

Pathology of Asbestosis—An Update of the Diagnostic Criteria

Report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society

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● Asbestosis is defined as diffuse pulmonary fibrosis caused by the inhalation of excessive amounts of asbestos fibers. Pathologically, both pulmonary fibrosis of a particular pattern and evidence of excess asbestos in the lungs must be present. Clinically, the disease usually progresses slowly, with a typical latent period of more than 20 years from first exposure to onset of symptoms.

Differential Diagnosis: Idiopathic Pulmonary Fibrosis.—The pulmonary fibrosis of asbestosis is interstitial and has a basal subpleural distribution, similar to that seen in idiopathic pulmonary fibrosis, which is the principal differential diagnosis. However, there are differences between the 2 diseases apart from the presence or absence of asbestos. First, the interstitial fibrosis of asbestosis is accompanied by very little inflammation, which, although not marked, is better developed in idiopathic pulmonary fibrosis. Second, in keeping with the slow tempo of the disease, the fibroblastic foci that characterize idiopathic pulmonary fibrosis are infrequent in asbestosis. Third, asbestosis is almost always accompanied by mild fibrosis of the visceral pleura, a feature that is rare in idiopathic pulmonary fibrosis.

Differential Diagnosis: Respiratory Bronchiolitis.—Asbestosis is believed to start in the region of the respiratory bronchiole and gradually extends outward to involve more and more of the lung acinus, until the separate foci of fibrosis link, resulting in the characteristically diffuse

pattern of the disease. These early stages of the disease are diagnostically problematic because similar centriacinar fibrosis is often seen in cigarette smokers and is characteristic of mixed-dust pneumoconiosis. Fibrosis limited to the walls of the bronchioles does not represent asbestosis.

Role of Asbestos Bodies.—Histologic evidence of asbestos inhalation is provided by the identification of asbestos bodies either lying freely in the air spaces or embedded in the interstitial fibrosis. Asbestos bodies are distinguished from other ferruginous bodies by their thin, transparent core. Two or more asbestos bodies per square centimeter of a 5- μ m-thick lung section, in combination with interstitial fibrosis of the appropriate pattern, are indicative of asbestosis. Fewer asbestos bodies do not necessarily exclude a diagnosis of asbestosis, but evidence of excess asbestos would then require quantitative studies performed on lung digests.

Role of Fiber Analysis.—Quantification of asbestos load may be performed on lung digests or bronchoalveolar lavage material, employing either light microscopy, scanning electron microscopy, or transmission electron microscopy. Whichever technique is employed, the results are only dependable if the laboratory is well practiced in the method chosen, frequently performs such analyses, and the results are compared with those obtained by the same laboratory applying the same technique to a control population.

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The observations and conclusions reported here represent the work of an international committee of North American, European, and Australasian pathologists, organized under the auspices of the College of American Pathologists and the Pulmonary Pathology Society. This article updates the previous guidelines for the histologic diagnosis of asbestosis and its distinction from other pulmonary fibrotic disorders¹ and is intended to be used as a basis for communication between pathologists, pulmonologists, oncologists, radiologists, occupational

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hygienists, and epidemiologists. The aim of this new edition is to define the morphologic features of asbestosis at its various stages, relate exposure levels to specific tissue reactions, and evaluate the grading scheme published in the first report. Although these guidelines primarily focus on pathologic diagnosis and risk assessment, clinical and radiologic presentations are also included. Epidemiology is considered, and techniques for the assessment of asbestos fiber burden are evaluated.

The initial guidelines also dealt with mesothelioma, lung cancer, and benign, asbestos-related pleural diseases, but attention here is confined to asbestosis and disorders with which it may be confused.

HISTORIC BACKGROUND

The use of asbestos dates back to preclassic times, at least 5000 years. The heat resistance and tensile strength of asbestos were used by ancient Cypriot civilizations to manufacture clothes, whereas, in Finland, archaeological remains have identified ceramics containing anthophyllite asbestos. The early Greeks used asbestos in lamp wicks, and the Romans incorporated asbestos in cremation clothes.

The hazardous health effects of asbestos were, to our knowledge, first recorded by the Greek geographer Strabo (in *Geographia*, book 10), reporting on a lung disorder among slaves weaving asbestos cloth. Large-scale industrial exploitation of asbestos began in the 1870s, and in 1898, attention was drawn to "injury to the bronchial tubes and lung" among asbestos-carding, silk-operating, and hemp-spinning workers,^{2(p171)} although at the time, the prevailing view was that asbestos was inert in human tissue. The first detailed account of death from asbestosis appeared in 1907,³ and thereafter, a series of reports described a chronic lung disease in asbestos workers that was neither tuberculosis nor silicosis. In 1917, the radiologic features of this disease were first described,⁴ and in 1927, the term *pulmonary asbestosis* was introduced.⁵ In 1930, a landmark epidemiologic study of asbestos textile workers showed a high incidence of lung fibrosis that correlated with exposure intensity and duration.⁶ With the recognition of the health hazards came a requirement for governmental regulatory control of asbestos dust in the workplace, which resulted in dust-suppressive measures being introduced in the United Kingdom in 1933.

Until the 1930s, measurements of airborne dust were rare, and hygiene equipment was limited to counting fibrous particulates. In 1922 and 1937, the impinger and the midget impinger were introduced, respectively, in the United States, expressing particle concentrations of millions of particles per cubic foot. Thermal precipitators were the preferred early hygiene tools in the United Kingdom, as was the konimeter, in South Africa. The aim was to control and monitor dust levels in the workplace. Epidemiologists have subsequently used such hygiene measurements to evaluate asbestos exposure in risk analyses.

By the 1930s, there were anecdotal case reports of lung cancer complicating asbestosis,⁷⁻⁹ but the association between lung cancer and asbestosis was not fully established until 1949, when lung cancer was reported in 13% of 235 men dying with asbestosis, compared with 1.2% of 6884 men dying with silicosis.¹⁰ In 1951, a histologic survey of 1205 industrial postmortems found

that 14% of the 121 asbestosis cases were accompanied by primary lung cancer.¹¹ In 1955, 2 further publications provided irrefutable evidence of the association between lung cancer and asbestosis. The first was a case-control study performed in 11 Californian hospitals,¹² and the second, a retrospective cohort mortality study of asbestos textile workers in the United Kingdom.¹³ The latter found an 11-fold increase in lung cancer among long-term workers, all of whom had concomitant asbestosis.

Reports of pleural cancer in persons with asbestosis date from the 1940s and were substantiated by a report of 33 cases of diffuse pleural mesothelioma in a crocidolite mining area of South Africa in 1960,¹⁴ at a time when the very existence of malignant mesothelioma was still controversial. The diagnosis of this tumor would remain problematic until the emergence of immunohistochemistry and electron microscopy in the 1970s.

Methodology for workplace dust monitoring had evolved since its introduction in the first part of the 1920s. In 1965, the modern membrane-filter method and a standardized approach to fiber counting were introduced. Fibers were interpreted as all structures with a length to diameter ratio of 3:1 or more (an arbitrary figure accepted by the Asbestosis Research Council). Pathogenic and respirable fibers were deemed to be those greater than 5 μm long and less than 3 μm in diameter. Fibers with these dimensions became known as *regulated fibers* or *World Health Organization fibers*. They were assessed by light microscopy, which meant that only fibers greater than 0.25 μm in diameter were visualized (irrespective of fiber length). Thus, regulated fibers represent only a small proportion of those in a dust cloud. Furthermore, light microscopic methods do not permit an accurate distinction of asbestos from nonasbestos fibers (ie, qualitative data are not possible). To make that distinction would require energy-dispersive x-ray analysis and selected-area electron diffraction, techniques that only later became available.

In a series of landmark studies in the United States and Germany, researchers drew attention to the importance of fiber length in relation to mesothelioma induction in animals.¹⁵⁻²⁰ The investigators concluded that the induction of mesothelioma was determined primarily by the physical dimensions of the fibers, the most dangerous being those greater than 8 μm in length and less than 0.25 μm in diameter. Long fibers were recognized to be more tumorigenic than short fibers. This led to the suggestion that other nonasbestos fibers of similar fiber dimensions might be just as hazardous as asbestos, an hypothesis that was subsequently supported by reports of erionite-induced mesothelioma in Turkey²¹ and animal experiments showing lung fibrosis and mesothelioma induction following erionite inhalation.²² On a dose per dose basis, erionite and amphiboles appeared to be equally potent.

In the 1970s, a number of epidemiologic studies were undertaken to determine the risk of disease after asbestos exposure, culminating in a state of the art document entitled *Biological Effects of Mineral Fibres*.²³ By the end of the decade, there was firm epidemiologic evidence that asbestos-induced disease related to fiber type as well as to cumulative asbestos dose. Chrysotile appeared to be less fibrogenic and far less tumorigenic than the commercial amphiboles crocidolite and amosite.

Since 1980, there has been considerable investment in the epidemiologic analysis of various asbestos-exposed cohorts to determine, in particular, exposure-response data for asbestosis. This was greatly facilitated by the 1980 International Labour Office system for the radiologic classification of pneumoconiosis²⁴ and the emergence of sophisticated electron microscopic analytical methods, which allowed more accurate assessment of fiber burden, fiber size, and fiber type.

A number of pathologic definitions of asbestosis exist, and pathologists have not applied them uniformly. During the past 25 years, 2 comprehensive descriptions of the pathologic characteristics of asbestosis have emerged. The Pneumoconiosis Committee of the College of American Pathologists and the National Institute of Occupational Safety and Health provided the first such description in 1982.¹ Their document set forth the proposed minimum histologic criteria for asbestosis and formulated a grading scheme for lung fibrosis. The minimum criteria necessary for a diagnosis of asbestosis were the finding of "discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of asbestos bodies" in histologic sections. Although the essential requirement for asbestosis is the presence of diffuse interstitial fibrosis in association with asbestos bodies, several outstanding issues exist and these problems still bedevil discussions on this topic. These issues concern the minimum number of asbestos bodies necessary and the degree of fibrosis required to enable the pathologist to diagnose asbestosis with confidence. The College of American Pathologists–National Institute of Occupational Safety and Health criteria did not specify the minimum number of asbestos bodies required, despite an inherent understanding that the definition phrasing implies more than one asbestos body. Unfortunately, there was no reference to the required asbestos body number per lung sectional area examined.

The grading scheme for fibrosis (asbestosis) was not universally accepted. Most notably, Churg and coworkers²⁵ sought to highlight that the disease process asbestosis required "diffuse" interstitial fibrosis and that this condition was distinct and different from small airways mineral-dust disease, where multifocal peribronchiolar fibrosis may be seen after the inhalation of a variety of mineral dusts, including asbestos, silicates, metal oxides, and coal. Similar changes may be seen commonly in the lungs of tobacco smokers.²⁶ It was recognized that the determination of early/minimal asbestosis in current or ex-smokers would be highly problematic, with potential for misclassification of cases.

A number of key publications emerged in the 1980s. With respect to the pathologic diagnosis of asbestosis, Roggli and Pratt²⁷ noted that 2 asbestos bodies in a 4-cm², Perl-stained section correlated with a 10-fold increase of asbestos bodies greater than the upper limit for a control reference population. In a series of accepted asbestosis cases studied by Roggli et al,²⁸ the authors reported more than 5 asbestos bodies per 1 cm² in 95% of cases, and more than 2 asbestos bodies per 1 cm² of lung sectional area in 100% of cases. In iron-stained sections, 2 asbestos bodies in a 2- × 2-cm² section corresponded to approximately 2000 asbestos bodies per gram of dry lung tissue on light microscopy.²⁹ Because asbestos bodies and fibers were not evenly distributed, more than one section needs to be examined. That evidence was accepted by most authori-

ties and served to underpin the later Helsinki definition of asbestosis (see below).³⁰

In 1984, the Ontario Royal Commission heard evidence that the threshold cumulative dose of asbestos necessary for clinical manifestations of asbestosis was between 25 and 200 fibers/ml–yrs (fibers/ml × number of years) of cumulative exposure. In contrast, a no-effect threshold level of asbestos (less than which there was no subsequent risk) was not recognized for malignant mesothelioma.³¹

Also in the 1980s, the mineralogic study of lung tissue in humans and animals was expanded. The focus was now to correlate disease with respirable (ie, inhaled, deposited, and retained) fiber counts at the site of tissue injury and to characterize the retained particulates. Various workers sought to study lung material from published cohorts. Lung fibrosis showed a dose-response relationship with retained amphibole asbestos, but not with chrysotile. Malignant mesothelioma incidence in Canadian chrysotile miners correlated with the contaminant amphibole tremolite, but did not correlate with chrysotile.³² It emerged that amphiboles are far more potent in the induction of asbestosis, lung cancer, and malignant mesothelioma than chrysotile. Meta-analyses have estimated that, for mesothelioma induction, the risk differential on a fiber per fiber basis is 1:1, 100:1, and 500:1 for chrysotile, amosite, and crocidolite, respectively. For lung cancer, estimates indicate a risk differential of 1:10 to 1:50 for chrysotile and commercial amphiboles, respectively.³³

In 1997, 19 participants from 8 countries met in Finland to discuss the diversity of asbestos-induced disorders, from which arose the so-called Helsinki Criteria for the definition of asbestosis.³⁰ The criteria required diffuse interstitial fibrosis *and* either 2 or more asbestos bodies within a section area of 1 cm² *or* a count of uncoated asbestos fibers that falls within the range recorded by the same laboratory for asbestosis. This definition clarified the minimum requirements of asbestos bodies per section area and recognized that, in some cases, mineralogic analysis of lung tissue was an acceptable biomarker of asbestos exposure. The participants also advocated a modified version of the 1982 grading scheme. A subsequent workshop in Adelaide, Australia, updated the Helsinki, Finland, report.³⁴

In 2002, an expert panel considered the health effects of asbestos and synthetic vitreous fibers, debating, in particular, the influence of fiber length in human disease.³⁵ The overwhelming opinion was that short fibers (<5 μm long) played no role in the induction of disease (fibrosis or tumors) in humans, but it was suggested that lung fibrosis may be induced by fibers shorter than those necessary to induce mesothelioma and lung cancer.

In summary, although much has been learned from scientific research into asbestos-related disease, there exist several outstanding issues. The pathogenesis of asbestosis is incompletely understood, as is the mechanism of asbestos-induced carcinogenesis. A number of confounders, most notably smoking, for asbestosis and lung cancer have compromised the interpretation of human studies.

MINERALOGY OF ASBESTOS

Asbestos is a generic name for a variety of silicate minerals that occur naturally in a fibrous form. They all exhibit, to a greater or lesser degree, high tensile strength and high resistance to heat and chemical attack. As shown in Table 1, the asbestos minerals can be divided into 2

Table 1. Types of Asbestos

| Serpentine | Amphiboles |
|------------|--|
| Chrysotile | Commercially exploited Amosite Crocidolite Noncommercial amphiboles Tremolite Actinolite Anthophyllite |

distinct groups, chrysotile and the amphiboles. The distinctions between the various forms of asbestos are based on mineralogic, structural, and chemical differences but translate into fibers with different biologic properties. Chrysotile has formed the vast bulk (>90%) of asbestos used in most countries, but the smaller amount of amphibole employed has differed in type from country to country. In North America, for example, most of the amphibole used has been amosite, whereas in the United Kingdom and Australia, there has been more exposure to crocidolite than to amosite.

Chrysotile is a magnesium silicate that, in its finest form, the fibril appears by electron microscopy as a hollow tube. The fibers have a positive surface charge. Larger and longer fibers of chrysotile are often curved. Chrysotile is relatively unstable in the lung. It fragments readily into short fibers and fibrils that are easily phagocytized by macrophages. Chrysotile is particularly unstable in acid environments, such as the macrophage phagolysosome, and dissolves by progressive removal of both magnesium and silicon from the fiber.³⁶ It has been estimated from *in vitro* chemical observations that in the lung, fibrils of chrysotile should dissolve in less than a day,³⁶ and carefully controlled studies in rats using high concentrations of inhaled, long (>20 µm), Canadian chrysotile fibers have shown a clearance half-time of 11 days.³⁷ Similarly, estimates of the clearance half-life in humans have been in the range of a few weeks to a few months.³⁸ However, fiber burden studies on experimentally exposed animals and on human lungs from exposed individuals show that some chrysotile fibers persist, perhaps because they are sequestered (probably in fibrous tissue) and thus protected from dissolution.

The amphiboles are a large mineral group, of which only a few members (Table 1) cleave into the very long, thin, fibrous form that defines asbestos. As opposed to chrysotile, amphibole forms of asbestos are stable within the lung; they do not fragment and are not sensitive to chemical attack. Thus, clearance half-lives for amphiboles are much longer than for chrysotile. In rats exposed to greater than 200 fibers per cubic centimeter, the amosite clearance half-life was estimated at more than 400 days,³⁹ and in humans, clearance half-lives for amphiboles are on the order of decades.³⁸

Amphibole forms of asbestos are often divided into those with considerable commercial exploitation (amosite and crocidolite) and those that are encountered largely as intrusions into other mineral deposits (tremolite, actinolite, anthophyllite); thus, tremolite is found in many chrysotile ore beds, and an amphibole that has been variously labeled as tremolite, richterite, or winchite is found in vermiculite ore from Libby, Montana.⁴⁰ However, the biologic properties of the amphiboles appear to

relate to fiber length and the length to width (aspect) ratios rather than to chemical composition, with thin, high-aspect ratio fibers more dangerous in their ability to induce disease than shorter and broader fibers.^{41,42} Thus, the amphibole found at Libby, Montana, behaves much like amosite in producing asbestosis.⁴³

In addition to fiber size and aspect ratio, experimental evidence and human epidemiologic data suggest that the persistence of a fiber within the lung is a crucial determinant of its pathogenicity.^{41,42} Although most studies have focused on the induction of mesothelioma, durable fibers, such as amosite or crocidolite, also induce considerably more fibrosis (asbestosis) in animals exposed to high doses of long fiber than do chrysotile or synthetic fibers with low biopersistence.⁴⁴⁻⁴⁶

In humans, fiber-burden studies have shown that asbestosis appears at much lower fiber burdens in individuals with amosite exposure than in individuals with chrysotile exposure,^{47,48} and the persistence of amphibole fibers in the lung is believed to be the reason why workers with amphibole exposure and radiologic asbestosis are more likely to see progression of their disease than are workers with chrysotile exposure and asbestosis.⁴⁹

The importance of fiber size and durability in disease induction is also confirmed by the findings from Turkey at a site where the soil and volcanic tufts contain the zeolite fiber, erionite. This fiber is not a form of asbestos but is comparable in size to amphibole asbestos and is also biopersistent.^{50,51} Most attention has been directed to the high incidence of mesothelioma in that region, but the same fibers also produce a significant incidence of interstitial pulmonary fibrosis comparable in every other aspect to asbestosis (>15% of the local population as studied by chest x-ray).⁵¹

ANALYSIS OF TISSUE MINERAL-FIBER CONTENT

The application of microscopic analytical techniques to demonstrate retained mineral particles in lung tissue has provided useful information for understanding occupational- and environmental-related lung disease, particularly regarding dose-response relationships in the various asbestos-related diseases.⁵²⁻⁵⁴ Mineralogic analysis contributes to the assessment of the intensity of past exposure, especially when data from other sources are unavailable, unreliable, or difficult to interpret quantitatively.

Techniques have been developed to measure the relative numbers of uncoated and coated fibers in lung tissue. Fibers are generally defined as particles with an aspect ratio (length to width) of 3:1 or greater, and most have relatively parallel sides. Regulatory fibers comprise only those fibers greater than 5 µm in length. Many different analytic techniques are available; some are costly, require specialist technical expertise, or are available in specialist centers only.

Because many of the important mineral particles are less than the optic resolution of the light microscope, light microscopic techniques always underestimate the retained mineral fiber content. As a consequence, there may be a poor correlation with exposure history.

Asbestos is ubiquitous, and some is always likely to be found in the lungs of the general, nonindustrially exposed population. It is, therefore, important that results found in a specific case be compared with those for the background population, and for this reason, control ranges need to be

established for each laboratory performing these analyses, especially because the protocols for mineral analysis vary among laboratories.⁵⁵ Ideally, but rarely practical, individual case results should be compared with ranges established for the relevant local population.

Subjects with asbestosis have higher amphibole asbestos fiber counts than those with pleural plaques or mesothelioma.^{47,48,56–58} Also, there is a good correlation between amphibole, but not chrysotile, asbestos fiber levels and grades of asbestosis. This is not surprising because chrysotile fibers clear relatively rapidly from the lung, whereas amphibole fibers tend to persist for many years.

Tissue Selection

Both formalin-fixed and fresh lung tissue can be used for these procedures, but within one laboratory, different samples from the same individual may differ 3-fold and up to 10-fold in very small samples.^{55,56,59} Consequently, analyses of transbronchial samples should only be undertaken in exceptional circumstances and the results interpreted with considerable caution. Optimal samples for mineral analysis comprise 2-cm³ blocks from 3 anatomic sites in the contralateral lung (in tumor cases) or either side (in nontumor cases), usually from the apical upper, apical lower, and basal segments of the lung. To be representative, the samples should not contain tumor or large areas of pleural fibrosis. Mineral fiber analysis can also be carried out on lung tissue retrieved from paraffin-wax blocks and bronchoalveolar lavage samples.

Methods of Tissue Dissolution and Fiber Retrieval

Separation of the fibers from the lung tissue should leave the fibers in as close to their natural state as possible, that is, without altering their dimensions and chemistries. The lung tissue is usually digested with wet chemical agents, such as sodium hypochlorite or potassium hydroxide, and the resulting digestate is put in a standard counting chamber⁵⁹ or collected on a membrane filter and examined by light or scanning electron microscopy. Alternatively, pieces of the filter can be placed on grids for transmission electron microscopic evaluation. The dry weight to wet weight ratio varies and should, therefore, be determined for each sample, and the results expressed as per gram of dry lung. Ashing methods are not generally satisfactory because of artifactual fragmentation of fibers. Limited periods of low temperature plasma ashing may be used, but prolonged periods alter the dimensions of the fibers, resulting in artifactually higher numbers of smaller fibers.⁵³ Care needs to be exercised to avoid contamination during sampling and preparation.

Counting and Measuring Mineral Fibers

Routine light microscopy allows a basic assessment of the type of dust. For example, ferruginous bodies can be identified in 5- μ m sections and more easily with Perl stain or the examination of thick unstained (20 μ m) sections. The pathologist should be able to distinguish those ferruginous bodies formed on the transparent, fibrous cores typical of asbestos bodies, from those formed on nonasbestos minerals, such as carbon, iron oxide, rutile, aluminum oxide, chromium oxide, mullite, kaolin, mica, talc, and glass. The latter are sometimes referred to as pseudoasbestos bodies. Ferruginous bodies formed on erionite or refractory ceramic fibers may be indistinguishable from true asbestos bodies by light microscopy alone,

although in practice, such pseudoasbestos bodies are rare in most localities.

Ferruginous body formation varies according to a number of factors including fiber type, length, concentration (fiber burden), quantity of iron within the lung, and other host factors. Therefore, counts of asbestos bodies do not show a consistent relationship to fibers. Thus, the quantification of asbestos bodies may not accurately reflect the total concentration of mineral fibers in the lung. For example, a higher proportion of a given number of amosite fibers form asbestos bodies than the equivalent number of crocidolite fibers, whereas a small proportion (0.14% on average) of chrysotile fibers form asbestos bodies.⁶⁰ Churg⁶¹ has analyzed 600 asbestos bodies from 82 subjects who were not asbestos workers and found that 98% had an amphibole core and 2% a chrysotile asbestos core. It may, therefore, be assumed that ferruginous bodies with a thin core nearly always represent amphibole asbestos.

Phase-contrast light microscopy is a relatively easy, inexpensive method that allows a basic quantitative assessment of fiber burden.⁵⁹ An appropriate volume of digestate is placed in a standard counting chamber, and both coated and uncoated fibers are counted. However, the method cannot distinguish between fiber types (ie, cannot specifically identify asbestos and nonasbestos types) and has a resolution limit for fibers of 0.2 μ m diameter.

These light microscopic methods are technically simple, inexpensive, and widely available but have several limitations. A comparative study of light to electron microscopic counts has shown a disproportionately high ratio of coated to uncoated fibers when fiber counts are low, so one cannot easily extrapolate from counts of asbestos bodies to numbers of uncoated fibers.⁶⁰ Electron microscopy, although more expensive and time-consuming, is more sensitive and can provide a breakdown of fiber types.⁶²

Transmission electron microscopy (TEM) is the most sensitive for detecting the smallest fibers. Pieces of the membrane filter bearing the digestate are placed on the electron microscope grid, and the filter is eliminated with an appropriate solvent. Counting is usually performed at a magnification between $\times 15\,000$ and $\times 20\,000$, which permits detection of fibrils as small as 1 nm in diameter. Fiber counts are usually 3-fold higher with TEM than with scanning electron microscopy. Transmission electron microscopy also allows the study of particle morphology and the use of electron diffraction for the identification of fiber type. Diffraction analysis is limited with a scanning electron microscope (ie, reflection electron diffraction with examination of Kikuchi lines⁶³), and details on internal particle structure are often better appreciated by use of TEM. Nonfibrous minerals can also be readily identified by TEM, although control reference ranges are more problematic to establish because of the complexity of the particles inhaled.

Scanning electron microscopy is a technical and scientific compromise between light microscopy and transmission electron microscopy. It can be used to determine the numbers and dimensions of fibrous and nonfibrous, inorganic particulates and to assess the relative proportions in which they are present. It requires minimal tissue preparation and has the advantage (unlike TEM) of allowing the examination of larger areas of tissue.

It is usually performed at $\times 1000$ to $\times 5000$ magnification and has a resolution limit for fibers of approximately $0.05 \mu\text{m}$ in diameter. Thus, it does not resolve the finest fibers, such as individual chrysotile fibrils.

Both scanning and transmission electron microscopes may be equipped for energy-dispersive x-ray analysis. Energy-dispersive x-ray analysis identifies the chemical composition of individual particles, which is often, in itself, sufficient to identify fiber type. Selected-area electron diffraction, which can be performed with TEM, provides information on crystalline structure, which can be of value when different fibers have similar chemical compositions, for example, anthophyllite and talc.

Interlaboratory and Intralaboratory Variation

There is considerable interlaboratory variation in results obtained on the same lung, probably because of irregularity in the distribution of asbestos in the lung and the methodological differences in tissue preparation, choice of analytic tools (scanning electron microscopy or TEM), magnifications adopted, and counting procedures. Laboratories assessing fiber burden should have a well-defined, standardized protocol for the digestion, preparation, and examination of the samples because there are numerous steps within the analytic process that can lead to loss or fracture of particles, resulting in correspondingly low or high artificial values. Interlaboratory comparisons have generally shown that reliable results can be obtained, although absolute values often differ. Generally, samples with low counts are consistently reported as low, and conversely, samples with high counts are consistently reported as high for each laboratory, demonstrating the importance of each laboratory having its own reference values.⁶⁴

ASBESTOSIS

Asbestosis is defined as diffuse pulmonary fibrosis caused by the inhalation of excessive amounts of asbestos fibers. All types of asbestos have been implicated to a greater or lesser degree, and there appears to be a dose-response relationship between the concentration of fibers in the lung and the severity or extent of the fibrosis.^{52,65} Asbestosis typically occurs in individuals with prolonged and heavy exposure to asbestos, and the disease may progress even after exposure has ceased. The diagnosis of asbestosis is usually based on the exposure history, clinical findings, and radiographic features. Biopsy is seldom required, but if thought ethically acceptable, it may be helpful when differential diagnostic considerations cannot be resolved on clinical or radiographic grounds alone.

Clinical Aspects

In contrast to the asbestosis seen in the first half of the 20th century, and even thereafter, many cases of asbestosis encountered nowadays represent asymptomatic disease, identified on radiologic investigation or by histologic assessment of lung parenchyma remote from a resected lung cancer. When asbestosis is symptomatic and progressive, the clinical features are essentially identical to those encountered with other forms of diffuse interstitial lung disease, such as usual interstitial pneumonia (UIP), taking the form of an insidious onset of breathlessness and dry cough. There may also be chest pain related to associated disorders, such as benign asbestos pleuritis or,

in patients with severe breathlessness, respiratory muscle fatigue from the increased respiratory work required to inflate fibrotic lung.^{66,67} Finger clubbing or central cyanosis may or may not be present.^{66,67}

Most cases of asbestosis are diagnosable as a probability exercise on clinical and radiologic grounds,⁶⁷⁻⁶⁹ without recourse to histologic examination, from the following findings:

1. A history of moderate to heavy asbestos exposure, typically, but not always, occupational and often protracted for many years. However, asbestosis is not an invariable outcome of substantial or even heavy asbestos exposures. In general, when the cumulative exposure has been substantial to heavy, the likelihood of clinical asbestosis and its severity are correspondingly greater, with a shorter latency interval between the commencement of exposure and the subsequent symptomatic onset of the disease.⁶⁷
2. Clinical signs of interstitial fibrosis in the form of end-inspiratory crackles on auscultation of the lung fields, especially in the lower zones.^{66,67}
3. Detection of reticular-linear diffuse opacities in the lower zones of the lung fields on radiologic examination (see following section);
4. Classically, restrictive impairment of lung function;⁶⁷
5. Usually, but not always, associated parietal pleural fibrous plaques and/or diffuse pleural fibrosis.⁶⁷

Criteria 1 and 3 are obligatory for the clinical diagnosis, which is further supported by criterion 5. When 1 or more of the criteria 5, 2, or 4 (in declining order of importance) are not fulfilled, the confidence index for the diagnosis declines correspondingly.

Pulmonary function tests usually demonstrate a restrictive impairment of lung function with a reduction of lung volume and forced vital capacity, diminished carbon monoxide diffusing capacity, and often hypoxemia on arterial gas analysis. Lung volume measurements have low specificity and sensitivity, the lack of sensitivity being explicable in part by the wide range of reference values.⁶⁷ Of greater significance is longitudinal assessment of lung volumes, with a greater than average, age-related decline for 3 to 5 years (with at least 3 serial measurements).⁶⁷ A reduction in diminished carbon monoxide diffusing capacity appears to be a more useful assessment, but it simply reflects a loss of parenchymal function and is affected, for example, by emphysema.⁶⁷

Coexistent airflow obstruction with reduced forced expiratory volume in 1 second is often explicable by tobacco smoking,^{67,70} but one study of lung function among Chinese asbestos workers⁷¹ recorded mild airflow obstruction in the female workers (all nonsmokers) and in smoker male workers, as shown by a reduced forced expiratory volume in 1 second. After adjustment for covariates, asbestos exposure, asbestosis, and pleural abnormalities correlated with lung restriction and mild airway obstruction that was independent of smoking.

Histologic diagnosis of asbestosis is most useful in the following circumstances: (1) when the clinical or radiologic features are atypical or nondiagnostic, for example, when the history of asbestos exposure is equivocal, and a biopsy of lung is carried out (optimally a wedge biopsy); (2) when histologic examination shows lung parenchyma

remote from a lung cancer or mesothelioma in surgical resection specimens; or (3) at autopsy.

An important differential diagnosis that arises in cases of asbestosis—especially when there is clinical-radiologic controversy about the diagnosis—is determining whether the disorder represents asbestosis or another interstitial disorder, such as one of the idiopathic interstitial pneumonias, especially UIP. One point of distinction is that UIP tends to be more rapidly progressive than asbestosis, which is usually either static or only slowly progressive,⁶⁹ although cases of rapidly progressive asbestosis do occur.⁷² About 50% or fewer cases progress after cessation of asbestos exposure.⁶⁷

Clinical asbestosis can be induced by cumulative asbestos exposure amounting to an estimated 25 fibers/ml-yr,^{31,67} and Browne⁷³ and Churg⁷⁴ have indicated that a “dose” in the range of 25 to 100 fibers/ml-yr is required for the development of asbestosis. One Chinese study,⁷⁵ based on chest radiographs of workers involved in the manufacture of asbestos products, found a 1% prevalence of grade I asbestosis (according to the Chinese system of grading), at a cumulative exposure of 22 fibers/ml-yr. Green et al,⁷⁶ in an autopsy study on the South Carolina asbestos textile workers, reported that histologic asbestosis was usually detectable with exposures in excess of 20 fibers/ml-yr, and a few cases were found with estimated cumulative exposures of 10–20 fibers/ml-yr (histologic examination being the most sensitive and specific means for the diagnosis of asbestosis). From an analysis of cases in the German Mesothelioma Register, Fischer et al⁷⁷ reported that a requirement for asbestos exposure amounting to 25 fibers/ml-yr for the diagnosis of asbestosis—including minimal histologic asbestosis—would lead to underrecognition of 42% of asbestosis cases and false-positive diagnoses in 24%.

Estimates of cumulative asbestos exposures required for induction of asbestosis have diminished during the years. Burdorf and Swuste⁷⁸ referred to a lifetime risk of asbestosis of 2 per 1000 cases at 4.5 fibers/ml-yr, and Dement et al⁷⁹ mentioned “a few” asbestosis deaths following exposures of less than 5 fibers/ml-yr. In South Africa, Sluis-Cremer⁸⁰ also recorded “slight” asbestosis following exposures to amphibole asbestos, estimated to have been as low as 2 to 5 fibers/ml-yr; however, Browne⁸¹ has rightly criticized that estimate because it was derived from average airborne fiber concentrations and did not represent an assessment of individualized exposures for the asbestosis cases. By way of a decision-tree approach to assessment of asbestosis, Burdorf and Swuste⁷⁸ suggested that for any probability of exposure defined by industry, evidence of direct exposure to asbestos amounting to, or in excess of, 5.0 fibers/ml for more than 1 year is enough for “ascertainment” of asbestosis (ie, >5.0 fibers/ml-yr). Even so, the development of asbestosis following seemingly low exposures of this type raises 2 distinct issues. The first is whether the patients with asbestosis had sustained other unrecognized exposures to asbestos because substantial concentrations of amphibole fibers in lung tissue are observed occasionally in the lung tissue of patients with only minor asbestos exposures (as evaluated from the work and exposure history).^{82,83} The second issue, as mentioned above, is whether the disorder represents coincidental idiopathic diffuse interstitial fibrosis⁶⁷ or interstitial disease related to some identifiable factor other than asbestos, and in this

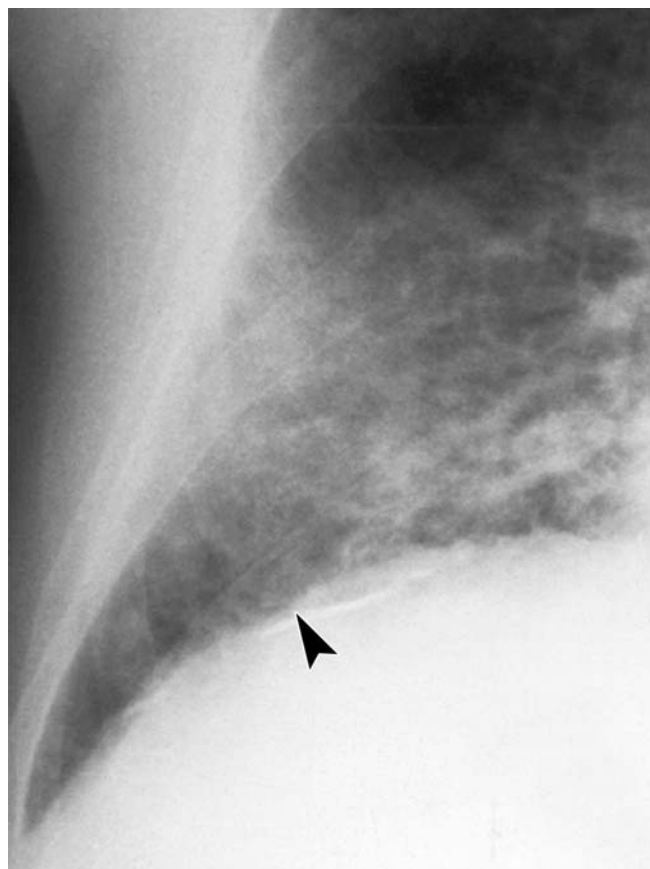


Figure 1. Posterior-anterior chest radiograph with limited view of the right lower lobe in a patient with asbestosis demonstrating small, irregular opacities. There is a calcified pleural plaque (arrowhead) projecting within the central tendon of the right hemidiaphragm.

latter circumstance, a probabilistic diagnosis of asbestosis becomes, in part, one of exclusion.

Imaging and Asbestos

The radiologist’s role in the assessment of an individual exposed to asbestos is complementary to that of the clinician and the pathologist. Biopsy material is not usually available, and the diagnosis is commonly predicated on clinical assessment, exposure history, and radiologic data. The imaging findings assume greater importance when the patient is exposed to cigarette smoke, and the cause of the patient’s dyspnea is multifactorial. Imaging also plays an integral role in differentiating other causes of fibrosis from asbestosis including: silicosis, sarcoidosis, hypersensitivity pneumonitis, nonspecific interstitial pneumonitis (NSIP), and to a lesser extent, idiopathic pulmonary fibrosis.^{84,85}

Chest Radiography

The chest radiograph remains the common entry point into the diagnostic-imaging algorithm. It is available worldwide and is associated with an accepted classification scheme for the evaluation of the pneumoconioses.⁸⁶ Asbestosis typically presents with small, irregular opacities at the lung bases (Figure 1). As the disease progresses, these opacities coalesce and become coarser, leading to a honeycomb pattern of small cysts. Association with pleural plaques increases the specificity of the diagnosis.

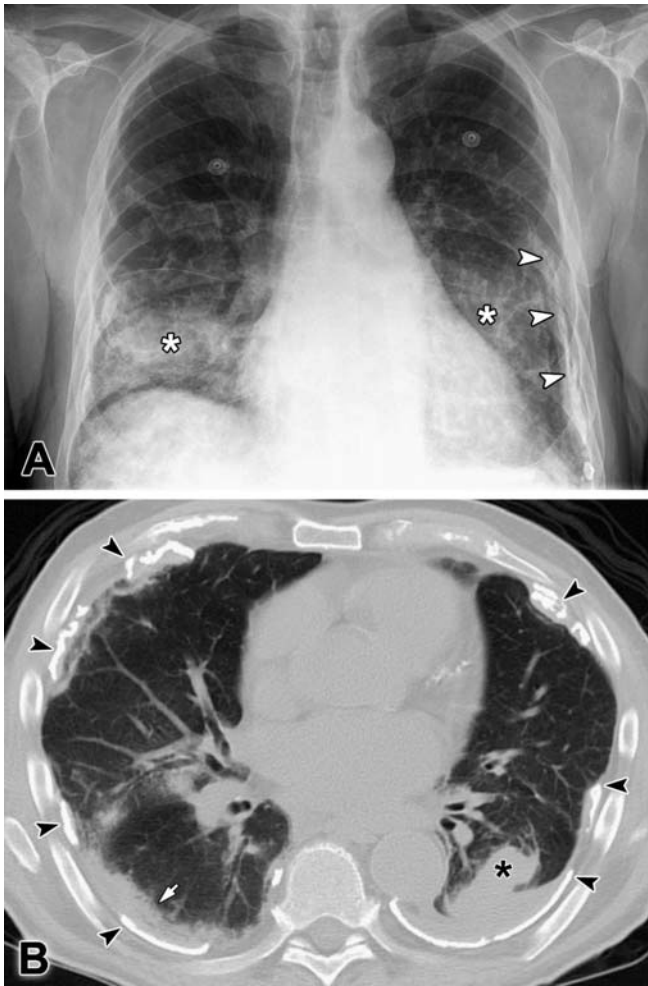


Figure 2. A, Posterior-anterior (PA) chest radiograph demonstrates extensive, calcified pleural plaques in both profile (arrowheads) and en face (asterisks). B, Axial chest computed-tomography slice through the lower lobes demonstrates a variety of parenchymal pathology not visualized on the PA chest radiograph, including round atelectasis (asterisk), calcified pleural plaques (arrowheads), and fibrosis (arrow).

However, there are significant problems associated with the chest radiograph and the diagnosis of asbestos-associated complications. The chest radiograph findings are normal in 10% to 18% of patients with biopsy-proven asbestosis, and at least 10% of pleural disease is not identified.^{87,88} It is estimated that the positive predictive value for an abnormal finding from a chest radiograph alone is approximately 40%.⁶⁸ The positive predictive value may be lower if the prevalence of asbestosis in the study population is less than 5%. Despite the acknowledged problems associated with the chest radiograph, it is still useful as an epidemiologic tool and as a diagnostic test in patients with characteristic, extensive disease and a confirmed history of exposure.⁸⁹

Extensive pleural disease is readily identified on chest radiography (Figure 2, A and B); however, the pleural density prevents accurate assessment of the underlying lung parenchyma. This problem, along with poor interobserver agreement between expert readers in patients with minimal disease, has highlighted the benefits of cross-sectional imaging.⁸⁹

Computed Tomography

Cross-sectional imaging in the chest and especially high-resolution computed tomography (HRCT) have changed the approach to chronic infiltrative lung disease. Conventional computed tomography and HRCT are more sensitive and specific than chest radiography in the diagnosis of both parenchymal and pleural diseases related to asbestos.^{90,91}

Meticulous computed tomography-histopathologic correlation from Akira et al^{92,93} defined the HRCT findings in patients with asbestosis. Isolated "dotlike" structures in the periphery of the lower lung on HRCT correlate with peribronchiolar nodular fibrosis found on histologic section. Many of these peripheral dots are associated with the peripheral pulmonary arteries and form branching structures that do not reach the pleural surface (Figure 3, A through C). Other HRCT findings associated with asbestosis include pleural-based intralobular and interlobular lines, ground-glass attenuation, and honeycombing. High-resolution computed tomography is most useful when the chest radiographic findings are normal or minimally abnormal. There is overlap between the HRCT appearances of asbestosis and UIP.

Diffuse fibrotic involvement of the visceral pleura is represented as widespread pleural thickening with costophrenic angle blunting on computed tomography and is associated with parenchymal bands and rounded atelectasis (Figure 4).⁹⁴ Parietal pleural involvement shows well-circumscribed areas of pleural thickening and correlates with the presence of pleural plaques (Figure 5). Despite the increased sensitivity of HRCT compared with radiography, it is important to recognize that the finding of a normal examination by computed tomography does not exclude the presence of asbestosis.⁹⁵

High-resolution computed tomography is emerging as an important tool for quantification of fibrosis^{96,97} and for elucidating the role of emphysema in dyspneic cigarette smokers who have a history of asbestos exposure. Copley et al⁹⁸ have demonstrated the ability to quantify the contribution that asbestosis, diffuse pleural thickening, and emphysema makes in the physiologic deficit and dyspnea suffered by an individual patient.

Macroscopic Features

Asbestosis is best observed in lung specimens that have been fixed by the instillation of formalin for 1 or 2 days.⁹⁹ The disease ranges in severity from subtle findings that are not visible macroscopically to advanced disease characterized by small, fibrotic lungs with honeycombing (Figure 6, A and B). The changes tend to be more severe in the lower lobes and periphery of the lung. Fibrosis is seen as linear or irregularly shaped areas of firm, gray tissue, and there may be accentuation of secondary lobular septa. Pleural adhesions are variably present. The honeycomb change seen in advanced cases is represented by subpleural cysts measuring up to 15 mm in diameter (Figure 7). Airways are generally unremarkable, although there may be areas of traction bronchiectasis in severely fibrotic areas. Lymph nodes may be enlarged but show no significant abnormalities on their cut surface. In exceptional cases, asbestosis has been described as being most severe in the upper lobes,¹⁰⁰ but it has to be asked whether those cases represented another form of interstitial lung disease in a patient with coincidental asbestos exposure.

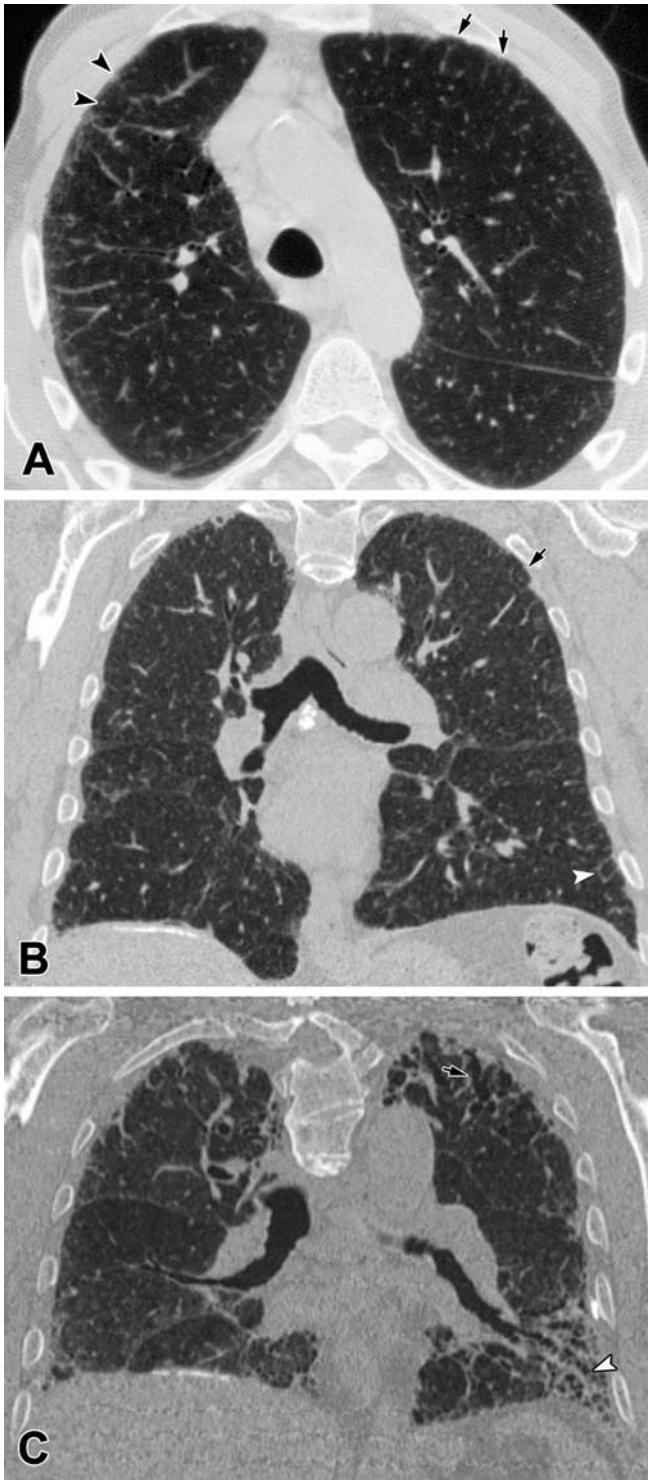


Figure 3. A, High-resolution axial computed-tomography (HRCT) slice at the level of the aortic arch in a patient with asbestosis, which shows peripheral “dotlike” (arrowheads) and branching structures (arrows). B, Coronal reconstruction of axial HRCT data demonstrates peripheral, interlobular septal lines (arrowhead) and “dotlike” structures (arrow). There is a calcified pleural plaque in the central tendon of the right hemidiaphragm. C, Coronal reconstruction of axial HRCT data demonstrates more advanced asbestosis, with honeycombing and traction bronchiectasis at the left base (arrowhead) in association with parenchymal bands (arrow).

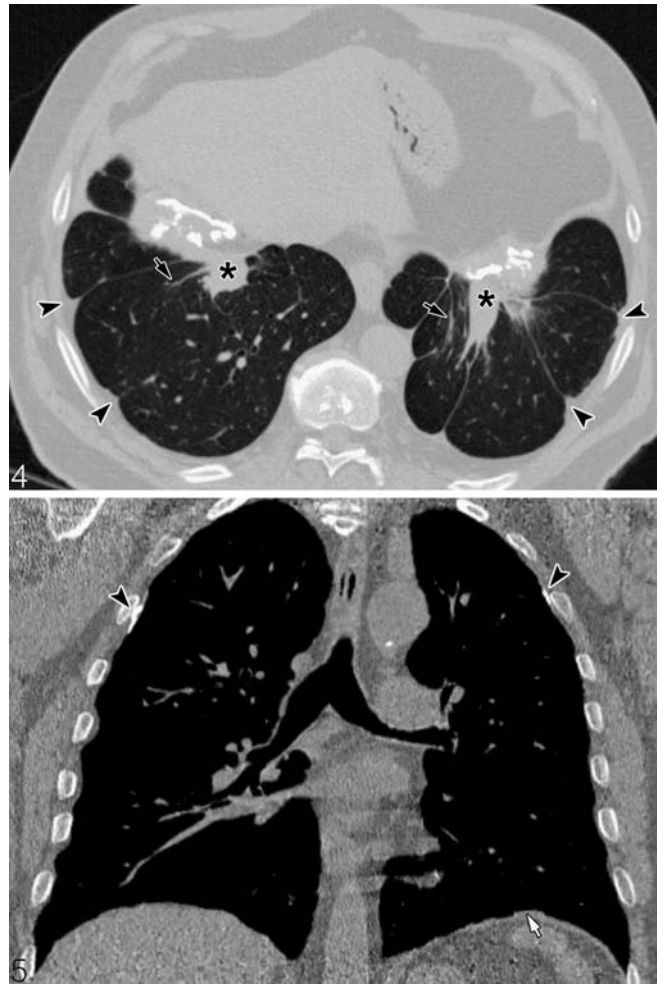


Figure 4. Axial chest computed tomography at the level of the dome of the diaphragm in a patient with diffuse visceral pleural fibrosis shows bilateral pleural thickening (arrowheads), parenchymal bands (arrows), and areas of round atelectasis (asterisks).

Figure 5. Coronal reconstruction of axial high-resolution computed tomography data demonstrates subtle, parietal pleural plaques, both calcified (arrowheads) and noncalcified (arrow).

Rare cases with massive fibrosis have also been reported, but those were likely related to concomitant exposure to silica dust.

A minor degree of diffuse, visceral pleural fibrosis is commonly seen (Figure 8), and most cases of asbestosis are associated with parietal pleural plaques. The latter form well-circumscribed areas of fibrosis located on the surface of the diaphragm or the posterolateral chest, particularly in relation to the ribs. Plaques are ivory-colored, raised, and smooth or knobby, often with an irregular outline. They are frequently calcified but many more are identified at autopsy than by radiography. It is emphasized that the term *asbestosis* applies exclusively to asbestos-induced pulmonary interstitial fibrosis, and it should not be used for any form of benign asbestos pleural disease.^{1,101}

A sampling scheme for histologic examination of cases of asbestosis was described previously.¹ The committee recommends that, for autopsy specimens, minimal sampling should include blocks from the peripheral and central portions of each lobe of both lungs (10 blocks

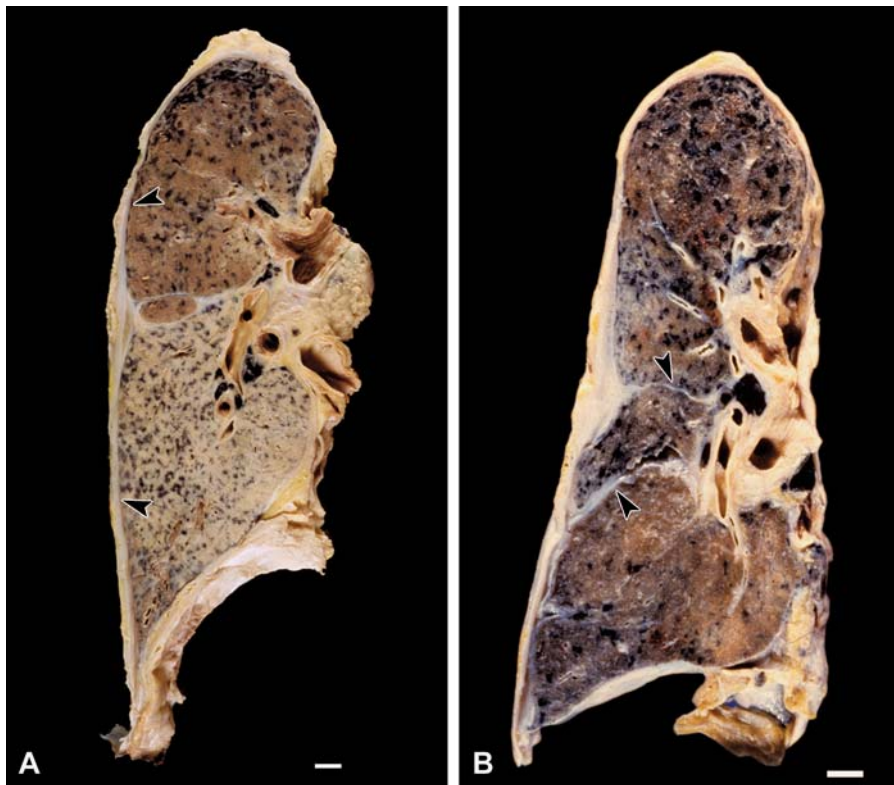


Figure 6. A, Right lung of a patient who was a crocidolite asbestos sprayer demonstrates advanced asbestosis that is most severe in the lower lobe. In addition, there is marked thickening of the visceral pleura (arrowheads). B, Right lung of a 71-year-old patient with asbestosis who was an amosite and crocidolite asbestos sprayer. There is thickening of the visceral pleura that extends into the fissures (arrowheads).

minimum), and for pneumonectomy specimens, samples should include peripheral and central blocks from each lobe. For lobectomy specimens, at least one peripheral and one central section should be sampled. To the extent possible, areas immediately adjacent to tumor should be avoided.

Microscopic Findings

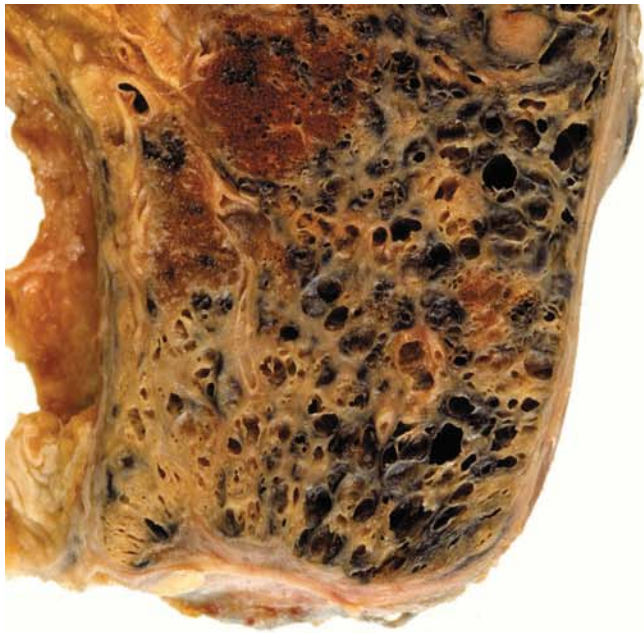
The microscopic diagnosis of asbestosis requires an appropriate pattern of interstitial fibrosis plus the finding of asbestos bodies. Both components must be present. Fibrosis in asbestosis is always paucicellular, lacks any significant degree of inflammation, and is collagenous rather than fibroblastic.

In early asbestosis, the fibrosing process is limited to the walls of alveoli immediately around the bronchioles (Figure 9, A). From this centriacinar position, fibrosis extends outward until it ultimately links adjacent bronchioles; at which time, the initial, predominantly peribronchiolar pattern of fibrosis may no longer be evident (Figure 9, B through D). Like UIP, the disease is most severe subpleurally, but as it advances, the fibrosis extends inward a considerable distance from the pleura. At that stage, a variety of morphologic patterns may be seen. Some cases resemble UIP, whereas others are more like fibrotic, nonspecific interstitial pneumonia, and still others do not match any other form of interstitial fibrosis. Asbestosis is characterized as having a lower lobe and peripheral distribution, similar to UIP, but with the temporal and spatial homogeneity of the fibrotic variant of nonspecific interstitial pneumonitis. Fibroblast foci are uncommon, seen only occasionally (Figure 10). If these foci of immature fibrosis are at all conspicuous, another diagnosis (such as UIP) should be considered. Honey-

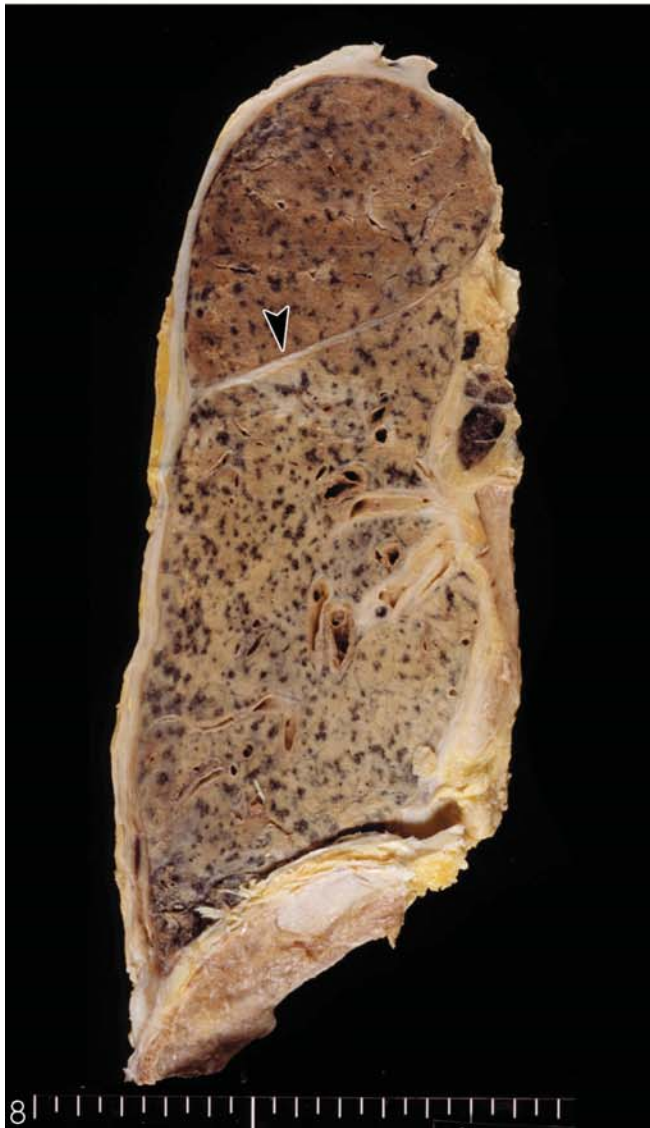
combing may be seen in advanced cases, but it is seldom as severe as in UIP (Figure 11, A through D).

Asbestos exposure may also be associated with fibrosis of the walls of the respiratory bronchioles and alveolar ducts (Figure 12), which is sometimes incorrectly referred to as *peribronchiolar fibrosis* and, therefore, is liable to be confused with the fibrosis of the alveolar walls around the bronchioles, which is truly peribronchiolar. A better term recommended here is *bronchiolar wall fibrosis*. Some authors accept bronchiolar wall fibrosis in the absence of alveolar septal fibrosis (and in association with asbestos bodies) as very early asbestosis, whereas others do not. Some have proposed the term *mineral dust airways disease* to refer to the isolated finding of bronchiolar wall fibrosis in association with a variety of dusts, such as silica, asbestos, iron, or aluminum oxide.¹⁰² Similar lesions may be observed from exposure to cigarette smoke.²⁶ This continues to be an area of controversy, and the arguments for and against the inclusion of bronchiolar wall fibrosis alone under the heading of asbestosis have been presented elsewhere.^{74,101} The committee believes that bronchiolar wall fibrosis should not be referred to as *asbestosis* and prefers the term *asbestos airways disease* for bronchiolar wall fibrosis associated with asbestos bodies.

The second feature necessary for a histologic diagnosis of asbestosis is the finding of asbestos bodies. Asbestos bodies are golden-brown, beaded, or dumbbell-shaped structures with a thin, translucent core (Figure 13, A through D). They form from the deposition of an iron-protein-mucopolysaccharide coating on the surface of an inhaled asbestos fiber by alveolar macrophages. In asbestosis, these bodies are typically found embedded within fibrous tissue, but they may also be observed within alveolar spaces or within the cytoplasm of



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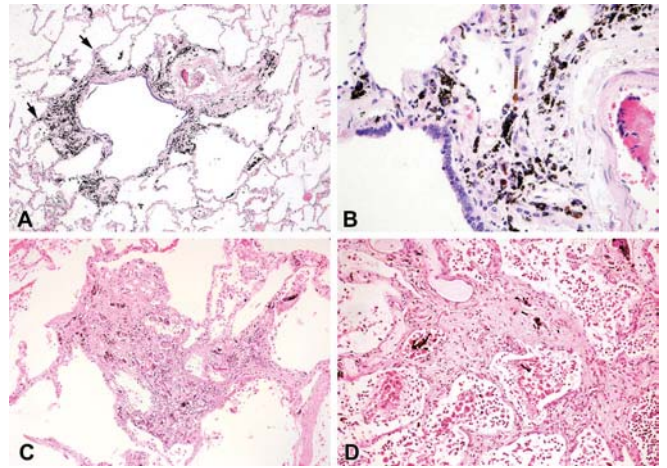


Figure 9. A, Grade 1 asbestosis consists of fibrosis involving the bronchiolar wall and extending to the first layer of alveoli (arrows). B, Higher magnification shows asbestos bodies embedded within the fibrous tissue. C, Grade 2 asbestosis consists of fibrosis involving more distant alveolar walls but which spares at least some alveoli between adjacent bronchioles. D, Grade 3 asbestosis consists of fibrosis involving all alveoli between 2 adjacent bronchioles (hematoxylin-eosin, original magnifications $\times 60$ [A and C], $\times 300$ [B], $\times 125$ [D]).

macrophages or multinucleate giant cells (Figure 14). They are most numerous around the bronchioles, but their presence there is often masked by deposits of carbon, and distinguishing between them is facilitated by the use of iron stains. Although asbestos bodies are typically formed on amphibole cores (Figure 15, A and B), chrysotile asbestos bodies are also observed in cases with chrysotile-induced asbestosis (Figures 16, A through C).¹⁰³ Asbestos bodies may also be observed within hilar lymph nodes, but that does not constitute asbestosis.¹⁰⁴

In most cases, asbestos bodies are readily identified in hematoxylin-eosin-stained sections, and several can commonly be found in a 2- \times 2-cm area of an iron-stained section. The committee recommends that a diagnosis of asbestosis should only be made when there is an acceptable pattern of alveolar septal fibrosis and an average rate of asbestos bodies of at least 2/cm² of lung.¹⁰¹ In rare cases, fewer bodies are seen, and the heavy fiber burden necessary for a diagnosis of asbestosis is only demonstrated by the more sophisticated techniques considered below. However, asbestos bodies are often distributed unevenly within the lungs, so that more than one section may need to be examined. Asbestos bodies should be distinguished from other ferruginous bodies or from pseudoasbestos bodies (see above), especially those with a black (Figure 17, A) or broad, yellow (Figure 17, B) core.^{53,74} The finding of asbestos bodies alone is insufficient for a histologic diagnosis of asbestosis and indicates only asbestos exposure.

←

Figure 7. This example of asbestosis shows honeycomb changes, with cysts up to about 15 mm in diameter. There is also diffuse visceral pleural fibrosis with blunting of the costophrenic angle.

Figure 8. In this patient with advanced asbestosis, there is diffuse visceral pleural fibrosis surrounding the lung and extending into the fissure (arrowhead).

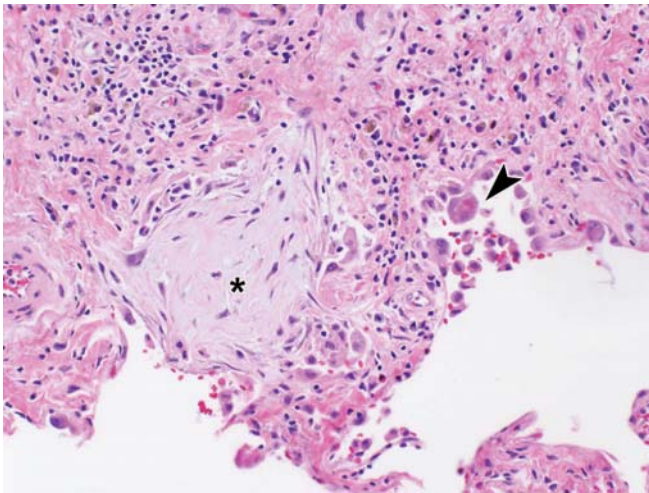


Figure 10. Fibroblastic foci, as seen in this case (asterisk), are uncommonly seen in patients with asbestosis. Cytoplasmic hyaline is also present in a nearby alveolar type II pneumocyte (arrowhead) (hematoxylin-eosin, original magnification $\times 150$).

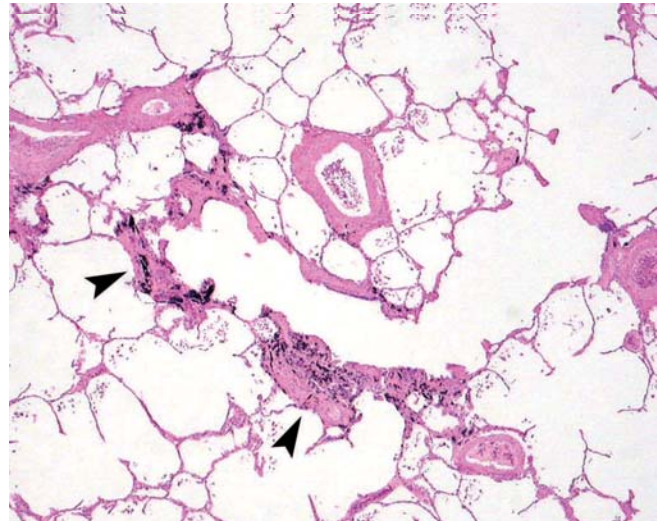


Figure 12. Asbestos airways disease consists of bronchiolar wall fibrosis (arrowheads) without fibrotic thickening of alveolar septa. This pattern should not be referred to as asbestosis (hematoxylin-eosin, original magnification $\times 70$).

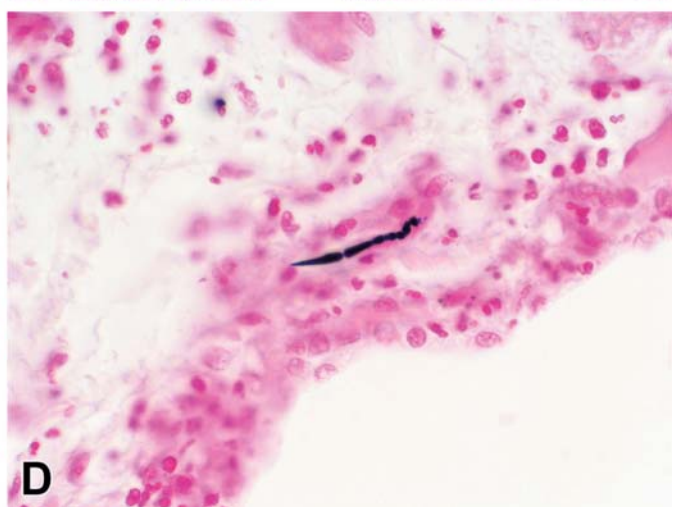
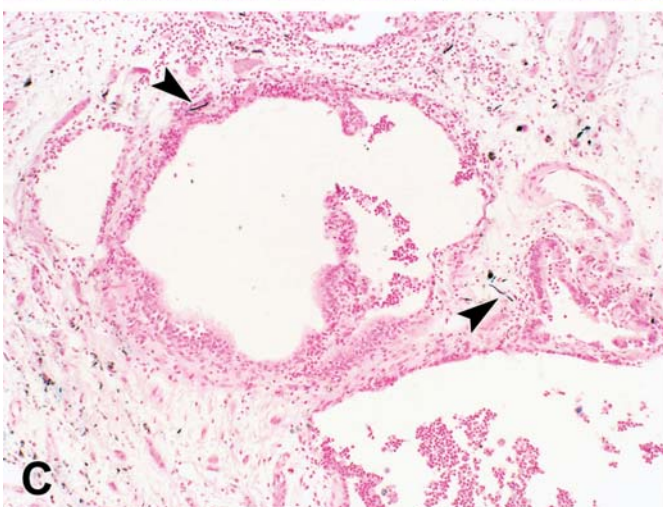
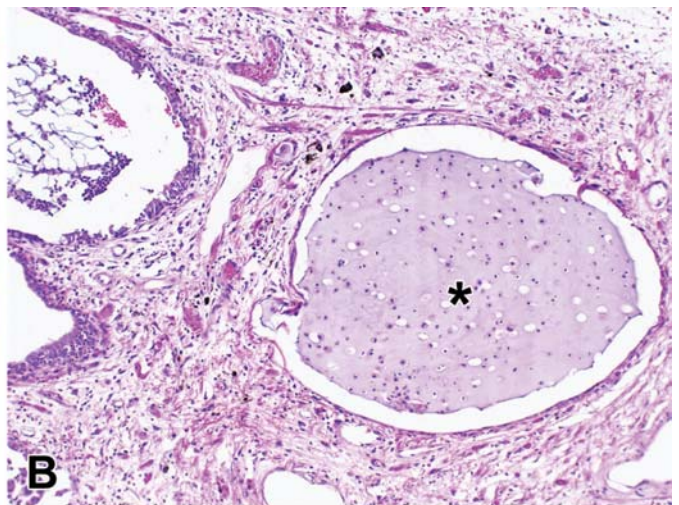
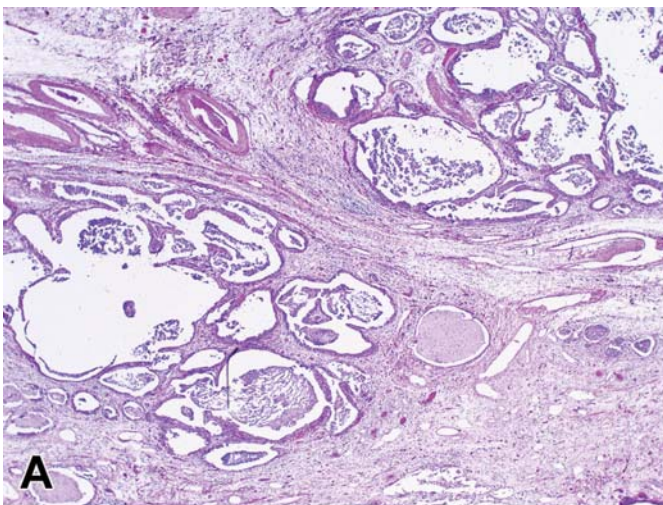


Figure 11. A, Low-power view shows fibrotic lung with honeycomb changes. B, Mucous-filled honeycomb cysts (asterisk) are present in this case of grade 4 asbestosis. C, At this magnification, asbestos bodies are just visible (arrowheads). D, Higher magnification shows the upper asbestos body from C (hematoxylin-eosin, original magnifications $\times 15$ [A], and $\times 70$ [B]; Perl iron, original magnifications $\times 70$ [C] and $\times 440$ [D]).

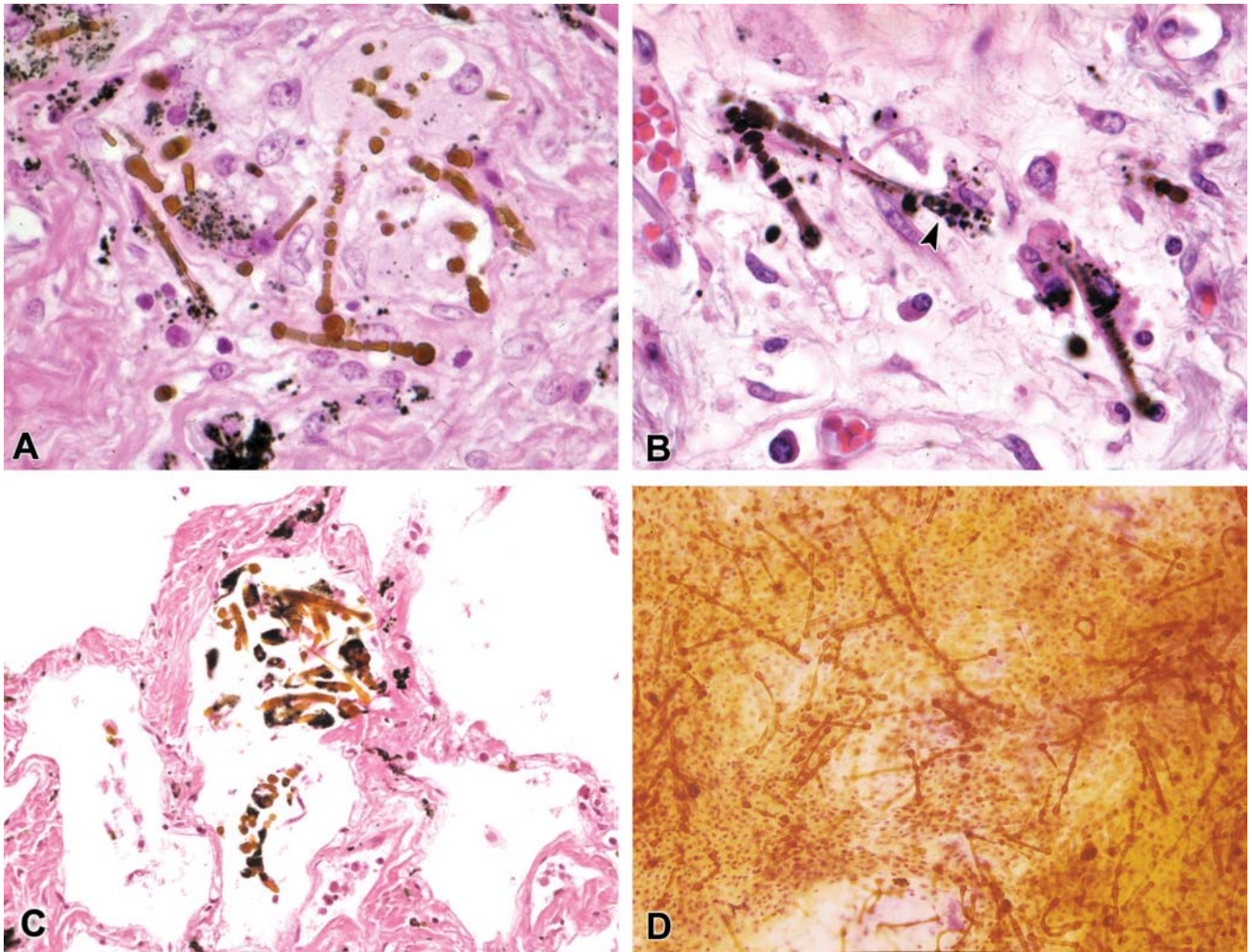


Figure 13. A, In this case of asbestosis from a crocidolite sprayer, asbestos bodies are embedded within the fibrous tissue. They consist of golden-brown, beaded structures with a thin, translucent core. B, Asbestos bodies in this case of asbestosis are embedded within fibrous tissue and are associated with pigment deposition (arrowhead). C, Asbestos bodies in this case from an amosite asbestos miner are lying free within the alveolar space. D, Numerous asbestos bodies are present within this sputum cytology sample from an insulator (hematoxylin-eosin, original magnifications $\times 440$ [A and B] and $\times 150$ [C]; Papanicolaou stain, original magnification $\times 150$ [D]).

Asbestosis typically has a latency period of 15 years or more from initial exposure until diagnosis. However, some of the early cases evolved much more rapidly, presumably related to historically high exposures.^{2,5} Such cases generally exhibited small fibrotic lungs without honeycomb changes but with numerous asbestos bodies in histologic sections. We suggest the term *accelerated asbestosis* for such cases, analogous to the term *accelerated silicosis* that has been applied to rapidly evolving pulmonary fibrosis caused by massive exposure to silica.¹⁰⁵ Although accelerated asbestosis is now rarely encountered in industrialized nations, such disease is always likely to develop if asbestos dust control is neglected, which is especially the case in developing countries. Accelerated asbestosis is characterized by diffuse shrinkage of the lower lobes by a combination of collapse, collagenous fibrosis filling the alveolar lumina, and the deposition of many asbestos bodies (collapse sclerosis or atelectatic induration). The upper lobes, on the other hand, exhibit earlier stages of asbestosis, with diffuse fibrosis confined to the centriacinar areas, and

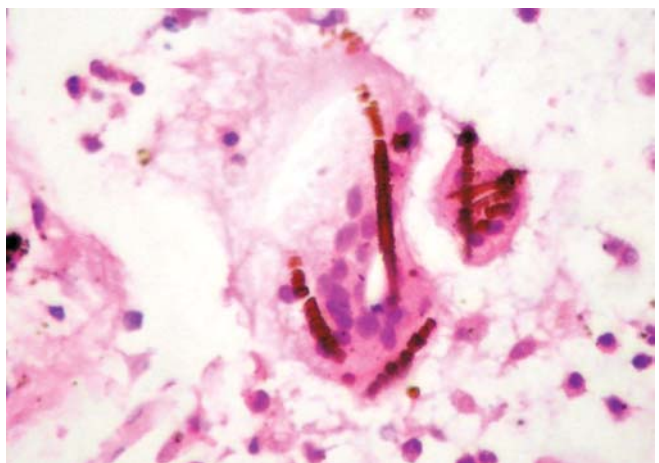


Figure 14. Several asbestos bodies are present within the cytoplasm of a multinucleated giant cell (hematoxylin-eosin, original magnification $\times 440$).

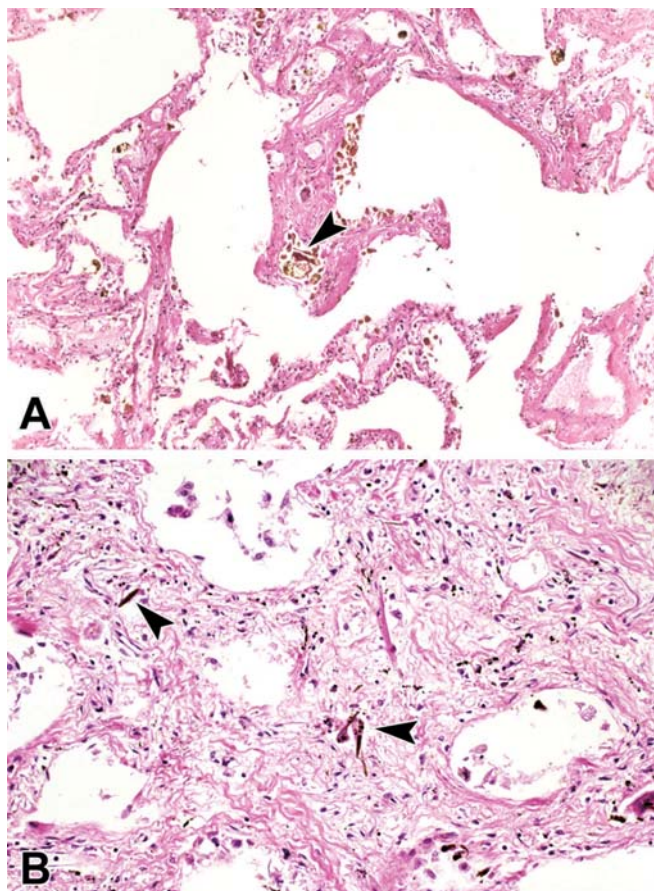


Figure 15. A, In this example of asbestosis from a South African miner, asbestos bodies are just visible at this magnification (arrowhead). B, Asbestosis from a South African miner. Note asbestos bodies (arrowheads) (hematoxylin-eosin, original magnifications $\times 20$ [A] and $\times 150$ [B]).

numerous asbestos bodies within or around the fibrotic lesions. Inflammation is scant or absent. In the experience of the committee, accelerated asbestosis is only caused by amphibole asbestos. Contrary to its silicotic counterpart, however, accelerated asbestosis progresses surprisingly slowly after it has fully evolved, with very little progression evident radiologically. The prognosis is correspondingly better in accelerated asbestosis than in accelerated silicosis.

A variety of other histologic abnormalities may be observed in asbestosis, but they are nonspecific. There may be type II pneumocyte hyperplasia, and in occasional cases, these cells may contain cytoplasmic hyaline, indistinguishable from that seen in alcoholic liver damage (Figure 18, A and B).¹⁰⁶ Small spicules of bone, with or without marrow elements, may develop in a variety of fibrotic lung disorders, including asbestosis.¹⁰⁷ Variable numbers of alveolar macrophages are seen and, in some cases, may be sufficiently numerous as to suggest desquamative interstitial pneumonia. In some cases, the macrophages are associated with laminated concretions, known as *pulmonary blue bodies*.¹⁰⁸ These represent extruded lysosomal residual bodies and, again, are not unique to asbestosis. Perivascular fibrosis may also be found, and vessel walls may be thickened by fibrosis, with consequent narrowing of the lumen (the changes of nonspecific endarteritis obliterans).

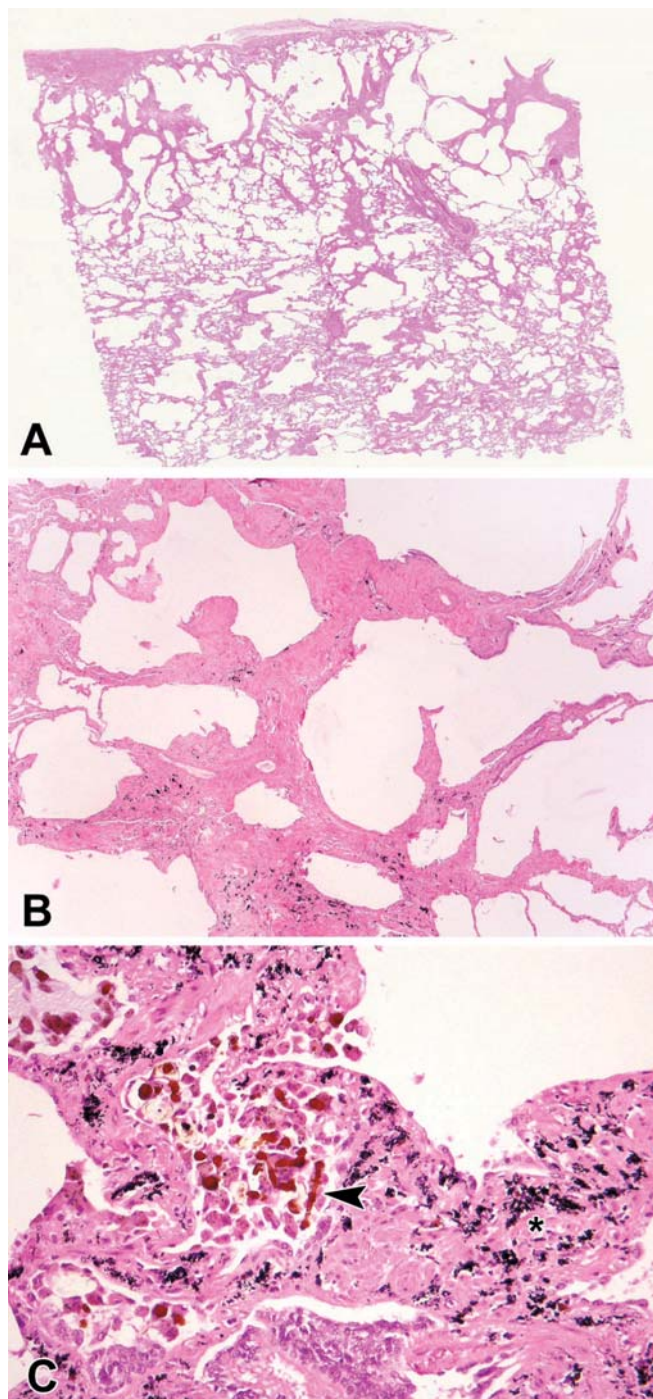


Figure 16. A, Whole mount of the lung in a Canadian case from a chrysotile asbestos miner showing diffuse interstitial fibrosis. B, The alveolar septa are markedly fibrotic. C, Asbestos bodies are present within a distorted alveolar space (arrowhead). Pigment is present within the fibrotic alveolar septa (asterisk) (hematoxylin-eosin, original magnifications $\times 10$ [A], $\times 70$ [B], and $\times 300$ [C]).

Cases have been reported in which asbestos bodies and a history of asbestos exposure are associated with a pattern of hypersensitivity pneumonia or organizing pneumonia,^{109,110} but the causative role of asbestos in those cases is unproven. It is the consensus of the committee that such cases should not be referred to as asbestosis.

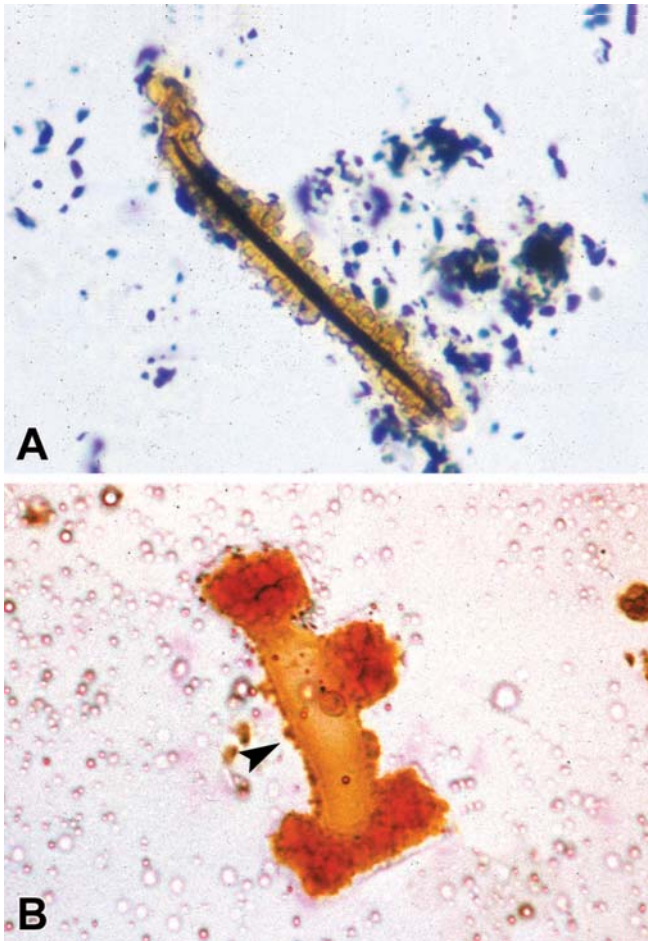


Figure 17. A, Pseudoasbestos bodies, like this one with a black core, should be distinguished from true asbestos bodies. B, This pseudoasbestos body has a broad, yellow sheet, silicate-type core (arrowhead) (hematoxylin-eosin, original magnification $\times 730$ [A]; unstained filter preparation, original magnification $\times 730$ [B]). Figures reprinted, with permission, from Roggli VL, Butnor KJ. *Pneumoconioses*. In: Leslie KO, Wick MR, eds. *Practical Pulmonary Pathology: A Diagnostic Approach*, Philadelphia, PA: Churchill Livingstone; 2005:312 (figure 9.27), 319 (figure 9.51).

Asbestosis is usually diagnosed histologically in lobectomy or pneumonectomy specimens resected because of cancer, or at autopsy. If a clinical diagnosis cannot be rendered and the patient requests a lung biopsy, video-assisted thoracoscopic surgery is required as transbronchial biopsies rarely provide sufficient tissue.¹⁰¹ However, the finding of asbestos bodies or asbestos fibers in bronchoalveolar lavage samples may also assist in the diagnosis of asbestosis when quantitative methods are employed (Figure 19, A and B).^{111,112}

Differential Diagnosis (Borderline Cases)

Asbestosis needs to be distinguished from other forms of pneumoconiosis, such as silicosis and mixed-dust pneumoconiosis. The hallmark of silicosis is the silicotic nodule, a localized area of rounded, whorled, hyalinized collagen. Silicotic nodules typically predominate in the upper lung zones, whereas asbestosis tends to predominate in the base.¹⁰⁵ The hallmark of mixed-dust pneumoconiosis is mixed-dust fibrosis, an irregular area of centriacinar interstitial fibrosis associated with dust deposits.¹¹³ The finding of asbestos bodies and the more

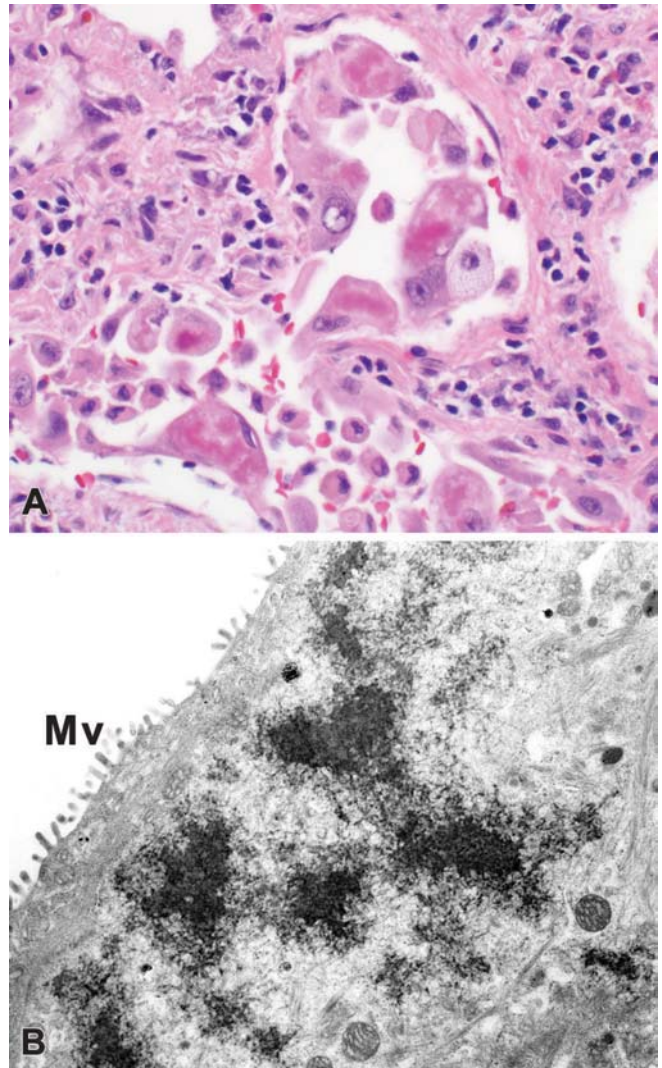


Figure 18. A, Cytoplasmic hyaline as seen in these alveolar, type II pneumocytes may be seen in some cases of asbestosis. B, Ultrastructurally, the hyaline material is irregular, electron dense, and free within the cytoplasm of a type II pneumocyte. Microvilli are present at the apical surface (hematoxylin-eosin, original magnifications $\times 440$ [A] and $\times 25\,000$ [B]).

diffuse nature of the fibrotic process distinguish asbestosis from mixed-dust pneumoconiosis. Although it is possible that an individual patient may have both asbestosis and silicosis or mixed dust pneumoconiosis, it is the authors' collective experience that this is distinctly unusual.

Asbestosis should similarly not be confused with lung diseases associated with cigarette smoking. The honeycomb changes seen in advanced cases of asbestosis are quite distinct from the centrilobular emphysema associated with cigarette smoking. The former develop in areas of subpleural basal fibrosis and rarely exceed 15 mm, whereas centrilobular emphysema predominates in the upper lobes and consists of black, "punched out" lesions that often measure many centimeters across. Such emphysematous bullae are often traversed by delicate strands representing residual blood vessels.⁹⁹ They are not associated with any marked degree of fibrosis. Respiratory bronchiolitis-associated interstitial lung disease is commonly encountered in smokers. It is characterized

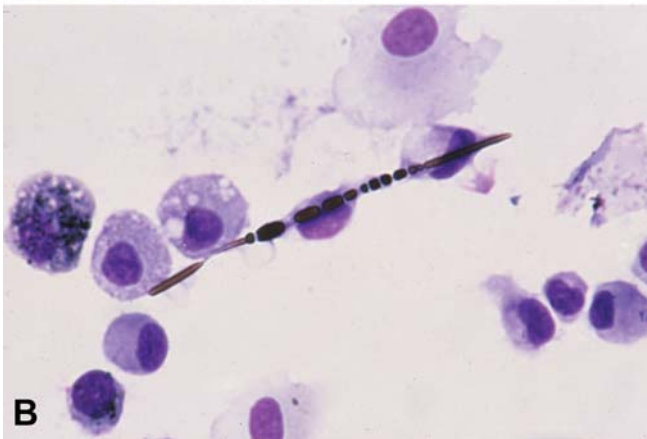
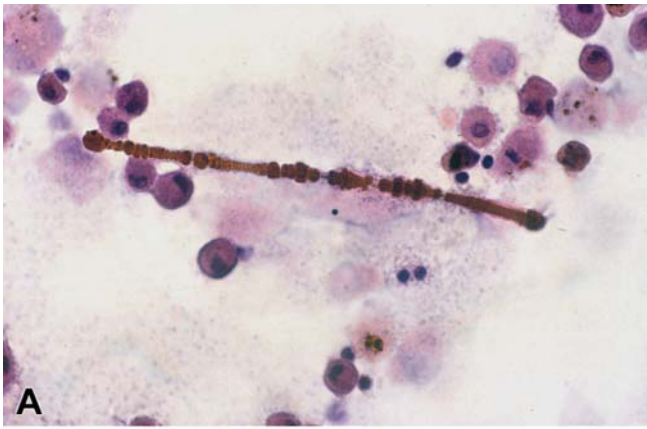


Figure 19. A and B, Asbestos bodies with beaded, ferruginous coating and thin, translucent core are present within bronchoalveolar lavage fluid (Wright-Giemsa, original magnifications $\times 440$ [A] and $\times 880$ [B]).

by foci of bronchiolar wall and alveolar septal fibrosis associated with numerous pigmented macrophages filling the centriacinar airspaces. Many asbestos workers smoke, and the lesions of asbestosis- and cigarette-induced lung disease may, therefore, coexist. Extreme examples of this account for some cases of desquamative interstitial pneumonia-like reactions described in patients with asbestos exposure.¹¹⁴

A more difficult area is the distinction between idiopathic pulmonary fibrosis and asbestosis (Table 2). The most common pattern of idiopathic pulmonary fibrosis is UIP. This is characterized by temporal heterogeneity, represented by densely hyalinized areas of fibrosis, alternating with areas showing fibroblastic foci,

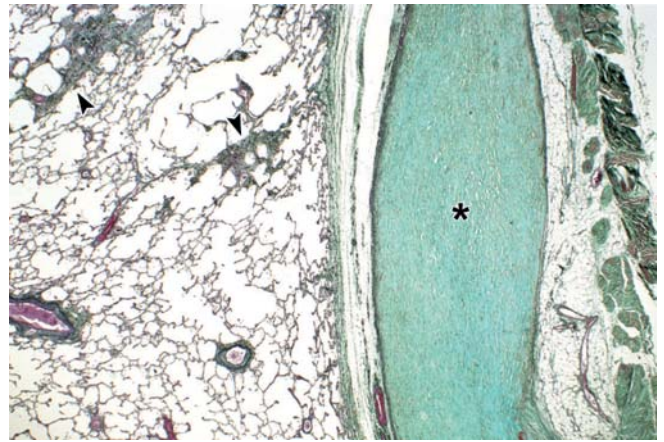


Figure 20. This low-power magnification of lung and chest wall from a patient with asbestosis shows parietal pleural plaque (asterisk) with a basket-weave pattern. Subjacent lung parenchyma contains several foci of fibrosis (arrowheads) (Masson trichrome, original magnification $\times 10$).

and yet others consist of nearly healthy lung. Honeycomb changes are frequently found in UIP. As noted, some cases of asbestosis resemble UIP, while others resemble fibrotic nonspecific interstitial pneumonitis,¹¹⁵ but in general, the presence of readily identified asbestos bodies permits the distinction of asbestosis from these other interstitial lung disorders. As noted above, the presence of frequent fibroblast foci is against a diagnosis of asbestosis. Pleural plaques (Figure 20) provide evidence of asbestos exposure, but they develop at relatively low levels of exposure and may, therefore, be present in patients with other fibrotic lung disorders.⁶⁵ In difficult cases, fiber analysis may be necessary to determine the etiology of the fibrotic process (see following section).

Role of Fiber Analysis

Methods for detecting the presence and quantities of asbestos fibers in lung tissue samples were reviewed in an earlier section. Suffice it to say here that fiber analysis should be considered an adjunctive technique in the assessment of asbestosis and cannot substitute for, or overrule, the histopathologic diagnosis of asbestosis as outlined above. Most studies have shown that patients with asbestosis have in excess of a million fibers per gram of dry lung tissue.¹¹⁶ Fiber analysis may also be useful for excluding a diagnosis of asbestosis in individuals with diffuse pulmonary fibrosis and a history of asbestos exposure but who lack the necessary histopathologic

Table 2. Differential Diagnostic Features for Asbestosis and Idiopathic Interstitial Pneumonias

| Histologic Feature | UIP | Asbestosis | NSIP |
|-------------------------------|--|--|---------------|
| Distribution | Subpleural accentuation, lower lung zone | Peribronchiolar with subpleural accentuation | Diffuse |
| Honeycomb changes | Common | Uncommon except in advanced cases | Uncommon |
| Fibroblast foci | Conspicuous | Rare | Inconspicuous |
| Asbestos bodies | Absent | Frequent ^a | Absent |
| Inflammation | Minimal, typically localized to honeycomb foci | Minimal | Variable |
| Pleural fibrosis ^b | Uncommon | Common | Uncommon |

Abbreviations: NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

^a In a small percentage of cases, asbestos bodies are not easily demonstrable. Fiber analysis is indicated in such cases when the exposure history is compelling.

^b Parietal pleural plaques and/or diffuse visceral pleural fibrosis.

Table 3. Histologic Grading^a Scheme for Asbestosis

| Grade | Description |
|----------------------|---|
| Grade 0 | No appreciable peribronchiolar fibrosis, or fibrosis confined to the bronchiolar walls |
| Grade 1 ^b | Fibrosis confined to the walls of respiratory bronchioles and the first tier of adjacent alveoli |
| Grade 2 ^b | Extension of fibrosis to involve alveolar ducts and/or ≥ 2 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 ≥ 2 adjacent respiratory bronchioles |
| Grade 4 | Honeycomb changes |

Source: Modified from the scheme presented in Craighead et al.¹

^a An average score is obtained for an individual case by adding the scores for each slide (0 to 4), then dividing by the number of slides examined.

^b Grade 1 and, to a lesser extent, grade 2 need to be distinguished from smoking-induced peribronchiolar fibrosis and mixed-dust pneumoconiosis.

criteria.^{65,117} As noted in a previous section, some individuals are poor at coating asbestos fibers and, thus, do not readily form asbestos bodies. In such cases, light microscopy has a limited role in the assessment of the overall lung fiber burden.

It is the consensus of the committee that cases of asbestosis (ie, asbestos-induced fibrosis) that do not meet the histologic criteria outlined in this document are rare. In such cases, analysis of lung tissue samples by an experienced laboratory using electron microscopic techniques may be useful. Cases with diffuse interstitial fibrosis and an asbestos fiber burden within the range of values observed for bona fide cases of asbestosis, as determined for a given experienced laboratory, are likely examples of asbestos-induced pulmonary fibrosis (ie, asbestosis). The asbestosis range for a laboratory refers to the retained amphibole fiber counts in cases of asbestosis (meeting the aforementioned morphologic criteria). The chrysotile count is not included because of the low biopersistence of the fiber. Conventional biologic reference range values are defined as including 95% of observed values for that group. The critical value to determine as the lower range value is the fifth percentile, that is, the value below which the lowest 5% of cases fall, and above which are 95% of cases.

Grading Schemes

A number of schemes have been reported for grading the extent and severity of asbestosis. These may be of particular value in epidemiologic studies and should only be applied to cases meeting the histopathologic criteria for the diagnosis of asbestosis. One such grading scheme is that proposed by the College of American Pathologists and National Institute for Occupational Safety and Health Asbestos Committee, a 12-point grading scheme that has been shown to be consistently reproducible with good interobserver agreement.¹ A simplified 4-point version of this scheme has been described by Sporn and Roggli.¹⁰¹ A modified grading scheme, based on the histologic criteria presented in this document, is provided in Table 3.

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