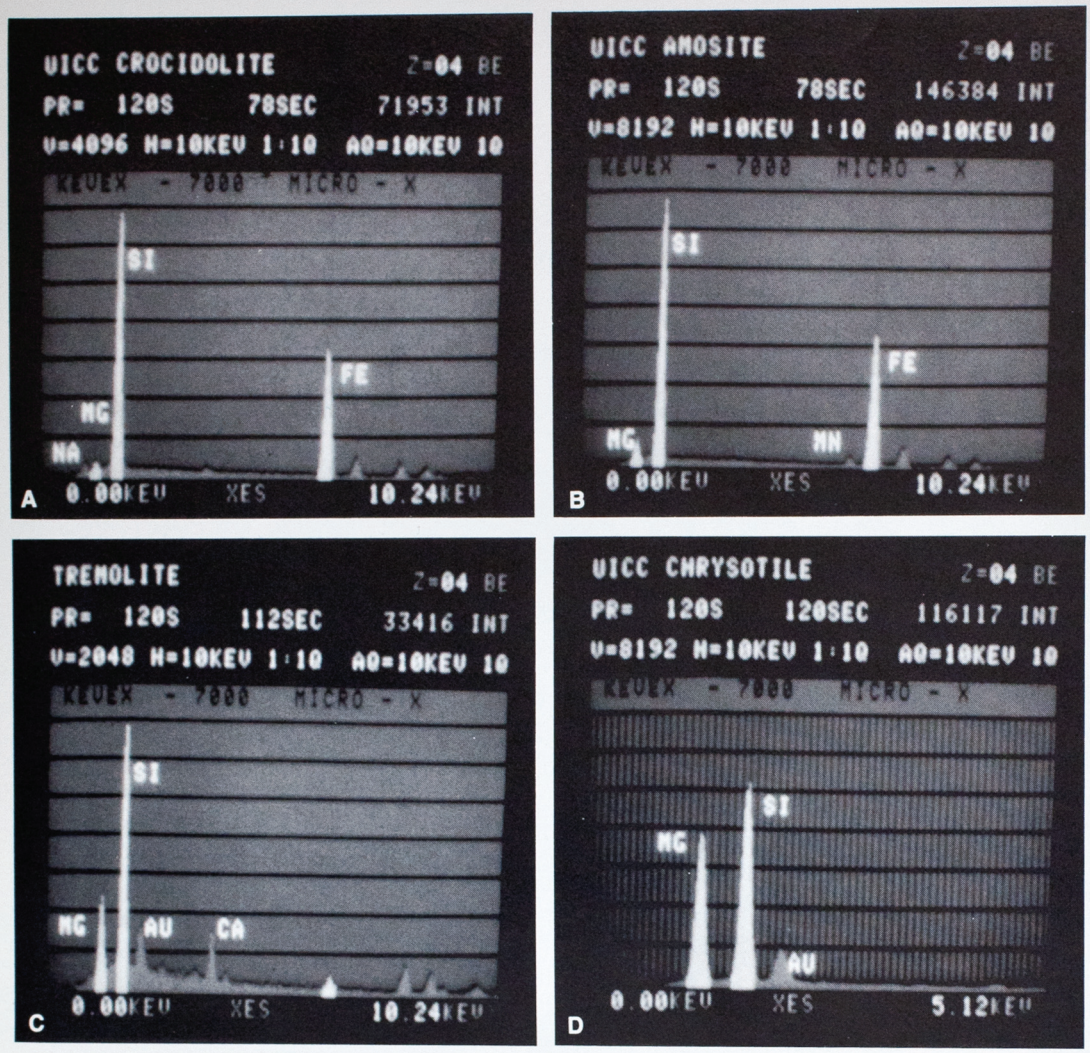

FIGURE 36-13. Energy-dispersive x-ray spectra of four different asbestos fiber types. (**A**) Amosite has peaks for silicon, iron, magnesium, and sometimes manganese. (**B**) Crocidolite has peaks for silicon, iron, sodium, and magnesium. (**C**) Tremolite has peaks for silicon, magnesium, and calcium. (**D**) Chrysotile has peaks for magnesium and silicon. The gold peak in (**C**) and (**D**) results from sputter-coating the specimen with this metal.

TABLE 36-1
Asbestos Content of Lung Tissue in Patients With Asbestos-Associated Diseases *versus* Normal Controls*

Diagnosis	Number of Cases	AB/g	UF/g
Asbestosis	76	37,800 (600–1,600,000)	330,000 (18,000–12,500,000)
Mesothelioma	67	1390 (1–1,600,000)	32,100 (1200–9,300,000)
PPP	40	1450 (6.8–18,900)	26,000 (800–243,000)
Carcinoma of the lung			
With Asbestosis	48	33,400 (620–352,000)	307,000 (18,500–7,800,000)
With PPP	25	1880 (23–18,900)	30,900 (3500–160,000)
With neither asbestosis nor PPP	70	170 (1–32,000)	14,700 (700–262,000)
Normal controls	20	2.9 (0–22)	3100 (400–16,900)

** Values are median counts per gram of wet lung for asbestos bodies or uncoated fibers 5 μm or greater in length. Ranges are indicated in parentheses.*

AB/g, asbestos bodies per gram, determined by light microscopy; PPP, parietal pleural plaques; UF/g, uncoated fibers 5 μm or greater in length per gram, determined by scanning electron microscopy.

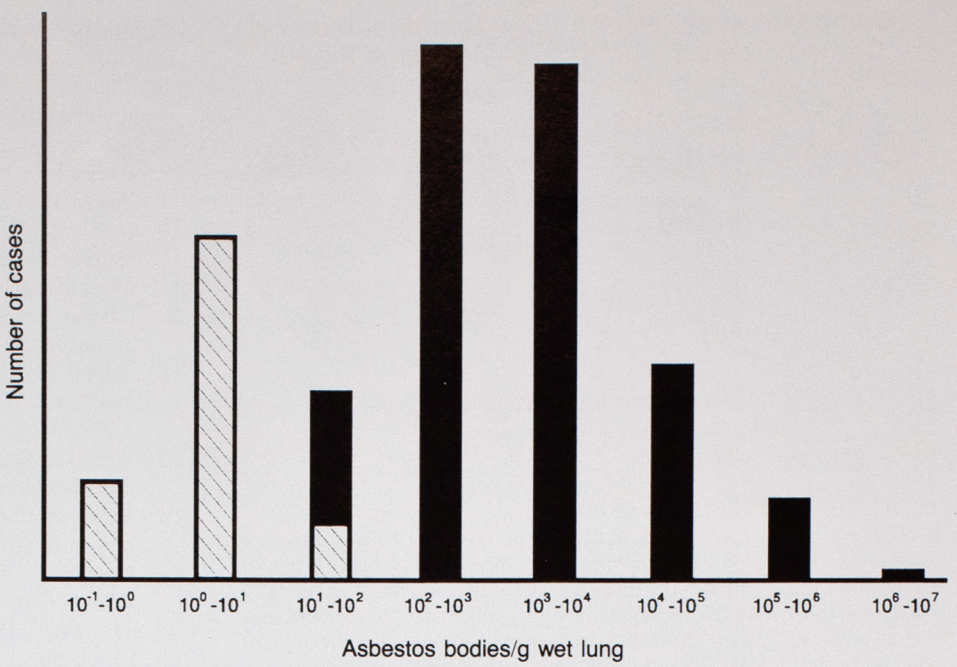

FIGURE 36-14. Distribution of asbestos body counts in 143 patients with malignant mesothelioma. The normal values are in the range of 0 to 20 asbestos bodies per gram of wet lung. The logarithmic scale has values ranging from 0.1 (10^{-1}) to 10 million (10^{7}) asbestos bodies per gram as determined by light microscopy. The data are consistent with a biphasic log normal distribution: 17% of cases have a mean of 0.15 and standard deviation of 0.21, and 83% of cases have a mean of 2.96 and standard deviation of 1.21. In the chi-square goodness-of-fit test, $\chi^2 = 1.19$, $P = 0.28$). The first distribution (*hatched area*) has values that overlap with those of the general population.

A study of five patients with rounded atelectasis showed results well within the range of values for patients with pleural plaques.[86] A study of seven patients with diffuse pleural fibrosis demonstrated fiber burdens intermediate between those of patients with plaques and those of patients with asbestosis.[87] In a large series of 120 patients with pleural plaques in which AB counts were determined by light microscopy, the median value was 145 AB/g. A histogram of the distribution of AB counts in these 120 cases showed a unimodal distribution; 72% of patients have AB counts outside of the normal range.[86] Approximately 67% of fibers analyzed by EDS in patients with pleural plaques are commercial amphiboles.

The pulmonary asbestos burden in patients with carcinoma of the lung and a history of occupational asbestos exposure is somewhat related to whether or not there is evidence of other asbestos-related tissue injury, although there is considerable overlap in this regard.[86] The highest levels of asbestos are found in patients who have histologically proven asbestosis; the 48 patients that I studied had a median AB count of 33,400 AB/g (range, 620–352,000 AB/g). The median concentration of fibers 5 μm or greater in length was 307,000 fibers/g (range, 18,500–7,800,000 fibers/g; see Table 36-1).

Intermediate values are observed for patients with lung cancer and pleural plaques who lack histologic features of asbestosis. The median AB count for 25 such individuals was 1880 AB/g (range, 23–18,900 AB/g), and the median concentration of fibers 5 μm or greater in length was 30,900 fibers/g (range, 3500–160,000 fibers/g).

The lowest values were observed in 70 patients with neither plaques nor asbestosis (see Table 36-1). However, approximately one half of patients with pleural plaques and lung cancer, and one fourth to one fifth of patients with a history of asbestos exposure and lung cancer, but lacking plaques or asbestosis, had lung asbestos burdens exceeding the fifth percentile for patients with asbestosis and lung cancer.[86] Some investigators have suggested that the association between asbestos exposure and lung cancer should be based on tissue asbestos burdens rather than on the presence or absence of asbestosis (see Asbestos and Carcinoma of the Lung).[88]

Relatively few studies have examined the relationship between type of exposure to asbestos and pulmonary asbestos burden.[78,82,89,90] In a study of 188 patients with asbestos-associated diseases and 18 patients with normal lungs and no known exposure to asbestos, the highest fiber burdens were observed among asbestos insulators.[86] Intermediate levels were found in shipyard workers, excluding insulators, and in individuals with other industrial exposures to asbestos. Somewhat lower levels were noted among railroad workers exposed to asbestos during the steam locomotive era. The lowest levels among occupationally exposed individuals were observed among automotive brake repair workers and manual laborers.

Interestingly, household contacts of asbestos workers often have pulmonary asbestos burdens similar to those of workers with light or moderate direct industrial exposure to asbestos.[82,86,91] In contrast, occupants of buildings with asbestos-containing materials may have fiber burdens indistinguishable from those of individuals with no known occupational exposure.[82,86] It should be noted that a wide range of values may be observed among individuals within any one group, and consequently there may be a considerable overlap of values between exposure categories.[82,86] This variation in fiber burden among individuals within the same exposure category may be related to variations in duration and intensity of exposure, cofactors such as cigarette smoking, and individual variability in clearance efficiency.[86]

The elemental composition of fibers recovered from human lung tissue samples can be determined by means of EDS (Fig. 36-15).[8,12,13,31,38,45,76,77,82,84,86,89] The results of analysis of more than 900 coated fibers (*i.e.*, ferruginous bodies) and 2500 uncoated fibers 5 μm or greater in length from more than 250 patients are shown in Figure 36-14. Approximately 94% of coated fibers and 56% of uncoated fibers have a composition indicative of commercial amphiboles (*i.e.*, amosite or crocidolite). Only 1.4% of coated fibers and 3% of uncoated fibers are chrysotile. This disparity in fiber types may be related to the tendency for chrys-

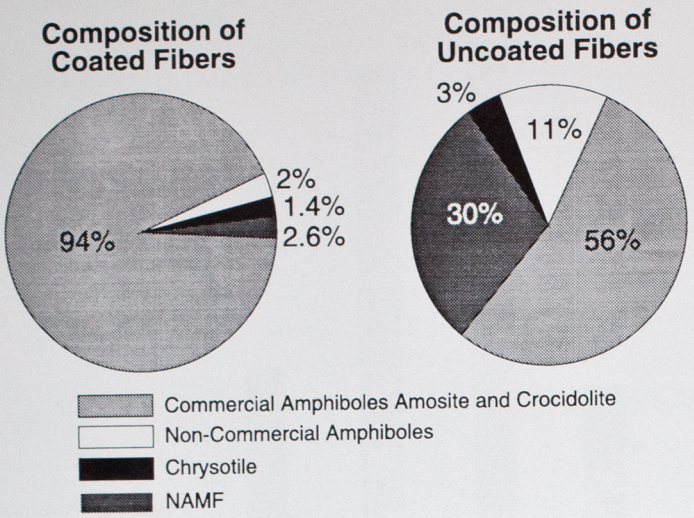

FIGURE 36-15. Proportions of the various types of fibers forming the cores of ferruginous bodies (*left*) and the composition of fibers 5 μm or greater in length (*right*). The data are derived from more than 3400 analyses in more than 250 patients, including more than 900 ferruginous bodies and more than 2500 uncoated fibers. Commercial amosite or crocidolite amphiboles account for the majority of fibers analyzed; only a small percentage is chrysotile. Note that more than 97% of ferruginous bodies are true asbestos bodies.

otile to break down into fibrils that are less than 5 μm in length.[2] Such fibers are cleared from the lungs more rapidly than are the long amphibole fibers, which are retained for prolonged periods.[92] Noncommercial amphiboles, which may be a contaminant of chrysotile ore, account for 2% of coated fibers and 11% of uncoated fibers. More than 97% of coated fibers have an asbestos core and thus are true ABs.

Nonasbestos mineral fibers that become coated are usually recognizable by light microscopy as ferruginous bodies with black or broad yellow cores (see Color Fig. 36-1; see Fig. 36-3).[8] Nonasbestos mineral fibers account for 30% of uncoated fibers. These include talc, silica, rutile, aluminum silicates, other silicates, fibrous glass, aluminum-rich fibers, iron-rich fibers, apatite, copper-zinc, tin, and iron-chromium.[86,93,94] The biologic significance of nonasbestos mineral fibers is largely unknown. However, there is no evidence to date, with the exception of erionite, that nonasbestos mineral fibers are of any significance in the causation of mesothelioma.

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