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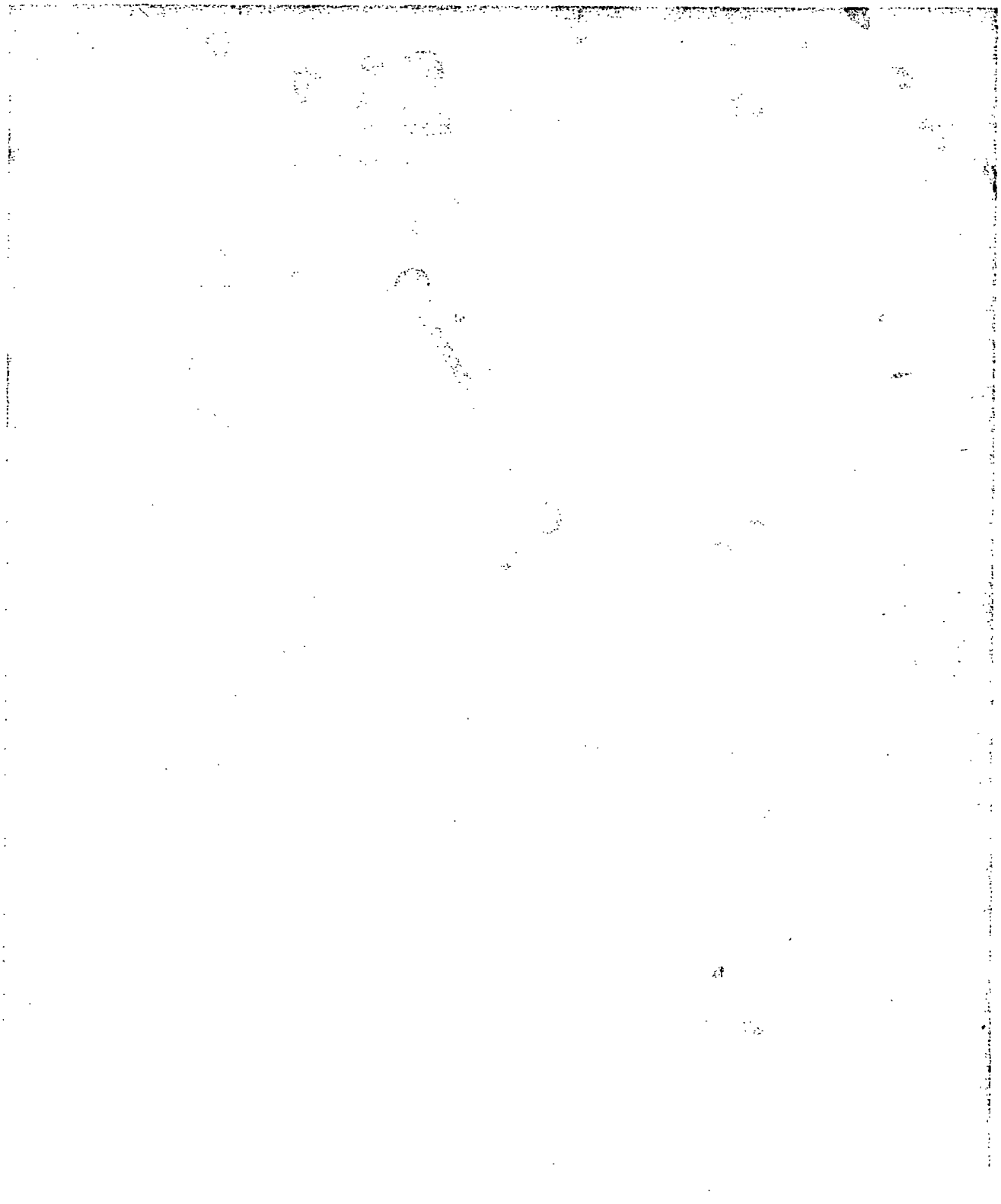
Asbestos-Associated Diseases

Special Issue

Archives of Pathology and Laboratory Medicine

Report of the Pneumoconiosis Committee of the College of American Pathologists and the National Institute for Occupational Safety and Health

John E. Craighead, MD, Chairman



Typical ferruginous body within pulmonary macrophage. Note delicate, thin walls of alveoli. Asbestosis was not evident in this tissue despite the presence of asbestos bodies (Prussian blue and eosin).

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The Pathology of Asbestos-Associated Diseases of the Lungs and Pleural Cavities: Diagnostic Criteria and Proposed Grading Schema

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The observations and conclusions summarized herein represent the work of a committee of North American pathologists that was organized under the auspices of the National Institute for Occupational Safety and Health (NIOSH) and the College of American Pathologists to evaluate the pathology of asbestos-associated diseases and to establish standards for the grading of asbestosis. This effort was undertaken because of the need to develop a common basis for communication among pathologists, and between pathologists and radiologists, clinicians, pulmonary physiologists, occupational hygienists, and epidemiologists.

During the course of this study, it became clear that the detailed morphologic features of the asbestos-associated diseases of the pulmonary parenchyma of man have not been described fully in the medical literature. Thus, considerable attention was given to the histologic features of asbestosis at various stages of what is believed to be its evolutionary course. Because most published descriptions are concerned with disease that results from exposure to an undefined mixture of different types of asbestos, the lesions associated with the various types of asbestos also were studied comparatively, using collections of pathologic material from the United States and abroad.

A grading schema that is functional and widely accepted by pathologists would have considerable usefulness in future studies of the clinical and epidemiologic aspects of the disease. Because many pathologists are uncertain as to the criteria for the diagnosis of asbestosis, a generally accepted description of the lesions would assist in establishing uniformity for purposes of diagnosis.

Although this monograph addresses a variety of topics concerned with asbestos and asbestos-associated diseases, the committee was concerned primarily with the pathologic features of the pulmonary parenchymal disease associated with exposure to asbestos. Several outstanding books, conference proceedings, and committee reports that examine in detail the mineralogy and public health aspects of asbestos and the asbestos-associated diseases have been published in recent years. We refer the interested reader to them for more detailed presentations (see the "Bibliography").

HISTORIC BACKGROUND

The fire-resistant properties of asbestos have been appreciated by man since ancient times. Although the mineral apparently was used in the fabrication of ceramics and textiles before the industrial revolution, it was not until the middle of the 19th century that commercial mining began. At that time, asbestos first was used in roofing materials and cement in the United States. During the next several decades, it was incorporated into commercial textile products in both North America and Europe. By the turn of the century, the industrial applications of asbestos seemed almost limitless and demand escalated. With the expanding recognition of asbestos as a commercially extractable mineral, mines were opened in many parts of the world.

It is unlikely that asbestosis was recognized as a disease before the term *pneumonokoniosis* was introduced by Zenker in 1867.[1] Early in the 20th century, a few case reports from Europe and the United States indicated a possible association of exposure to asbestos dust with pulmonary fibrosis; in 1924 the term *asbestosis* was introduced by Cooke.[2] By the 1920s and 1930s, the disease was more commonly recognized and series of

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cases appeared in the literature. Yet, the industrial use of asbestos increased. As the United States turned to the automobile for transportation, the use of asbestos in brake linings became commonplace. In the 1930s, the technique of spraying asbestos insulation in construction was developed, and shortly thereafter asbestos began to be used in the manufacture of insulation and pipe.

In the United States, the occurrence of bronchogenic carcinoma in a patient with asbestosis was noted by Lynch and Smith in 1935.[3] Their observation was soon confirmed by others, and over time an association was established. Although worldwide concern about the health effects of asbestos mounted, the problem became more critical during the mobilization that accompanied World War II. Warfare demanded ships and modern weaponry, and the war effort brought countless thousands of persons into industries that used asbestos.

Although Klemperer and Rabin described tumors known by the designation *mesothelioma* in 1931,[4] recognition of the association of the neoplasm with asbestos awaited the reports of Weiss[5] and Leichner[6] in the 1950s. In 1960, Wagner and his colleagues[7] noted the relatively common occurrence of this rare neoplasm in persons exposed to South African cape "blue" asbestos, a type composed of unusually long and thin fibers. Subsequent experiments documented the induction of morphologically similar pleural lesions in animals after the intrapleural introduction of asbestos and of man-made fibers that had similar physical properties.[8] Countless reports since that time have confirmed the etiologic association of asbestos with mesothelioma.

Clinical and pathologic evidence accumulated during the past several decades established the role of asbestos in the pathogenesis of diffuse pulmonary fibrosis. Evaluations of population groups by radiologists and epidemiologists documented the common occurrence of pleural plaques in persons exposed to asbestos. Definition of the role of asbestos in carcinogenesis required the efforts of epidemiologists, who established the association of asbestos with bronchogenic carcinoma and with neoplasms in other organs. Noteworthy among these studies are the work of Doll in 1955[9] and the more recent observations of Selikoff and his associates,[10] Enterline and Henderson,[11] and investigators at the National Cancer Institute[12] in this country.

OCCUPATIONAL AND NONOCCUPATIONAL EXPOSURE TO ASBESTOS

Although asbestos has been mined commercially since the turn of the century, it was not used widely in the United States until after 1930. Approximately 30 million tons of asbestos has been incorporated into construction materials and manufactured products in this country since then. Each year, US industry consumes more than 800,000 tons of asbestos. About one million living Americans either work or have worked in industries that manufacture asbestos products, and countless millions more are exposed to the several thousand asbestos-containing products that are available commercially. In addition, persons are exposed inadvertently to the breakdown products of the mineral during the reconstruction and renovation of buildings and because of the deterioration of manufactured materials that contain asbestos.

Because of its heat- and fire-resistant properties, as well as its high tensile strength and flexibility, asbestos finds its greatest use in the construction industry. About one third of the annual US consumption is incorporated into cement and cement products. Asbestos cement pipe and corrugated sheeting are the major products, among many others. The concentration of asbestos in cement varies considerably, but customarily is about 15% to 20%. Asbestos-containing products also are used in floor tile, insulation board, plastic, molding, and paint, as well as spackle, patching, and taping compounds. In addition, asbestos is used as a filler in the construction of buildings. In the past, asbestos in the form of a suspension was applied by spray guns in the construction of steel-girdered buildings to prevent fire damage. This application now is prohibited in the United States because of its unrestricted pollution of the ambient air.

Asbestos-containing products are used extensively to insulate electrical and heat-generating equipment and in the plumbing and shipbuilding industries. These products contain asbestos in amounts that range from 10% to almost 100%. Because the material is relatively uncontained and is manipulated during processing and use, breakdown products create a severe hazard. Thus, contamination of the environment often is subtle and the overall importance of the problem with regard to health is difficult to assess.

Almost two million persons are employed in automotive sales, service, and repair, of whom some 900,000 are believed to be exposed frequently to asbestos from automobile brakes and clutch repair. Additional thousands are exposed elsewhere in the transportation industries.

Asbestos is used in yarns and fabrics for protective clothing, safety curtains, and fire blankets. Asbestos-reinforced plastics are used in secondary industries too numerous to mention.

Contemporary standards adopted by the US Occupational Safety and Health Administration are based on the demonstration of fibers 5 μm or longer in ambient air using light microscopy. At present, no more than an average of 2 fibers per cubic centimeter of air during an eight-hour work period is permissible in the occupational setting. Criteria based on concentrations of "long" fibers are a practical but relatively crude means for assessing environmental pollution, because the "short" (ie, < 5 μm) asbestos fibers are not counted. Although long fibers are thought to play a major role in the pathogenesis of asbestosis and mesothelioma, the importance of short fibers in carcinogenesis and fibrogenesis in the lungs is uncertain.

Nonoccupational exposure to asbestos is particularly insidious. It occurs in persons who reside near asbestos mines and mills, construction and

building demolition sites, and asbestos dumps. Members of the household of asbestos workers may be exposed to contaminated work clothes. Avocational exposure occurs in those undertaking do-it-yourself home repairs and auto body work. Obviously, it is difficult to document the severity of these types of exposure.

MINERALOGY OF ASBESTOS

The term *asbestos* refers to a family of naturally occurring, flexible, fibrous hydrous silicate minerals that are relatively indestructible and heat-resistant, and have a high length-to-breadth ratio (aspect ratio). Although fibrous minerals are ubiquitous in the earth's crust, only a few types have commercial importance: (1) chrysotile, derived from serpentine rock, and (2) crocidolite, amosite, and anthophyllite, which are classified as amphiboles (Fig 1).

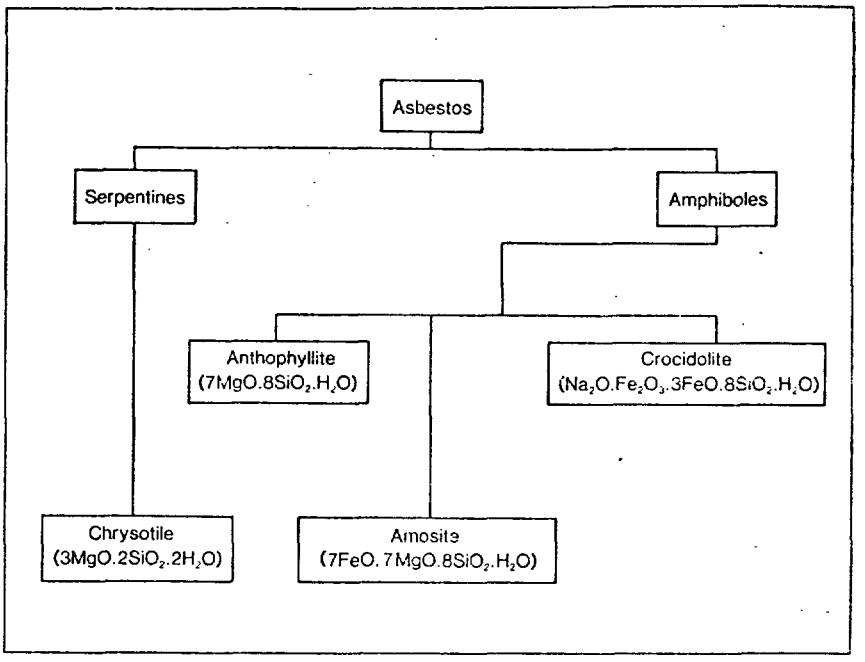


Fig 1.—Mineralogic classification and chemical composition of common commercial types of asbestos (from *New England Journal of Medicine*, 1982;306:1446-1455).

Fibers of both the serpentine and amphibole types consist of subunit fibrils. Individual serpentine fibers are made up of fibrils that have a layered, silicate structure, formed into scroll-like or concentric cylindric tubes. Presumably because of the high surface concentrations of magnesium hydroxide, these fibers exhibit a strong positive surface charge. The basic subunit of the amphibole is a silicon dioxide tetrahedron arranged in parallel chains and linked laterally by various cations. Amphiboles, in contrast to the serpentines, possess a slightly negative charge. Naturally occurring fibers of both types vary considerably in length, as well as in overall diameter. Fragmentation into shorter fibers and subunit fibrils occurs both with industrial processing and in tissue after inhalation (Figs 2 and 3).

Belts of serpentine rock are located in nearly every mountain chain in the world. Chrysotile is found cryptically in rocks and soils of several types, and in potable water in many parts of the United States. It is mined in California and Vermont.

About 8% of the earth's crust consists of amphibole rock minerals. Because of the complexity of the structure and chemistry of the amphiboles, a wide variety of geologic strata and soils contain fibrous and nonfibrous minerals somewhat akin to commercial amphiboles. The mineralogy and nomenclature of these substances is complex. Amphiboles often are found with commercial deposits of chrysotile; eg, Canadian chrysotile, which is used widely in the United States today, contains variable amounts of tremolite.

The different types of asbestos seem to vary with regard to their importance in the causation of disease. Crocidolite is generally considered to be the most "dangerous" asbestos because of its strong association with mesothelioma. It now is banned from importation into the United Kingdom, but it is still used to a limited extent in the United States. Amosite is used less widely in this country today. More than 95% of the asbestos used in the United States is chrysotile, which comes from either domestic or Canadian sources. However, it often is impossible to determine the type of asbestos a patient has been exposed to, because the various types of asbestos commonly are used interchangeably and as mixtures.

ASBESTOS FIBERS IN TISSUE

Two forms of asbestos fibers characteristically are found in the lungs. One, the uncoated, "bare" fiber, is identical to the inhaled particle unless altered by physical and chemical events in the tissue. Because of their narrow diameter, even relatively long fibers (> 5 μm) of inhalable size are detected only with difficulty by light microscopy; shorter fibers (which often are present in large numbers) are demonstrable only by electron microscopy. Polarized light microscopy is of limited use in detecting asbestos in lung tissue because these relatively thin fibers are only weakly birefringent. Similarly, the fibers cannot be identified positively in tissue by phase optics microscopy.

The second form of fiber, the asbestos body, is the hallmark of asbestos exposure (Color Fig 1). It consists of a fiber of variable length that is coated with proteins and iron compounds. The core of the fiber is transparent, colorless, and usually straight and unbranched; however, curved, branched bodies sometimes are seen. Their appearance has been described

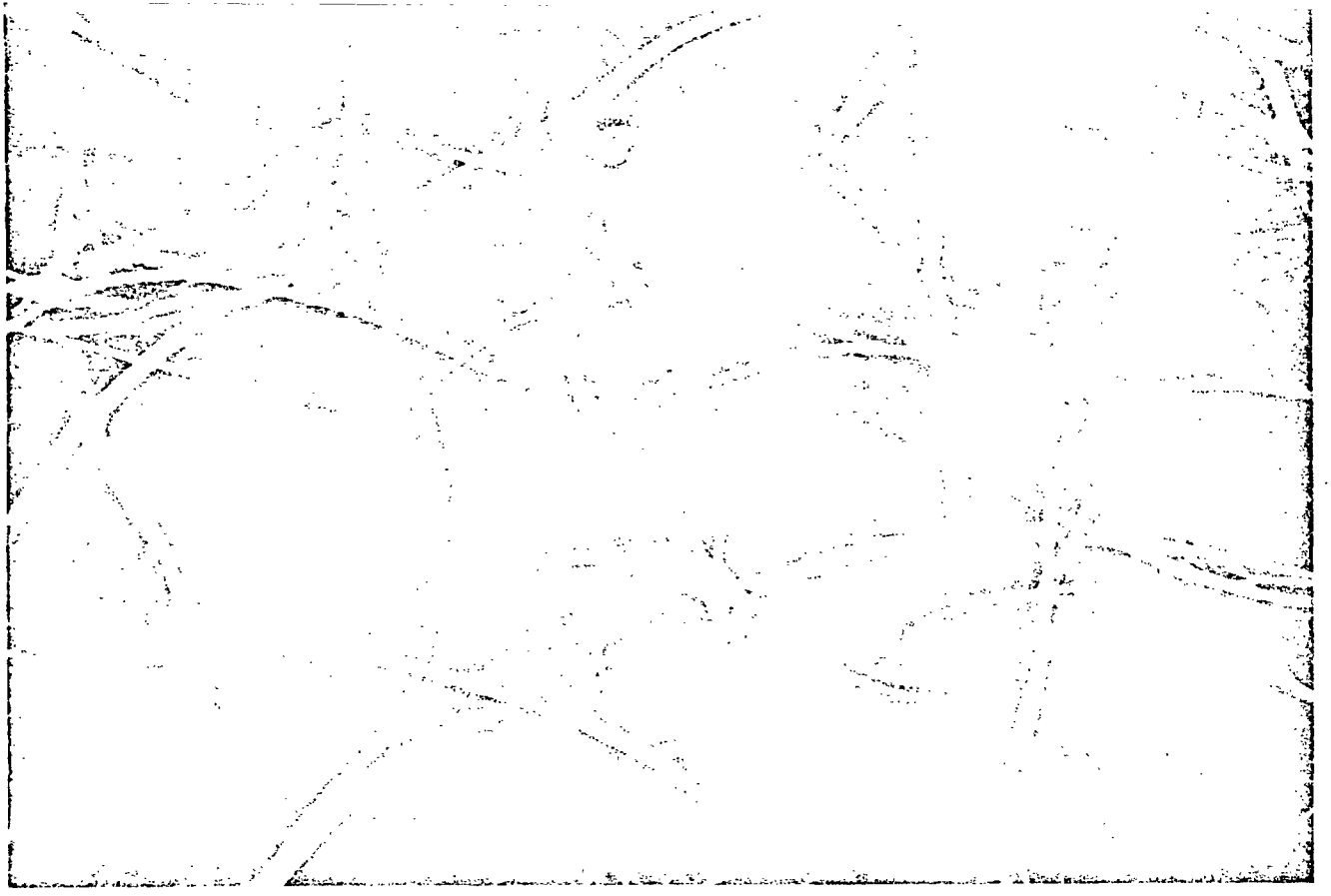


Fig 2.—Scanning electron micrographs of Canadian chrysotile (top, ×7,500; bottom, ×18,000). Note curled features as well as variable lengths and diameters of fibers. Top, Fibrillary makeup of individual fibers is evident. In tissue, fibers often break down into individual fibrils and thus may not be evident by light microscopy. All specimens in Figs 2 and 3 were prepared under auspices of Union Internationale Contre Cancer and consist of commercial products. Properties of minerals extracted from individual geologic deposits of asbestos differ, which may affect pathogenicity.

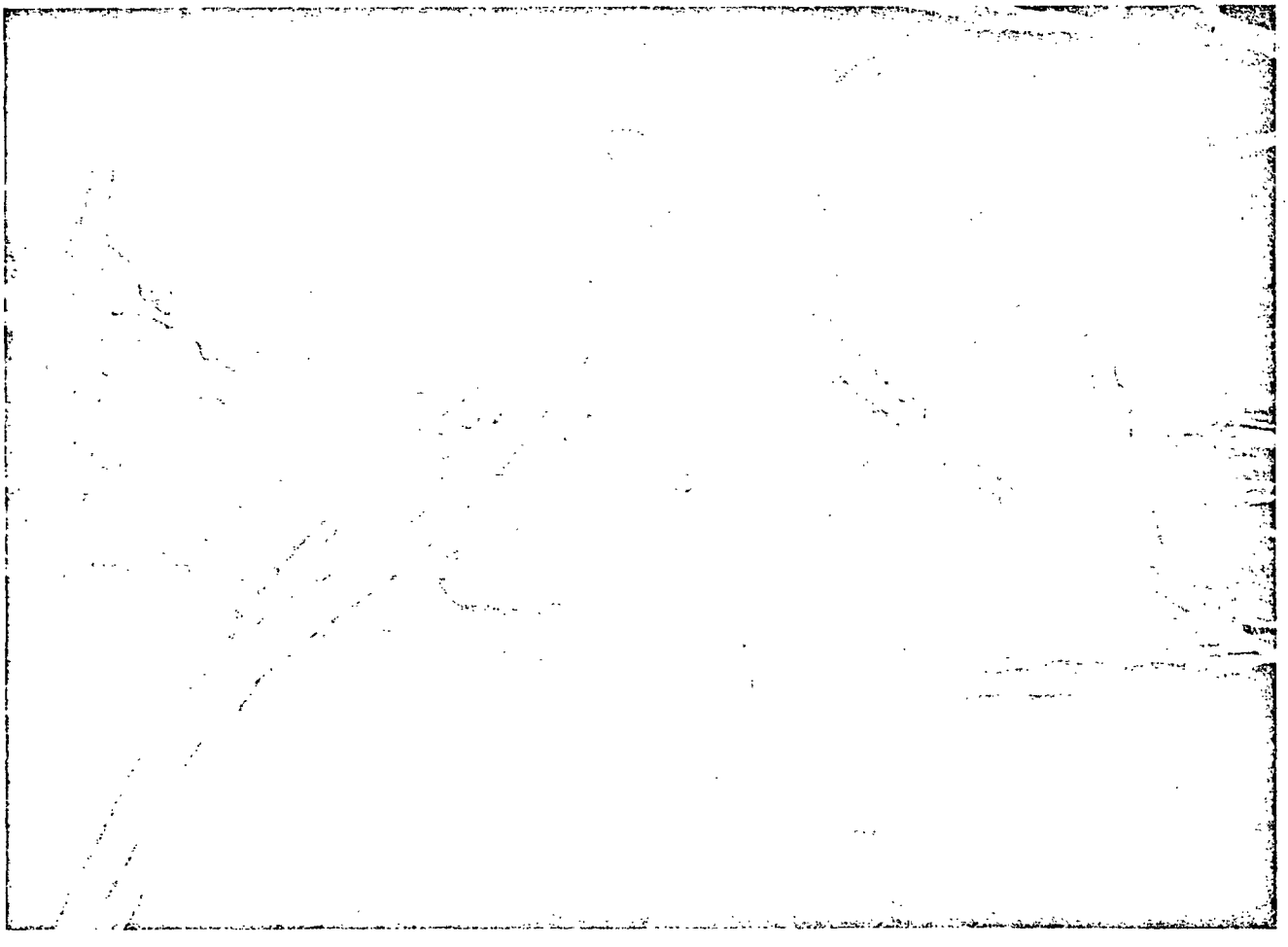


Fig 3.—Scanning electron micrographs of South African crocidolite (top, ×7,500; bottom, ×18,000). Note rodlike features of rigid fibers of crocidolite and their variable lengths and diameters. Fibular substructure of fibers is apparent. See Fig 2.

Color Fig 1.—Typical asbestos bodies in lung exhibiting grade 3 asbestosis. Note characteristic hollow cores of many fibers. Phagocytic multinucleate cells are unusually prominent in this tissue (hematoxylin-eosin).

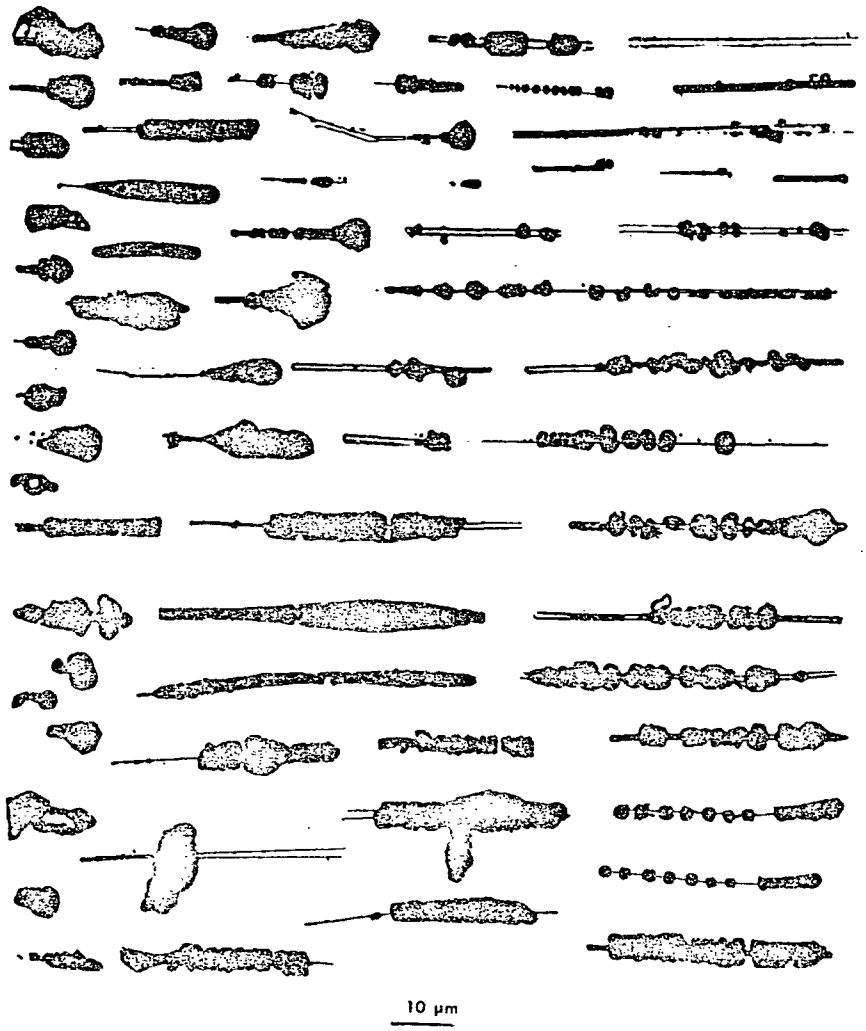


Fig 4.—Configurations of Prussian blue-stained asbestos bodies in lung with asbestosis. Bodies were identified in photomicrographs of lung and cut out to prepare montage. Asbestos bodies consist of an asbestos fiber core and surface deposits of protein- and iron-containing compounds.

as "dumbbell," "drumstick," "beaded-necklace," and "sausage," among other descriptors (Fig 4). Typical asbestos bodies are from 10 to more than 300 μm long, although the usual length is about 30 to 50 μm. However, much smaller bodies of various shapes often are seen free in the tissue or in the cytoplasm of macrophages. The width is less than 3 μm, whereas the core can vary from 0.1 to 1.0 μm. A histologic stain for iron often is helpful in demonstrating asbestos bodies in tissue and should be used when the bodies are not readily demonstrated in lesions believed to be due to asbestos exposure. The ratio of uncoated fibers to asbestos bodies in the lungs is high, often ranging from 5:1 to 10,000:1.[13]

The term *ferruginous body* has been suggested as a general descriptor for a fiber in tissue with an iron-protein coat.[14] Ferruginous bodies derived from a variety of inorganic and organic fibers have been identified in human lungs. Structures formed around carbon particles have black cores by light microscopy, and bodies formed on other silicates, eg, talc and mica, often have yellow cores. As most ferruginous bodies with colorless, transparent cores in human lungs consist only of asbestos, we prefer to use the more specific term *asbestos body*.[15,16]

When birefringent material is present in the lungs in large amounts, exposure to common silicates like mica, talc, and kaolinite is likely. In workers exposed to talc, the inhaled dust usually contains asbestos because small amounts of the fibrous

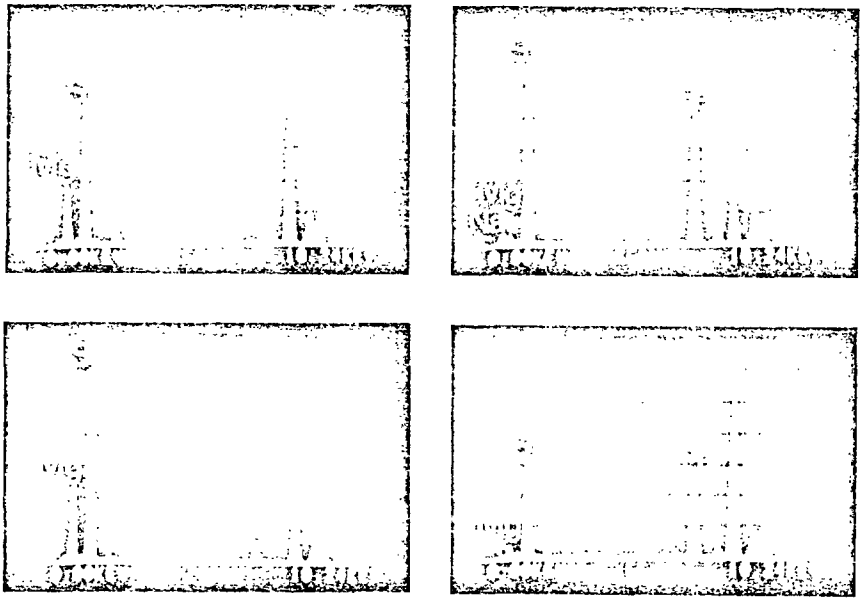


Fig 5.—Energy-dispersive x-ray spectrometry (microprobe) spectra of the four commercially important types of asbestos. Individual elemental components of fiber are displayed at various loci along horizontal axis of cathode ray image; height of peak indicates relative amount of each element present. Upper left shows chrysotile; upper right, crocidolite; lower left, anthophyllite; and lower right, amosite.

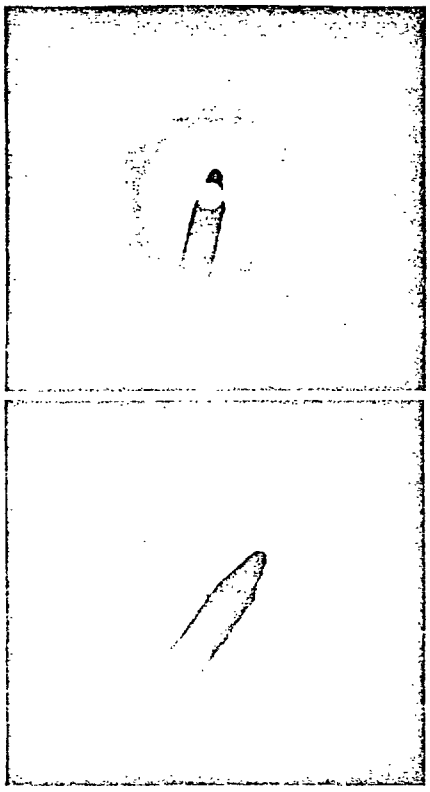


Fig 6.—Electron microscopic diffraction patterns of chrysotile (top) and crocidolite (bottom). Chrysotile pattern is distinctive. Crocidolite pattern is not specific, but is consistent with amphibole mineral. It is possible to identify mineral type using x-ray spectrometry and electron diffraction.

mineral customarily are present in commercial deposits of talc. Evidence of exposure to silica dust, eg, quartz, often is found in conjunction with asbestosis. Pulmonary disease consequent to a mixture of dusts, including asbestos, is an important consideration in some occupational groups, and this should be reflected in the diagnosis by the pathologist.

The mineralogic identification of either a specific fiber or a nonfibrous mineral in tissues is a difficult and time-consuming task that requires specialized equipment and highly trained personnel. Usually, it is necessary either to digest tissues in alkali or to incinerate them before analysis.

Light microscopic and ultrastructural methods have been developed for the identification and quantification of fibers and asbestos bodies in tissue (appendix 1). These techniques may be useful for documenting exposure in persons with no history of exposure, and for identifying the specific mineral or minerals involved. However, it is difficult to relate the fiber content of tissue to the extent and severity of parenchymal disease of the lung.

The physical characteristics of particles in tissue vary, and in part reflect changes that occur after inhalation. For example, chrysotile fibers fragment into subunits and are leached of certain mineral constituents with the passage of time.[17] Ultrastructural examination of individual fibers by either scanning or transmission electron microscopy is not a useful technique for the identification of fibers because the individual fiber types have few specific structural features. Energy-dispersive x-ray spectrometry (electron probe) and electron diffraction transmission microscopy permit the chemical and crystallographic analysis of a fiber in tissue (Figs 5 and 6). Because of the specialized nature of these time-consuming techniques, they are of limited diagnostic usefulness.

ASBESTOS-ASSOCIATED PLEURAL AND PULMONARY DISEASE

Long-term exposure to asbestos may result in disease that is restricted to either the pleura or the pulmonary parenchyma, although lesions of varying severity commonly are present in both anatomic locations.

Pleural Plaques

Plaques of the parietal and diaphragmatic pleura often are found in persons exposed to asbestos.[18] In recent years, these lesions have been considered one of the pathologic and radiologic hallmarks of exposure. Plaques may prove to be the only evidence. The interval between the time of initial exposure and the development of plaques is not clearly defined, but ten to 20 years usually elapse before they become evident clinically (Fig 7). As might be expected, the prevalence in groups of workers exposed to asbestos increases with age. In some series of cases, more than 50% of the study group exhibited radiologic evidence of plaques 30 to 40 years after exposure[19-21] (Fig 8).

All commercial types of asbestos induce plaques. In one study, the prevalence differed 13-fold between workers in two regions mining the same vein of chrysotile in Quebec. Plaques are also found in members of the families of asbestos workers and in persons who reside in communities near asbestos mines and mills. They have been reported in persons exposed to mica, industrial talc (which contains asbestos fibers), fibrous diatomaceous earth, fibrous zeolite, and other silicates. Plaques commonly occur among members of the general population in certain areas of Finland,[21] various places in central Europe, and in a few localities in Turkey.[22] Because evidence of occupational exposure in these areas is usually lacking, it has been suggested that the lesions are due to the inhalation of fiber and minerals that are found in soils and geologic outcrops.

The plaques on the parietal pleura typically are located on the posterolateral aspect of the lower part of the thorax and on the dome of the thoracic surface of the diaphragm (Figs 9 and 10). Customarily, they are not found adjacent to the apices of the lung or in the costophrenic angles. Plaques also are situated at scattered sites on the peritoneal surfaces of the abdominal cavity, but these are relatively rare lesions.

Thin plaques usually are smooth and grayish white, whereas the thicker lesions are ivory-white and either have a smooth surface or are coarsely nodular. The size and shape vary: whereas plaques on the surface of the diaphragm typically are round and disklike, those located over the intercostal spaces are elongate and have an irregular configuration (Figs 11 through 13). Plaques customarily do not form on the visceral pleura, although this surface often is either diffusely or focally thickened by fibrous tissue. This latter lesion ranges in severity from a simple loss of translucency to a shell of white, fibrous tissue that encases the whole lung. When honeycombing of the lung parenchyma exists, the surface may

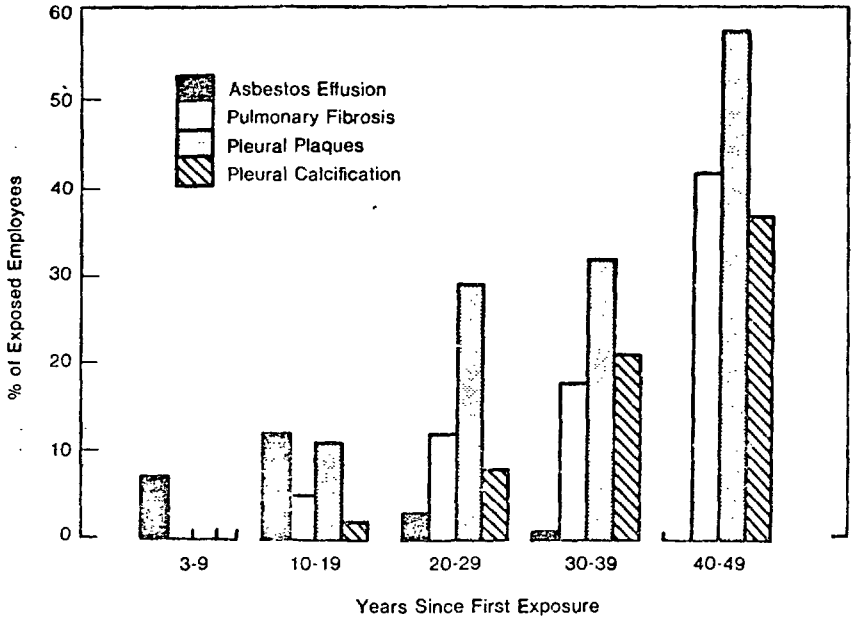


Fig 7.—Clinical occurrence of various asbestos-associated lesions among industrial workers chronically exposed to airborne mineral fibers. Data are based on physical examinations and roentgenograms obtained systematically during 50-year period (from Epler and Gaensler[74]).

Fig 8.—Chest roentgenogram of 68-year-old construction contractor who was hospitalized for treatment of recurrent transitional cell carcinoma of bladder. There were no unusual respiratory complaints. Calcified plaques on parietal pleural surface of rib cage, pericardium, and diaphragm were incidental finding.

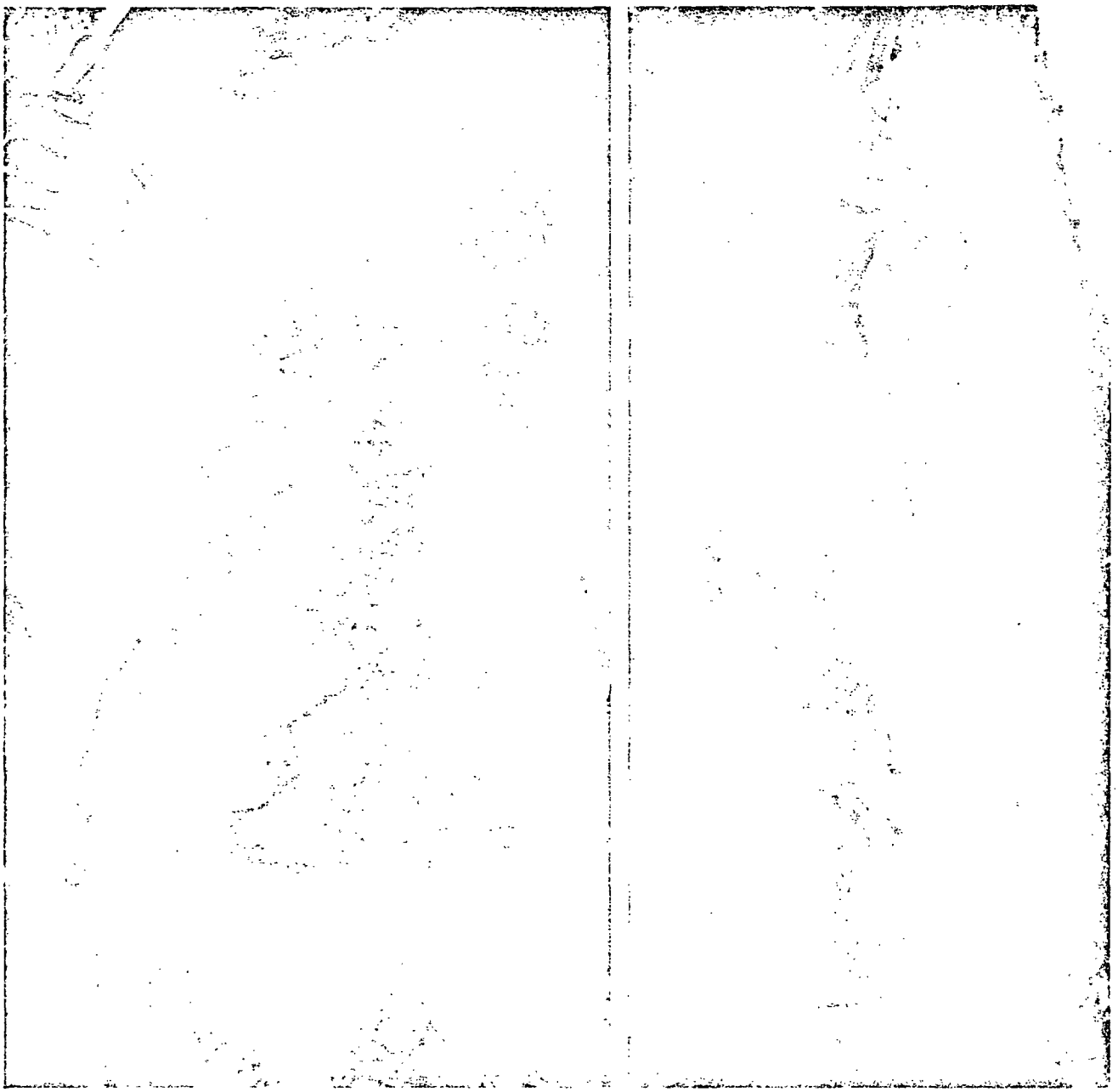


Fig 9.—Parietal pleural surfaces of thoracic cages of two Finnish men at autopsy. Lungs and mediastinal structures have been removed. Left, Note nodularity of plaques. Right, Note smooth, confluent, sheetlike plaques. Diaphragmatic surface exhibits large, circumscribed, disklike plaques. There was no history of occupational exposure to asbestos.

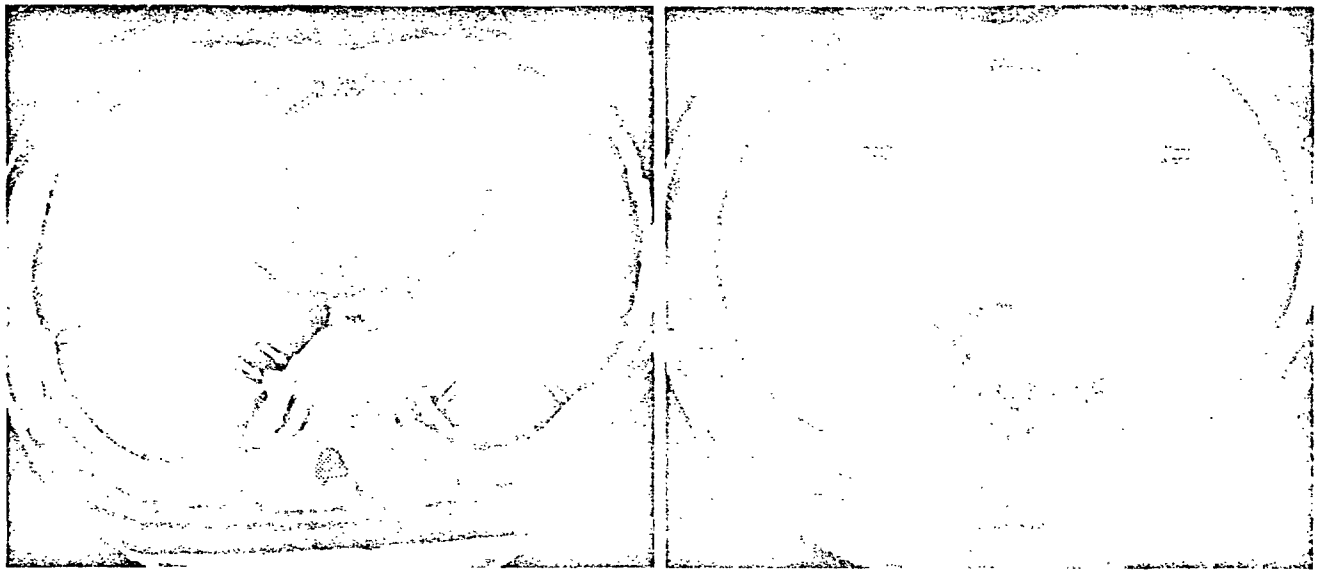
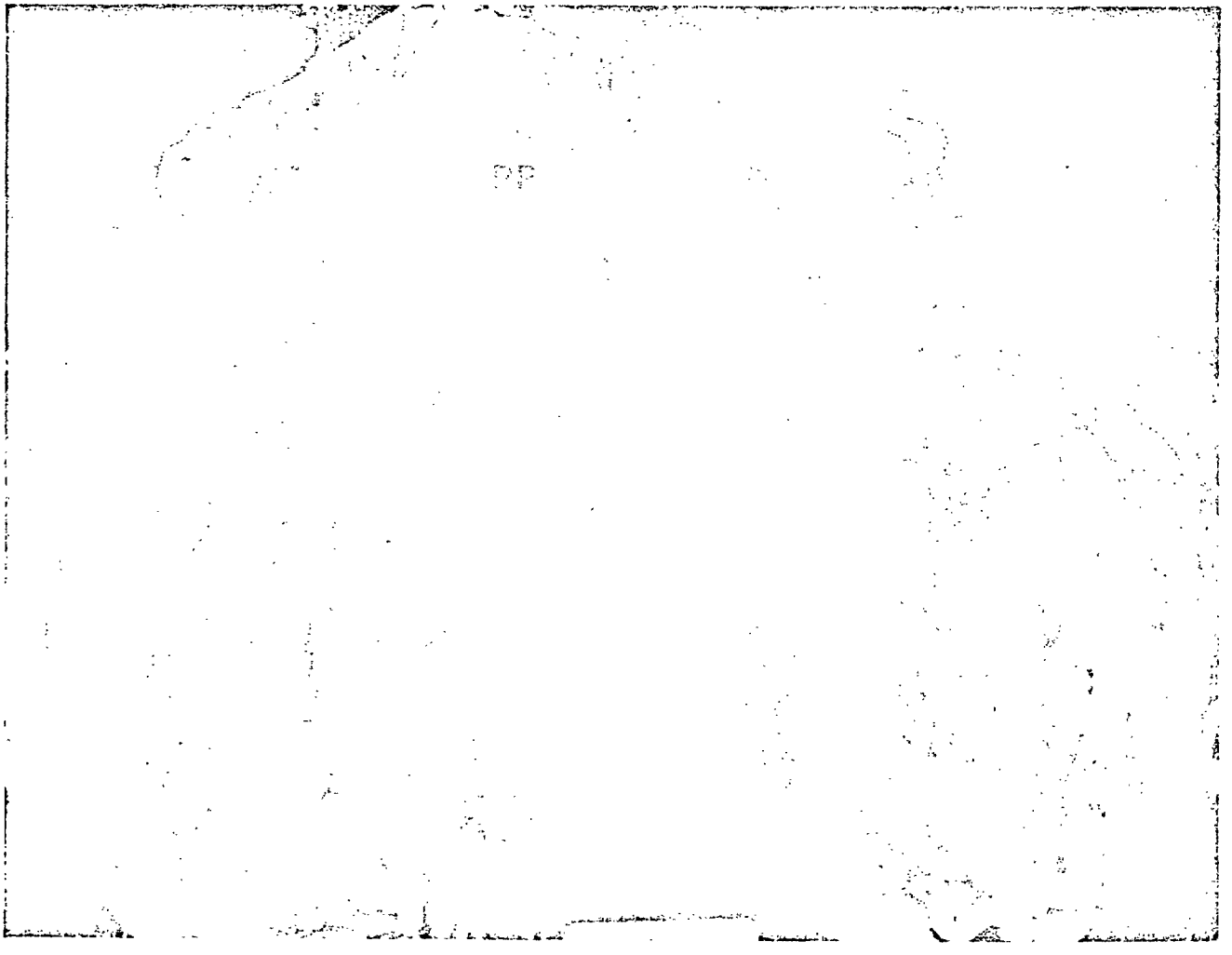


Fig 10.—Computed tomograms of pleural plaques (arrows). Left, Calcified paravertebral and peripheral plaques. Right, Calcified mediastinal, paravertebral plaques (from Preger[75]).

Fig 11.—Parietal pleural surface and parietal pericardium (PP) of diaphragm of American man with history of occupational exposure to asbestos. Disklike configuration and nodularity are typical of these lesions.



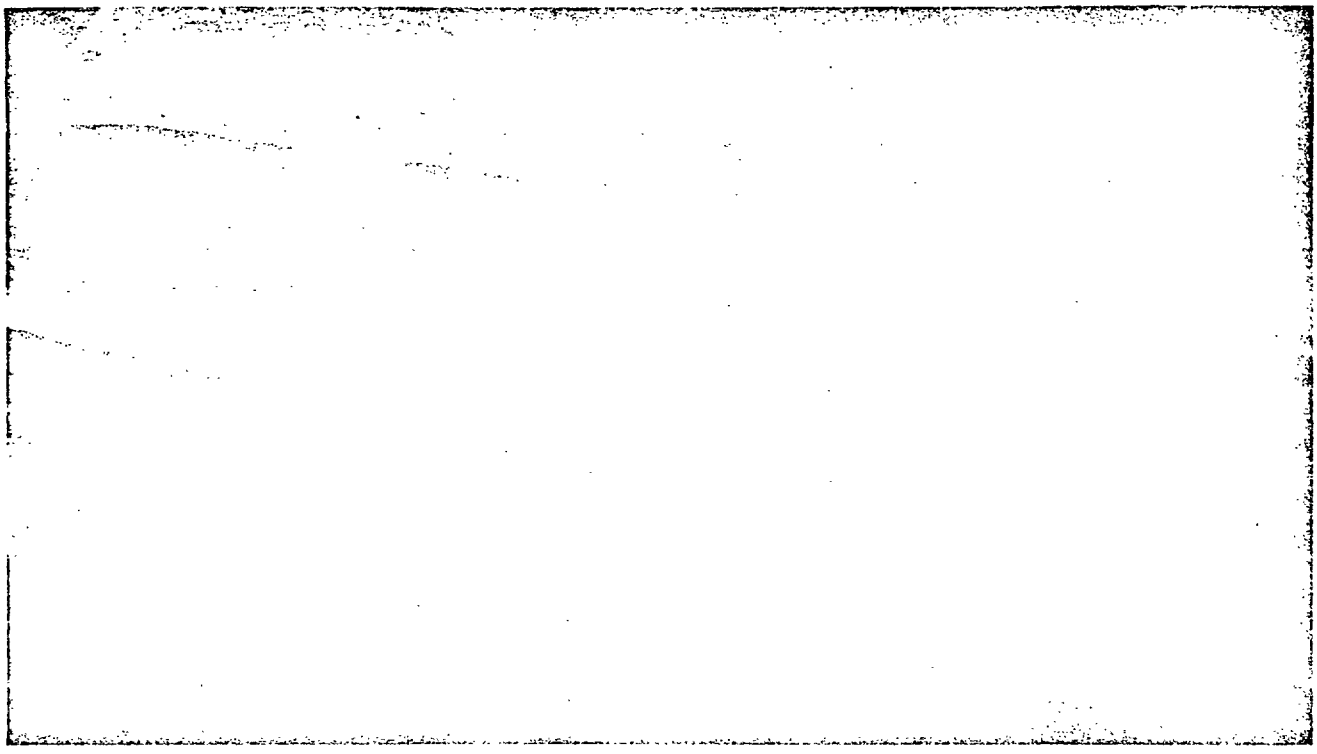
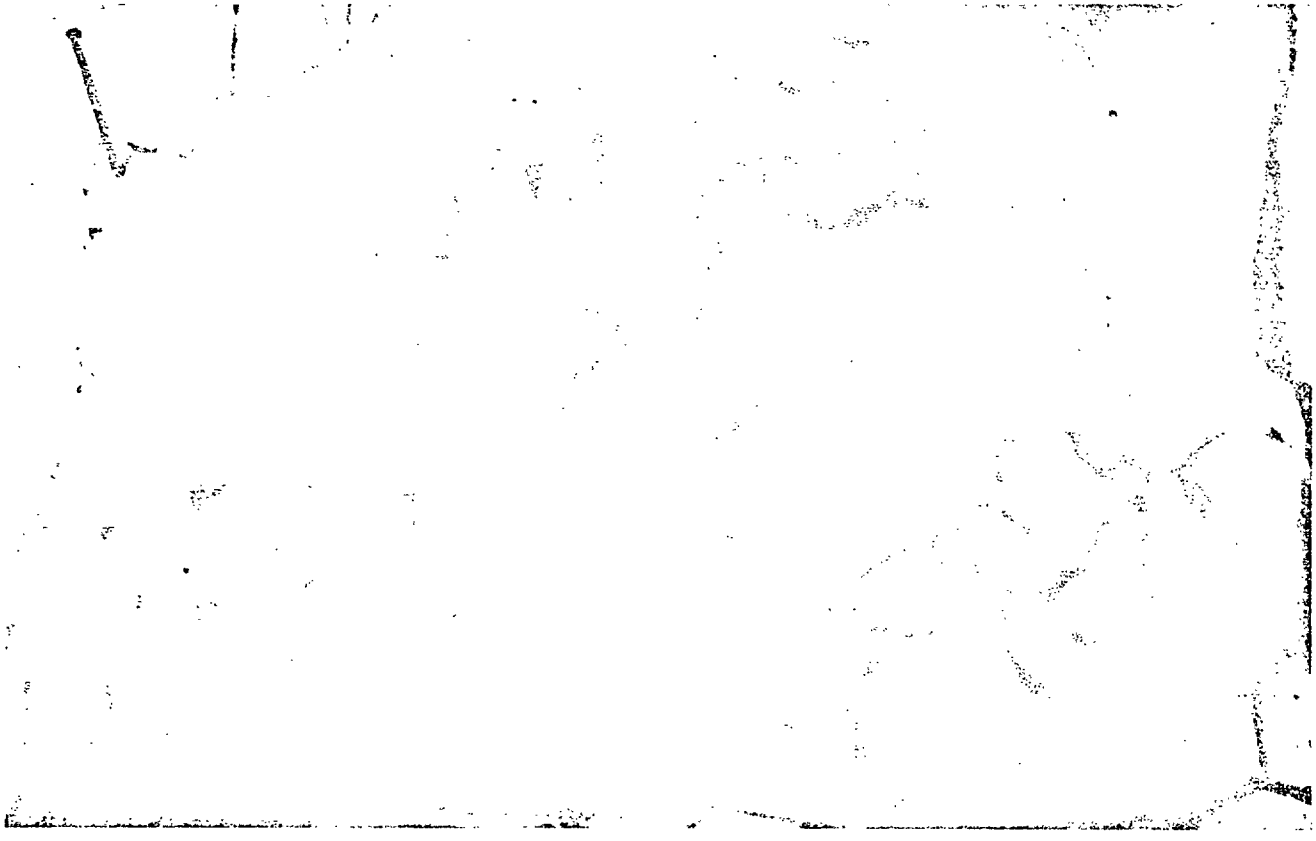


Fig 12.—Roentgenogram of calcified plaques adjacent to ribs in autopsy specimen. Plaques appear to originate on inner surface of ribs and grow onto surface of intercostal muscle (from Preger[15]).

Fig 13.—Nodular plaques on pleural surface of membranous diaphragm of Finnish man with no known occupational exposure to asbestos.



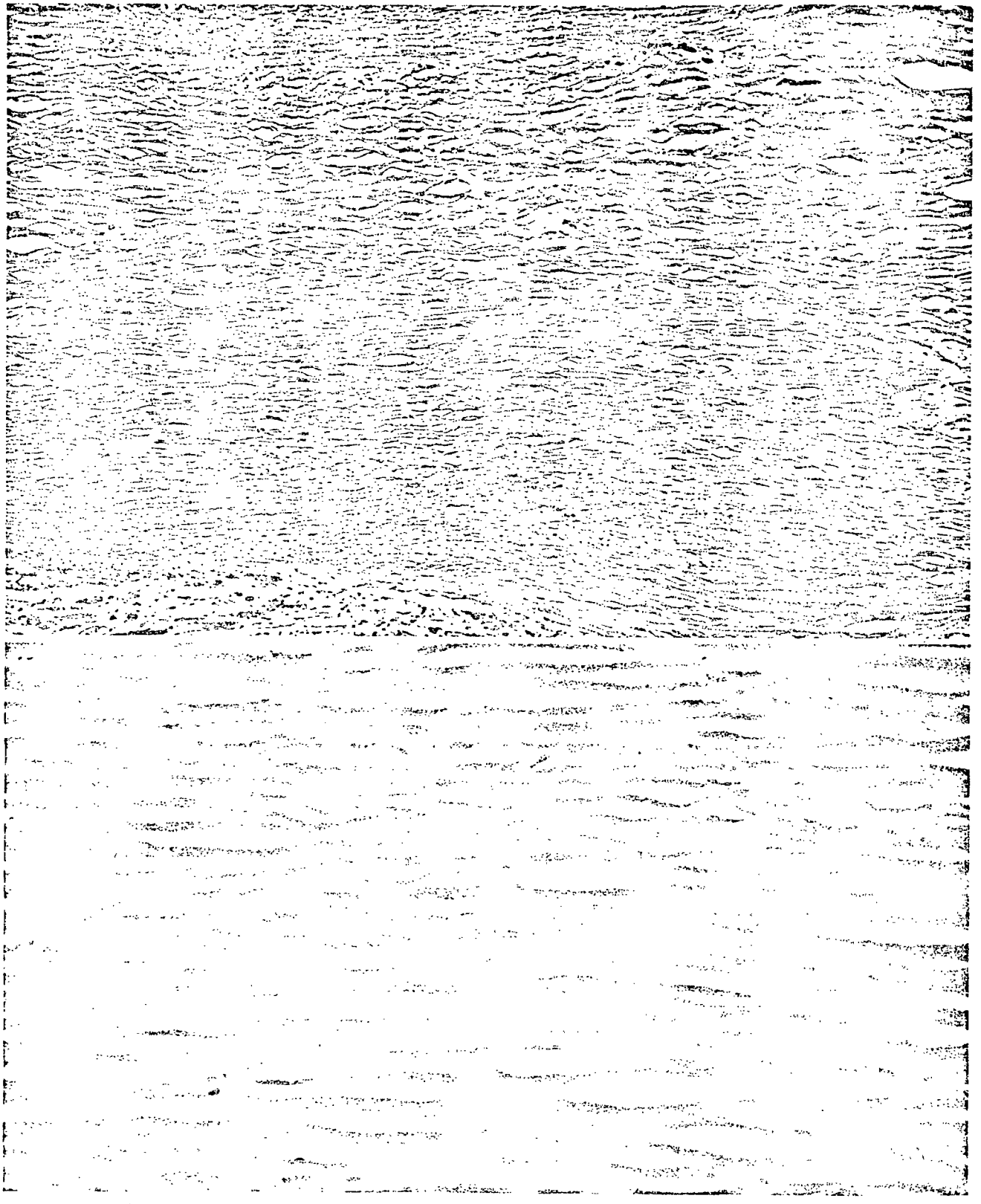


Fig 14.—Microscopic features of typical pleural plaque. Note "basket-weave" arrangement of collagen bundles and relative acellularity of tissue. These lesions usually are not vascularized.

have a coarse nodularity that resembles a cirrhotic liver. Adhesions between the visceral and parietal pleura are common, particularly at the lung bases. The degree of pleural thickening does not reflect the severity of the pulmonary parenchymal disease and it can occur in the absence of fibrosis. Pleural pigmentation is not a feature of asbestosis and its presence suggests exposure to other types of dust.

Microscopically, pleural plaques consist of dense strands of hyalinized, relatively acellular, nonvascular collagen lined by a surface of mesothelial cells. The collagen fibers lie parallel to the surface and show a reticulated mesh appearance, the so-called basket-weave pattern (Fig 14). The collagen fibers in nodular plaques have a whorled arrangement. Occasional plaques exhibit elastic fibers and scattered, thin-walled blood vessels. Inflammatory cells are not present, but may be found nearby. Calcification is a common but variable feature that has proved useful in radiologic epidemiology. Occasionally, fibers of asbestos can be found in plaques by electron microscopy after either digestion or incineration of the tissue.

Asbestosis

Asbestosis is pulmonary fibrosis consequent to the accumulation of airborne asbestos in the lungs. It does not refer to the lesions of the pleura already described. The severity of the disease varies. It depends in large part on the type and duration of exposure, the concentration of dust in the ambient air, and the fiber "burden" of the lung. Factors unique to the host (eg, immunologic responsiveness, concomitant disease processes, exposure to other types of dust, and cigarette use) also are believed to be important, although their relative significance in the evolution of the disease is uncertain. Asbestosis is a chronic and often progressive disease. Although decades usually elapse before its signs and symptoms become clinically evident, shorter latency periods have been noted in asbestos workers who experienced exceptionally heavy exposure.

Gross Features.—The pathologic features of the advanced stages of pulmonary asbestosis have been recorded in the classic descriptions of the disease. As expected from physiologic studies and the chest films, the lungs are small and firm. The cut surface is striking because of its dark-brown color. Gray streaks of fibrous tissues outline interlobar and lobular septa and focally interdigitate the lung tissue. The visceral pleura is thickened by dense collagenous tissue (Fig 15). The occurrence of adhesions varies.

The parenchymal fibrosis, which is linear and reticular, is most prominent in the lower lobes. The bronchi are normal unless the patient has been a heavy smoker or other diseases exist. The tracheobronchial lymph nodes do not have characteristic changes. Commonly, they are enlarged and brown-black, but are neither firm nor fibrotic.

In advanced cases, the parenchyma exhibits honeycombing that is most prominent subpleurally and in the lower lobes (Color Fig 2). In contrast with emphysema, the airspaces of the honeycomb lung result from tissue fibrosis, with retraction of the residual structures (Fig 16). These revised cavities have diameters that range from 1 to 15 mm, and have visibly thickened walls. No evidence indicates that exposure to asbestos contributes to the development of emphysema. Although progressive, massive fibrosis (as in coal workers' pneumoconiosis[23] and silicosis[24]) has been described in persons with asbestosis, it is rare and usually consequent to exposure to a mixture of dusts.

The evaluation of fibrosis of the parenchyma on gross examination of the lungs requires a careful inspection of slices of tissue that have been inflated by the intratracheal instillation of fixative solution. Because the lesions of advanced asbestosis usually are most prominent in the lower lobes and subpleural tissue, a detailed description of the gross changes is mandatory. In addition, photographic documentation is recommended. The pathologist should attempt to determine the relative proportion of a whole lung section that exhibits fibrosis.

Although these features are typical of the overt case of asbestosis, the lungs of others with less severe exposure exhibit only moderate degrees of parenchymal fibrosis that are not clearly evident on gross examination. In the evaluation of these specimens, the histologic assessment of the lungs using the diagnostic criteria to be summarized may be pivotal in establishing a diagnosis.

Microscopic Features.—The severity of the histologic changes in the lungs in asbestosis varies, presumably in large part because of differences in the intensity and duration of exposure. At one extreme, the features of typical asbestosis are obvious after a brief examination of a tissue section; at the other, the lesions are subtle, for they may be identified only at scattered sites in representative histologic sections of the pulmonary tissue. It should be remembered that the lower lobes and subpleural regions of the lung are involved most severely by the disease. Pathologists must critically evaluate the lesions of pulmonary fibrosis using the criteria to be cited before implicating asbestos. A history of exposure is supportive but *not* definitive evidence. Conversely, its absence does not exclude the diagnosis because so many cryptic forms of exposure exist.

Correlative evaluation of experimental and human materials has provided insight into the morphogenesis of the disease at an early stage of evolution. Inasmuch as the pathologist often is obliged to establish a diagnosis in cases with undocumented exposure and mild disease, this section will emphasize the lesions we believe occur early in the pathogenetic sequence of events. Accordingly, an attempt has been made to develop a construct based on our concept of the disease from its initial stages to the more severe, overt form.

Little is known about the development of the early lesion of asbestosis in man. Thus, the evolution of the process must be inferred from a study of animals exposed to asbestos in inhalation chambers.[25-28] Asbestos seems to be deposited first in the respiratory bronchiole and the alveolar duct. Some observers believe an acute polymorphonuclear leukocyte

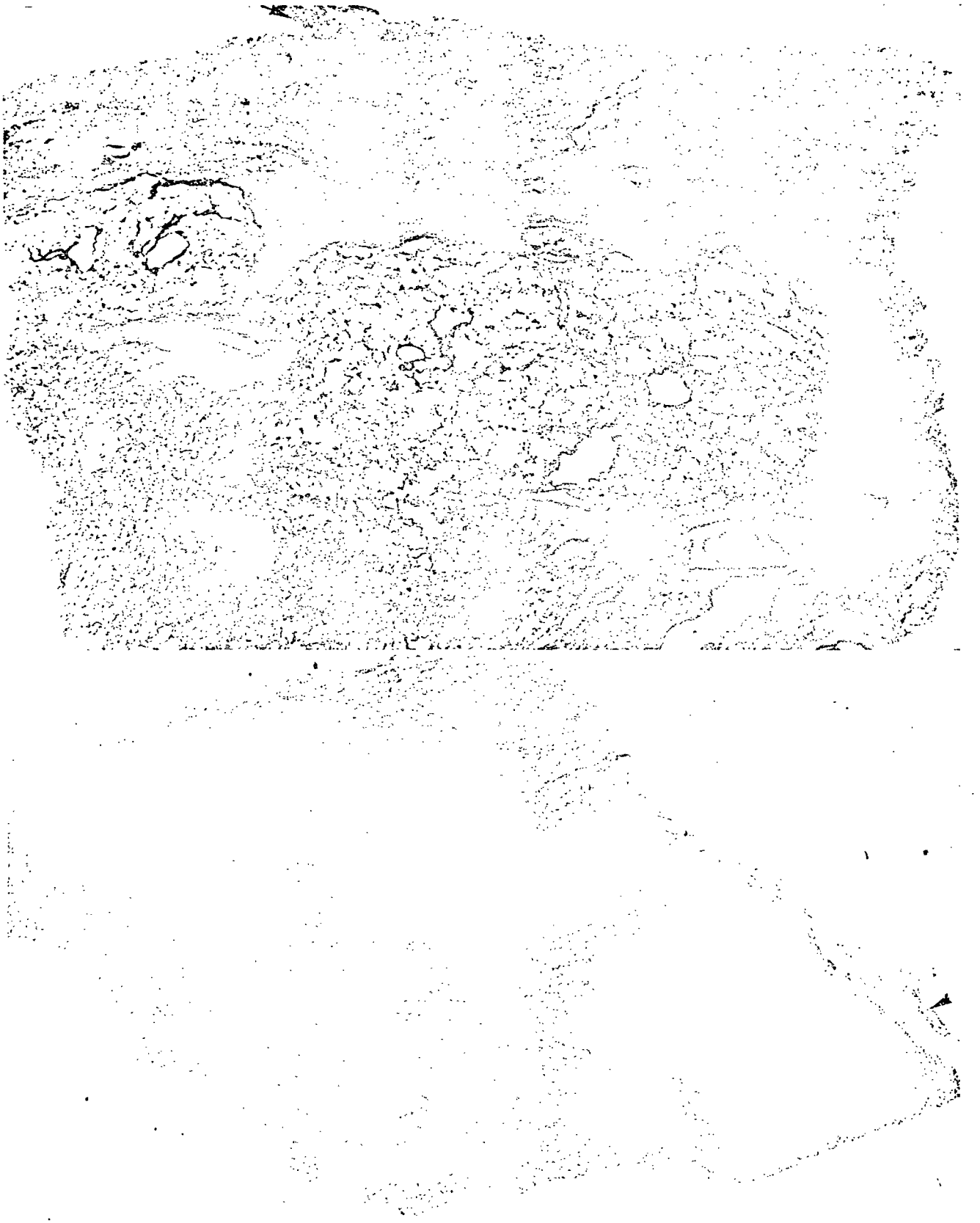


Fig 15.—Examples of fibrosis of visceral pleura (top) and interlobar septum (bottom) in lungs of two English dockworkers with long histories of exposure to asbestos. There is pulmonary asbestosis, grade 2B. Note adhesions (arrow and arrowhead) to parietal pleura. In contrast with plaques, which typically are found on parietal pleura, these lesions often are vascularized and consist of irregular bundles of nonhyalinized fibrous tissue. Involvement of interlobar septum (bottom) is typical of asbestosis (hematoxylin-eosin).

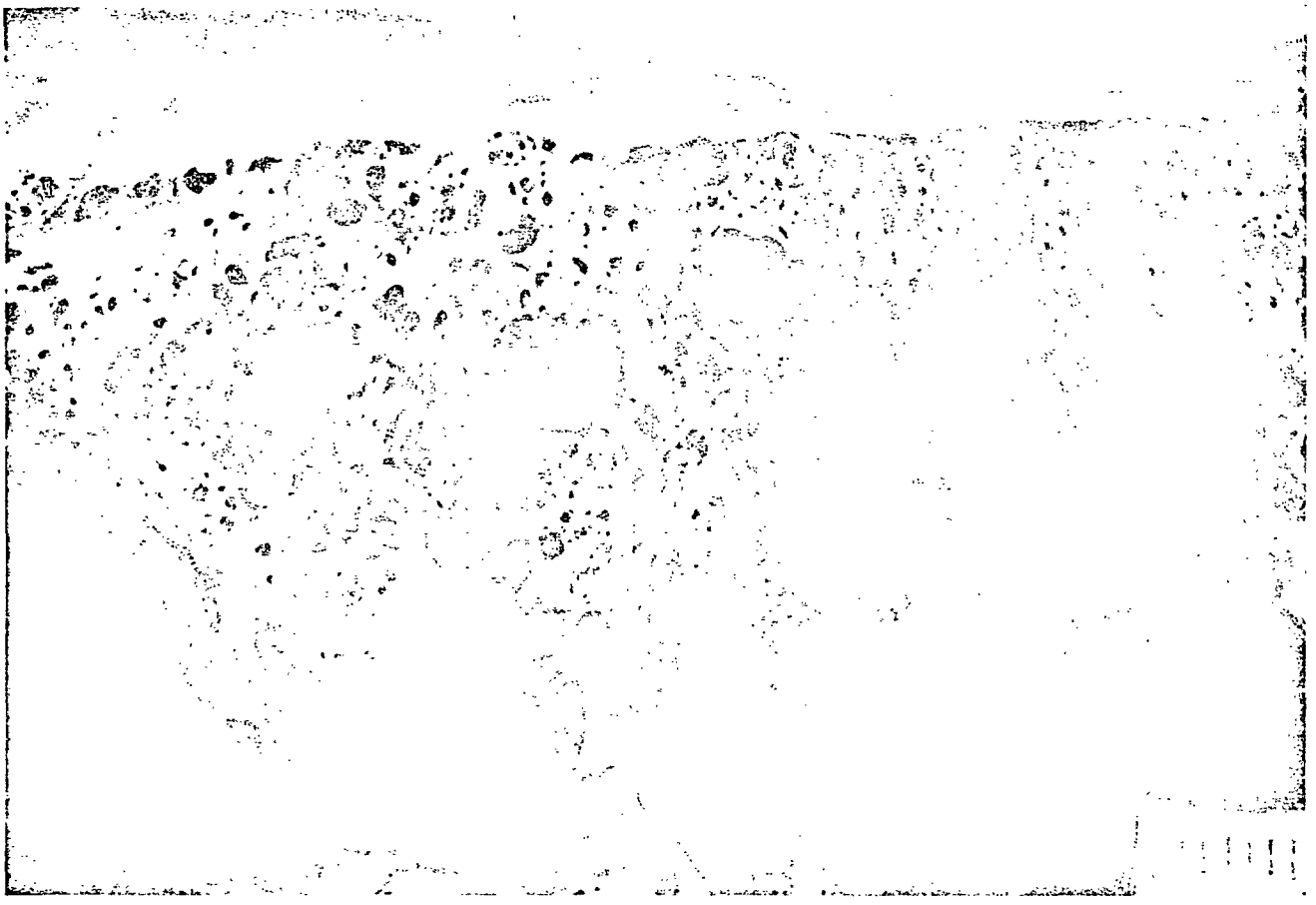


Fig 16.—Fixed portion of upper lobe of lung of insulation worker. Note diffuse reticular fibrosis and associated honeycombing in subpleural tissue.

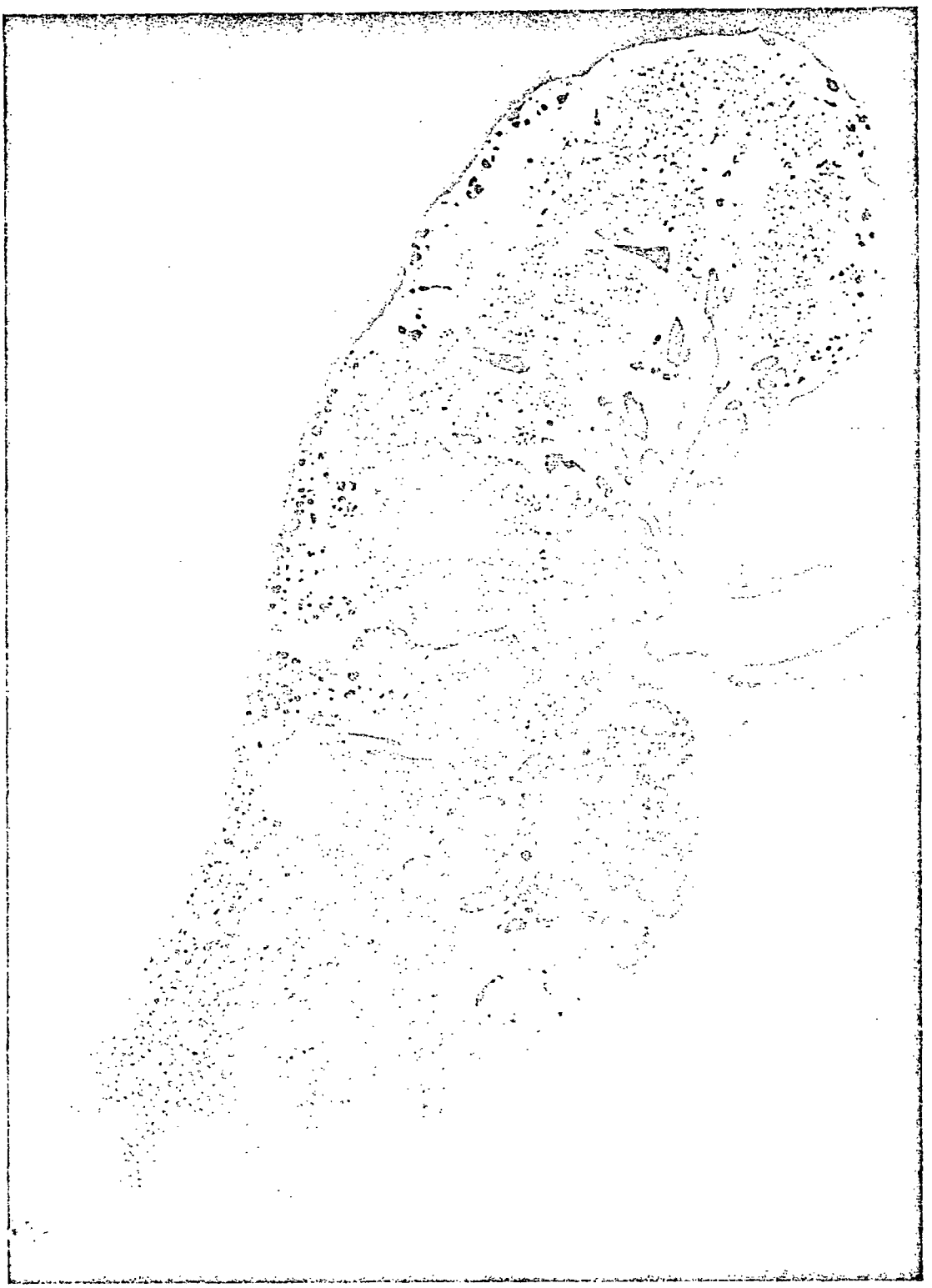
response is provoked as an early and transient reaction to dust deposition[29,30] (J. Abramowitz, MD, personal communication, June 8, 1981). Although this might occur, the macrophage usually is the prominent cell in the distal airways at the time of pathologic examination.

In the respiratory bronchioles, the lesion associated with asbestos deposition consists of a thickened wall attributable to the accumulation of reticulin and collagen. Either cuboidalization of the epithelial cells or both squamous cell and goblet cell metaplasia can be observed in the mucosa. In typical early asbestosis, only an occasional pulmonary subunit is affected (Figs 17 and 18). Thus, histologic sections obtained from representative sites throughout the lungs must be examined.

The criteria that permit the pathologist to establish the diagnosis of asbestosis have evolved during a review of many cases of the disease. Presently, the minimal features that permit the diagnosis are the *demonstration of discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of asbestos bodies.* These morphologic findings, although adequate to establish the diagnosis of asbestosis in an early evolutionary stage, have not been shown to result in functional and radiologic alterations. *The demonstration of asbestos bodies in the absence of fibrosis is insufficient evidence to justify the diagnosis of asbestosis.* Conversely, a definitive diagnosis of asbestosis cannot be made in cases that show characteristic fibrosis in the absence of asbestos bodies, even in a patient with a history of exposure. Because asbestos bodies are unevenly distributed in tissue, an adequate number of samples should be examined thoroughly.

In the lesions, asbestos bodies are located either in the walls of the bronchioles or in the airspaces, where they are often closely associated with macrophages. When only a single asbestos body is found in a histologic section, it is necessary to demonstrate additional bodies (either in deeper sections of the same block or in other samples of tissue) to establish the diagnosis of asbestosis.

Initially, first-order respiratory bronchioles are affected by the fibrotic process; in more advanced stages, the second- and third-order branches and alveolar ducts are involved. Concomitantly, the terminal bronchioles



Color Fig 2.—Thin sections (≈300 mm) of freeze-dried left lung of 51-year-old man with grade 4C asbestosis. Note diffuse fibrosis with honeycombing that is particularly prominent in basal portions of lower lobe, and in subpleural parenchyma. Honeycombing is typical of end-stage diffuse pulmonary fibrosis of many different causes, but prominence of lesions subjacent to pleura and in lower lobes of this case is typical of asbestosis.

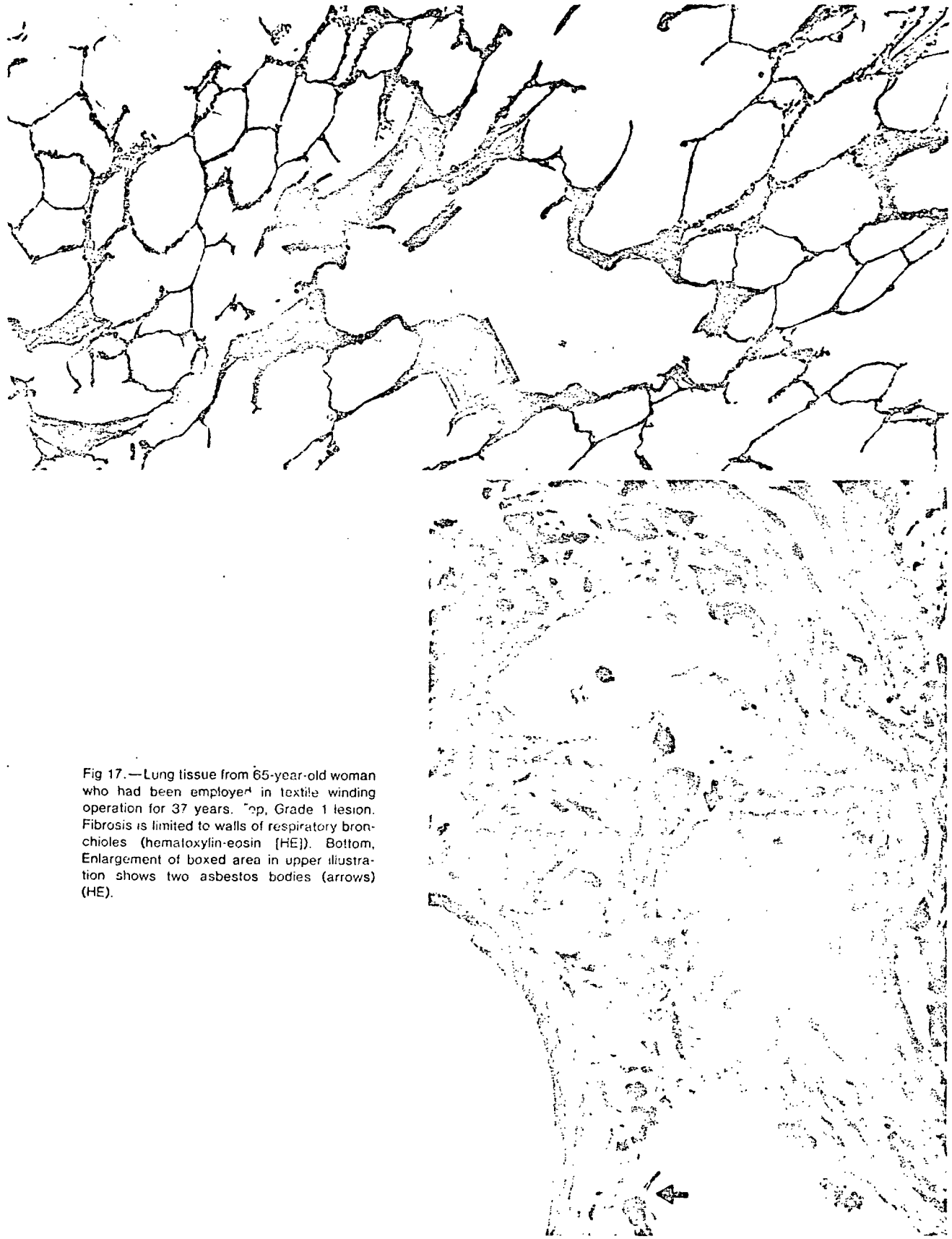


Fig 17.—Lung tissue from 65-year-old woman who had been employed in textile winding operation for 37 years. Top, Grade 1 lesion. Fibrosis is limited to walls of respiratory bronchioles (hematoxylin-eosin [HE]). Bottom, Enlargement of boxed area in upper illustration shows two asbestos bodies (arrows) (HE).

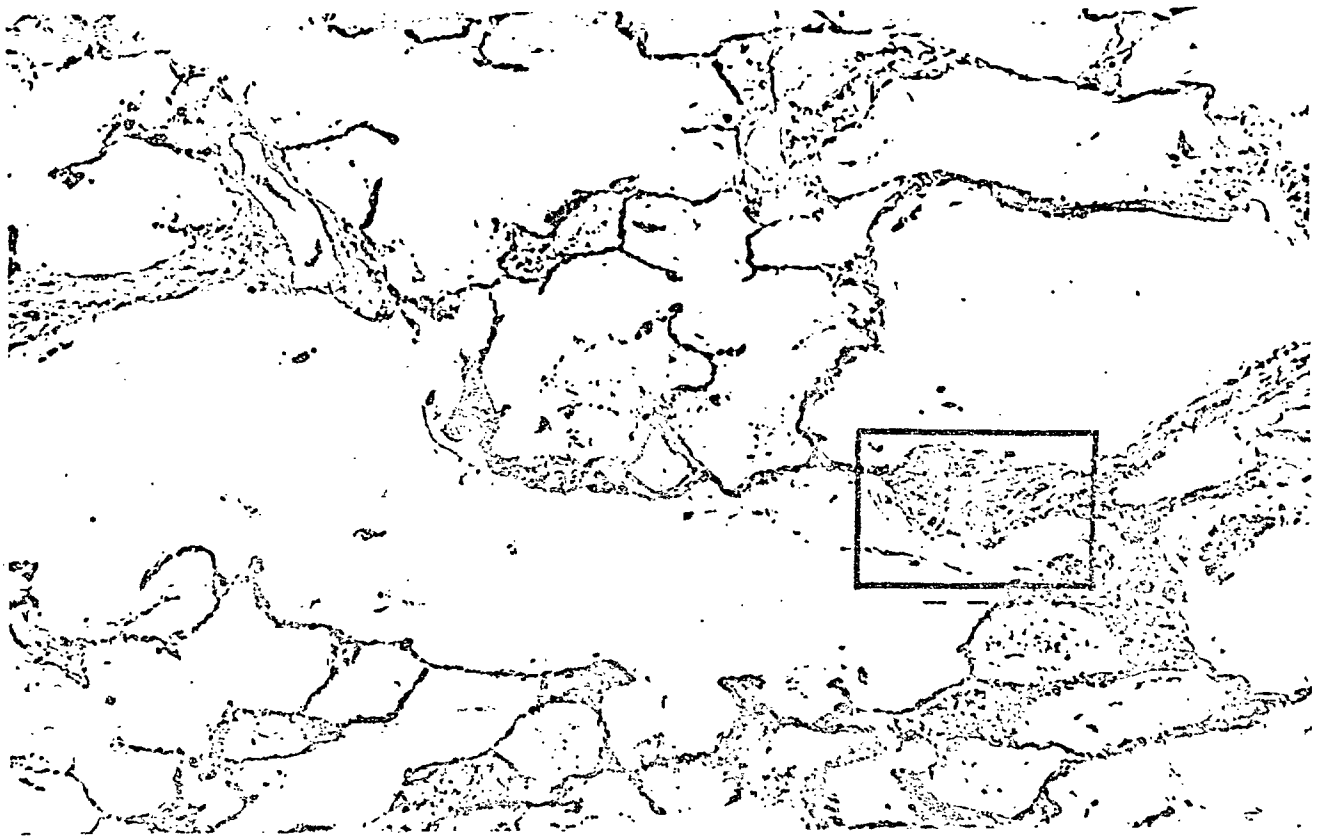


Fig 18.—Lung tissue from 64-year-old man who had been employed as spinner in textile mill for 34 years. Top, Grade 2 lesion. Fibrosis is primarily located around respiratory bronchioles, but there is extension into adjacent alveolar septae (hematoxylin-eosin [HE]). Bottom, Enlargement of boxed area in upper illustration shows several asbestos bodies (arrows). There are fragmented bodies and anthracotic pigment in the fibrotic tissue and pulmonary macrophages (HE).

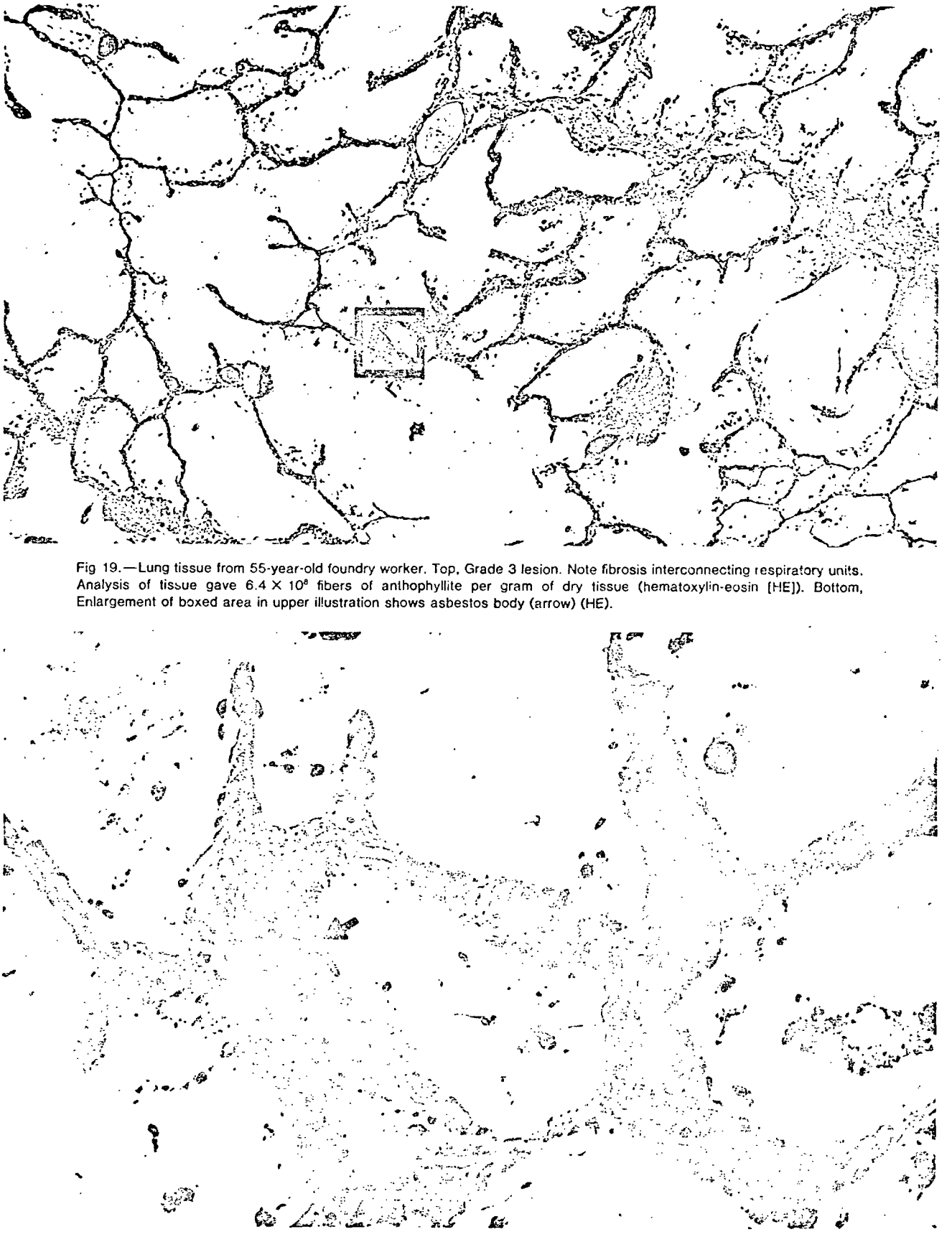


Fig 19.—Lung tissue from 55-year-old foundry worker. Top, Grade 3 lesion. Note fibrosis interconnecting respiratory units. Analysis of tissue gave 6.4×10^6 fibers of anthophyllite per gram of dry tissue (hematoxylin-eosin [HE]). Bottom, Enlargement of boxed area in upper illustration shows asbestos body (arrow) (HE).

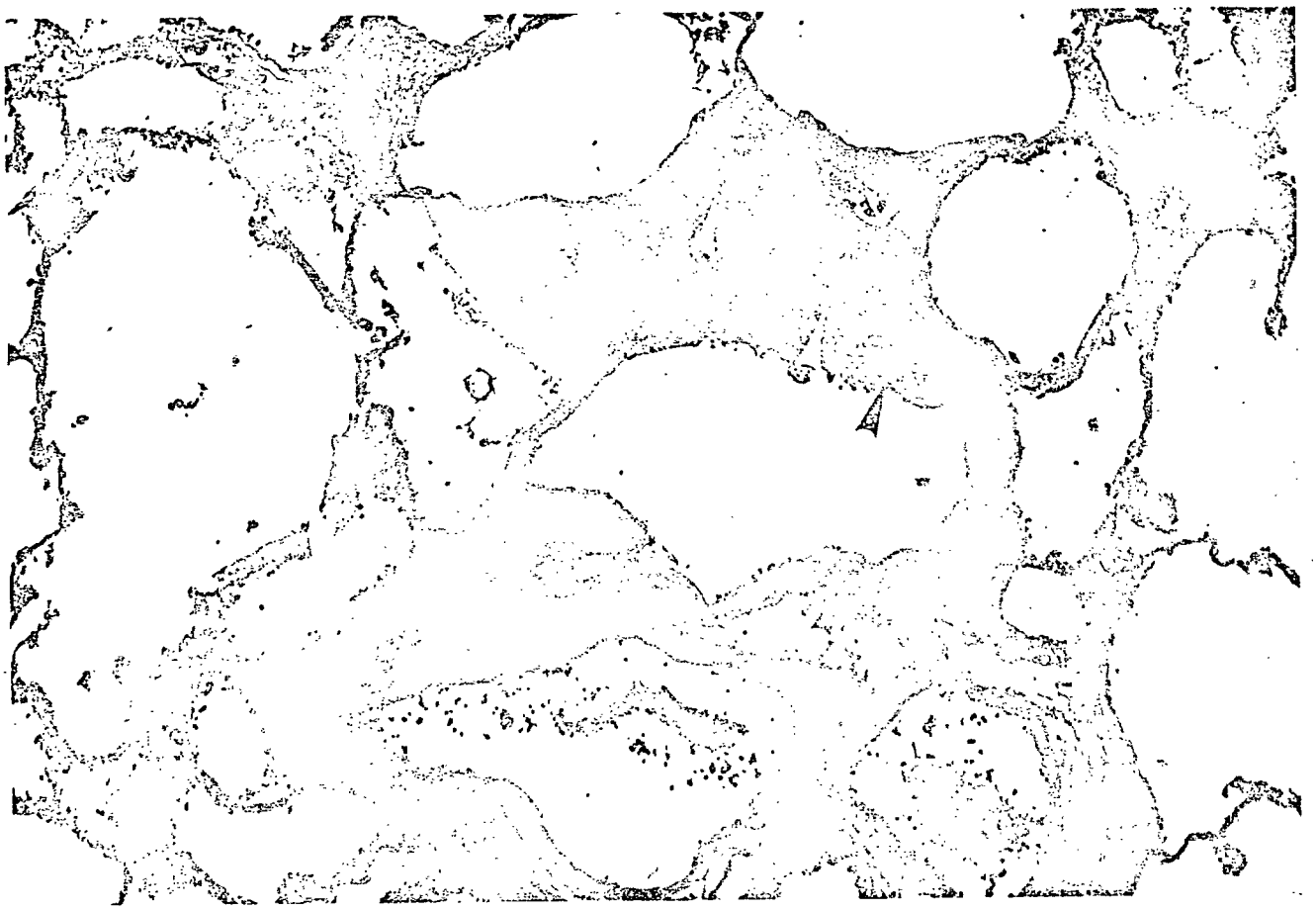


Fig 20.—Grade 2 lesions in lung of occupationally exposed worker with undocumented period of exposure to asbestos. Arrowheads indicate multinucleate giant cells and asbestos bodies (hematoxylin-eosin).

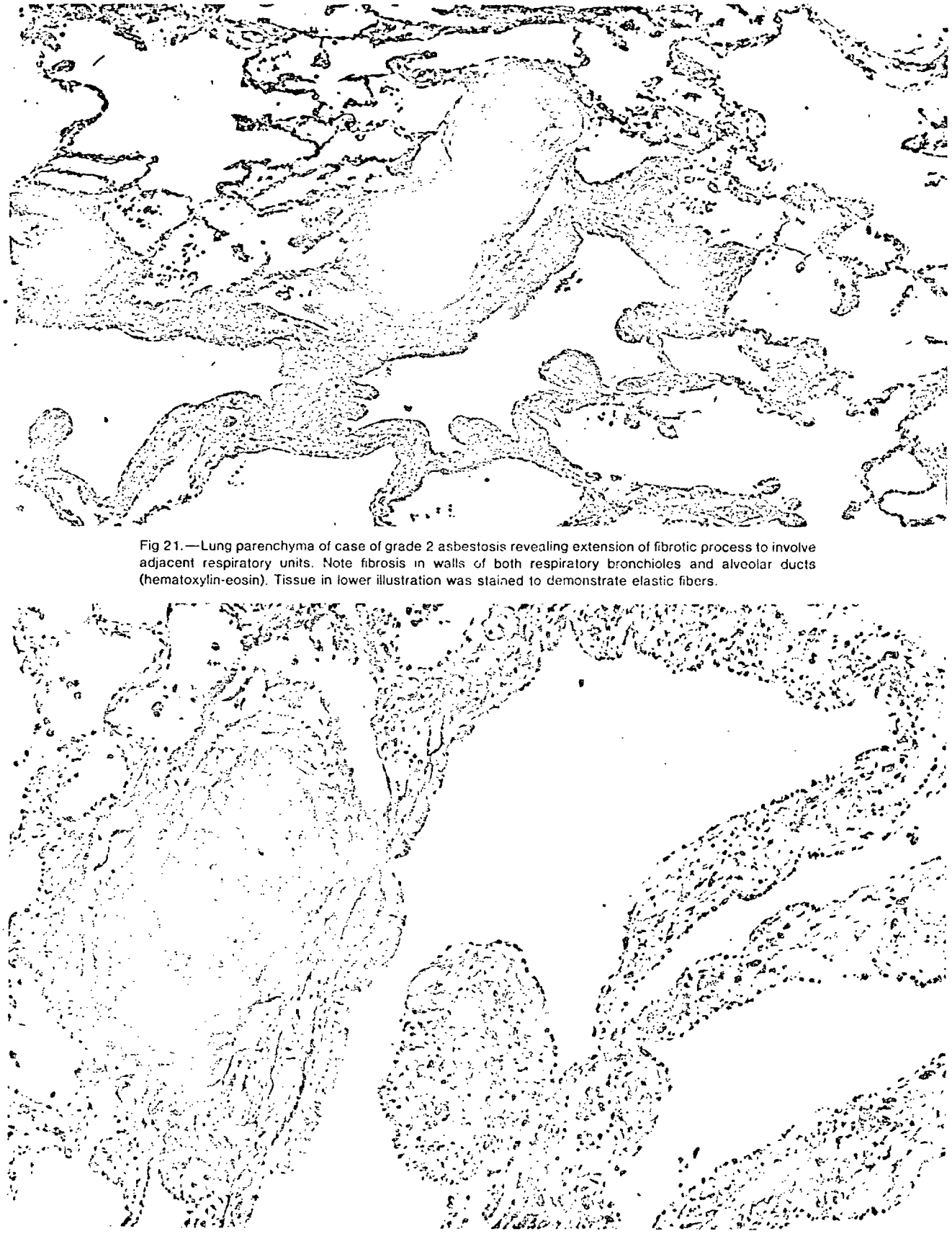


Fig 21.—Lung parenchyma of case of grade 2 asbestosis revealing extension of fibrotic process to involve adjacent respiratory units. Note fibrosis in walls of both respiratory bronchioles and alveolar ducts (hematoxylin-eosin). Tissue in lower illustration was stained to demonstrate elastic fibers.

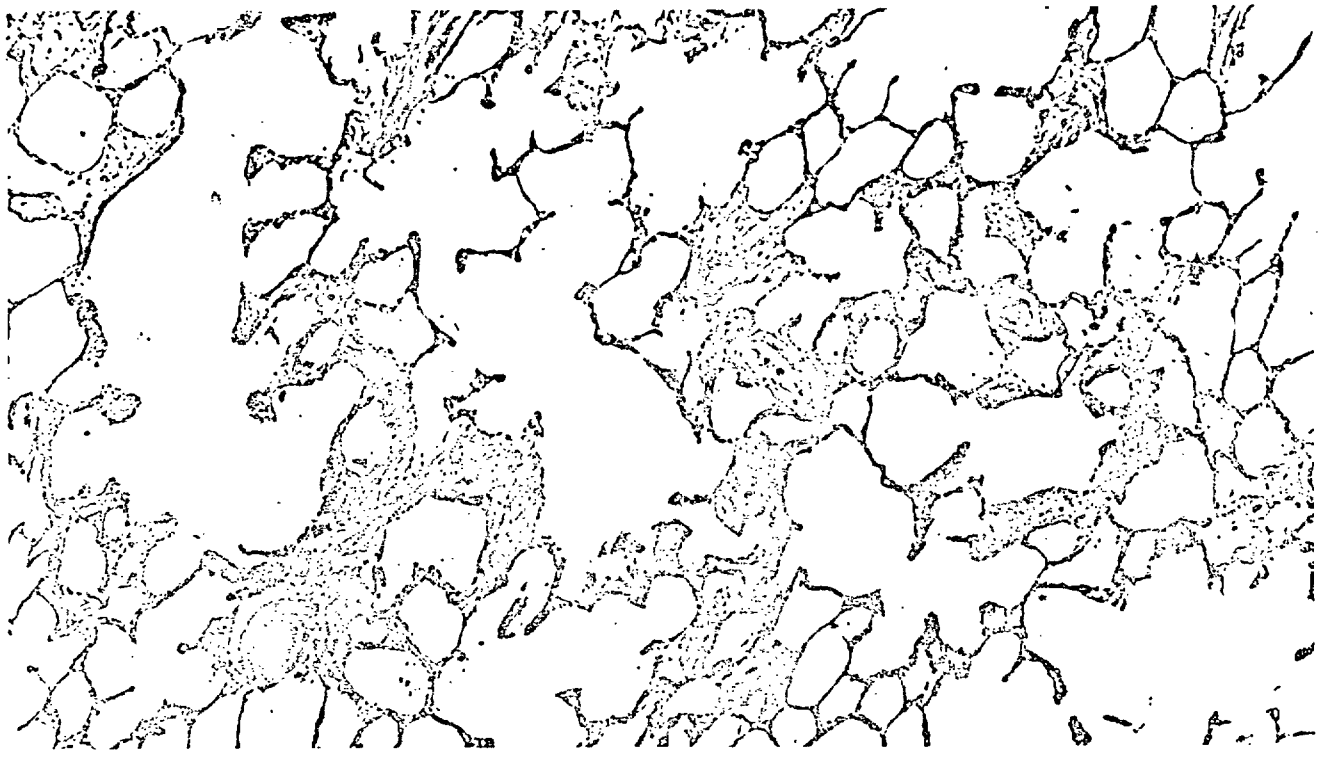


Fig 22.—Lung tissue from 48-year-old man who worked for 26 years in manufacture of chrysotile-coated textile products. This is grade 3 lesion. There is peribronchial and diffuse interstitial fibrosis (hematoxylin-eosin).

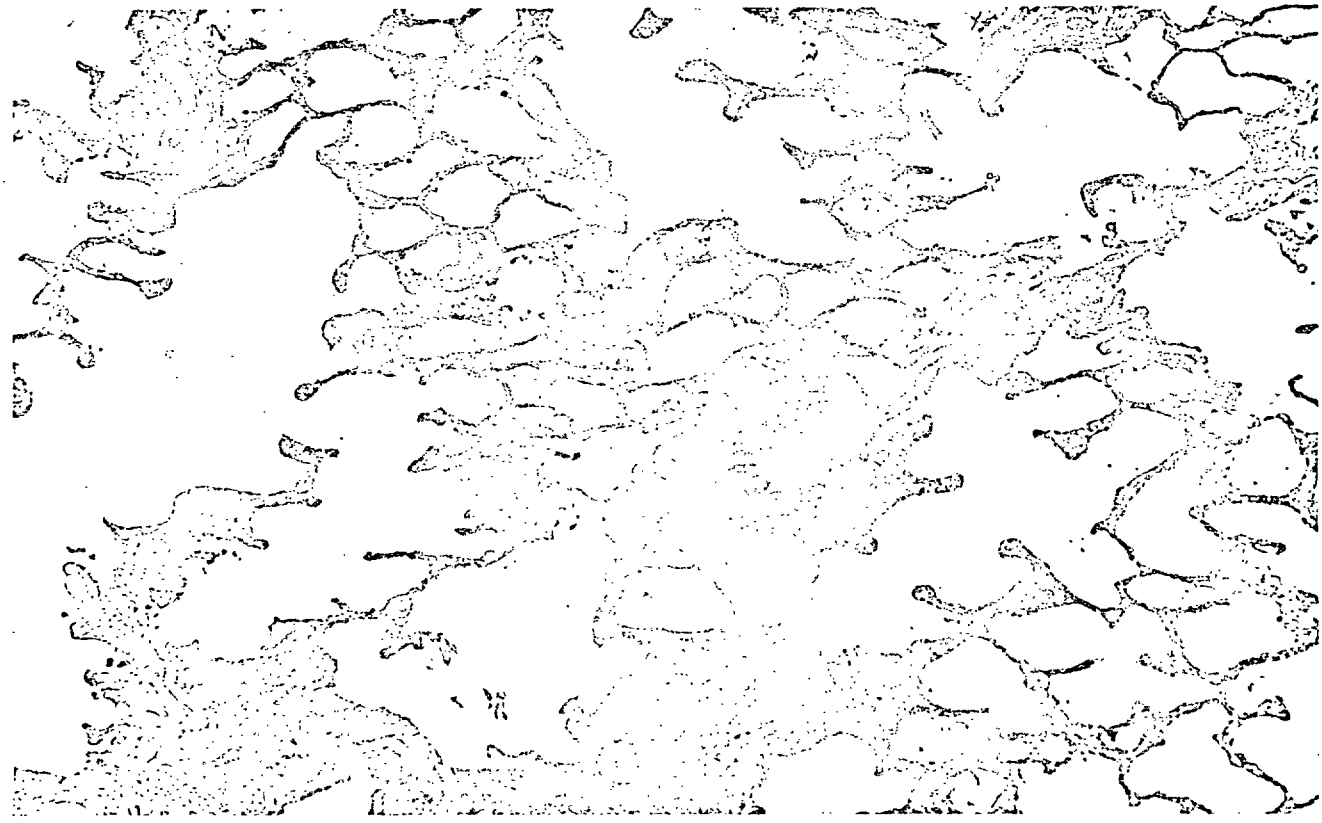
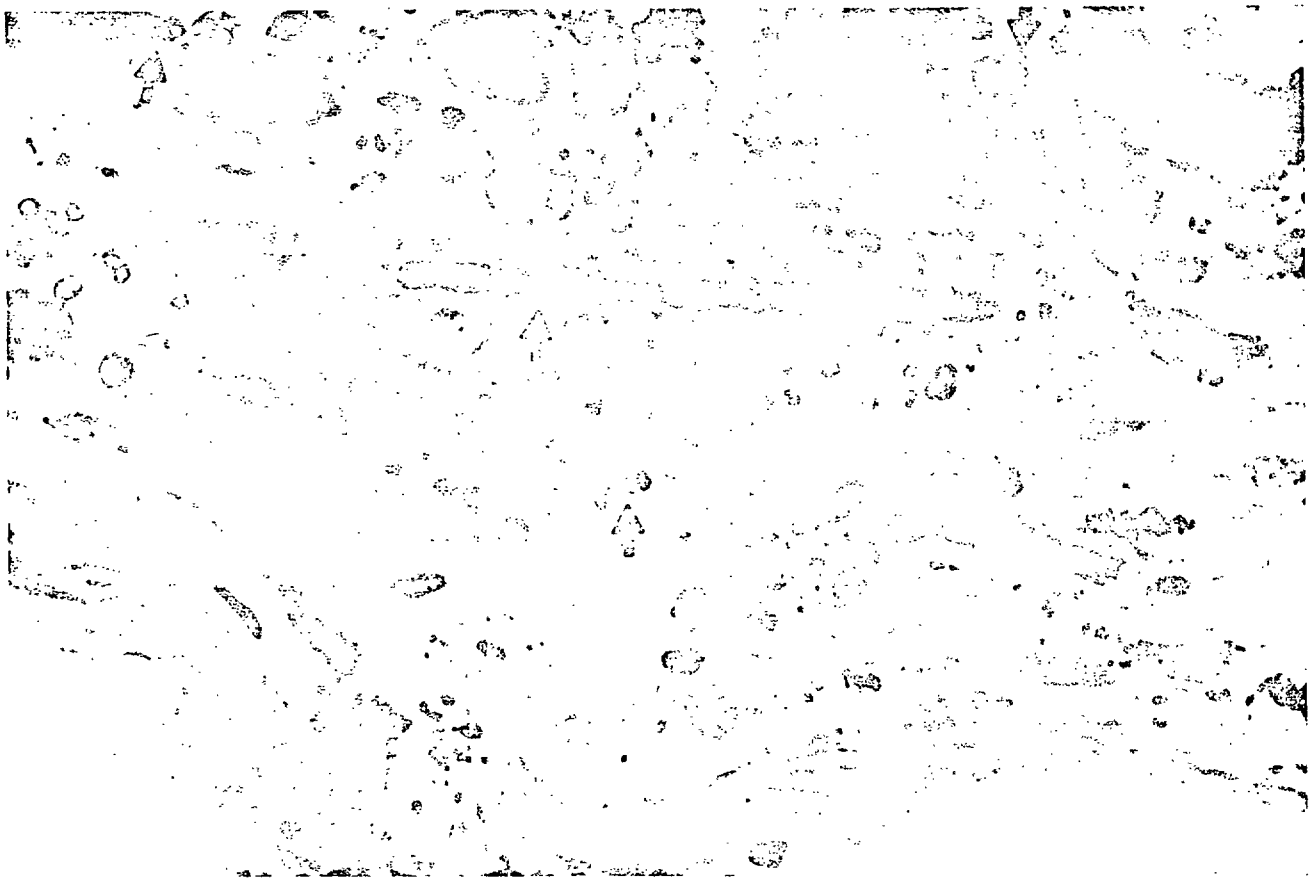


Fig 23.—Upper left and right, Grades 2 to 3 lesions. Fibrosis is centered around respiratory bronchioles and involves adjacent respiratory units (hematoxylin-eosin [HE]). Lower left and lower right, Asbestos bodies (arrows) in boxed areas of upper left and upper right illustrations, respectively (HE).



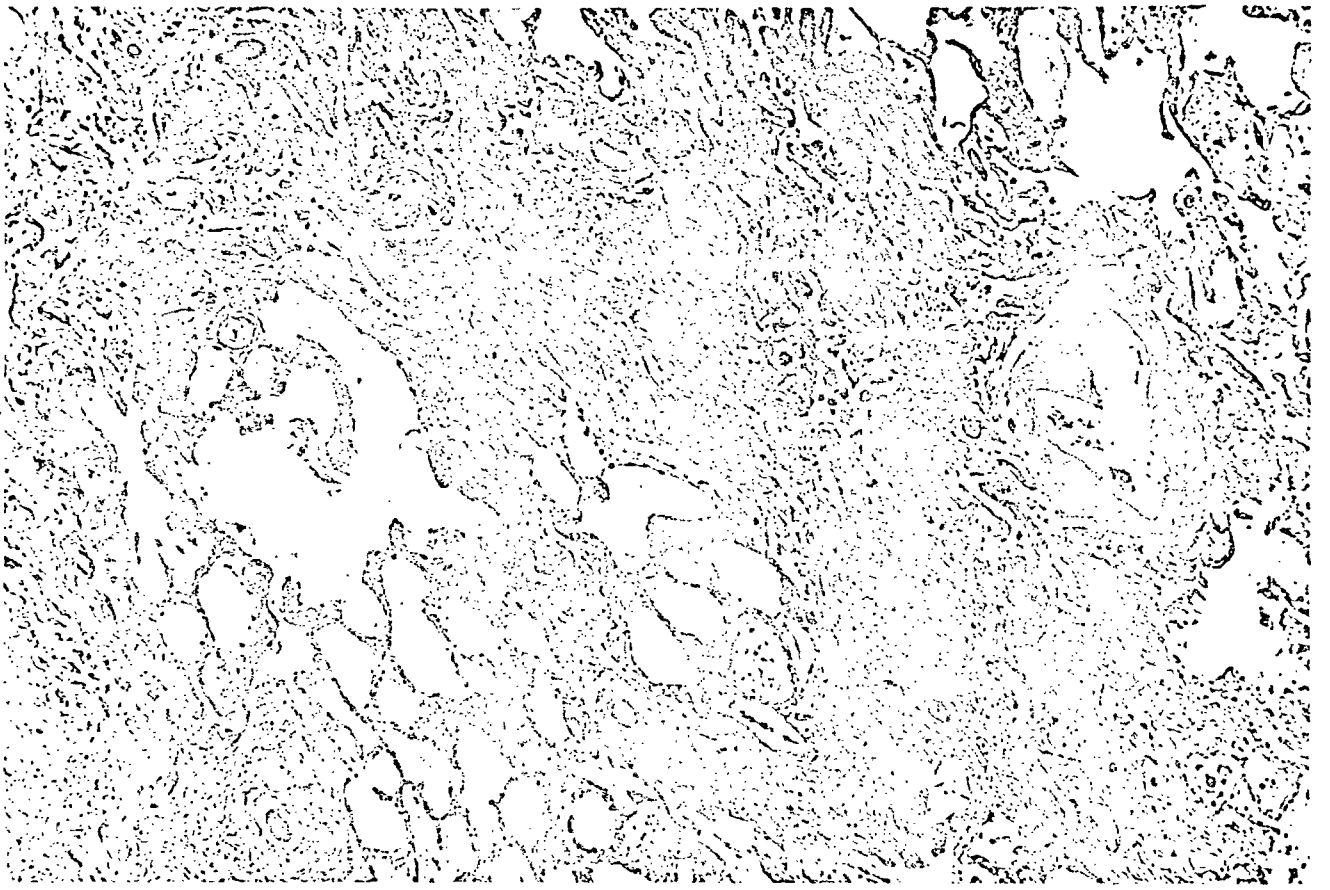


Fig 24.—Lung tissue of 48-year-old man who worked 26 years in manufacture of chrysotile-coated textiles. Lesion is grade 3, but elsewhere grade 4 lesions were found (hematoxylin-eosin).

exhibit changes. Often the septa adjacent to the respiratory bronchioles are affected so that the fibrosis appears to radiate out from the immediate vicinity of the affected subunit. This process involves variable numbers of acini (Figs 19 through 21).

With further progression of the process, increasing amounts of adjacent lung tissue are affected, seemingly in a centrifugal fashion (Figs 22 through 24). In later stages, the parenchyma is diffusely involved, although the overall structural continuity of the lung is preserved (Fig 24). As the scarring process progresses, the parenchyma is obliterated by fibrous tissues, and fibrous-walled cysts form, particularly in the subpleural and paraseptal regions of the lower lobes (Fig 25). At this stage in the evolution of the disease, peribronchial and perivascular fibrosis also is seen. Asbestos bodies often are observed in and around the lymphatic vessels adjacent to these structures.

Asbestos bodies usually are obvious in the advanced stages of the disease (Fig 26). However, this is not invariably the case, because fibers are cleared from the lungs and undergo dissolution and fragmentation with time. Thus, paradoxically, in some cases it may be difficult to demonstrate asbestos bodies. In our experience, this is a rare occurrence. In the absence of asbestos bodies, there is no satisfactory means to establish the diagnosis in histologic material. Although the demonstration of asbestos fibers by the electron microscopic study of tissue digestates (appendix 1) provides evidence of exposure, ultrastructural technique cannot be used to establish definitively the etiologic role of asbestos in disease.

Multinucleate giant cells are a variable feature of the lesion; in some cases they are prominent, whereas in others they rarely are seen (Figs 4 and 27). Infiltrates of lymphocytes and plasma cells are found in scattered sites in the lungs of some patients. The importance of this inflammatory process is uncertain, although it could be related to the immunologic reactions that have been described in some patients with asbestosis. Interstitial cellular infiltrates usually are not prominent in asbestosis.

The finding of macrophage accumulations in air spaces is of no diagnostic usefulness because this feature is commonly associated with the smoking of cigarettes and other forms of pulmonary injury. However, in occasional cases of asbestosis, prominent numbers of macrophages in the air spaces and the histologic picture suggest the pattern of desquamative interstitial pneumonitis (Fig 28).

Cytoplasmic hyaline bodies have

been described in the reactive cuboidal cells that line the air spaces of the lungs in asbestosis.[31] Although this cellular lesion often is seen in asbestosis, it is not specific because similar changes occasionally are found in idiopathic fibrosis and other types of pulmonary disease[32] (Fig 29).

No systematic studies of the tracheobronchial tree and the pulmonary vasculature have been reported in documented cases of asbestosis. There seems to be no specific lesion attributable to asbestos in the airways proximal to the terminal bronchioles. Sclerotic pulmonary vascular changes are evident in advanced cases of the disease. Although this may be secondary to the parenchymal lesion and the related hypoxemia, there is insufficient information available to establish the pathogenesis of the lesion.

Asbestos workers often are exposed to respirable mineral dusts of a nonfibrous type. The pathologist should be alert to the possibility of exposure to a mixture of dusts, even in lungs that exhibit large numbers of asbestos bodies. Modern analytic techniques now make it possible to document the presence of such minerals as silica, talc, feldspar, and other aluminum silicates in lung tissue (Figs 30 and 31).

Assay Techniques.—The demonstration of asbestos bodies in lung tissue with typical fibrotic lesions is required to establish the diagnosis pathologically. In our experience, these structures are not distributed uniformly in the tissue, even in advanced forms of the disease. Thus, multiple histologic sections must be studied. As previously noted, most of the asbestos fibers in the lung tissue are not coated and are usually relatively small (ie, < 5 μm long). Uncoated short fibers of chrysotile cannot be visualized by bright-field, phase, or polarization light microscopy, and do not stain by the Prussian blue technique. Amphibole fibers are more easily identified in tissue by light microscopic techniques.

Methods have been developed for the semiquantitative assessment of asbestos bodies and fibers in digestates and incinerated samples of lung tissue. These are research techniques, subject to considerable variation in inexperienced hands, and their value for the pathologist who is occasionally responsible for the autopsy of a subject with asbestosis is doubtful (appendix 1).

Despite variations introduced by the techniques in use, the burden of pulmonary fibers in members of the general population is many times less than in asbestos workers. The data for persons with modest exposure often are less definitive. The demonstration and measurement of asbestos fibers in lung tissue by these approaches are not a substitute for careful histologic study and the demonstration of asbestos bodies in association with the typical lesions of the disease.

METHODS FOR PATHOLOGIC STUDY

Postmortem Studies

A complete examination of the respiratory tract, including the larynx and thoracic cavity, is critical to the thorough evaluation of the suspected case of asbestosis. When pleural lesions, eg, adhesions and plaques, are widespread or a mesothelioma is present, the thoracic contents should be removed en bloc. Often this is a difficult and time-consuming task, but it will yield detailed information with regard to the severity and distribution of the disease.

Because pleural plaques often are found in the absence of significant pulmonary disease and a documented history of exposure to asbestos, examination of the parietal pleura is a mandatory routine procedure in good autopsy practice. Plaques often are overlooked and their importance as an indicator of exposure to asbestos is not universally appreciated. Unless other considerations dictate, one lung should be inflated through the major airway with buffered formalin; ideally, the perfusion pressure should be regulated to 25 cm H_2O. Apparatuses have been fabricated for permanent installation in the morgue, or for rapid assembly for temporary use. After fixation for at least 24 hours at a sustained pressure, the lungs should be sliced for gross assessment and blocks of tissue prepared for microscopic study. We believe that the lungs can be evaluated adequately if tissue blocks are obtained from the apices of each lobe and, in addition, the diaphragmatic portions of the lower lobes. Samples also should be prepared to include (1) the visceral pleura and subpleural tissue, (2) deep parenchyma, and (3) portions of major bronchi, with adjacent parenchyma from each lobe. Examination of the lungs in this manner is necessary because the lesions of asbestosis are distributed irregularly and tend to be most severe beneath the pleura and in the lower lobes. The blocks should be appropriately labeled so that the distribution of lesions can be assessed subsequently. Obviously, additional blocks of tissue can be selected to evaluate other grossly evident lesions at the discretion of the pathologist.

The processing of tissue requires no special techniques. When asbestos bodies are common in lung tissue, they can be detected readily using 5- to 6-μm-thick sections stained with hematoxylin-eosin. The standard iron stain helps identify these structures. Without this stain, one may overlook many asbestos bodies, even when using high magnification to screen the tissue.

The use of thick sections (eg, $\approx$30 μm) has been recommended by several workers to help demonstrate asbestos bodies. Although this technique increases the mass of lung tissue examined, it introduces artifacts and complicates the detailed evaluation of the lung tissue. Thick-section examination is an ancillary technique that can be used when asbestos bodies are not identified in tissue sections of standard thickness.

Lung Biopsy

The radiologic demonstration of diffuse fibrotic pleural and parenchymal disease in a person with documented occupational exposure to asbestos customarily is considered ample to establish the diagnosis of asbestosis. Lung biopsy rarely is justified in such patients unless the evidence suggests other complicating, treatable conditions. Accordingly, biopsy of the lung should be carried out when the nature of the pulmonary lesion is obscure.

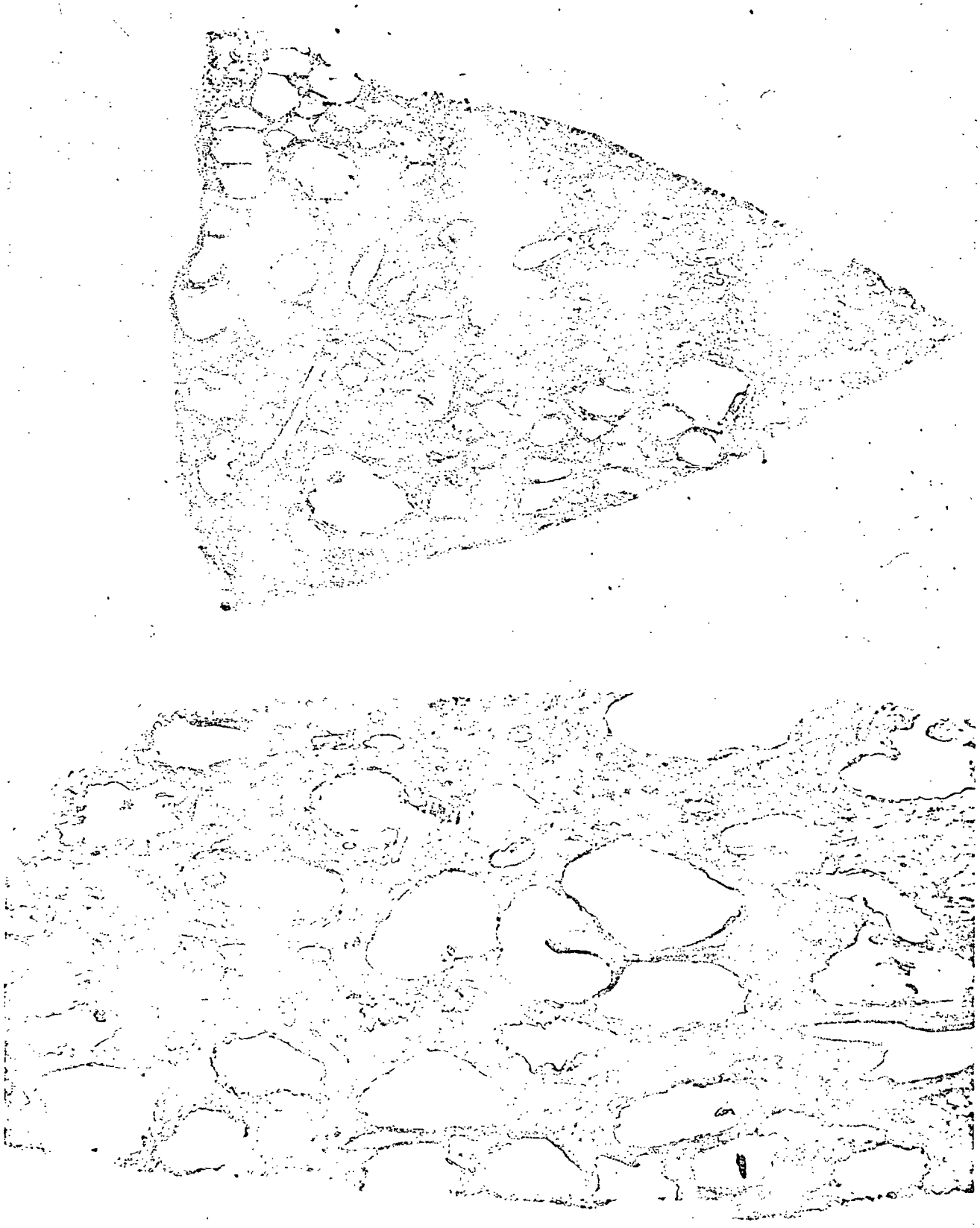
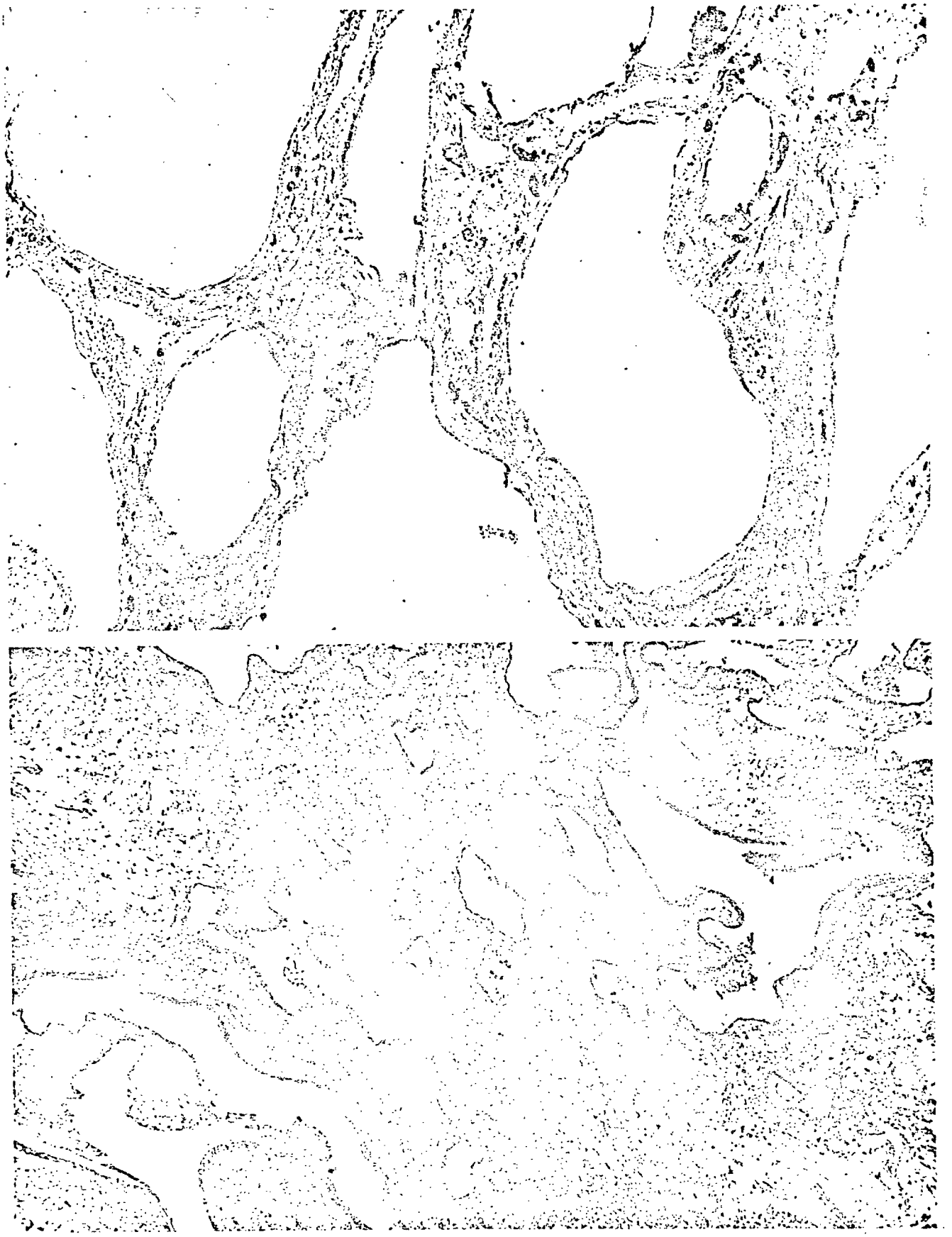


Fig 25.—Grade 4 lesions. There is diffuse fibrosis and honeycomb formation. Lining of cyst spaces by bronchiolar epithelium is variable feature (hematoxylin-eosin).



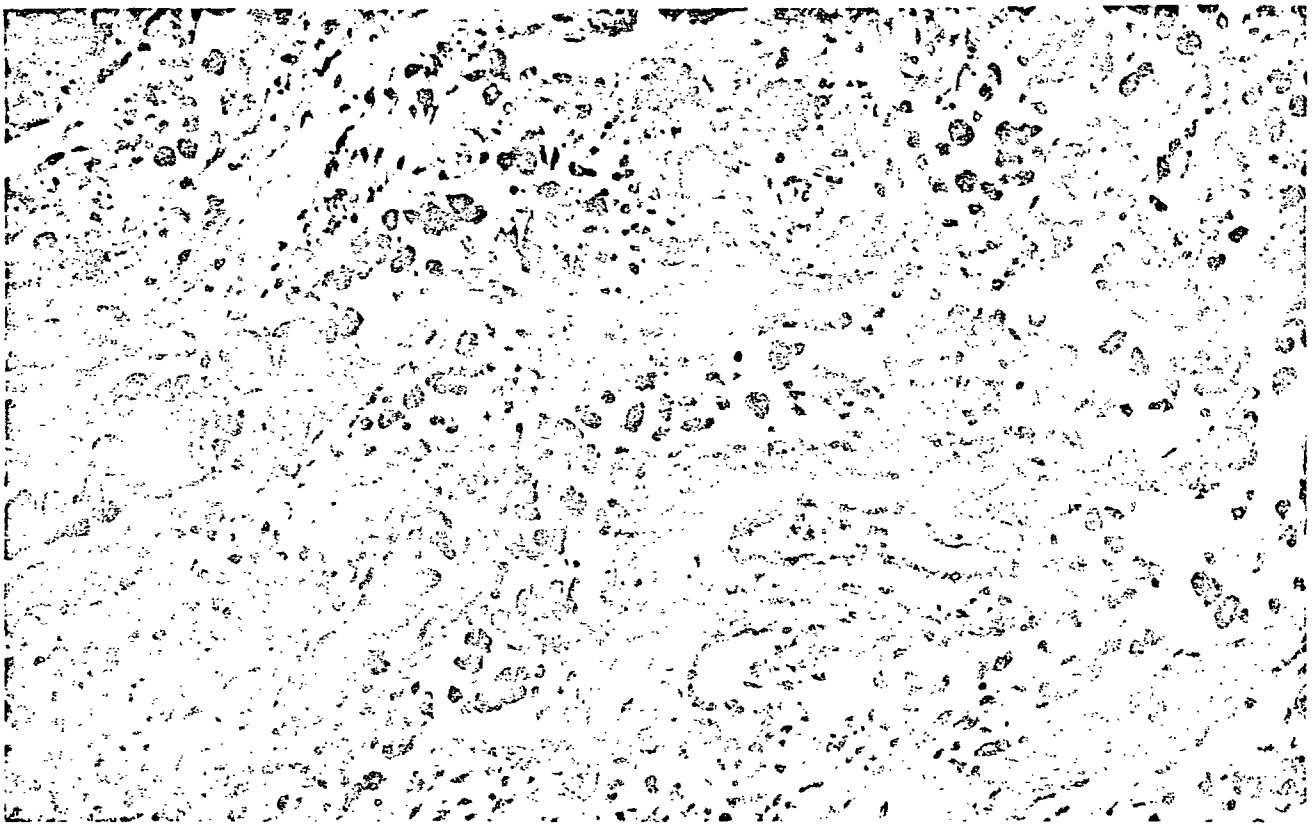
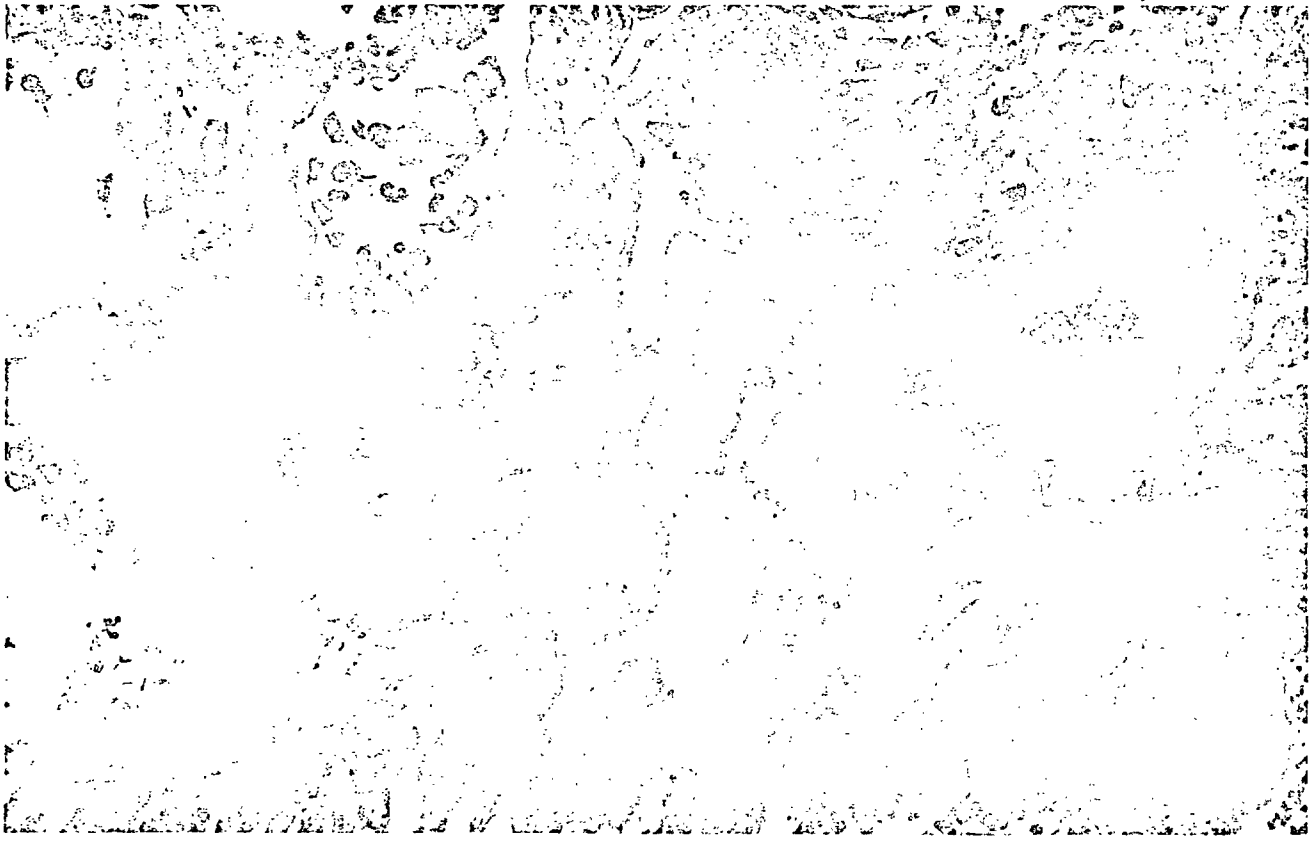


Fig 26.—Grade 3 asbestosis. Occasionally only "heads" of asbestos bodies are evident in histologic material. They are seen as golden spheres (arrowheads) that approximate pulmonary macrophages in size (hematoxylin-eosin).



As noted, the lesions of asbestosis often have a spotty distribution when the disease is of either mild or moderate severity. Adequate sampling of the lung parenchyma is critical and open lung biopsy is strongly recommended. Transthoracic needle aspiration and transbronchial biopsy usually do *not* yield sufficient tissue to permit a diagnosis in these cases. Samples of tissue collected by these techniques cannot be used to exclude the diagnosis of asbestosis.

A biopsy procedure that yields inflated, well-fixed tissue has been described.[33] Areas of relatively normal-appearing and fibrotic lung tissue are identified and sampled to examine tissue at various stages in the evolution of the disease. Severely fibrotic tissue may show honeycombing and is of limited use for pathologic interpretation because this lesion is not specific. The tips of the lingula and middle lobe are to be avoided because they often are scarred nonspecifically. A wedge biopsy specimen should be preserved in an inflated state at the time of surgery. The lung is maintained in distention by the anesthesiologist while a wedge is isolated with two sets of clamps. The surgeon cuts between the clamps and the wedge of tissue is given to the pathologist, who fixes it with the clamps in place to prevent collapse. A technique for either vascular or bronchial perfusion of biopsy specimens has been described.[34] Often, it is useful when the specimen is collapsed.

Sputum and Lavage Examination

Asbestos bodies usually are demonstrable in sputum specimens from persons chronically exposed to the mineral dust and can be present when changes in the chest roentgenogram are not evident.[35,36] The bodies are found in the mucin and in close association with clusters of alveolar macrophages (Fig 32). The presence of asbestos bodies in the sputum cannot be used as a diagnostic criterion of asbestosis. On the other hand, most asbestos workers with restrictive pulmonary function and radiologic lesions yield sputum with asbestos bodies. Asbestos bodies in sputum strongly suggest past exposure to asbestos and reflect the presence of a significant asbestos burden in the lungs.

Systematic studies of persons exposed to asbestos using the technique of bronchopulmonary lavage have not yet been reported. This approach undoubtedly would provide large numbers of pulmonary macrophages for examination, and thus might prove to be a sensitive indicator of exposure.

CLINICAL FEATURES OF ASBESTOSIS

Asbestosis is clinically indistinguishable from other forms of diffuse pulmonary fibrosis. The clinical picture ranges from dyspnea associated with exertion to respiratory failure accompanied by cardiac decompensation. In addition to exertional dyspnea, symptoms of early disease include a nonproductive cough, fatigability, and a vague feeling of being "unwell." Obviously, these features are not specific because cardiovascular and neuromuscular disorders produce similar symptom complexes. As the fibrotic process progresses, shortness of breath becomes apparent at lesser levels of physical activity and ultimately occurs at rest. Cough may be troublesome and difficult to control, although sputum production is unusual in the absence of coexisting chronic bronchitis.

There are no specific symptoms and signs of early asbestosis, but end-inspiratory crackles (rales) occasionally are prominent at the lung bases. Crackles are found in a variety of conditions associated with relative underinflation of lung because they result from the rapid opening of peripheral lung units. They are not unique, nor are they more prevalent in asbestosis than in other conditions in which similar pathologic factors exist. Thus, the clinician should be cautious in attributing specificity to these sounds or even considering them a sensitive means for detecting early asbestosis. As the disease progresses, lung volume reduction leads to a pattern of rapid, shallow breathing. Hypoxemia develops when significant ventilation-perfusion discrepancies develop and gas exchange fails. Occasionally it is clinically manifested as cyanosis, initially on exercise, and in the later stages at rest. As with other forms of advanced respiratory diseases, clubbing of the digits can be present, but it is neither specific nor common in asbestosis.

Effusions of serous fluid occasionally occur in persons with pleural and parenchymal disease due to asbestos. The prevalence seems to be dosage related. Usually, the fluid accumulations are relatively small and often they are asymptomatic (Fig 7).

PHYSIOLOGIC FEATURES OF ASBESTOSIS (PULMONARY FUNCTION)

In considering the physiologic consequences of exposure to asbestos dust, one must distinguish between alterations encountered early in the course of the respiratory disease (such as might be found in a working population) and the impaired lung function associated with well-established, advanced asbestosis (which is accompanied by the characteristic clinical and roentgenographic findings). In the former case, spirometrically determined lung volumes and expiratory flow rates are affected adversely in a dose-related manner, at least in the experience of some investigators. This effect can precede roentgenographic evidence of the disease. Similarly, total lung capacity and exercise ventilation become abnormal in relation to the level of exposure to dust. Thus, vital capacity and forced expiratory volumes and flows reflect cumulative exposure. In some cases, diffusing capacities are a sensitive measure of parenchymal disease. That maximum expiratory flow limitation occurs in the early stages of asbestosis is not surprising in view of the pathologic demonstration of bronchiolar lesions in the initial stages of the disease. However, it should not be assumed that clinically significant functional impairment necessarily accompanies early morphologic lesions. Determinations of pulmonary diffusing capacity can be used to separate persons with well-established asbestosis from those who do not have roentgenographically detectable alterations. Although the diffusing capacity is abnormal in advanced disease, it is not a particularly sensitive means for

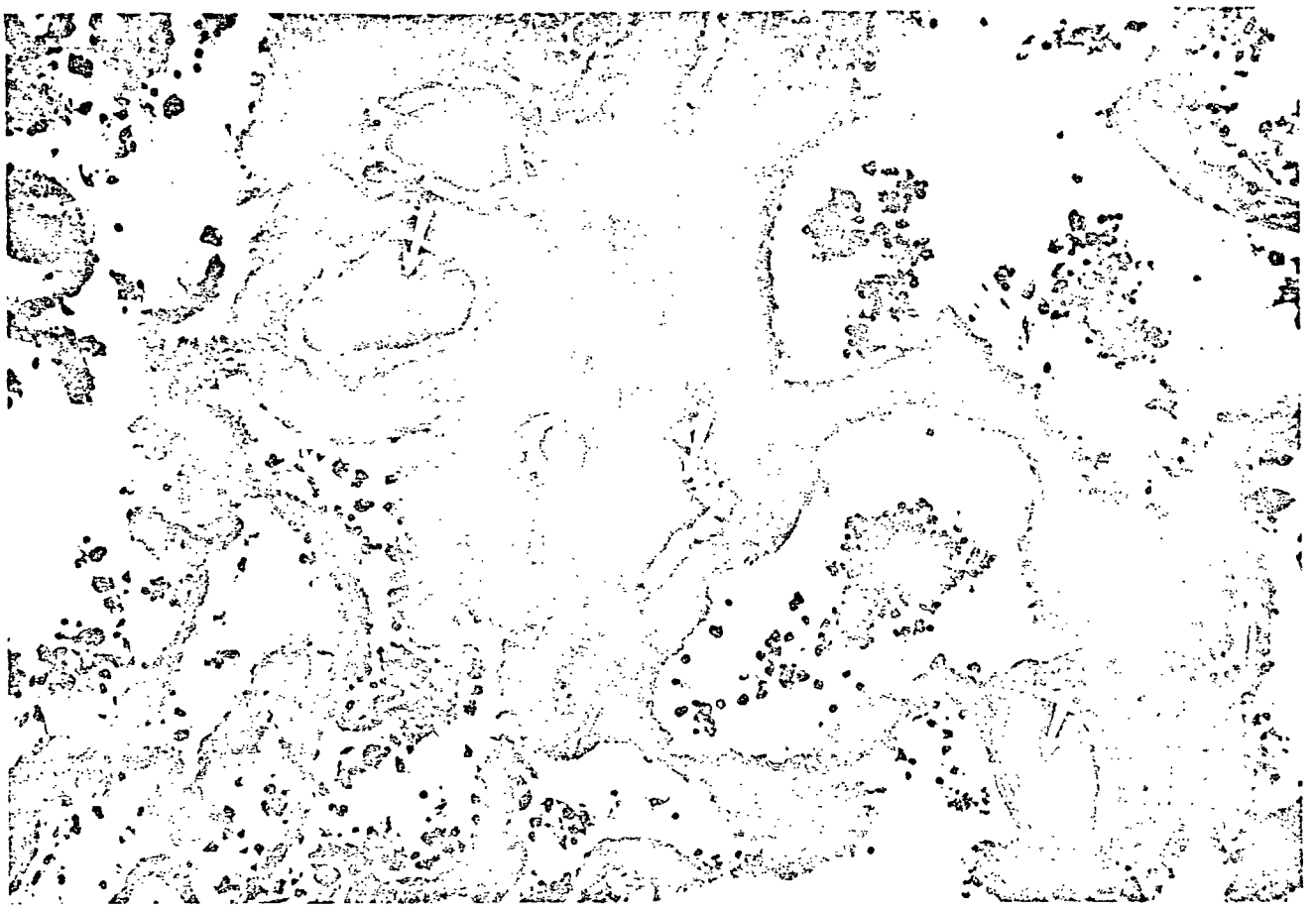
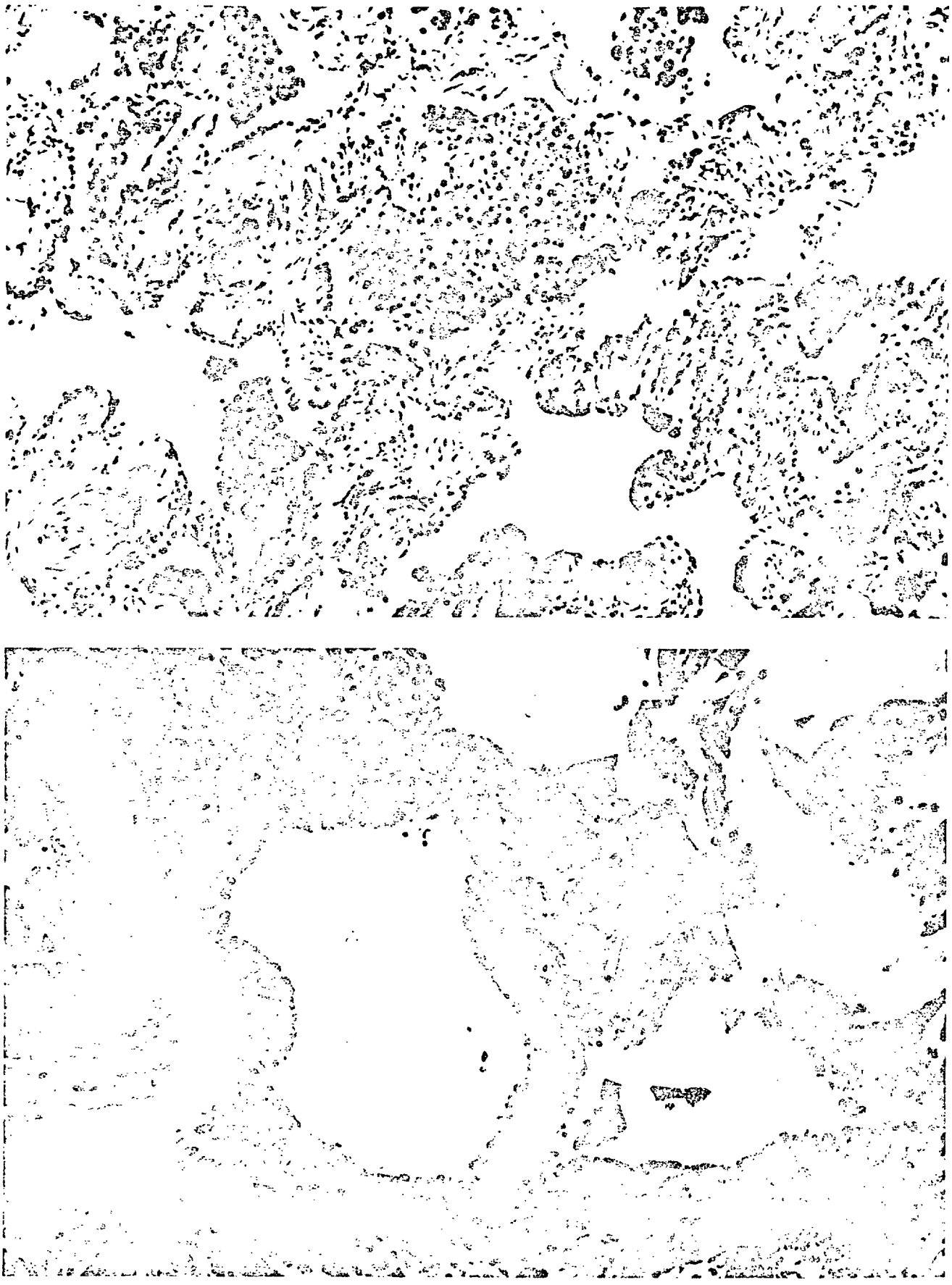


Fig 27.—Grade 3 asbestosis exhibiting prominent numbers of multinucleate cells, many of which contain asbestos fibers and bodies (arrows). Evidence of phagocytosed fibers is variable feature. Multinucleate cells are particularly prominent in case material from Finland, where anthophyllite exposure occurs (hematoxylin-eosin).



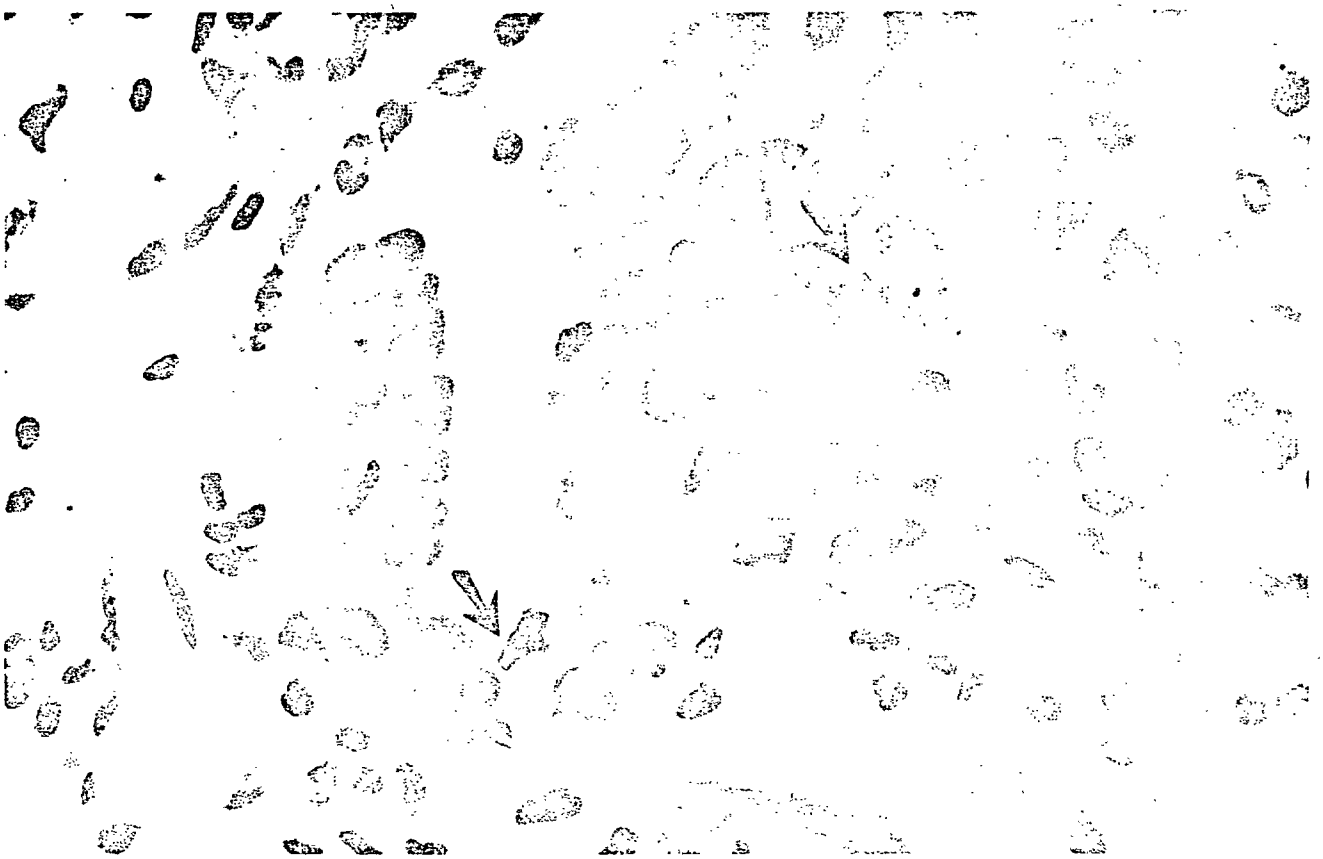
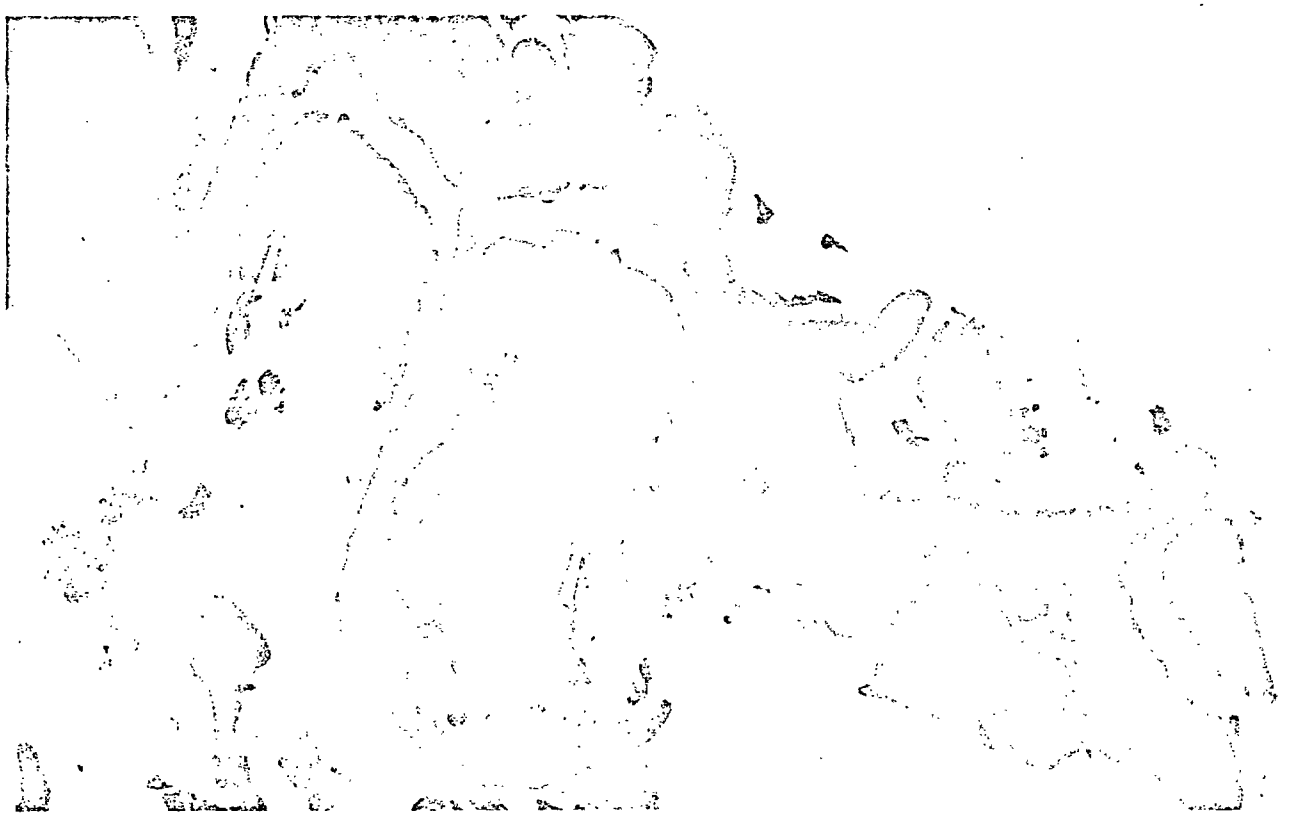
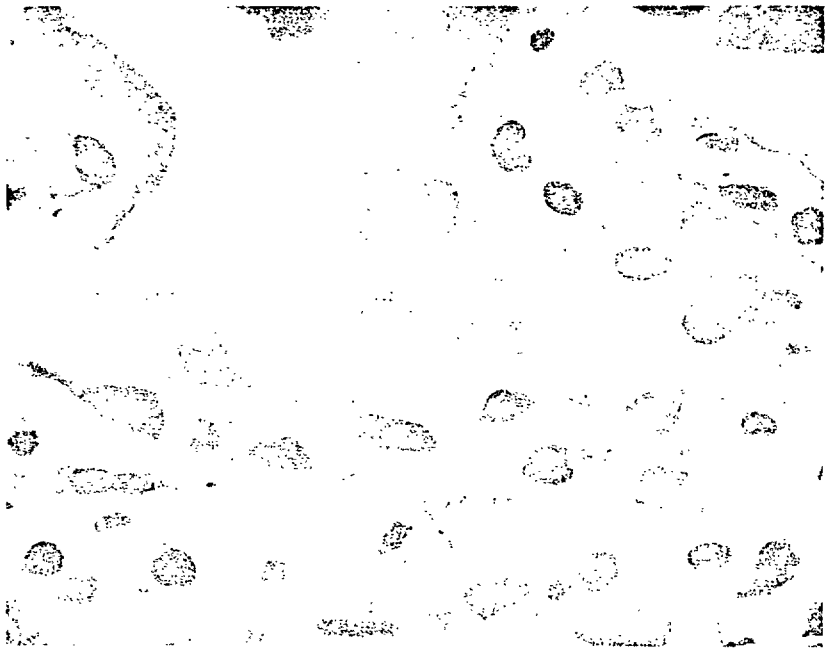
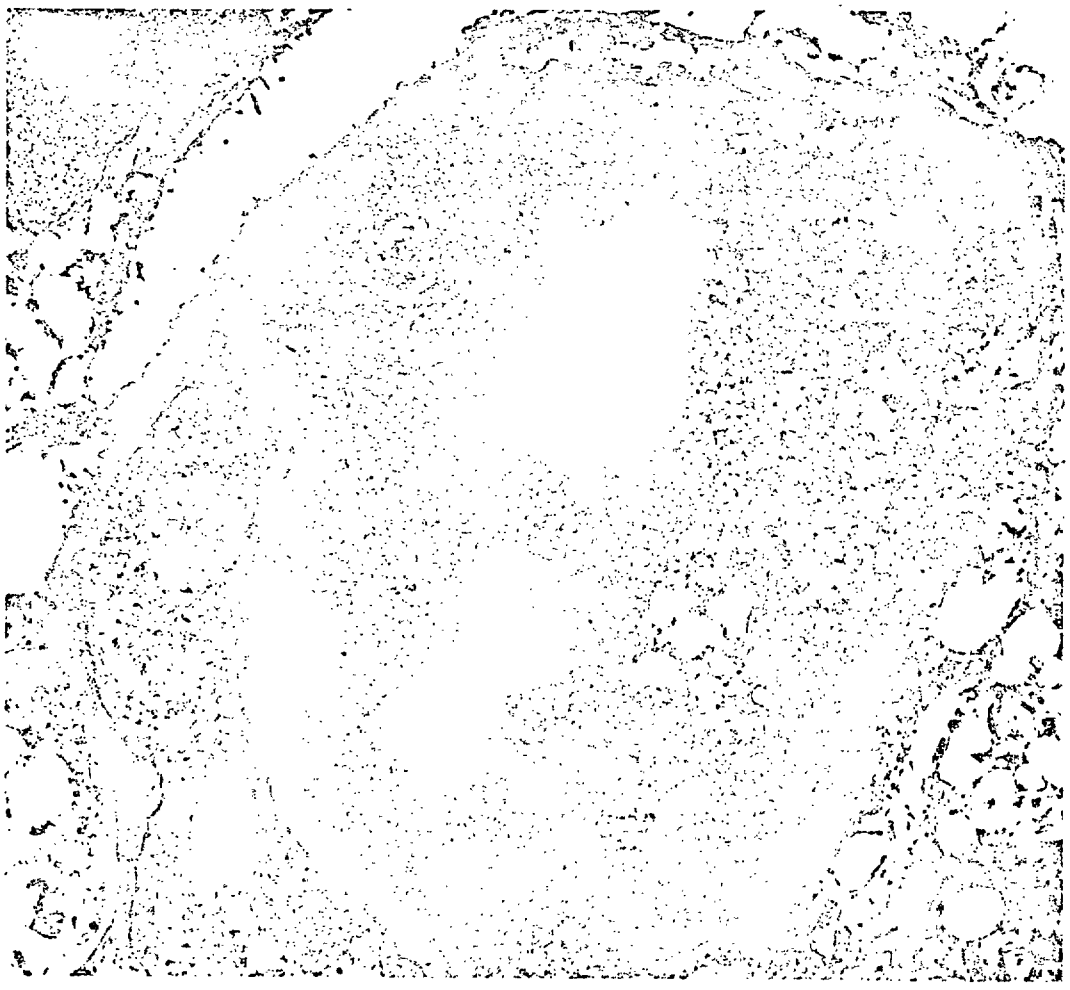


Fig 28.—Prominent accumulations of macrophages in air spaces of lungs of patient exhibiting grade 3 fibrosis. This nonspecific cellular response occasionally resembles tissue reaction observed in desquamative interstitial pneumonitis. Arrows indicate subtle asbestos bodies.







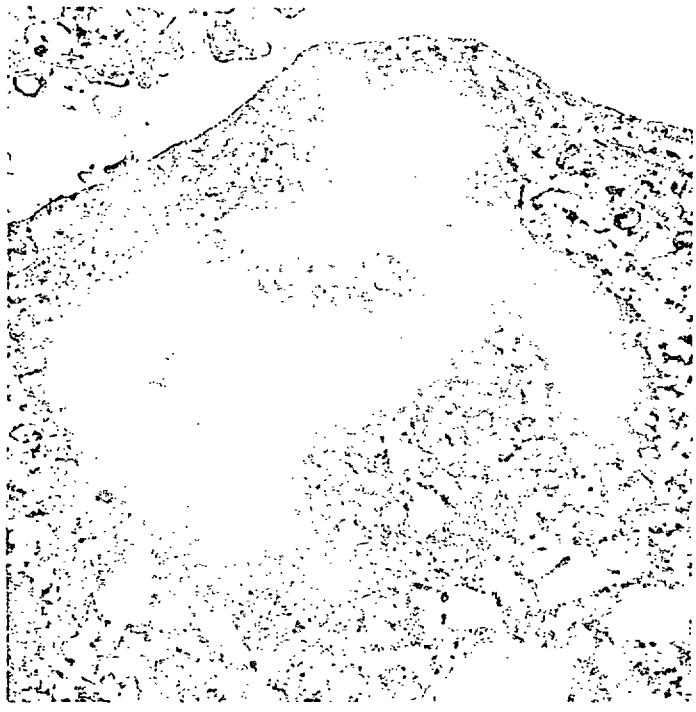
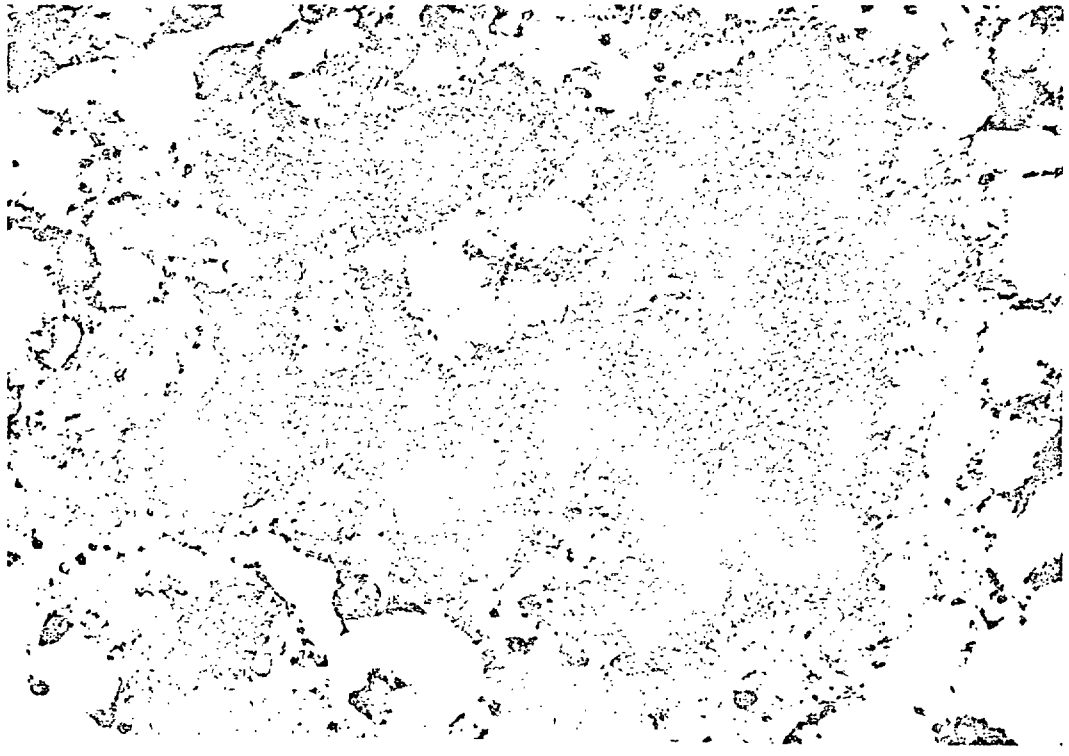


Fig 29.—Network of flocculent hyaline material in alveolar epithelial cell in lung of patient with asbestosis (upper left). This enlarged cell has large nucleus with prominent nucleolus (hematoxylin-eosin, original magnification ×1,250). Upper right and lower left, Electron micrographs demonstrate dense core of inclusion. Lower right, Meshwork of fibrils comprise it (uranyl acetate-lead citrate) (from Kuhn and Kuo[31]).



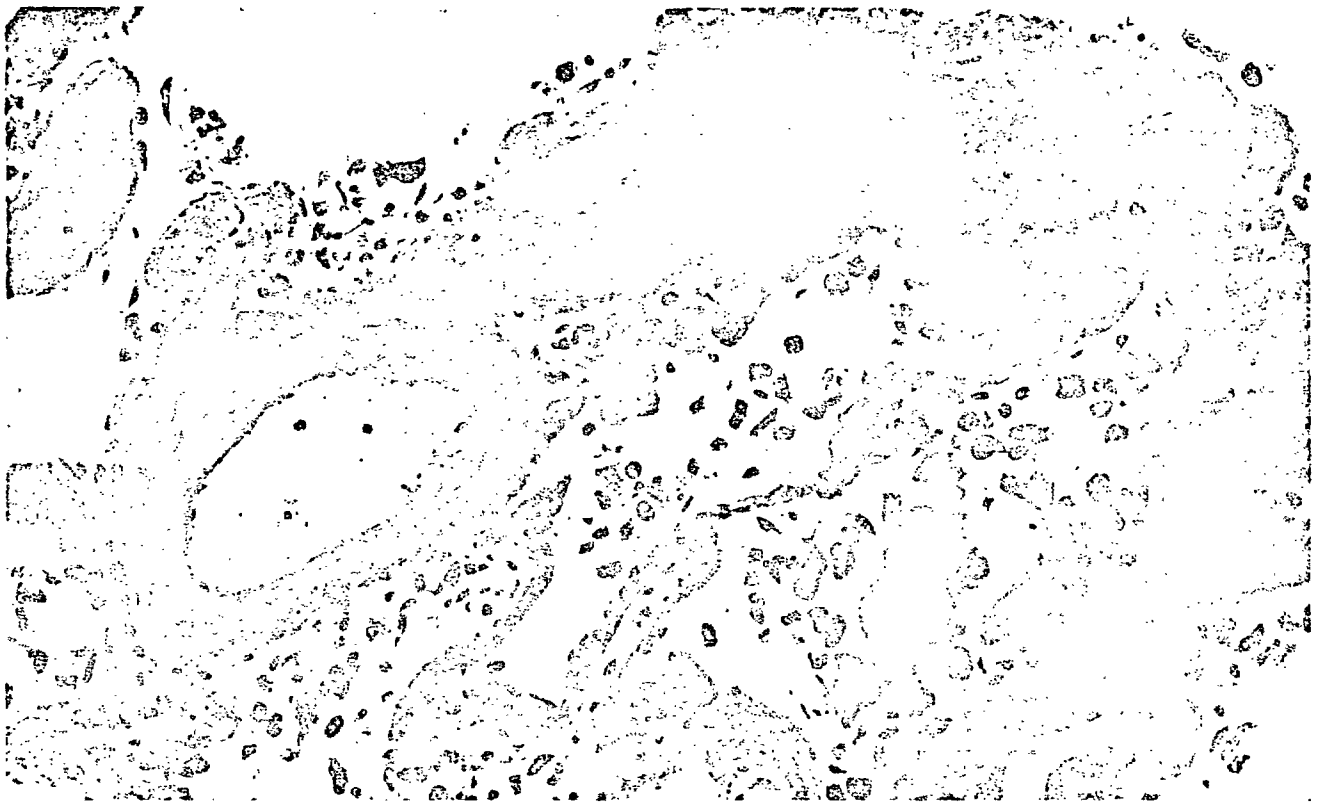
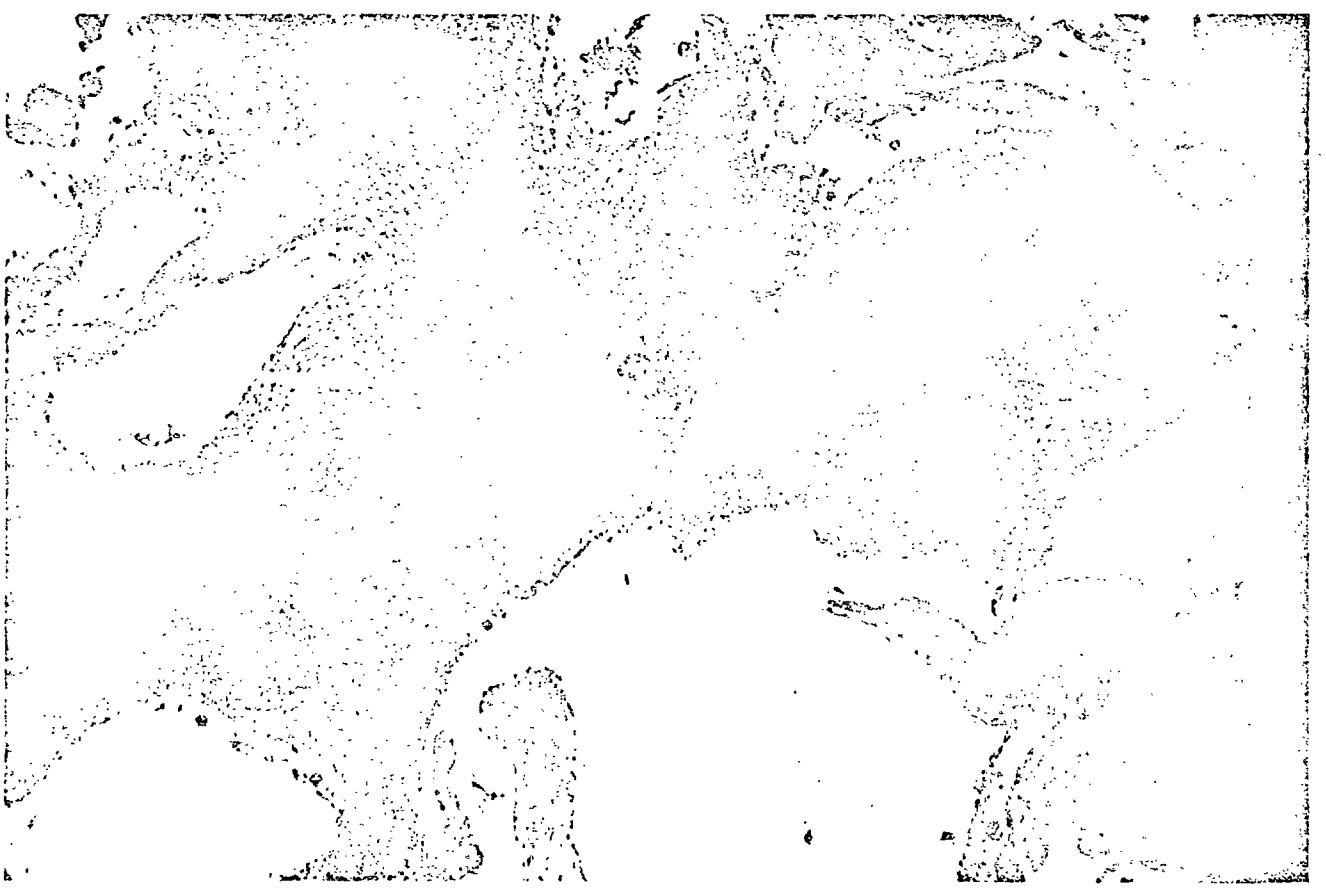


Fig 30.—Lung tissue of patient with advanced asbestosis and evidence of exposure to dusts other than asbestos. Analysis of similar dust maculae in this lung showed crystalline aluminum silicates and anthracotic pigment (hematoxylin-eosin).

Fig 31.—Confluent nodular lesion consistent with silicosis superimposed on lesions of asbestosis. Note deposits of anthracotic pigment and prominent accumulations of mononuclear cells in and around silicotic nodules (hematoxylin-eosin).



Not AMA

Fig 32.—Papanicolaou-stained sputum smears showing asbestos bodies associated with pulmonary macrophages. Arrow indicates uncoated portion of asbestos fiber (×450). These specimens were obtained from worker in amosite asbestos pipe insulation plant (from McLarty et al[36] and from Rogli et al[76]).

Not AMA

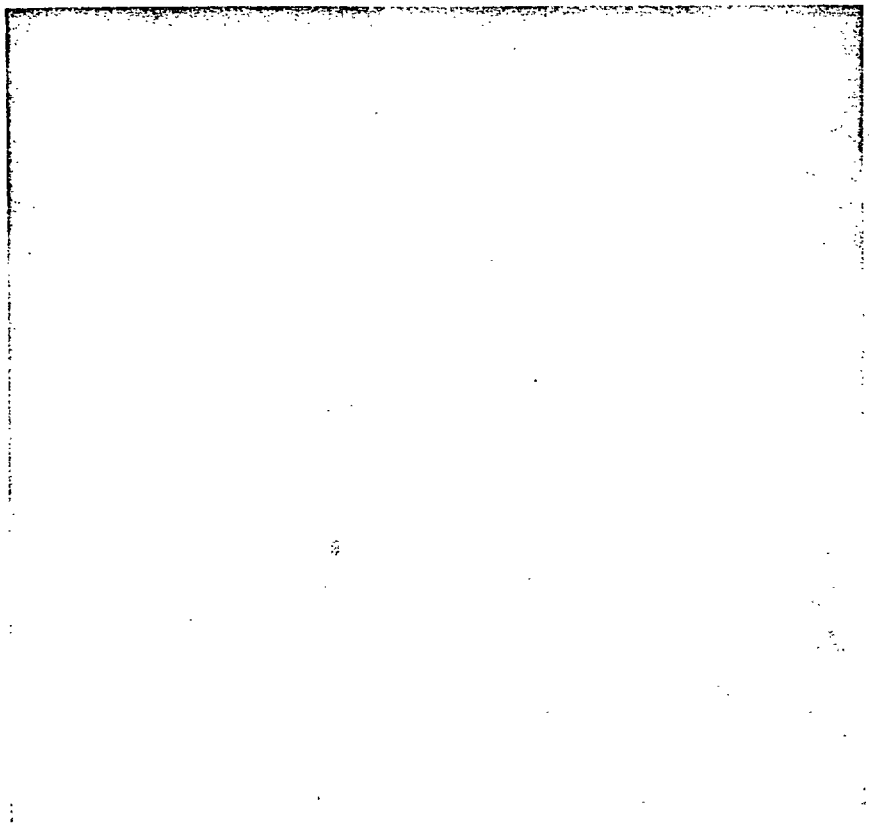


Fig 33.—Roentgenogram of 68-year-old man who worked for 35 years as insulator. He had no history of cigarette use. His overall health was considered good until about two years before death, when exertional dyspnea was noted. About five months before death, he was forced to retire because of severe respiratory distress. Radiologic examination disclosed evidence of asbestosis and right pleural effusion. Note linear streaks and small irregular opacities in lungs, and "shaggy" heart border. At autopsy, there was grade 3 asbestosis (from *Pathology Annual*, 1980;2:77-104).

demonstrating a dose relationship in a working population. However, in one study, abnormal diffusing capacity correlated with the severity of the histologic lesion demonstrated in the lung biopsy specimen.[37]

ROENTGENOGRAPHIC FEATURES OF ASBESTOSIS

The earliest roentgenographic evidence of pulmonary fibrosis due to asbestos inhalation appears in the lower lung zones. Typically, small, linear, and irregular opacities are located symmetrically at the lung bases. The densities usually have a "fine" character, but at times are somewhat coarse. The middle and upper lung zones become involved as the fibrotic process progresses. Subsequently, the densities increase in number and size. Eventually, these opacities may obliterate the definition of normal adjacent structures, resulting in the so-called shaggy heart and an indistinct diaphragm (Fig 33). Massive conglomerate and coalescent densities are uncommon, but the changes of the honeycomb lung are evident in late stages of the disease. Diffusely distributed small, rounded opacities generally are not expected as the result of exposure to "pure" asbestos, but are encountered when there also has been exposure to silica dust. Although roentgenographic features of asbestosis are nonspecific and can be seen in any form of diffuse pulmonary fibrosis, the presence of diaphragmatic plaques and pleural thickening associated with fibrosis in the lower lobes strongly suggests the diagnosis.

Often, but not invariably, asbestosis is a progressive disease, either with or without continued exposure. Using paired serial chest roentgenograms, evidence of progression was evaluated in workers in the asbestos-building products industry.[38] The appearance of the small, irregular opacities that are believed to indicate pulmonary fibrosis was related to cumulative exposure to dust. Progression of pleural thickening and plaques, however, was influenced by the duration of exposure and the elapsed time from initial exposure, but not to cumulative dosage.

MESOTHELIOMA

Malignant mesotheliomas of the pleura and peritoneum either are exceptionally rare or never occur in persons not exposed to asbestos. It is now apparent that asbestos plays an important role in the pathogenesis of these tumors. Although the relative risk is difficult to determine (as the prevalence in the general population is negligible), mesothelioma accounts for about 10% of all deaths in some occupational groups. In a recent study of insulation workers, 112 peritoneal and 63 pleural mesotheliomas were identified among 2,271 deaths, a prevalence of 8%.[39] By comparison, there were 486 deaths (21%) from lung cancer in the same group. Mesothelioma typically develops many years after the initial exposure; in most series, no increase in frequency is observed before 25 to 30 years have passed, and cases with a latency of more than 40 years have been reported.[40]

The protracted interval between exposure and the development of the tumor is important with regard to our expectations for the future occurrence of mesotheliomas. Because a substantial number of shipyard and industrial workers were exposed to asbestos during World War II, an increasing incidence can be expected during the remaining decades of this century.

A rigidly defined relationship to dosage has not been established for mesothelioma, although most cases are found among members of occupational groups that experienced heavy exposure. The neoplasm also occurs in persons with relatively limited exposure. The tumor is found in persons with asbestosis and pleural plaques, but many cases were associated with neither.

Malignant mesothelioma in its fully developed form is a diffuse tumor that

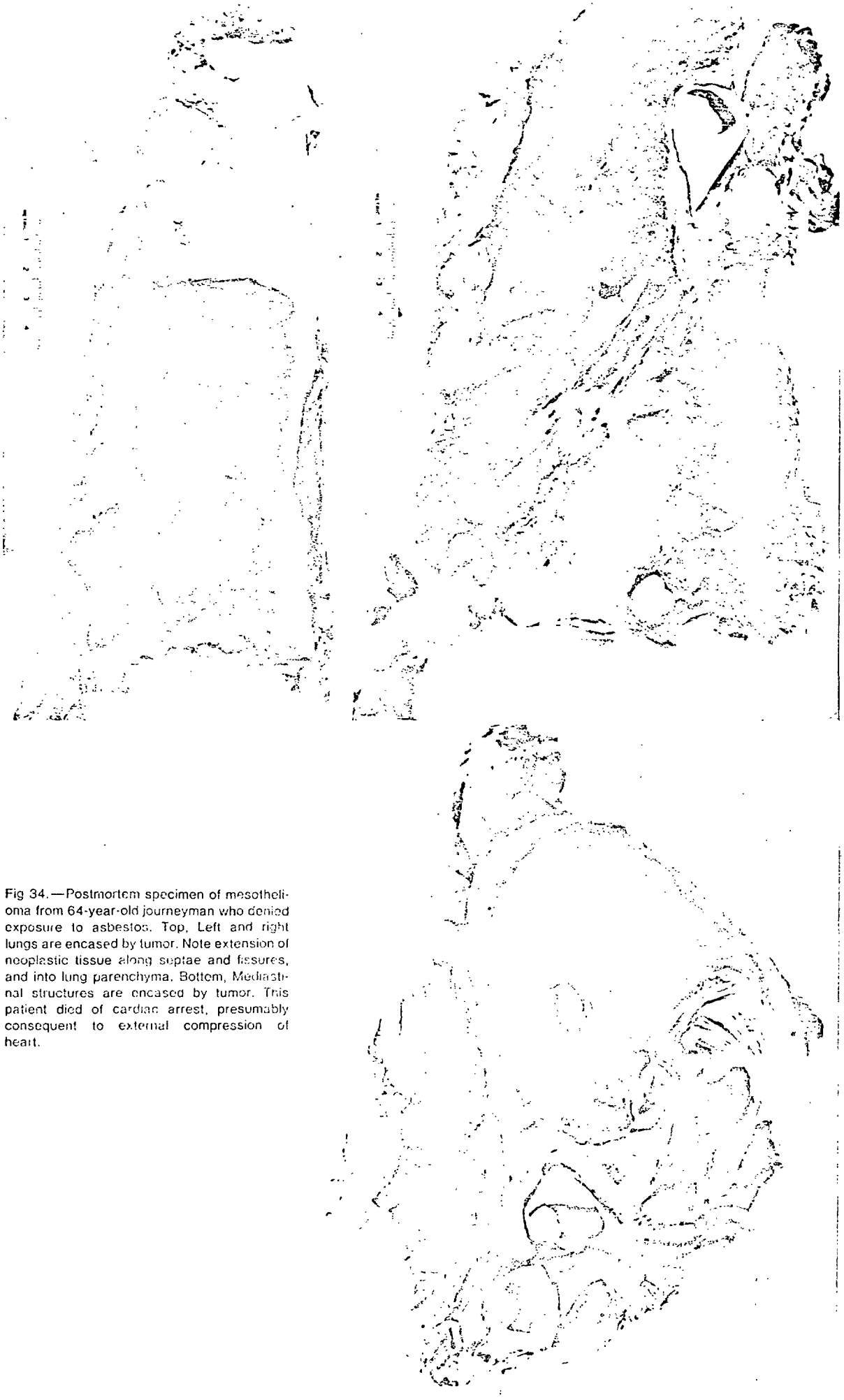


Fig 34.—Postmortem specimen of mesothelioma from 64-year-old journeyman who denied exposure to asbestos. Top, Left and right lungs are encased by tumor. Note extension of neoplastic tissue along septae and fissures, and into lung parenchyma. Bottom, Mediastinal structures are encased by tumor. This patient died of cardiac arrest, presumably consequent to external compression of heart.

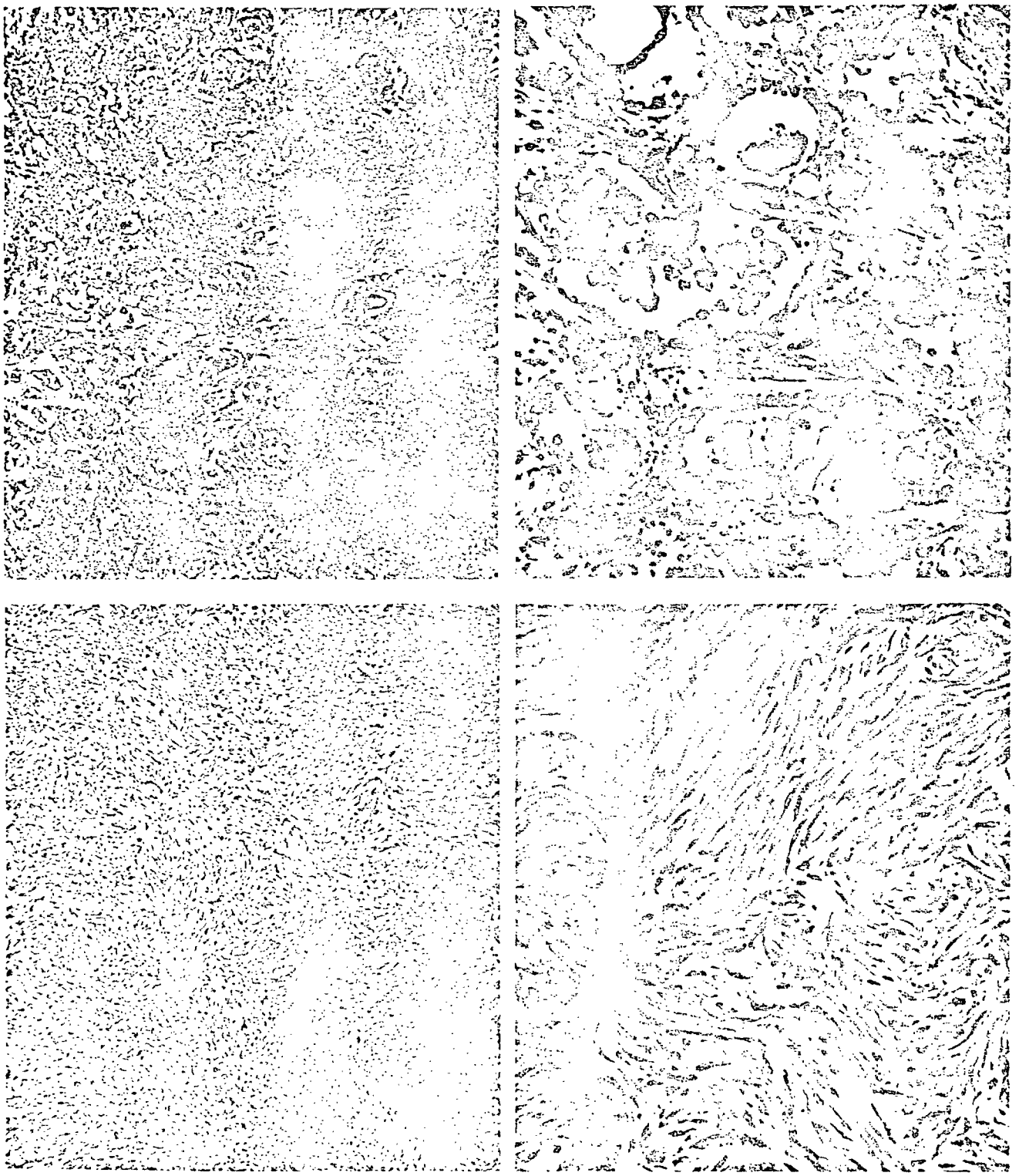


Fig 35.—Histologic features of mesotheliomas. Upper left, Typical epithelial mesothelioma of tubulopapillary type (hematoxylin-eosin [HE], ×50). Upper right, Tumor shown at upper left illustrating spaces lined by cuboidal cells, and formation of papillary structures within spaces (HE, ×500). Lower left, Typical sarcomatous mesothelioma (HE, ×50). Lower right, Tumor pattern shown at lower left illustrating spindled cells forming storiform pattern. This pattern of growth is common in sarcomatous mesotheliomas (HE, ×500).

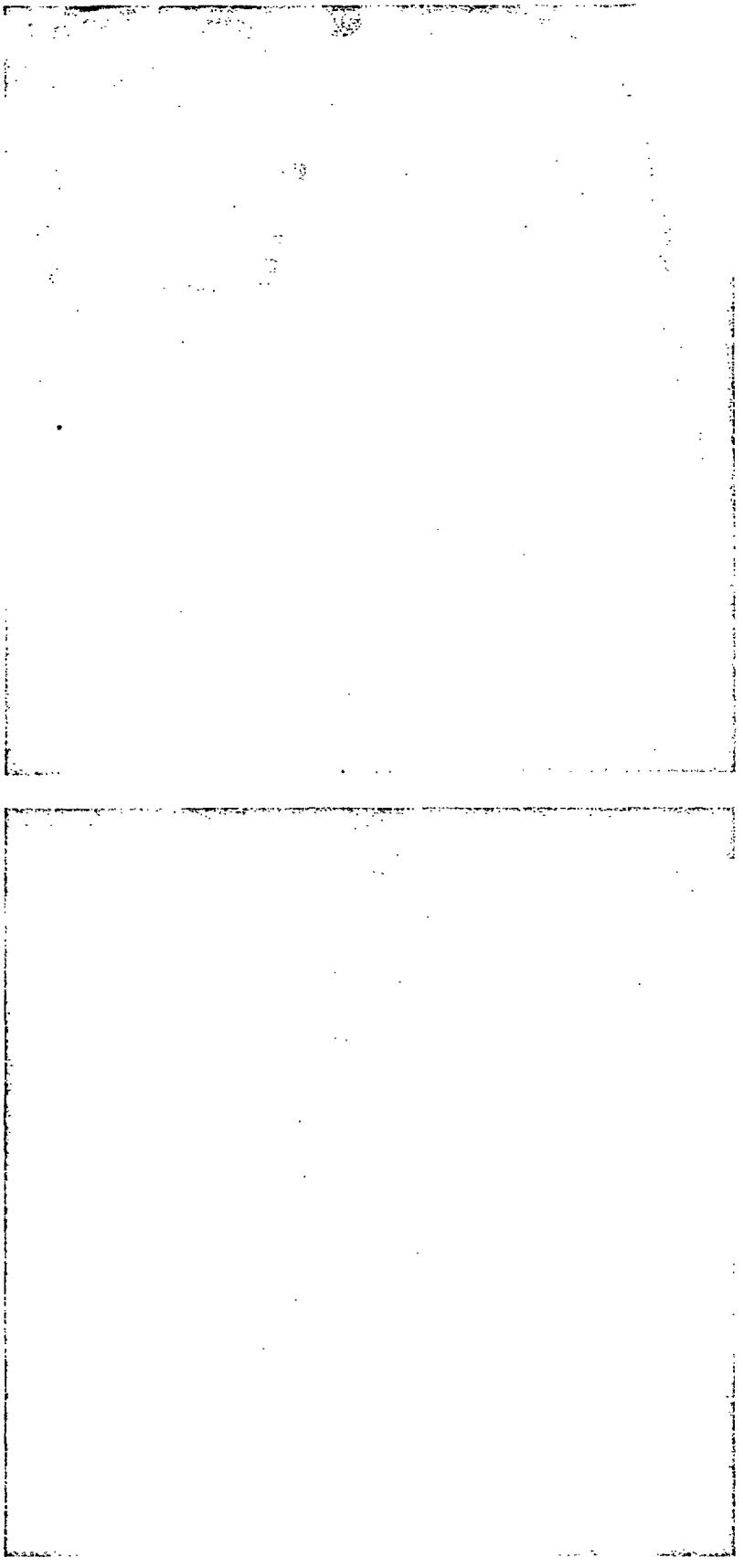


Fig 36.—Roentgenograms of 76-year-old furnace worker with long history of cigarette use. He was hospitalized terminally and died without treatment. Radiologic studies demonstrated immobile right diaphragm and pleural effusion (top). Circumscribed cavitary lesion was found by tomography. Postmortem examination showed pulmonary asbestosis (grade 1), noncalcified plaques in pleura, and well-differentiated cavitary squamous cell carcinoma. Right pleural cavity contained 300 mL of fluid (bottom).

tends to surround one and sometimes both lungs and mediastinal structures (Fig 34). In the abdomen, it encases the bowel, often leading to obstruction. Less commonly, pleural mesothelioma is a discrete mass that invades lung. In early cases, it may be difficult to distinguish the tumor grossly from pleural plaques (eg, at the time of exploratory thoracotomy). For this reason, the pathologist is advised to obtain multiple samples of the lesion when biopsy is performed for the purposes of diagnosis. Although plaques are found in persons with mesothelioma, no evidence suggests that mesotheliomas are derived from plaques. Asbestos bodies are customarily not found in the tumor tissue.

Mesothelioma may penetrate the diaphragm and invade viscera. Metastases once were considered to be an indicator that a tumor was not a mesothelioma. However, metastases, particularly within lung and local lymph nodes, are not rare. A characteristic feature of mesothelioma is the tendency to grow along needle tracts and through surgical incisions.

The microscopic patterns of mesothelioma are numerous and not clearly defined, particularly in the case of the sarcomatous tumors (Fig 35). Mesotheliomas are grouped generally into epithelial, sarcomatous, and mixed types. Detailed descriptions of the gross and microscopic features of malignant mesotheliomas are beyond the scope of this monograph and are published elsewhere.[40] Assistance in the diagnosis of mesothelioma is provided by panels of pathologists in both the United States and Canada (appendix 2).

The most crucial step in the diagnosis of malignant mesothelioma is to distinguish these tumors from primary bronchogenic adenocarcinomas, and from metastatic carcinoma and sarcoma. The autopsy finding of a typical gross appearance and the absence of another primary neoplasm are useful, but care should be taken to rule out the occasional adenocarcinoma of lung that spreads over the pleura. Staining for mucins often is helpful in differentiating an adenocarcinoma from a mesothelioma. The carcinomas often contain PAS-positive, diastase-resistant mucin within cytoplasmic droplets, whereas epithelial cells in mesotheliomas may contain glycogen that is removed by pretreatment with diastase. The epithelial cells of the mesothelioma often contain droplets of hyaluronic acid that do not react with the Schiff reagent. This acid polysaccharide stains with either colloidal iron or Alcian blue; it can be removed by digestion with testicular hyaluronidase. The demonstration of hyaluronic acid by electrophoresis of tumor tissue also may be valuable.[41]

Electron microscopy probably is of little help in establishing the diagnosis, because the ultrastructural features of mesothelioma are similar to those of many carcinomas and sarcomas. Specifically, the epithelial types show the features of secretory cells, including the formation of lumina, whereas the sarcomatous forms are similar ultrastructurally to fibrosarcomas and malignant fibrous histiocytomas.

In recent immunocytochemical studies, material resembling carcinoembryonic antigen was demonstrated consistently in both bronchial adenocarcinomas and bronchioloalveolar carcinomas, but not in mesotheliomas.[42] On the other hand, intermediate fibers made up of keratin usually were found in the cells of mesotheliomas.[42] These new histochemical approaches may prove helpful to the pathologist.

CARCINOMA OF THE LUNG

The association of lung cancer with exposure to asbestos has been established conclusively by epidemiologic studies conducted in a number of different population groups. Asbestos-associated lung cancer usually has a latency period in excess of 20 years, but generally occurs at an earlier age than does lung cancer in nonexposed persons[43] (Fig 36). All histologic types are represented, although in some series adenocarcinomas predominate.[44] The latter neoplasms tend to be located in areas of fibrosis and thus are more common in the lower lobes[45,46] (Fig 37).

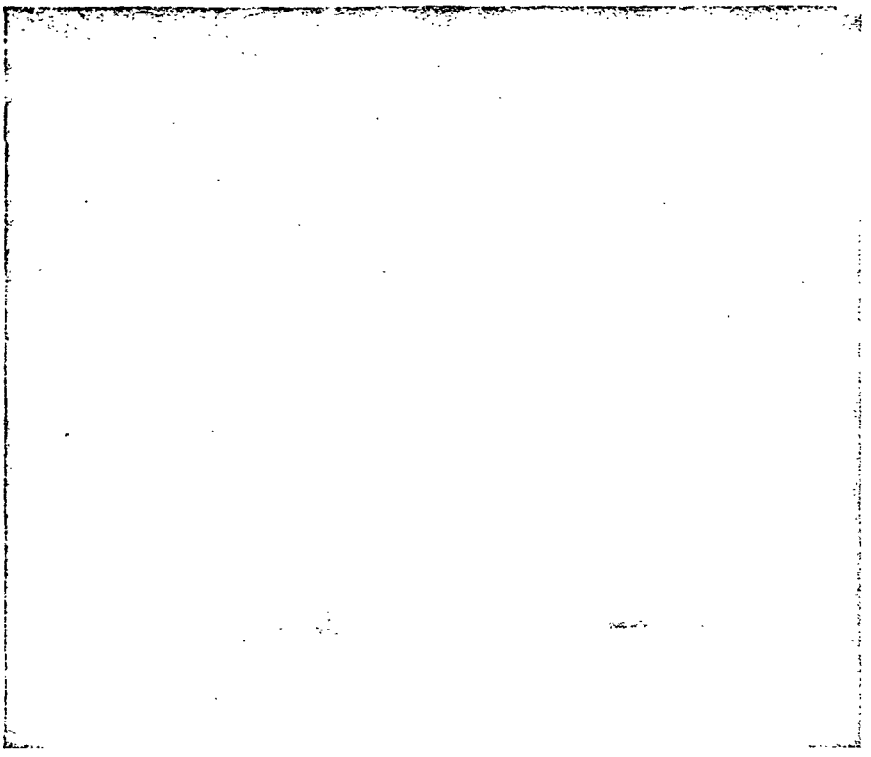
The relationship of the number of asbestos bodies and uncoated fibers in the lungs with the pathogenesis of the neoplasm has not been resolved. The greater the cumulative exposure to asbestos, the higher the risk of lung cancer developing.[47-49] All types of asbestos seem to be carcinogenic; however, the relative carcinogenicity of each type of asbestos is not defined and remains a matter of controversy.

Asbestos workers who smoke have an incidence of lung cancer higher than that of nonexposed smokers and of those who work with asbestos but do not smoke.[50] In one study of insulation workers, nonsmokers had an approximately fivefold increase in the risk of lung cancer compared with a nonsmoking population.[51] This increase in prevalence of neoplasms in nonsmoking asbestos workers has not been found in most studies. On the other hand, the risk of lung cancer was increased greater than 50-fold in asbestos workers who smoked, compared with nonsmokers who lacked exposure to asbestos.[50,51] These observations cannot be accounted for on the basis of an additive effect of two independently acting carcinogens, which suggests that asbestos and cigarette smoke act synergistically.[52]

PATHOGENETIC IMPORTANCE OF DIFFERENT TYPES OF ASBESTOS

Asbestos is not one, but a number of different, commercially available, fibrous minerals that have different physical and chemical properties. Fiber length and diameter, as well as the fiber aspect ratio (ie, ratio of length to diameter) are critical with regard to transport of particles in the respiratory tract. The diameter of the fiber is a major determinant of the depth of penetration into the lung.[53]

All types of asbestos can produce pulmonary fibrosis, and no evidence suggests that the morphologic features of the lesions differ. This statement must be qualified, however, because much of the case material available for study represents severe, far-advanced disease in which subtle differences in the pathogenicity of the dust and the morphologic aspects of the lesion would be difficult to discern. In addition, documentation of exposure to only one type of mineral



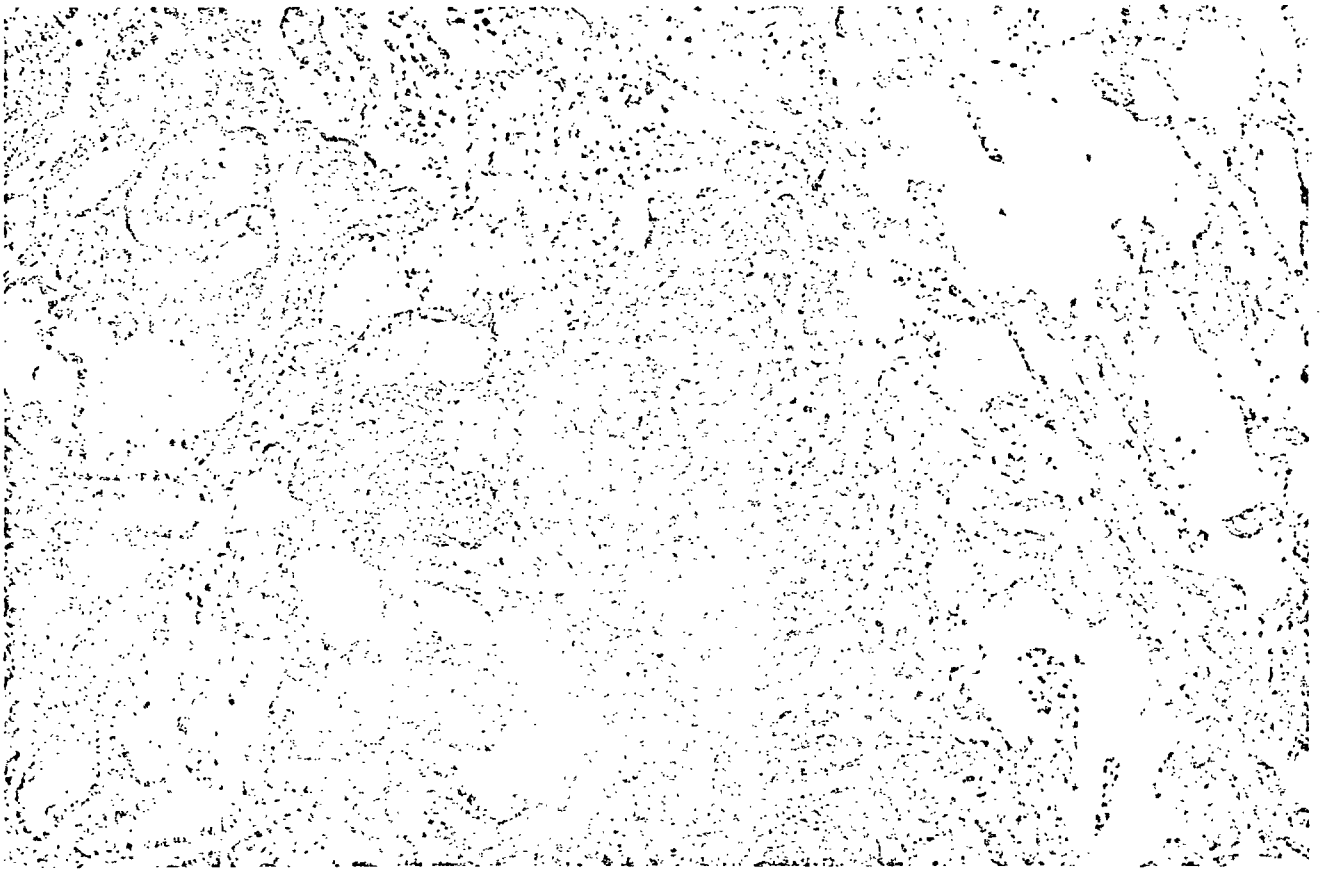


Fig 37.—Top, Chest roentgenogram of 44-year-old man whose chest film had been normal three years earlier. Solitary right lower-lobe lesion is seen, with slight increase in linear, reticular marking in both lower lung fields. No pleural changes are evident. Patient had been exposed to asbestos for 17 years while working as boiler tender in Navy. He had smoked two to three packs of cigarettes per day for 30 years. Ventilation perfusion scan was normal, except for evidence of chronic obstructive pulmonary disease. Patient underwent right lower lobectomy. Bottom, Right lower-lobe lesion proved to be adenocarcinoma, presumable arising in scar. Asbestotic lesions of varying severity were located elsewhere in specimen (see Figs 21 and 28). This finding emphasizes importance of thorough evaluation of pulmonary tissue in persons exposed to asbestos (hematoxylin-eosin).

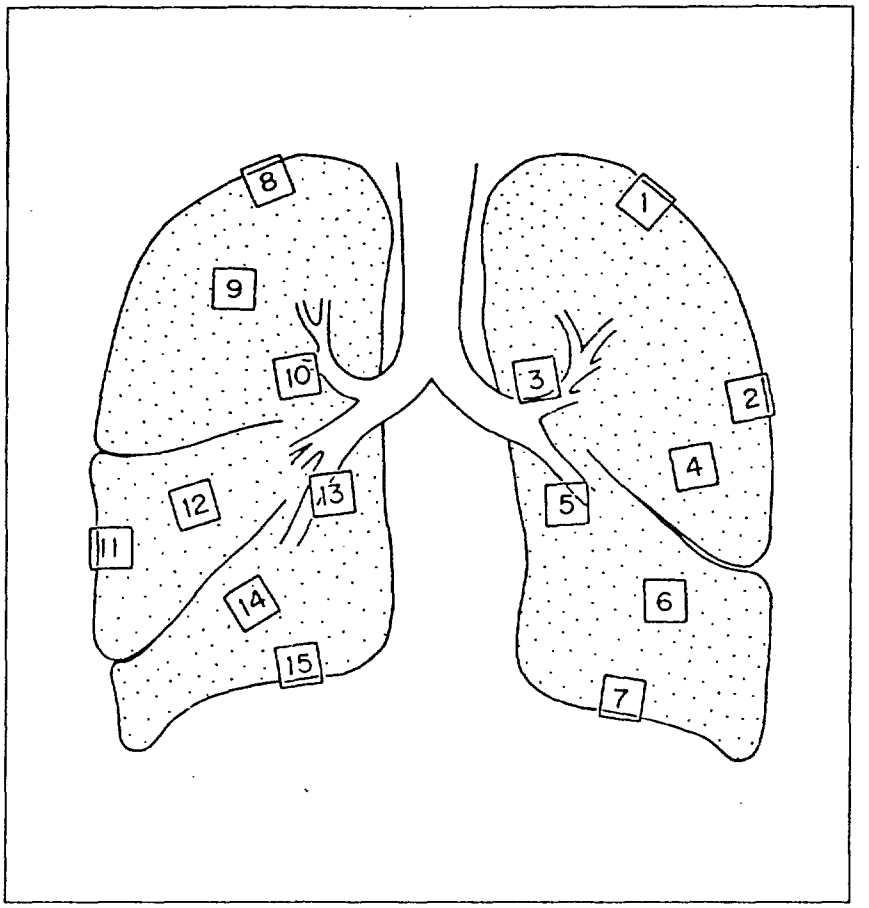


Fig 38.—Recommended sites for preparation of tissue sections in left lung. Right lung is sampled in similar manner, although specimens are also prepared from middle lobe.

can rarely be established with certainty. From a practical point of view, it must be emphasized that many commercial asbestos products contain mixtures of more than one type of fiber. Because exposure may occur over a worker's lifetime, and because industrial processes change and are often poorly documented, it is rare when only one type of fiber is involved in the disease.

The physical characteristics of the fiber seem to be of paramount importance in mesothelioma. When either naturally occurring or man-made fibers are introduced experimentally into the pleural cavity of rats, those fibers longer than 8 μm and of a diameter less than 1.5 μm produce mesotheliomas with a high degree of efficiency.[8] Because the chemical composition and origin of the material does not seem to be critically important, the aspect ratio of the asbestos particles must be a factor that determines the pathobiologic properties of a mineral species. A possible confirmation of this notion has come from recent reports of mesothelioma that developed in persons who lived in areas of Turkey where the soil and building materials contain large amounts of a zeolite fiber, erionite.[22] These fibers are similar in size and shape to many types of amphibole asbestos, but they are dissimilar structurally and chemically.

The importance of different types of asbestos in the pathogenesis of mesothelioma in man has been explored in numerous epidemiologic studies. Anthophyllite failed to produce the tumor, even though pleural plaques occur commonly in populations exposed to this mineral.[54] The apparent benignity of anthophyllite is believed to reflect the relatively broad diameter of its fiber. Mesotheliomas were strongly associated with crocidolite. However, the physical characteristics of this mineral type (and, thus, the prevalence of mesothelioma) differ from one mine to another. Crocidolite from the Transvaal region of South Africa is considerably less likely to induce the tumor than are the fibers extracted in the Northwest Cape region.[7] The importance of chrysotile in the etiology of mesothelioma is less clear, and the question remains a subject of controversy.

HOST FACTORS IN ASBESTOSIS

Although persons may differ in their susceptibility to the pathologic effects of asbestos, the possibility is not well documented. A genetic predisposition to asbestosis has been suggested. In two studies, HLA-B27 was demonstrated more commonly in persons with asbestosis than in members of the general population.[55,56] Subsequent investigations failed to confirm this observation.[57] Additional detailed studies using carefully selected groups of patients and controls will be required before possible association between a specific histocompatibility antigen and disease can be established.

Immunologic aberrations have been documented in blood sera of workers exposed to asbestos, especially those with roentgenographic evidence of disease. Considerable clinical evidence suggest that disturbances of immunoregulation may be operative in asbestosis. For example, impaired expression of cell-mediated immunity has been demonstrated.[58-60] Persons with asbestosis also exhibit altered humoral immune responsiveness, as exemplified by the occurrence of non-organ-specific autoantibodies (rheumatoid and antinuclear factors) in relatively low concentrations in the blood serum.[61,62] Increased concentrations of serum secretory immunoglobulin are frequently noted. The pathogenetic and clinical significance of these immunologic alterations have not been defined. Because similar aberrations are observed in other forms of interstitial lung disease, the finding lacks diagnostic significance.

Appendix 1: Methods for the Assessment of Lung Fiber Concentrations

Techniques have been developed to measure the relative numbers of uncoated and coated asbestos bodies in lung tissue. Most of the studies thus far reported have been performed on autopsy specimens, although biopsy material also can be used. Although these techniques seem simple, laboratories differ in the number of fibers demonstrated in tissues from persons with seemingly comparable degrees of exposure. Experience and critical control of variables are required to obtain meaningful data. Unfortunately, as of this writing only a few laboratories in North America accept specimens of tissue for routine quantitative study. (Interested parties should write to the authors for further information.)

The size (particularly length) and the relative number of coated and uncoated particles in the lung influence the sensitivity of the method. Because some asbestos fibers either break down into smaller subunits in tissue over time or are inhaled as small particles, the burden of dust in the lung may not be reflected accurately in light microscopic counts of fibers longer than 5 μm. In addition, the various types and sizes of fibers are probably cleared from the lung at different rates. These considerations provide some basis for the observation that particle counts by light microscopy do not correlate directly with the severity of the pulmonary parenchymal disease.

Both formalin-fixed and fresh lung tissue can be used in the techniques to be described. Contamination of the fixative and glassware with asbestos theoretically is a problem because many municipal water supplies contain fibers in concentrations of 1 to 5×10^6/L. This may prove to be an important consideration in some laboratories.

Examination of histologic sections from patients with asbestosis has demonstrated the uneven distribution of asbestos bodies in the lungs. This finding has been confirmed by quantitative studies.[13,63] In addition to seemingly random variation within a given area of parenchyma, short fibers tend to concentrate under the pleura. An uneven distribution of fibers seems to be greater in scarred lungs. These factors should be borne in mind when selecting tissue for analysis; for example, variations in fiber distribution may make the use of small biopsy specimens unreliable.

Most published studies used one of the following two techniques. In one, fixed lung tissue is dissolved in sodium hypochlorite (Chlorox). The resulting slurry is washed to remove organic debris and the material collected on a membrane filter. The filter then is mounted on a slide and examined in a light microscope to demonstrate fibers and asbestos bodies.[64-66] Alternatively, pieces of the filter can be placed on electron microscope grids and the fibers transferred to the grid by dissolving the filter in an appropriate solvent. This method has the advantages of (1) gentle chemical digestion, (2) maximal concentration of the sample (a feature of great importance in persons whose exposure has been minimal), and (3) the preservation of a permanent sample for light and electron microscopy. These preparations are excellent for counting asbestos bodies by light microscopy and uncoated fibers by electron microscopy, but are not suitable for counting uncoated fibers by light microscopy.

Ashcroft and Heppleston described an alternate method.[67] Tissue is dissolved in concentrated potassium hydroxide solution and an appropriate volume of the digestate is placed in a standard counting chamber to be examined by phase-contrast microscopy. Generally, this method neither produces as much concentration of the sample as the technique just described, nor is the counting chamber sample permanent. However, it does permit counting of long (> 5 μm) uncoated fibers by light microscopy.

Determination of the number of asbestos bodies in lung tissue digestates provides a quick, although somewhat crude, estimate of the pulmonary burden of fibers. When many bodies are found by this method, the result usually can be considered indicative of substantial exposure to asbestos (although the actual values found in patients with occupational exposure vary from laboratory to laboratory). When small numbers of bodies are identified, occupational exposure is less certain. As discussed in the section entitled "Asbestos Fibers in Tissue," refined analytical studies are required to document the types of minerals present in tissue. The numbers and types of asbestos fibers and bodies found in patients with various asbestos-related diseases are detailed in several reports.[68,69]

Appendix 2: Mesothelioma Panels

Panels of experienced pathologists were established by the Union Internationale Contre Cancer (UICC) Working Group on Asbestos and Cancer in 1964 to provide a referral mechanism for the diagnosis of this relatively rare tumor. The function of these panels was recently evaluated.[70] In 1972, the US panel reviewed 168 cases. Of the lesions, 70% were considered either probable or definite mesotheliomas and 16% were thought to be possible mesotheliomas. In the remainder, the diagnosis of mesothelioma was rejected. Members of the panel customarily concurred; in only 10% of the cases was there substantial disagreement.

The present US panel organized under the auspices of the UICC is chaired by Charles Carrington, MD (Department of Pathology, Stanford University, Stanford, CA 94305). The Canadian panel is chaired by W. T. E. McCaughey, MD (Clinical Studies Unit Bldg, 60 Ruskin Ave, Ottawa, Ontario, Canada K1Y 4M9).

Appendix 3: Pathologic Grading of Asbestosis

The classification and grading of morphologic lesions has potential use in epidemiologic investigations and correlative studies of various aspects of disease. A useful system should be functional and acceptable to the pathologist who is expected to apply it consistently and in a reproducible fashion. In addition, the interobserver variability must be sufficiently low to permit the application of the system to studies that involve large numbers of cases and, thus, different pathologists.

In 1965, the Working Group on Asbestos and Cancer of the UICC recommended a classification schema for asbestosis that was based on both the assessment of the severity of fibrosis and the extent of the changes in the lung as a whole.[71] Shortly thereafter, Hinson et al[72] proposed a grading protocol based on gross and microscopic criteria that could be applied to pulmonary fibrosis in general, and to asbestosis specifically. To the best of our knowledge, this grading system has not been applied systematically in large-scale studies.

Grading protocols for the radiologic assessment of the pneumoconioses are at an advanced stage of development. Groups of radiologists working largely under the auspices of the UICC and the International Labor Organization (ILO) proposed protocols that were generally accepted and have been applied in numerous epidemiologic studies. Moreover, it has been possible to train many radiologists in many parts of the world in the application of the system. The UICC and ILO grading systems were developed with silicosis and coal workers' pneumoconiosis in mind, and were not as applicable to asbestosis as might be desired. Because of this problem, the standard UICC and ILO systems were amalgamated into the UICC-ILO 1971 system (updated in 1980), which now is used universally for all pneumoconioses, including asbestosis. To date, no attempt has been made to correlate the radiologic severity of disease with studies of pathologic material.

A universally acceptable grading system for pathologic evaluation of fibrotic lungs would have relevance to the clinical and radiologic investigation of asbestosis. In addition, it could provide a common language for communication among pathologists and with other groups in the health fields.

The histologic grading system proposed here is a further modification and extension of the protocol of Hinson et al,[72] although it is based exclusively on microscopic criteria. It presupposes systematic study of the lung tissue at the time of autopsy and requires the representative sampling of the lungs described earlier (see "Methods for Pathologic Study) (Fig 38). Although perfusion fixation would be highly desirable, the schema is applicable to lung tissue obtained under less-than-ideal conditions of fixation (ie, without perfusion). It also can be used in the evaluation of lung biopsy material, accepting the limitations of the sample. Under this circumstance, evaluation of the pathologic material might appropriately be carried out in conjunction with radiologic studies to assess the distribution of disease.

GRADING OF ASBESTOSIS

The grading system is intended only for the semiquantitative estimation of the degree of asbestosis, and not as an aid to diagnosis. Therefore, the diagnosis of asbestosis should be established before grading is attempted. Because fibrosis of the peribronchiolar and interstitial tissues is the key lesion in asbestosis, this grading system is based solely on the evaluation

Table 1.—Semiquantitative Evaluation of Asbestosis*

Lobe†	Slide	Severity	Extent	Score	Average Score for Lobe
RUL	1	1	1	1	...
	2	1	2	2	1.5
RML	1	2	2	4	...
	2	3	2	6	5.0
RLL	1	2	3	6	...
	2	3	3	9	7.5
LUL	1	1	2	2	...
	2	2	2	4	3.0
LLL‡	1	3	3	9	9.0
Total	...	...	...	...	26.0
Grade§	...	...	...	...	5.2

*Description of a hypothetical case.
†RUL indicates right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; and LLL, left lower lobe.
‡Second slide missing.
§Grade is total score divided by the number of lobes examined.

Table 2.—Asbestosis Grading Schema*

Grades From Products							
Score	1	2	3	4	6	8, 9	12
Magnitude of increase	...	2X	1.5X	1.3X	1.5X	1.5X	1.3X
Straight Grades							
Score	1+	2+	3+	4+	5+	6+	7+
Magnitude of increase	...	2X	1.5X	1.3X	1.25X	1.2X	1.1X

*Quantitative comparison of incremental intervals between histologic grades, determined either as a product (severity × extent) or as an evaluation of sequential changes in disease severity.

of fibrosis. Numbers of asbestos bodies, macrophages, and inflammatory cells within the tissues and changes in the epithelium are not considered.

Each histologic slide is evaluated from two perspectives. Initially, the severity of the lesion either in or surrounding the bronchioles is assessed and the numeric score recorded. Then, the proportion of the bronchioles in the section that have any degree of involvement is evaluated (not just the proportion involved to the most severe degree). This grade, which represents extent of disease, is recorded as a letter score.

To establish an overall grade for a tissue section, the distribution letter score is converted to a number and multiplied by the lesion score. To characterize the disease of a patient, the products of the scores of all the slides are added and the sum divided by the number of slides examined. This average indicates the degree of disease. Table 1 gives data from a hypothetic case to demonstrate the suggested format for recording data.

ASBESTOSIS GRADING SCHEMA

Severity

Lesions associated with individual respiratory bronchioles are evaluated. The grade is based on the most severe lesion in the slide, not a visual average of the changes found in the various individual respiratory units, as follows.

Grade 0: No fibrosis is associated with bronchioles.

Grade 1: Fibrosis involves wall of at least one respiratory bronchiole with or without extension into the septa of the immediately adjacent layer of alveoli; no fibrosis is present in more distant alveoli.

Grade 2: Fibrosis appears as in grade 1, plus involvement of alveolar ducts or two or more layers of adjacent alveoli; there still must be a zone of nonfibrotic alveolar septa between adjacent bronchioles.

Grade 3: Fibrosis appears as in grade 2, but with coalescence of fibrotic change such that all alveoli between at least two adjacent bronchioles have thickened, fibrotic septa; some alveoli may be obliterated completely.

Grade 4: Fibrosis appears as in grade 3, but with formation of new spaces of a size larger than alveoli, ranging up to as much as 1 cm; this lesion has been termed *honeycombing*. Spaces may or may not be lined by epithelium.

Extent

The proportion of the respiratory bronchioles involved by the disease process is assessed. The grades pertain to the relative numbers of bronchioles in the slide involved by *any degree* of fibrosis—not just the numbers involved to the maximum degree as recorded under severity—as follows.

Grade A (1) Only occasional bronchioles are involved—most show no lesion.

Grade B (2): More than occasional involvement is seen, but less than half of all bronchioles are involved.

Grade C (3): More than half of all bronchioles are involved.

Multiplication of the scores for severity and extent requires explanation because it might be argued that a product score is inappropriate. For example, a product score of 4 obtained on a tissue with grade 4 severity with an extent score of A has implications with regard to disease that differ from a tissue with grade 2 severity and grade B extent. Although theoretically the validity of this argument cannot be refuted, in the evaluation of our case material the severity and extent of the lesions were not found to vary independently, but seemed to be interdependent. Thus, severe lesions are usually found when disease is widespread in the tissue.

The second concept, which argues for the multiplication of the severity and extent scores, relates to the range of possible scores that result (Table 2). Thus, the products of grades (1×1, 1×2, 2×3, etc) produce a series of eight possible scores (1, 2, 3, 4, 6, 8, 9, and 12). As shown in Table 2, the magnitude of increment between products remains relatively constant throughout the range. This is not the case when a numeric grading system (1+ through 7+) is used (Table 2).

Appendix 4: Preliminary Evaluation of Grading Schema

We evaluated the proposed grading system using pathologic material in the files of the Armed Forces Institute of Pathology, Washington, DC. In this study, we were interested only in determining the applicability of the system to a series of cases of asbestosis of varying degrees of severity and assessing preliminarily both the interobserver and intraobserver variations in scoring. Two tissue sections from each of 20 representative cases were chosen by John Rust, MD, of the Pulmonary Disease Section, Armed Forces Institute of Pathology. Nine pathologists (ourselves and Dr Rust) then reviewed the material microscopically. All 40 slides were examined once by each participant, and 20 slides were evaluated twice, once in the morning and again in the afternoon. The results of an analysis of intraobserver variability in the evaluation of the 20 histologic sections are given in Table 3. As can be seen, observers scored slides differently on the two occasions, but the average algebraic difference between the morning and afternoon readings for the group as a whole was −0.3. Disregarding temporal considerations, the variability was 0.47, which is 4% of the total possible range of 0 to 12. When the mean of all differences in the scoring of individual slides is evaluated, the average difference was only 1.3 (ie, 10.8% of the total possible range). This latter analysis magnified differences maximally. We concluded that the degree of intraobserver variability was acceptable.

The average scores of the nine pathologists on all 40 slides for morning and afternoon readings are given in Table 4. As might be expected, differences between observers were found, but the SD of the mean score (6.5) for all readings was 0.8. This SD is 12% of the mean value, or 7% of the total range.

The coefficient of correlation between the scores of every possible pair of pathologists on individual slides was evaluated. The average of all coefficients was .69 ($P < .0001$).

Parametric statistical methods were used in these evaluations. It could be argued that this approach is inappropriate as the "scores" are not a true measure of disease. Accordingly, a nonparametric analysis was also carried out.[7] In this evaluation, the data on the cases were arranged in order of increasing severity as determined by each pathologist, and the agreement in ranking by the observers was analyzed. When the coefficient of concordance was determined, the overall concordance among the pathologists as a group was +.71 ($P = .001$).

Additional analyses were performed to address objections to a grading system based on the multiplication of the extent and severity scores. The measures of severity and extent were evaluated individually by determining the agreement between all possible pairs of pathologists. With both measures, it was found that the scores of the pairs of observations were identical for more than half of the slides reviewed. In nine of ten slides, the maximum discrepancy was only one grade.

The preliminary evaluation was carried out by pathologists who have a special interest in pulmonary disease. The members of the group had worked together to evaluate pathologic material from almost 200 cases of asbestosis. It would be unrealistic to suggest that they are unbiased subjects for a test of the proposed grading system. Nonetheless, it is evident that agreement among members of the group with regard to evaluating both severity and extent of the lesions was excellent.

At this juncture, further evaluations of the grading system by pathologists with different backgrounds seems appropriate. In addition, studies should be undertaken to determine whether the pathologic and radiologic grades correlate.

Table 3.—Evaluation of Asbestosis Grading Schema*

Pathologist	Mean Algebraic Difference	Mean Random Difference	Mean Absolute Difference
1	0.5	0.5	1.6
2	−0.7	0.7	1.0
3	−0.3	0.3	1.6
4	0.1	0.1	1.1
5	−0.6	0.6	1.8
6	−0.1	0.1	1.3
7	−0.3	0.3	1.0
8	−0.7	0.7	1.3
9	−0.7	0.7	1.3
Average	−0.3†	0.47‡	1.3§

*Intraobserver variation in the evaluation of disease grade for 20 histologic sections examined by nine pathologists in the morning and afternoon of the same day.

†Afternoon grades were slightly lower than the morning grades.

‡Score is 4% of total range (0 to 12).

§Score is 10.8% of total range (0 to 12).

Table 4.—Asbestosis Grading Test*

Pathologist	Slide A (AM)	Slide A (PM)	Slide B (AM)	Average
1	7.4	7.8	7.9	7.7
2	7.1	6.4	7.1	6.9
3	8.0	7.7	7.0	7.6
4	6.6	6.7	7.5	6.9
5	6.8	5.9	7.0	6.5
6	5.4	5.4	5.6	5.5
7	5.6	5.3	4.4	5.1
8	6.8	6.1	6.3	6.4
9	6.1	5.5	5.7	5.8
Average	6.6	6.3	6.5	6.5 ± 0.8†

*Mean of the grades determined on 20 histologic sections by nine pathologists in the morning and afternoon of the same day.

†The SD is 12% of the mean.

During its deliberations the Committee consulted many scientists and pathologists in this country and abroad, including the following.

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Frank Whitwell, MD, Broadgreen Hospital, Liverpool, England

Ralph Yodaiken, MD, NIOSH, Rockville, Md

J. C. Wagner, MD, of the Medical Research Council, Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan, graciously provided case material for the study of the committee, including the material shown in Figs 15 and 31, and spent many hours discussing his views on the pathologic aspects of the disease with the chairman. We wish to acknowledge the interest and help of Peter C. Elmes, MD, director of the unit, and the members of his staff.

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Jack Abramowitz, MD, of the Institute of Occupational Health, Johannesburg, South Africa, made available to the committee material from his country for study.

The collection of pulmonary diagnostic material assembled by the late Averrill A. Liebow, MD, was used in this study. The Department of Pathology, University of California (San Diego), gave us access to the collection.

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The illustrations shown in Fig 9 were supplied by L. O. Meurman, MD, University Hospital, Turku, Finland.

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The material shown in Fig 19 was supplied by D. Groth, MD, NIOSH, Cincinnati.

The material shown in the color figure on the inside back cover was supplied by Serge Massé, MD, University of Sherbrooke, Quebec.

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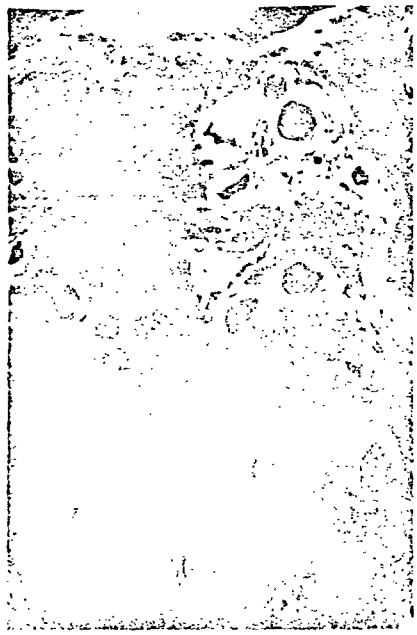

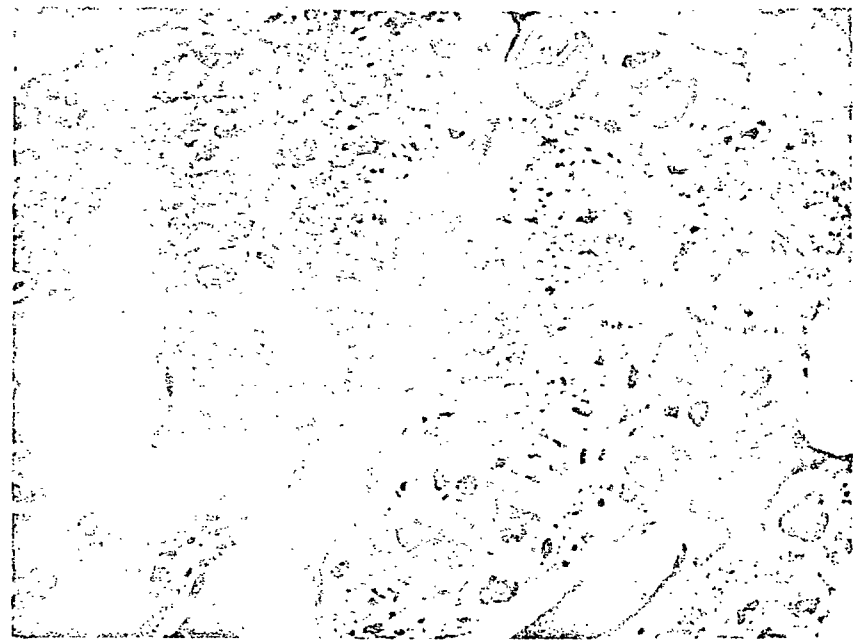

Unfixed lung of Canadian chrysotile worker. Upper left, Note diffuse interstitial fibrosis and brownish discoloration attributable to hemosiderin accumulations in macrophages. Upper right, Note diffuse parenchymal fibrosis and honeycomb lesions that are particularly striking adjacent to visceral pleura. Bottom, Note fibrous thickening of visceral pleura. There is dense parenchymal fibrosis and honeycombing, which is particularly prominent in lower lobe. Accumulations of anthracotic pigment account for gray-black discoloration of fibrotic parenchyma.