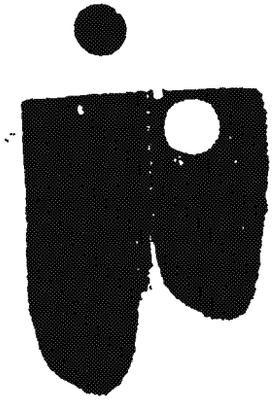

Pathology of Human Asbestosis: A Critical Review

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Although health hazards related to exposure to asbestos dust have been recognized since ancient times, it was not until after the widespread usage of asbestos during the Industrial Revolution that asbestos-related pulmonary disease was identified and defined in modern terms.[1] Dr. H. Montague Murray is generally credited with the first description of asbestos-related pulmonary disease, which was reported to a British parliamentary committee in 1906.[2] The patient was a 33-year-old man who had worked for 14 years in the carding room of an asbestos textile plant. In 1914, the German pathologist T. Fahr described the characteristic appearance of pulmonary interstitial fibrosis in a 35-year-old asbestos worker. Fahr called attention to crystals in the lung tissue and attributed the pulmonary fibrosis to asbestos exposure.[1,3] Dr. W.E. Cooke provided the first detailed description of asbestosis in the general medical literature in 1924 and subsequently coined the term asbestosis.[4] Since then, numerous cases of asbestosis have been published in the medical literature in workers exposed to asbestos dust through mining and milling, manufacture of asbestos products, or utilization of asbestos-containing products.[1]

Asbestosis has subsequently been defined by a number of investigators in slightly different ways,[5-7] but none of these definitions has gained wide acceptance or been uniformly applied by pathologists. The most comprehensive description of asbestosis and perhaps most widely cited definition are found in the 1982 report[8] of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health. This group defined the minimum features that permit the morphologic diagnosis of asbestosis as the "demonstration of discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of asbestos bodies." In addition, a scheme for the pathologic grading of asbestosis was proposed, and the intraobserver and interobserver variability for pathologists using this scheme was assessed. Although previous protocols for the histologic grading of asbestosis had been published,[9,10] they have not been applied systematically in large-scale studies.[8]

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Though comprehensive in its scope, the aforementioned description of asbestosis[11] leaves a number of questions unanswered. How many asbestos bodies must be observed before the diagnosis of asbestosis can be made? This point is not directly addressed, although the description of "asbestos bodies" presumably means at least two. Other investigators have suggested that one asbestos body is sufficient when found in the presence of diffuse interstitial fibrosis,[11] whereas others have stated that "clusters of three" asbestos bodies are needed.[12] Also left unspecified are the number of tissue sections that should be searched for asbestos bodies, the magnification to be used in the search, or whether hematoxylin and eosin (H&E) or iron-stained sections should be examined. In addition, the preferred staining method (H&E or Masson's trichrome) for assessing fibrosis is not identified. It is the purpose of this study to describe in detail the pathologic features of asbestosis, to address the questions outlined above, and to examine the role of quantification of tissue asbestos burden in our understanding of human asbestosis.

Asbestos and Asbestos Bodies

Asbestos, from the Greek word meaning "unquenchable," refers to a group of fibrous silicates with the qualities of thermal and chemical resistance, flexibility, and high tensile strength. As a result of these qualities, asbestos is an extremely useful material for many industrial applications, and thus it has been incorporated into more than 3,000 commercial products.[13] The two major types of asbestos are serpentine and amphibole forms (Table 1). Chrysotile is the sole fibrous member of the serpentine family of minerals, and it accounts for some 90% to 95% of asbestos used commercially. The fibers tend to be curly rather than straight, a feature that derives from mismatching of the sheet silicate and brucite layers in the crystal structure.[14] Chrysotile has a very unusual structure, which consists

TABLE 1.
Types of Asbestos

Serpentine
Chrysotile
Commercial amphiboles
Amosite
Crocidolite
Noncommercial amphiboles
Actinolite
Anthophyllite
Tremolite

of a magnesium silicate forming a sheet that is rolled up like a scroll. Consequently, each individual fibril has a central capillary that can be readily visualized at high magnification in a transmission electron microscope. Chrysotile fibers are composed of numerous individual fibrils, and the fibers have a tendency to split longitudinally into smaller fibrillar bundles or individual fibrils. The amphibole group includes commercially valuable forms, crocidolite and amosite, and the noncommercial forms, tremolite, anthophyllite, and actinolite.[15] The latter are primarily important as contaminants of other minerals, such as talc or chrysotile asbestos. All of the amphibole fibers tend to be straight and do not break apart into individual fibrils as readily as does chrysotile. The amphiboles are distinguished from one another based on differences in chemical composition.[14–16]

Asbestos bodies are the histologic hallmark of prior exposure to asbestos. They were first described as "pigmented crystals" in the lung by Marchand in 1906,[17] and early observers apparently confused these golden brown, segmented structures with fungi.[1] Cooke[4] and Gloyne[18] were among the first to recognize that these curious bodies had asbestos fibers at their core. They were initially termed asbestosis bodies, which was subsequently changed to asbestos bodies when it was discovered that they occurred in the lungs of some workers who did not have asbestosis.[1] Experimental animal studies showed that a number of fibrous dusts (fibrous aluminum silicate, silicon carbide whiskers, cosmetic talc, and fibrous glass), when administered by intratracheal instillation into the lungs of hamsters, resulted in the formation of structures indistinguishable from asbestos bodies. These findings led Gross et al.[19] to propose the noncommital term "ferruginous body" when the precise nature of the fibrous core was unknown. Churg and Warnock[20, 21] then employed energy dispersive spectrometry and electron diffraction to show that ferruginous bodies isolated from human lungs and having a thin, translucent fibrous core were virtually always true asbestos bodies.

The structure and development of the asbestos body has been described in detail by Suzuki and Churg[22] and more recently by Churg and Warnock,[23] and Morgan and Holmes.[24] Asbestos bodies form when an asbestos fiber is inhaled and deposited in the distal regions of the lung parenchyma. Here the alveolar macrophages attempt to phagocytose the fiber (but fail because of its size) and in the process cover the fiber with a layer of ferroprotein material. The iron component gives the structure its characteristic golden brown appearance and also gives a strong reaction with the Prussian blue stain. The peculiar segmentation is thought to be due to fragmentation of the smooth, sheath-like coating, and it is thought that further "weathering" and dissolution of the coating eventually occurs.[25, 26] This sequence of events has been supported by scanning electron microscopic observations of asbestos bodies isolated from human tissues.[27] Hence formation of asbestos bodies is a dynamic process, with fibers becoming coated, the coating material undergoing segmentation and dissolution, and the fiber eventually becoming uncoated and thus available to initiate the process all over again. Asbestos bodies are generally 2 to 5 μm in diame-

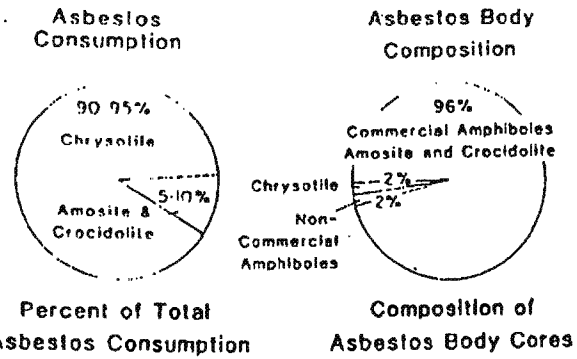

FIG 1.
The industrial consumption of asbestos by fiber type compared with the composition of the cores of asbestos bodies by fiber type. (From Roggli VL, Brody AR: Imaging techniques for application to lung toxicology, in Gardner DE, Crapo JD, Massaro DJ (eds): *Toxicology of the Lung*. New York, Raven Press, 1988, pp 117–145. Used by permission.)

ter,[23] although by scanning electron microscopy I have observed bodies that were only about 0.5 μm in diameter. Their length ranges from 10 to over 250 μm[23] and averages about 35 μm.[28] Fiber length is an important variable in determining the formation of asbestos bodies: Morgan and Holmes[29] have shown that fibers less than 20 μm in length rarely become coated, whereas virtually all fibers 80 μm or greater in length are coated. The vast majority of asbestos bodies isolated from human lungs have an amphibole asbestos core: commercial amphiboles, amosite or crocidolite, form the cores of most bodies isolated from the lungs of asbestos workers[16] and of men in the general population,[30] whereas noncommercial amphiboles, tremolite or anthophyllite, account for most of the bodies isolated from women in the general population.[30] This finding is possibly related to contamination of commercial talcum powder with tremolite and anthophyllite. The predominance of amphibole asbestos body cores is somewhat curious, considering that the bulk of asbestos used commercially is chrysotile asbestos (Fig 1). The reason for this anomaly apparently lies in the ready

FIG 2.
Comparison of the appearance of typical asbestos bodies with various types of pseudoasbestos bodies on Nuclepore filter preparations of lung tissue digests. **A,** typical asbestos bodies isolated from the lung of an insulator with asbestosis and pleural mesothelioma. Thin translucent cores are visible in several bodies *(arrowheads)*. Magnified 680×. **B,** pseudoasbestos bodies of the sheet silicate type, isolated from the lungs of an insulator with asbestosis and small cell carcinoma of the lung, have broad yellow cores *(arrows)*. True asbestos bodies are also present *(upper center* and *lower left)*. Magnified 520×. **C,** pseudoasbestos body isolated from the lungs of a coal worker has a black carbon core that is coated with segmented ferroprotein material. Magnified 800×. **D,** pseudoasbestos body with a dark, slightly curved core composed of chromium, isolated from the lungs of a metal polisher. Magnified 670×. (Part C from Roggli VL, Maslin JP, Shelburne JD, et al: Inorganic particulates in human lung: Relationship to the inflammatory response, in Lynn WS (ed): *Inflammatory Cells and Lung Disease*. Boca Raton, Fla, CRC Press 1983, pp 29–62. Used by permission. Part D from Roggli VL: Analytical scanning electron microscopy in the investigation of unusual exposures, in Romig AD, Chambers WF (eds): *Microbeam Analysis — 1986*. San Francisco, San Francisco Press, 1986, pp 586–588. Used by permission.)

fragmentation of chrysotile into shorter fibrils and the fact that asbestos bodies tend to form only on fibers that are 20 μm or greater in length.

As noted earlier, fibrous dusts other than asbestos can become coated with iron, or ferruginized, so that one must be cautious in identifying asbestos bodies by light microscopy. Fortunately, most of the nonasbestos ferruginous bodies, or pseudoasbestos bodies, can be distinguished from true asbestos bodies at the light microscopic level.[31] The typical appearances of true asbestos bodies and the more common types of pseudoasbestos bodies are illustrated in Figure 2. Bodies with broad yellow cores and prominent knobbed ferroprotein coating on the ends or sides usually have sheet silicate (e.g., talc) cores.[21, 31] A number of metal oxides can assume on occasion a fibrous form—e.g., aluminum oxide, chromium oxide,[32] iron oxide,[33] and titanium oxide—and these form ferruginous bodies with dark brown to black cores. In addition, coal dust and wood-stove dust may contain fibrous fragments of coal or burnt wood, and these too can form ferruginous bodies with black cores.[34] Finally, the fibrous zeolite known as erionite can form ferruginous bodies that at the light microscopic level are indistinguishable from asbestos bodies.[35] Zeolite bodies have not yet been reported in lung tissues from individuals in North America.

Pathologic Features

Gross Morphology

Asbestosis is characterized by linear interstitial fibrosis that tends to be more severe in the lower lobes.[8] These findings are in contrast to silicosis, which is characterized by nodular fibrosis that is more severe in the upper lobes.[34] Lungs with asbestosis have a reduced volume (Fig 3), which correlates with restrictive findings on pulmonary function tests. The weight of the lungs is increased, the consistency is firm, and close inspection of the cut surface demonstrates gray streaks of fibrous tissue (Fig 4). In advanced cases, honeycomb changes may be observed (Fig 5) and are most prominent subpleurally and in the lower lobes.[8] Progressive massive fibrosis has been rarely described in asbestosis, and it is usually the result of exposure to a mixture of dusts. In exceptional cases, fibrosis in asbestosis is more severe in the upper lobes.[36] The tracheobronchial tree and hilar lymph nodes do not show any characteristic changes in asbestosis.[8]

Although the gross features previously described may be observed in a number of chronic interstitial lung diseases, a useful feature in asbestosis is the frequently associated pleural involvement.[8] Diffuse pleural thickening is often present, and adhesions are variable. More characteristic of asbestos exposure is the finding of parietal pleural plaques, which are localized areas of ivory colored pleural thickening with either a smooth or knobby, "candle-wax dripping" surface (Fig 6). These are usually located over the domes of the diaphragm or on the posterolateral chest wall, running along

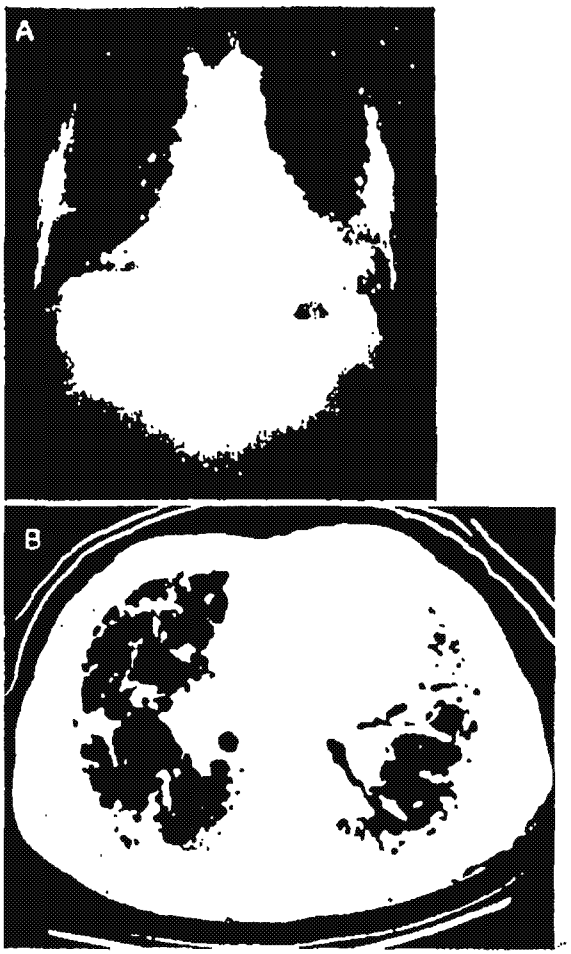

FIG 3.
A, posteroanterior chest roentgenogram from an insulator with asbestosis, showi small lung volumes and bilateral reticulonodular infiltrates most prominent in l lung bases. **B,** CT scan from the same individual, showing prominent intersti markings with honeycomb changes and peripheral accentuation. (Courtesy of I Colleen Bergin, Department of Radiology, Duke University Medical Center.)

the direction of the ribs.[37, 38] The plaques are frequently calcified. Th may develop after brief or low level exposures to asbestos and are oft found in the absence of parenchymal fibrosis.[37, 38] These pleural abn malities thus differ from the parenchymal disease in terms of epidemiolo clinical features, and prognosis,[39] and the term "asbestosis" should not

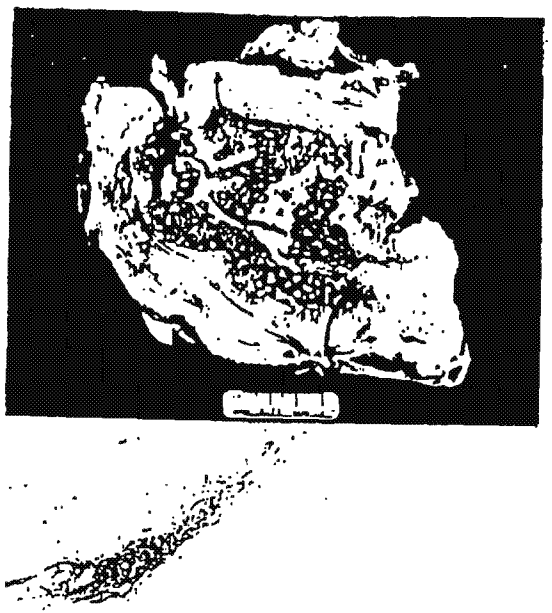

FIG 6.
A, Gross appearance of hemidiaphragm with parietal pleural plaque shows irregular, 10-cm plaque with both smooth and nodular areas, the latter resembling candle-wax drippings. **B**, photomicrograph of typical plaque shows bundles of acellular, hyalinized collagen arranged in a "basket-weave" pattern. A focus of chronic inflammation is present at the interface of plaque and adjacent pleura. H&E, magnified 68×. (Part A from Wain SL, Roggli VL, Foster WL: Parietal pleural plaques, asbestos bodies, and neoplasia: A clinical, pathologic, and roentgenographic study of 25 consecutive cases. *Chest* 1984; 86:707–713. Used by permission.)

distally to involve the terminal bronchioles and alveolar ducts in the fibrotic process. Ultimately, there is radial extension to alveolar septa surrounding these structures (Fig 8). The fibrosis is usually most severe in the subpleural regions and in alveoli in closest proximity to the bronchioles. Scarring and distortion of bronchioles occasionally results in the lining of adjacent alveoli by cuboidal bronchiolar epithelium, a process sometimes referred to

FIG 7.
Coronal section of lung from an insulator and cigarette-smoker showing moderate asbestosis and severe centrilobular emphysema. Note the visceral pleural thickening enveloping the lung and extending into the interlobar fissure.

as pulmonary adenomatosis. Secondary lobular septa may be of marked increased thickness due to collagen deposition, and there is often diffus fibrotic thickening of the visceral pleura. In the most advanced cases, larg zones of lung consist of alveoli with fibrotic walls, and there may be hon eycomb change. The latter is characterized by irregular, cystlike structur 1 to 15 mm in diameter, which are lined by cuboidal to low columnar ep ithelium and have fibrotic walls. Pools of mucus often accumulate in the spaces. A background of chronic inflammatory cells, consisting of lymph ocytes and plasma cells, is often scattered within the fibrotic interstitium. A bestos bodies may be found lying free within alveolar spaces or embedd within the fibrotic pulmonary interstitium (see Fig 8). The detection of a bestos bodies in histologic sections can often be enhanced by iron stai (e.g., Prussian blue), particularly when there are few bodies present. Fu thermore, connective tissue stains (e.g., Masson's trichrome) may facilita the assessment of the extent of pulmonary interstitial fibrosis. The fibro process tends to be patchy, so that many sections may need to searched to find the diagnostic features.[8]

Other histologic abnormalities are seen less commonly in patients w

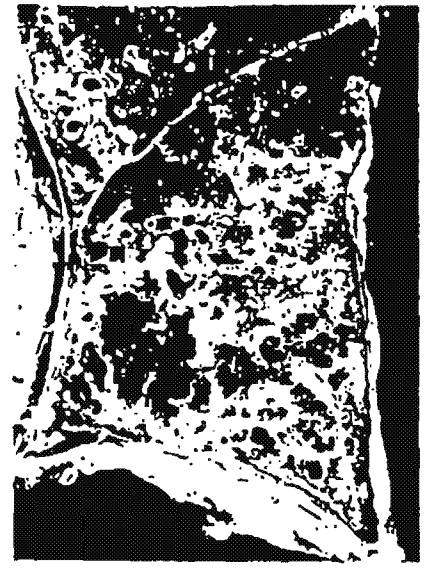

FIG 4.
Coronal section of the lower portion of the lung of an insulator with asbestosis. There is pale gray, linear interstitial fibrosis especially prominent in the lower lobe. Note the visceral pleural thickening laterally and adhesion of the diaphragm to the undersurface of the lung.

applied to the pleural lesions.[8, 39] Others have argued that when one considers that both pleural and parenchymal fibrosis derive from exposure to asbestos, the need for any distinction disappears.[40] One has only to consider the fact that asbestos exposure can produce asbestosis and malignant mesothelioma to see the fallacy in this argument.

Asbestos workers are more often than not cigarette smokers, and the pathologist must take care to distinguish abnormalities related to smoking from those related to asbestos. For example, severe emphysema of the centrilobular type may be present and can overshadow the fibrosis of asbestosis (Fig 7). Emphysema must be distinguished from honeycomb changes, and in this regard, distribution is a useful guide; emphysema tends to be most severe in the upper lobes, whereas honeycomb changes are most severe in the lower lobes. The cystic spaces of honeycombing are rather uniform, averaging about 0.5 cm in diameter and having visibly thickened, fibrotic walls. The spaces of emphysema are variable in size, ranging from just visible up to several centimeters across and do not have "walls." Strands (representing remnants of blood vessels) are often seen traversing emphysematous spaces, and grossly visible fibrosis is not an expected associated finding in centrilobular emphysema.[41] As is the case for most other pathologic changes in the lungs, the lesions of asbestosis can be best assessed by careful inspection of slices prepared from lungs that have been fixed under pressure by prolonged intrabronchial instillation of fixative solution.[8, 41]

FIG 5.
Coronal section of the left lung of an insulator with asbestosis and ca
squamous cell carcinoma of the right lower lobe. Note the honeycomb char
the medial portion of the lower lobe.

Histopathology

There is a range of microscopic changes in asbestosis depending up
severity of the process. These have been extensively illustrated in a
monograph,[8] and only the main features need be summarized her
two microscopic features that are the sine qua non for the histologic
nosis of asbestosis are pulmonary interstitial fibrosis and asbestos b
Experimental animal studies[12] and studies of autopsy lung tissue fr
bestos workers[8] suggest that the earliest changes of asbestosis invo
creased collagen deposition in the interstitium surrounding resp
bronchioles, although this idea has been challenged by some inv
tors.[43] With more extensive disease, there is extension both proxima

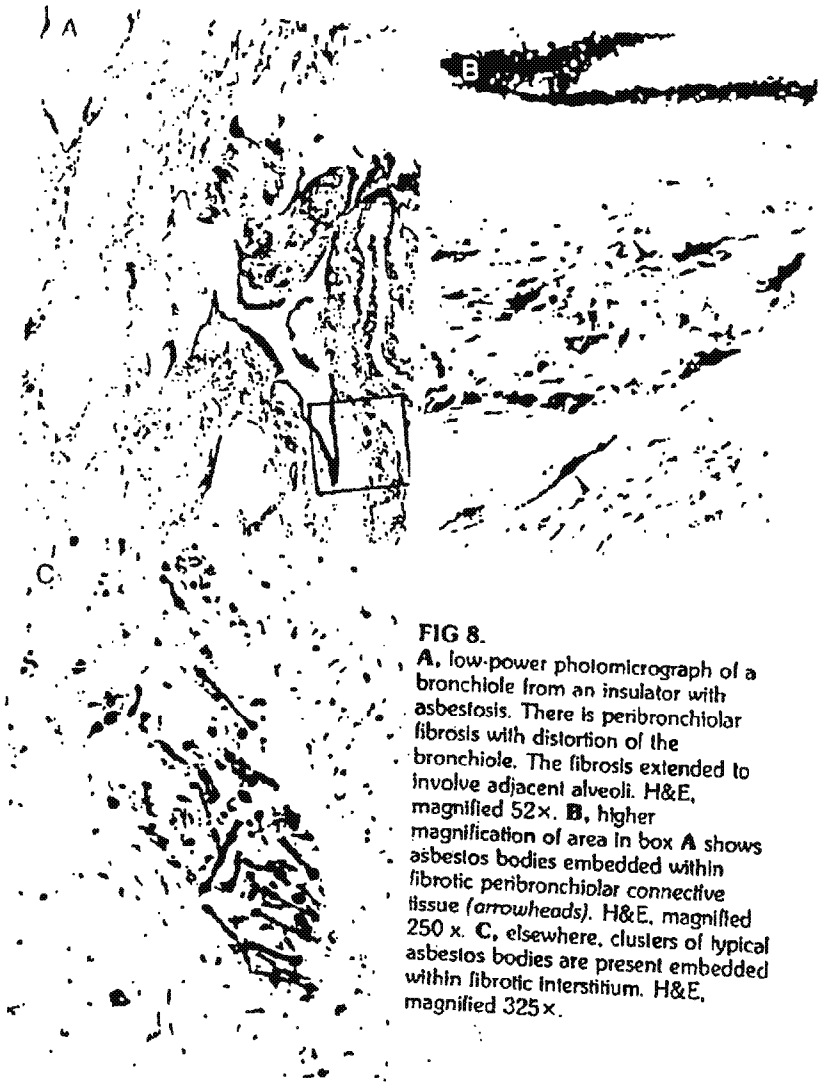

FIG 8.
A, low-power photomicrograph of a bronchiole from an insulator with asbestosis. There is peribronchiolar fibrosis with distortion of the bronchiole. The fibrosis extended to involve adjacent alveoli. H&E, magnified 52×. **B,** higher magnification of area in box **A** shows asbestos bodies embedded within fibrotic peribronchiolar connective tissue *(arrowheads).* H&E, magnified 250 x. **C,** elsewhere, clusters of typical asbestos bodies are present embedded within fibrotic interstitium. H&E, magnified 325×.

asbestosis (Table 2). Although increased numbers of alveolar macrophag are often seen within alveolar spaces in asbestosis, in some cases, the alv oli are packed with sheets of macrophages in a pattern similar to desqu mative interstitial pneumonitis (Fig 9). Occasionally, foreign body type ant cells may be seen within the alveoli or, less commonly, within the brotic interstitium. Hyperplastic alveolar type II cells often line the fibros alveolar septa in asbestosis, and in some cases (roughly 7% of all cas with histologically documented asbestosis in the author's series), these ty II cells contain irregular, waxy-appearing, deeply eosinophilic material (F 10). This cytoplasmic hyalin has the same tinctorial and ultrastructu characteristics as the alcoholic hyalin observed in hepatocytes.[44] Howev this abnormality is not specific to asbestos and probably represents a pec liar, nonspecific reaction to injury.[45] These uncommon histologic abn malities are in the author's experience observed in the more advanc stages of asbestosis.

Rarely observed in patients with asbestosis are the so-called pulmon blue bodies. These basophilic, laminated concretions are present in alv lar spaces and consist primarily of calcium carbonate.[46] They are not vi alized with polarizing microscopy in H&E-stained tissue sections, but brightly birefringent in filter preparations of tissue digests (Fig 11) or in stained histologic sections.[46] Their mechanism of formation is unknov although asbestos can cause abnormal accumulations of calcium salts the lung parenchyma in experimental animal models of asbestosis.[47] P monary blue bodies are not specific for asbestosis and may also be

TABLE 2.
Histologic Findings in 100 Cases of Asbestosis

Histologic Feature	Percent
Always present	
Asbestos bodies	100
Peribronchiolar fibrosis	100
Often present	
Alveolar septal fibrosis	82
Occasionally present	
Honeycomb changes	15
Foreign body giant cells	15
Pulmonary adenomatosis	10
Cytoplasmic hyalin	7
Desquamative interstitial pneumonitislike areas	6
Rarely present	
Osseous metaplasia (dendriform pulmonary ossification)	2
Pulmonary blue bodies	1

FIG 9.
Low-power photomicrograph of lung of patient with asbestosis showing alveoli packed with sheets of alveolar macrophages *(asterisks)*. This pattern resembles that seen in desquamative interstitial pneumonitis. H&E, magnified 68×.

served in patients with asbestos exposure who do not meet histologic criteria for the diagnosis of asbestosis.[46] An additional unusual process that is rarely observed in patients with advanced asbestosis is dendriform pulmonary ossification.[48] This is characterized by branching spicules of bone (often with bone marrow) in association with pulmonary scarring, apparently resulting from metaplasia of interstitial fibroblasts to osteoblasts. An-

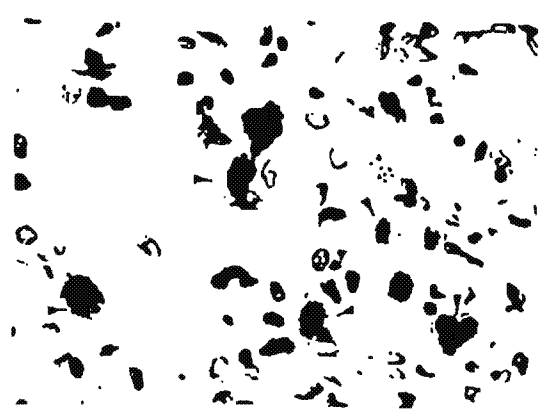

FIG 10.
Photomicrograph of lung of patient with asbestosis showing hyperplastic alveolar type II pneumocytes, many containing cytoplasmic hyalin *(arrowheads)*. This material has the same tinctorial characteristics as the hyalin found within hepatocytes in patients with alcoholic hepatitis. H&E, magnified 680×.

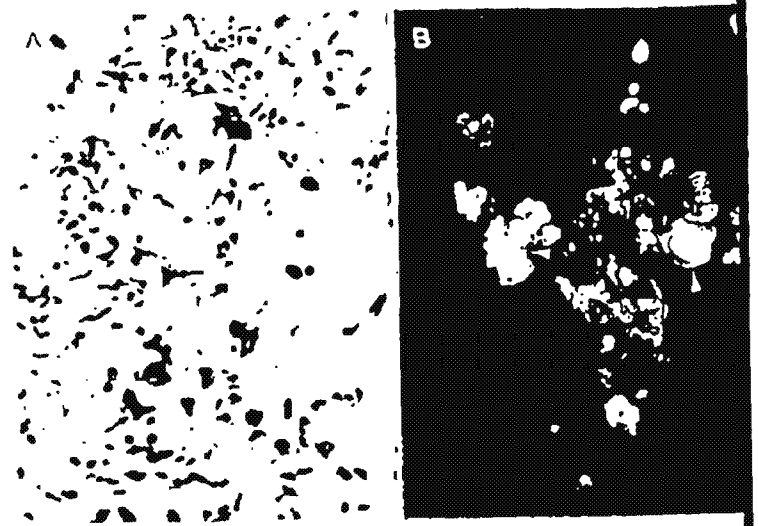

FIG 11.
A, these intraalveolar pulmonary blue bodies have a somewhat laminated app ance *(arrows)* and consist primarily of calcium carbonates. H&E, magnified 40 **B,** Nuclepore filter preparation of lung tissue digested in sodium hypochlorite, f same case illustrated in **A.** When examined by polarizing microscopy, the " bodies" are brightly birefringent and the laminations clearly visible *(arrowhe* Magnified 325×. (Courtesy of Dr. Fred Askin, Department of Pathology, Unive of North Carolina, Chapel Hill, NC.)

other peculiar association with asbestosis is *Aspergillus* pneumonia. Hi dal and Hecksher reported four cases of this unusual combination,[49] the author has personally observed five additional cases[50] (and unp lished observations). No other opportunistic fungal infections associa with asbestosis have to my knowledge been described. The mechan may involve the suppression of cell-mediated immunity by asbestos,[51] though the reason for the specific predisposition for *Aspergillus* specie not known.

It is not the purpose of this review to discuss asbestos-related malign cies, and the interested reader is referred elsewhere for detailed discuss of this subject.[8, 52] However, the pathologist should be aware of so nonneoplastic pulmonary parenchymal processes that can mimic neopl both clinically and radiographically, since he or she may be called upo examine such cases by frozen section. The author has observed sev cases of organizing pneumonia in patients with asbestos exposure who derwent thoracotomy for suspected malignancy. Organizing pneumoni a well-known mimicker of carcinoma of the lung.[53] Whether this proc has an increased incidence in patients with asbestosis or whether these

...ults are merely observed more closely for potential malignancy is unknown. In addition, a peculiar process known as rounded atelectasis (also known as folded lung syndrome) can occur adjacent to thickened, buckled pleura, and this lesion can radiographically resemble a peripheral coin lesion (Fig 12). Its radiographic features are described elsewhere.[51] On histologic examination, the lung parenchyma may be atelectatic or normal, although the overlying visceral pleura is invariably thickened. The patholo-

FIG 12.
A, lateral chest roentgenogram shows a peripheral mass posteriorly *(arrowheads).* **B,** CT scan from the same individual shows distorted bronchovascular bundles coursing into the mass which abuts the pleura. This radiographic appearance is characteristic of rounded atelectasis. (Courtesy of Dr. Colleen Bergin, Department of Radiology, Duke University Medical Center.)

...gist should look for asbestos bodies and peribronchiolar fibrosis in the ...jacent lung, since this process is frequently associated with exposure to ...bestos.[51]

Differential Diagnosis

Asbestosis must be distinguished from pulmonary injury secondary to i... lation of other toxic substances and also from other forms of pulmo... interstitial fibrosis. Peribronchiolar fibrosis may be associated with inh... tion of other mineral dusts, such as silica, iron oxides, or aluminum oxid... and with exposure to cigarette smoke,[43] although the percentage of s... airways with abnormalities due to these exposures is generally less ... that observed with asbestos exposure.[43, 55] Diffuse interstitial fibrosis ... also be seen with exposure to a variety of inorganic particulates.[34] T... the finding of peribronchiolar or diffuse alveolar septal fibrosis alone is ... sufficient for a diagnosis of asbestosis, and the identification of asbe... bodies in histologic sections is necessary to relate the fibrosis to asbe... This is also true for idiopathic pulmonary fibrosis of the usual or des... mative type, which has many features that overlap with asbestosis. Ind... since idiopathic pulmonary fibrosis is a diagnosis of exclusion, asbesto... one of the conditions that should be ruled out to make that diagnosis. ... presence of asbestos bodies and visceral pleural fibrosis are helpful ... tures in this regard, as is the identification of parietal pleural plaques.

Individuals who are occupationally exposed to asbestos are often ... posed to other dusts as well. For example, shipyard workers may rec... substantial exposures to silica, talc, or welding fumes as well as asbe... Crystalline silica constitutes one component of the lining of steam boile... ships and is sometimes still used in sandblasting. Individuals engage... boiler-scaling or sandblasting or working in the vicinity of these operat... often have silicotic nodules in the hilar lymph nodes and occasional... the lung parenchyma, especially in the upper lobes.[34] Shipyard welder... ten are exposed to asbestos, so that care should be taken to disting... welder's pneumoconiosis from asbestosis. Welders are exposed to n... oxides (especially iron oxide), and sheet silicates. Iron oxides appear a... terstitial deposits of dark brown to black spherical particles, often wi... golden brown rim.[34] There is very little collagen deposition in respons... these particles. Pseudoasbestos bodies with black or broad yellow c... may be identified in histologic sections. Among 12 cases of welder's p... moconiosis in shipyard workers from the author's consultation files, ... four cases satisfied histologic criteria for the diagnosis of asbestosis,[8] ... peribronchiolar fibrosis and true asbestos bodies.

Quantitation of Tissue Asbestos Burden

A number of studies have demonstrated that when digestion-concentra... techniques are employed to analyze adequate amounts of lung tis...

[illegible] found in the lung of virtually all adult [illegible] industrialized nations.[66, 67] Therefore, the mere demonstration of the presence of asbestos in tissue digests is of no particular value, and quantitative studies are required to understand the relationship between tissue fiber burdens and various disease processes. A variety of techniques have been described for the isolation and quantification of tissue asbestos content,[63–67] and it is beyond the scope of this review to consider these here. Rather, the intent is to review the information that has been obtained regarding the asbestos content of lung tissue in patients with asbestosis.

Relatively few studies have been published examining the asbestos content of lung tissue in series of patients with asbestosis.[68–71] The data from these studies and the author's own series are compared in Table 3. With the exception of the unusually high median count for asbestos bodies in the study by Ashcroft and Heppleston, and the high mean count for uncoated fibers by electron microscopy in the study by Wagner et al., the values are roughly similar among the reported series. This is rather remarkable considering the wide range of values obtained when different laboratories examine the same samples and considering the different techniques employed in each of the studies referred to in Table 3. For example, Ashcroft and Heppleston[69] used phase contrast light microscopy (PCLM) at a magnification of 400× and counted all visible fibers, enumerating coated and uncoated fibers separately. Whitwell et al.[68] used PCLM and counted all fibers greater than or equal to 6 μ in length, counting coated and uncoated fibers together. Warnock et al.[70] used transmission electron microscopy (TEM) and counted all fibers that exceeded 0.25 μm in length and had an aspect ratio (length to width) of 3 or greater. Wagner et al.[71] used the PCLM method of Ashcroft and Heppleston[69] as well as TEM. The present author's results were obtained by scanning electron microscopy (SEM) at a magnification of 1,000×, counting all visible fibers with a length greater than or equal to 5 μm.[16] The study by Warnock et al.[70] and the study by Roggli also counted asbestos bodies by conventional light mi-

TABLE 3.
Asbestos Content of Lung Tissue in Reported Series of Patients with Asbestosis*

Source	No. of Cases	Method†	Asbestos Bodies/gm Dried Lung	Uncoated Fibers/gm Dried Lung
Whitwell et al.[68]	23	PCLM	. . . .	8 (1.0–70)
Ashcroft and Heppleston[69]	22	PCLM	12.2 (0.49–192)	32 (1.3–493)
Warnock et al.[70]	22	TEM‡	0.123 (0.001–7.38)	5.68 (1.6–121)
Wagner et al.[71]	100	PCLM	. . . .	1.5 (0.001–31.6)
	170	TEM	. . . .	372 (<1.0–10,000)
Roggli (present study)	76	SEM‡	0.378§ (0.006–16)	3.3§ (0.18–125)

*Values reported are the median counts for millions (10^6) of asbestos bodies or uncoated fibers per gram of dried lung tissue, with ranges indicated in parentheses, except for the study of Wagner et al.,[71] where only the mean value could be obtained from the data presented.
†PCLM = phase contrast light microscopy; TEM = transmission electron microscopy; SEM = scanning electron microscopy.
‡In these two studies, asbestos bodies were counted by conventional light microscopy.
§Values multiplied by a factor of 10 (approximate ratio of wet to dry lung weight) for purposes of comparison.

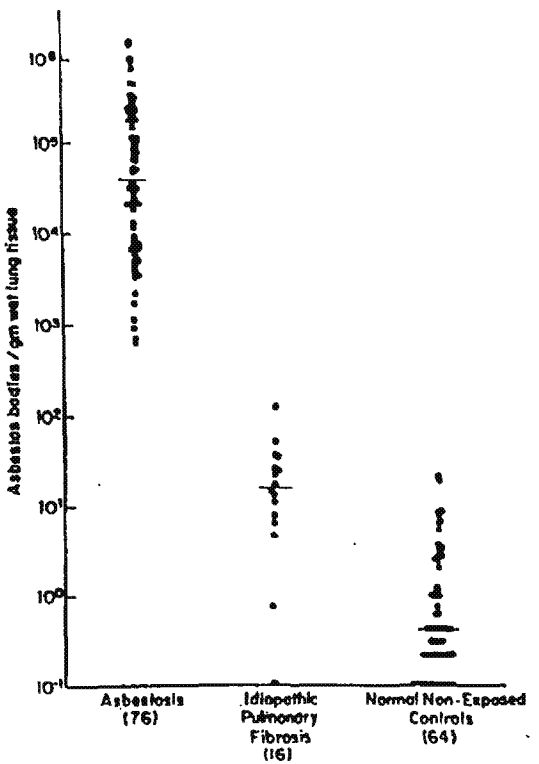

FIG 13.
Histogram of asbestos body counts in 76 patients with asbestosis, 16 patients with idiopathic pulmonary fibrosis, and 64 nonexposed "controls." Horizontal bars indicate median values. Note logarithmic scale.

count in my laboratory for uncoated fibers 5 μm or greater in length from individuals with normal lungs and no known occupational asbestos exposure is approximately 0.034 × 10^6 fibers/gm.

The asbestos body content of the lung in 76 patients with histologically confirmed asbestosis is shown in Figure 13 and is compared with the results from 16 patients with idiopathic pulmonary fibrosis (IPF) and with 64 nonexposed controls. The results are expressed on a logarithmic scale as asbestos bodies per gram of wet lung tissue (which can be approximately converted to bodies per gram of dry lung tissue by multiplying by a factor of 10).[15] The median count for the patients with asbestosis is 37,800 asbestos bodies per gram of wet lung tissue (AB/gm), whereas the median values for the patients with IPF is 16 AB/gm and for the controls is 0.4 AB/gm. There is substantial overlap between the IPF and "control" groups, although a few IPF patients with low-level asbestos exposure have slightly elevated values. It should be noted that for 95% of the cases of asbestosis, the asbestos body content is 1,700 AB/gm or greater. This finding is useful because, at this tissue asbestos body concentration, it has been shown that several asbestos bodies should be observed on most 2 × 2 cm histologic sections when the sections are stained for iron and systematically examined.[28] Thus the finding of asbestos bodies in histologic sections is a reasonable histopathologic discriminator between asbestosis and IPF.

A few studies have investigated the relationship between tissue asbestos burden and the fibrotic response in humans, and these are summarized in Table 4. The study by Whitwell et al.[68] shows a progressive increase in median total coated and uncoated fiber count from patients with mild (1+) to severe (3+) fibrosis. Ashcroft and Heppleston[69] showed similar progression in severity of fibrosis with increasing uncoated fiber count from no fibrosis to moderate (2+) fibrosis, but no further increase in fiber count from moderate to severe disease. The latter authors concluded that additional factors other than tissue fiber burden must be involved in the progression from moderate to severe disease.[69] Warnock et al.[70] graded the severity of fibrosis on a scale of 0 to 3+ based on visual inspection of the cut surface of inflation fixed specimens, with ½+ defined as microscopic fibrosis only (Table 4). Their data show no apparent correlation between the severity of fibrosis and total fiber content for all fibers 0.25 μm or greater in length as assessed by TEM. Wagner et al.[71] graded the severity of fibrosis microscopically on a scale of 0 to 4, which for the sake of convenience has been tabulated as 0 to 3 in Table 4 with their grade 1 fibrosis listed under ½+. Their data show a progressive increase in optically visible and electron microscopically enumerated fibers with increasing severity of asbestosis.

The relationship between histologic asbestosis score using the method recently proposed by the Pneumoconiosis Committee of the College of American Pathologists[8] and the tissue content of uncoated fibers 5 μm or

TABLE 4.
Severity of Asbestosis vs. Tissue Asbestos Content as Total Fibers/gm Dried Lung[a]

	Asbestosis Grade				
Study	0	½+	1+	2+	3+
Whitwell et al.[68]			8 × 10^6	14 × 10^6	37 × 10^6
Ashcroft and Heppleston[69]	2.4 × 10^6		20 × 10^6	200 × 10^6	133 × 10^6
Warnock et al.[70]	4.8 × 10^6	5.7 × 10^6	48 × 10^6	11 × 10^6	35 × 10^6
Wagner et al.[71]	0.005 × 10^6	0.009 × 10^6	0.015 × 10^6	0.12 × 10^6	1.2 × 10^6
	1.3 × 10^6	31.6 × 10^6	44 × 10^6	68 × 10^6	464 × 10^6

[a] Values indicated represent the median counts derived from the data presented in the reference that is cited. Asbestosis grade is as defined in each original source. First two studies employed phase contrast light microscopy whereas the study of Warnock et al. used transmission electron microscopy and the study of Wagner et al. used both (phase contrast results listed in Figure 2 of the latter study,[71] listed first, and EM results from Figure 1, listed below). Wagner et al. grading scheme has been modified to 0 to 3 simply for purposes of tabulation.

greater in length as assessed by SEM is shown in Figure 14. These data are based on the 36 autopsied cases of asbestosis from the author's consultation files for which tissue was available for analysis of asbestos content. There is a statistically significant ($P < .01$) relationship between histologic score and uncoated fiber content, although there is a wide range of scatter of the data points. The degree of correlation would likely improve with more extensive histologic and mineralogic sampling of the lungs and expression of the data as total lung burden rather than fiber concentration.[16] Furthermore, the intercept for the regression line is approximately 100,000 fibers per gram of wet lung (or one million fibers per gram of dry lung), which coincides with the lower limit of the range of values shown in Table 3. In addition, it can be seen from Figure 14 that very few patients with alveolar septal fibrosis (grade 4 or higher) have uncoated fiber counts less than 100,000 per gram, although some patients with fibrosis confined

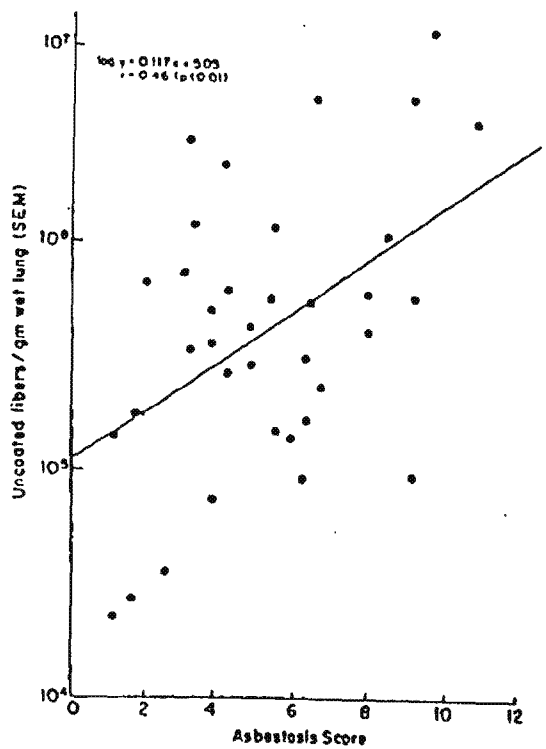

FIG 14.
Correlation between uncoated fiber count by scanning electron microscopy and histologic assessment of the severity of asbestosis for 36 autopsied cases, using grading scheme of College of American Pathologists and National Institute for Occupational Safety and Health.[8] The correlation coefficient (r) for the linear regression line is 0.46 ($P < 0.01$). *SEM* = scanning electron microscopy.

to the wall of small airways (grade 3 or less) have values well below this level. This observation is in agreement with the findings by Churg[17] of relatively low tissue asbestos burden in chrysotile miners with fibrosis confined to the walls of small airways. There is also a statistically significant association between histologic score and total (coated plus uncoated) fiber content as assessed by SEM, but not between histologic score and asbestos body content as measured by light microscopy (Table 5). Finally, in this study, there was no significant association between histologic score and patient age, duration of occupational exposure, or pack-years of smoking (see Table 5).

Warnock et al.[70] have reported finding large numbers of commercial amphiboles, noncommercial amphiboles, and chrysotile fibers in patients with asbestosis. These authors used analytical TEM and examined all detectable fibers 0.25 μm or greater in length. For comparison, the data from more than 1,200 fibers isolated from 76 patients with asbestosis and identified using analytic SEM are shown in Table 6. These data show that for fibers greater than 5μm in length, the vast majority (92%) are commercial amphiboles (mostly amosite with some crocidolite). Less than 2% are noncommercial amphiboles and less than 1% chrysotile. Of interest is the observation that for fibers in the stated size range, nonasbestos mineral fibers[34] are more common than chrysotile and noncommercial amphiboles combined.

Diagnostic Criteria

The histologic diagnosis of asbestosis is important because it provides independent assessment of the presence or absence of pulmonary interstitial

TABLE 5.
Correlation of Histologic Grade of Asbestosis With Tissue Asbestos Content and Other Parameters*

	Correlation Coefficient (r)	P
Uncoated fibers/gm (>5μm)SEM	0.46	<0.01
Total fibers/gm (coated and uncoated), SEM	0.44	<0.01
Asbestos bodies/gm, LM	0.26	NS
Smoking history, pk-yr	0.22	NS
Age	0.12	NS
Duration of exposure, yr	0.06	NS

*SEM = scanning electron microscopy; LM = light microscopy. pk-yr = packs smoked daily × no. years smoked.

BLE 6.
ergy Dispersive X-Ray Analysis Data on 1,215 Fibers From 76 Patients With Asbestosis

	Commercial Amphiboles	Noncommercial Amphiboles	Chrysotile	Other*
Coated	497	4	0	13
Uncoated	622	19	8	52
Total (%)	1,119 (92)	23 (1.9)	8 (0.6)	65 (5.5)

*Includes talc, silica, rutile, kaolinite, miscellaneous silicates, fiberglass, iron-rich fibers, and aluminum-rich fibers.

fibrosis resulting from inhalation of asbestos-containing dust. Based on the foregoing analysis, reasonable criteria for the histologic diagnosis of asbestosis can be established. Asbestosis may be defined as the presence of peribronchiolar fibrosis and asbestos bodies in histologic sections, with or without alveolar septal fibrosis. Since other experimental exposures can produce some peribronchiolar fibrosis,[43, 55] it is recommended that in the absence of alveolar septal fibrosis, a histologic diagnosis of asbestosis should be made only when the majority of the bronchioles show increased amounts of fibrous tissue. Occasionally the assessment of fibrosis can be difficult in uninflated tissue that is collapsed, congested, or consolidated by pneumonia, and the pathologist should be careful not to overinterpret such material as showing alveolar septal fibrosis.[74] In cases where the assessment of presence and extent of fibrosis is not straightforward on H&E-stained sections, it is recommended that Masson's trichrome stains be obtained to assist in this evaluation. Similarly, the pathologist should be careful not to interpret ferruginous bodies with black or broad yellow cores as asbestos bodies, and only structures with the typical morphology that has been described[8, 20, 21, 30, 31] should be interpreted as asbestos bodies. In cases where asbestosis is suspected and asbestos bodies are not readily identified on H&E-stained sections, it is recommended that iron-stained sections be prepared and examined systematically using a mechanical stage and a magnification of 200×.[28] With this approach, an average value of five or more asbestos bodies per cm^2 of tissue section area examined would be expected in 95% of our cases of asbestosis, and two or more asbestos bodies per cm^2 in all of our cases. Of course, asbestos bodies are not necessarily distributed evenly in histologic sections.[28] Therefore, more than one section should be examined in cases where asbestos bodies are sparse.

Fibrosis was confined to the peribronchiolar region in 18% of the cases in our series (see Table 2), and some investigators have challenged the inclusion of such cases in the definition of asbestosis on the grounds that ex-

[illegible] fibrosis.[43, 55] With regard to the first argument, the same is true of diffuse interstitial (i.e., alveolar septal) fibrosis as for peribronchiolar [illegible]; in either case, the finding of asbestos bodies in histologic sections greatly increases one's confidence that the fibrosis observed is related to asbestos exposure.[11] If one further restricts the definition to cases where the majority of bronchioles are involved, the chances of overdiagnosing such lesions as being asbestos related is further reduced. With regard to the second argument, it is true that progression from peribronchiolar to alveolar septal fibrosis has not been demonstrated experimentally, although the peribronchiolar area appears to be an early site of abnormality in experimental animal studies.[42] It should be noted that peribronchiolar fibrosis is a form of interstitial fibrosis, since the pulmonary interstitium includes not only the interstitium of the alveolar septa, but the subpleural connective tissue, secondary lobular septa, and connective tissue enveloping bronchovascular and bronchiolovascular bundles as well. All of these sites may show increased fibrous tissue deposition in individuals exposed to asbestos, and it is this writer's opinion that the preponderance of the evidence does justify inclusion of peribronchiolar fibrosis in the definition of asbestosis.

Other investigators have challenged the requirement of finding asbestos bodies in tissue sections before a histologic diagnosis of asbestosis is rendered. The justification for that opinion has been firstly the observation that chrysotile forms asbestos bodies less readily than do the amphiboles and many workers are exposed primarily to chrysotile,[75] and secondly that some individuals coat fibers to form bodies much less efficiently than others.[76, 77] With regard to the first argument, Holden and Churg[78] have shown that asbestos bodies are readily found in histologic sections of chrysotile miners with asbestosis, and that these asbestos bodies do in fact have chrysotile asbestos cores. With regard to the second argument, there have been a few cases reported of patients with pulmonary fibrosis where the asbestos body content of the tissue was low (less than 100 per gram of wet lung tissue) but the uncoated fiber content of the tissue by TEM was considered high.[76, 77] Such cases are apparently rare, as no similar cases were observed in our series of 76 patients with asbestosis. Furthermore, the 16 patients in our series with idiopathic pulmonary fibrosis who had relatively low asbestos body counts (see Fig 13) also had low uncoated fiber counts,[16] and it is unlikely that any of these cases were misclassified. The classification of the uncommon cases with interstitial fibrosis, absence of asbestos bodies in histologic sections, and elevated tissue asbestos fiber burden remains problematic, but the existence of cases of pulmonary fibrosis due to asbestos fiber inhalation that do not fulfill histologic criteria for the diagnosis of asbestosis seems plausible.

In consideration of the lack of a uniform method for the analysis of tissue mineral fiber content and the variable results obtained from different laboratories analyzing the same sample, it is not presently possible to recommend a specific tissue asbestos fiber content to be used as a criterion

[illegible] asbestos. Nonetheless, based on the data summarized in Table 3, it seems unlikely that a patient with clinically significant pulmonary interstitial fibrosis who has fewer than 10^6 fibers 5 μm or greater in length per gram of dry lung tissue (10^5 fibers/gm wet lung tissue) is suffering from asbestosis. Whereas the fibrogenicity of asbestos fibers 5 μm or greater in length is well established,[42,79–82] the fibrogenicity of fibers less than 5 μm in length remains unproved.[83] Therefore, no tissue level of fibers in the latter size range should at the present time be proposed as a criterion for the diagnosis of asbestosis.

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Forensic Toxicology Drugs-of-Abuse Testin

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The estimated annual cost of employee productivity lost due to alcol and drug abuse in the United States is estimated to be $100 billion.[1] T lower productivity seems to coincide with an increase in drug use indicat by reports from emergency room visits from 1980 to 1985 (Fig 1). Cc cern over increasing drug use and its costs has prompted a flurry of activ related to drugs-of-abuse screening and as a consequence, forensic uri drug testing is one of the fastest growing areas within forensic toxicology has been estimated that one-fourth of the largest firms in the United Sta have instituted programs for drugs-of-abuse screening and that four out 100 employees are subject to mandatory drug testing.[2] The federal g

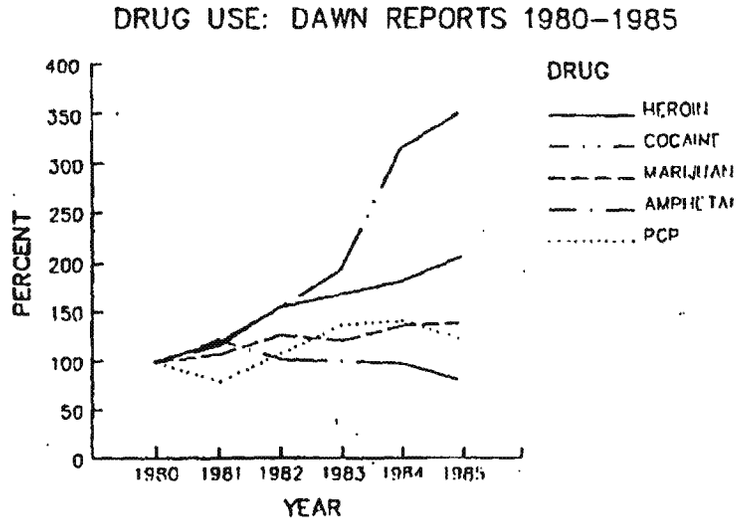

FIG 1.
Drug use based on Drug Abuse Warning Network emergency room reports. (I from Frank RS: Drugs of abuse: Data collection systems of DEA and recent tre *J Anal Toxicol* 1987; 11:237–241.

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