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Malignant Mesothelioma and Other Pleural Tumors

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Malignant mesothelioma, a relatively rare but unique cancer of the pleura and other serosal membranes, has been the subject of numerous epidemiologic, clinical, pathologic, and experimental studies during the past 30 years. The enormous interest has been generated by the rising incidence of this tumor, particularly after the recognition of asbestos as a main causative agent. The association between asbestos exposure and mesothelioma has been and continues to be the source of a great deal of litigation, with the pathologist frequently playing a pivotal role in establishing the diagnosis and the cause of this tumor.

Although a link between asbestos exposure and mesothelioma had been suspected before, it was not until 1960 that firm evidence was established.[1] It has since been documented by numerous studies in the United States, Canada, the United Kingdom, Australia, and South Africa.[2–6] As the association became clearer, government regulations curtailed asbestos use in industrialized nations. In Third World nations, however, unsafe practices in the use of asbestos are still commonplace, ensuring a place for mesothelioma as a cause of morbidity and mortality for years to come. Because of a long latency period from exposure to development, mesothelioma will continue to be a significant medical problem well into the twenty-first century.

By epidemiologic estimates, the number of new cases of mesothelioma in the United States has risen from 5000 in 1980 to 19,000 in 1985, and the number of deaths is predicted to reach 79,000 by 2030.[7] The wide range of this estimate reflects the difficulties in diagnosing mesothelioma accurately and the lack of adequate registries. It therefore behooves the pathologist to become well acquainted with the pathologic features of mesothelioma and other asbestos-related diseases (see Chap. 36).

Malignant mesothelioma is a rare tumor, accounting for only a small fraction of deaths due to cancer. However, several factors contribute to the interest in mesothelioma. The neoplasm is associated with exposure to asbestos occupationally or through environmental factors unrelated to the workplace. A definitive diagnosis of mesothelioma during life is difficult on the basis of small biopsy specimens or cytologic samples. Mesothelioma has a nonbiologic cause, yet it basically fulfills Koch's postulates for an infection in that an etiologic agent is known, the condition can be transmitted through inhalation of the agent, and it can be reproduced in experimental conditions.

Asbestos is only one of various minerals with a fibrous structure (Color Fig. 57-1). After asbestos fibers are inhaled, they work their way into the air passages, alveolar tissue, and the pleural space. An increased risk of mesothelioma has been observed from occupational exposures in mines where asbestos is crushed and in plants, mills, and shipyards where asbestos is used. An increased risk also exists for bystanders, including persons who work or live near asbestos mines and family members of asbestos workers. Unlike asbestosis, which is a dose-related effect of asbestos exposure, no threshold exists below which asbestos workers are safe from the development of mesothelioma. The incidence of mesothelioma increases as a power function of time from the first exposure, but latency in individual cases is impossible to predict. Many patients develop mesothelioma after only a few months of minimal incidental exposure to asbestos.[9,10] In various studies, exposure to asbestos has been established for 10% to 70% of all cases of mesothelioma.[11] Whether this reflects an inherent difficulty in obtaining an exposure history or some peculiarity of mesothelioma is unknown. Roggli thinks that 25% of the cases of mesothelioma occur without occupational asbestos exposure.[12] In most cases, however, coated and uncoated asbestos fibers are recovered in significant numbers from the lungs of patients with mesothelioma (Fig. 57-1).

Primary peritoneal mesotheliomas are more common in patients who report heavy exposure; pleural mesotheliomas predominate in patients exposed to moderate amounts of asbestos and in patients with only incidental exposure. Pleural plaques and pleural
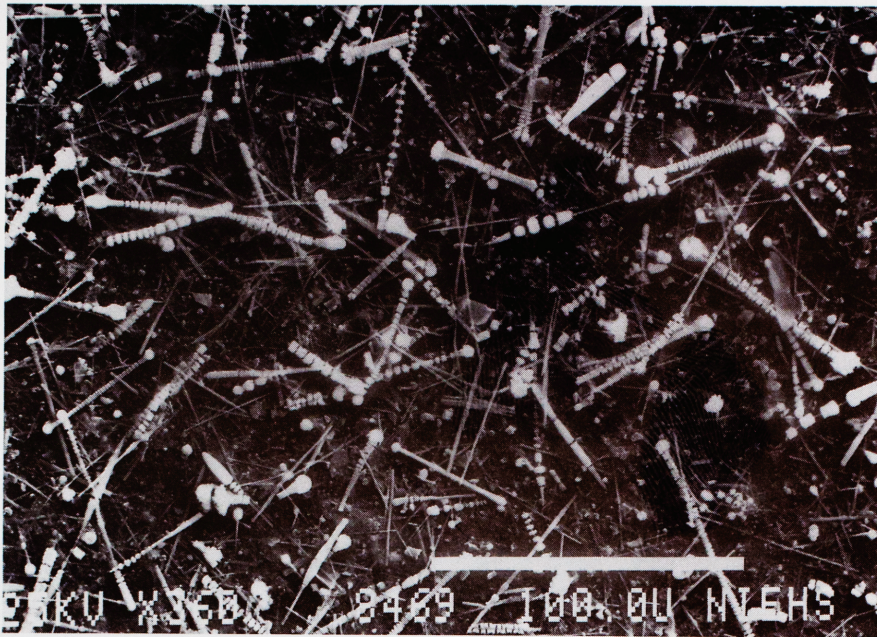
FIGURE 57-1. This nucleopore filter preparation contains amphibole asbestos. Note the numerous coated and uncoated fibers of various dimensions. (Original magnification × 3600; courtesy of V. Roggli, M.D., Durham, NC.)

fibrosis—two dose-related conditions linked to asbestos—are much more common in patients with peritoneal mesotheliomas than in patients with pleural mesotheliomas.

The diagnosis of mesothelioma depends on a constellation of findings, including a history of exposure, signs and symptoms, radiographic findings, and a pathologic diagnosis. Most patients with mesothelioma are diagnosed between 40 and 70 years of age. There is often a history of insidious onset of pain and shortness of breath. Even though the pain is pleuritic in nature, advanced pleural effusions may go undetected for months. Thoracentesis usually reveals voluminous bloody effusions with a high content of hyaluronic acid.

Cytologic examination of the effusion and small pleural biopsies usually prompts a differential diagnosis between mesothelioma and adenocarcinoma. Clinically, there is an overlap between mesothelioma and adenocarcinoma involvement of the pleural surfaces, and adenocarcinoma mimics mesothelioma closely in its pathologic features. Cigarette smoking is not a factor in the cause of mesothelioma.[13] However, cigarette smoking is synergistic to the role of asbestos in the development of lung cancer (Table 57-1).

Thoracotomy with full examination of the pleural space yields the greatest certainty of diagnosis, but it is an invasive procedure. An intermediate approach, thoracoscopy, with visual inspection of the pleural surface and direct biopsy of the lesion, is gaining acceptance in places where mesothelioma is endemic.[14] It is essential to submit specimens for a variety of techniques to establish the diagnosis. I subscribe to a multimodal approach to the diagnosis of mesothelioma in which cytology, conventional histology, special stains, immunohistochemistry, and electron microscopy play an important role.

NORMAL MESOTHELIUM AND ITS REACTION TO INJURY

The parietal mesothelium derives from the embryonic mesodermal layer through a process of a differentiation and attenuation until it becomes reduced to a thin layer of specialized epithelial cells supported by a vascularized connective tissue stroma. This process occurs in tandem with the development of the endodermally derived visceral mesothelium that forms the splanchopleura, which is the predecessor of the visceral pleura. Eventually, the two newly formed membranes form the thin serosal covering of the lungs and the inner aspects of the chest wall. In adults, the mesothelial cells appear rather quiescent in histologic sections, cytologic imprints, or tissue cultures.

The major role of the mesothelium is lubrication to facilitate the gliding motion of the lungs on the pleura. Lubrication is provided by mesothelial cells with profuse surface microvilli, a thick glycocalyx rich in sialic acid, and secretion of hyaluronic acid into the pleural space. These characteristics aid in differentiating mesothelial cells from pleural macrophages, which they superficially resemble. Unlike macrophages, mesothelial cells are not inclined to phagocytosis, and they lack a large number of lysosomes in the cytoplasm. In general, quiescent mesothelial cells possess only rudimentary surface projections and few organelles, including mitochondria, a small Golgi zone, and scattered glycogen granules.

After injury interrupts its integrity, the mesothelium can regenerate and attain full remesothelialization within 8 to 10 days, regardless of the size of the defect. The process is preceded by fibrin accumulation and migration of macrophages, but it seems unrelated to bone marrow totipotential precursor cells or free-floating reserve cells of uncertain origin once thought to be involved in the process of mesothelial replenishment. Evidence suggests that mesothelial repopulation occurs as the result of upward movement of submesothelial mesenchymal precursor cells or the centripetal migration of surface mesothelial cells.[15] Evidence for each of these theories is based on observations of mesothelial proliferation induced by injury.

In dealing with mesothelioma, the pathologist should think in terms of mesotheliomatous differentiation of a neoplasm, rather than a mesothelial histogenesis of these tumors. This hypothesis has the advantage of explaining the occurrence of mesotheliomas in places devoid of mesothelium, such as the lung parenchyma and bronchial mucosa.

Regeneration of mesothelium has been observed in clinical and experimental settings. During the acute phase of injury, de-

TABLE 57-1 Characteristics of Cancers Linked to Asbestos		
Characteristic	Lung Carcinoma	Malignant Mesothelioma
History of exposure	Usually present	Usually present
Latency period	10–30 yr	30–60 yr
Asbestos burden	Risk increases with dose	May occur with very low dose
Fibers in the lung	No increase in number of fibers	Increased number of fibers
Asbestosis	Not necessarily a factor	Asbestosis present in 25% of cases
Cigarette smoking	Synergistic effect	No relation
Distribution	More frequent in lower lobes	Diffuse on pleural surface
Pathogenesis	Carcinogens from smoke absorbed on asbestos	May be induced by other fibrous minerals
Casual relation	Difficult to prove in absence of asbestosis	Asbestosis not required for link to asbestos

nuded mesothelium appears highly vascularized, but it gradually returns to normal thickness as remesothelialization takes place. Although these are static observations subject to deductive subjectivity, they have led to Bolen's theory of a "multipotential subserosal cell."[16] According to this theory, the plump spindle cells in areas of pleural inflammation are totipotential mesenchymal precursors, capable of transformation into surface lining mesothelial cells. These cells and their progeny are capable of rapid proliferation, during which they acquire bizarre cytologic features, the source of considerable diagnostic difficulty.

According to Battifora, the multipotential subserosal cells can be identified by several characteristics.[17] Their long axis is parallel to the pleural surface. They are uniformly distributed and arranged in a bandlike fashion, and the bandlike layer of spindle cells is sharply demarcated from the underlying tissue. The sequence of events leading to the transformation of fibroblastlike cells from the subserosal layer into the cuboidal, epitheliallike cells near the surface has been investigated.[16] Initially, the fibroblastlike cells are positive only for vimentin, but as they migrate toward the surface, they acquire expression of low-molecular-weight keratin. They develop a greater amount of cytoplasm and a less spindly configuration.

Immunocytochemically, these subserosal cells are capable of dual expression of low-molecular-weight keratin and vimentin. They can express muscle-specific actin, which probably explains their ability to migrate upward.[17] After they have reached the surface, mesothelial cells acquire full-blown epithelial characteristics, including expression of high-molecular-weight keratin. They become covered by microvilli, show a concentric distribution of the intermediate filaments around the nuclei, and begin to secrete hyaluronic acid.

Throughout the response to injury, mesothelial cells preserve their potential for reacting and expressing mesenchymal and epithelial features. This is at the core of the recognition and diagnosis of mesothelioma in cytologic and histopathologic specimens. Whitaker does not believe that the surface mesothelium is regenerated from subserosal totipotential precursors; he thinks that these cells arise from the borders of the serosal defect through a process of redistribution that implies locomotion on the part of the migrating cells.[18] By time-elapse cinematography, he has observed centripetal migration of surface mesothelial cells at a speed of 25 nm/hour.[18] After the mesothelial and submesothelial layers have rearranged themselves and corrected the defect, they respect their normal topography.

Under normal circumstances, the band of keratin-positive, fibroblastlike multipotential subserosal cells is sharply demarcated from the underlying keratin-negative mesenchymal tissue, and the cells show no tendency for infiltration. Preservation of this normal topography is useful in the interpretation of biopsies showing irritated and inflamed pleura to avoid a false-positive diagnosis of malignancy. Reactive mesothelial cells are unique in that they have cytomorphologic features that resemble other cell types but emerge with their own distinctive morphology. In common with glandular epithelial cells, mesothelial cells possess microvilli, but theirs is a florid assortment of surface projections, much greater than any other cell type. Similar to keratin-rich squamous cells, mesothelial cells express intermediate filaments, but they are preferentially distributed in a concentric fashion around the nucleus. The keratin filament distribution of mesothelial cells is responsible for the sharp ectoendoplasmic demarcation, a feature not shared by other cell types. Mesothelial cells show only scant organelles, including mitochondria, lipid, and glycogen particles. These products can be visualized by routine and cytologic stains, a feature that can be put to practical advantage with the use of imprints. This situation sharply contrasts with the rich array of secretory granules displayed by epithelial cells.

ATYPICAL MESOTHELIAL HYPERPLASIA AND MESOTHELIOMA IN SITU

Despite the current better understanding of the origins of mesothelial cells and the sequence of events in the process of serosal repair, difficulties remain in the recognition of individual lesions affecting the pleura. In thoracoscopic biopsies, it is possible to appreciate lesions that fit the concept of mesothelioma *in situ* advanced by Whitaker and his colleagues.[20] In contrast, considerably less is known about the conditions that effect primarily the nonepithelial mesothelial cells of the pleura.

Epithelial Abnormalities

Reactive mesothelial hyperplasias occur in inflammatory processes that are localized (*i.e.*, lesion related), regional (*i.e.*, organ related), or systemic (*e.g.*, immune mediated) and can be the cause of considerable diagnostic difficulties. These processes are accom-

panied by pleural effusion with predictable cytologic features, which together with the clinical history allow their recognition. Considerable atypia of the mesothelial cells occurs in hyperplastic foci accompanying pulmonary infarction, recurrent pneumothorax, and reactive eosinophilic pleuritis.[21-23]

Outside the chest, diagnostic difficulties are encountered in the interpretation of hyperplasias associated with incarcerated hernial sacs, subserosal decidual reaction, endometriosis, and cirrhosis accompanied by ascites.[24-27] In cirrhosis, the hyperplasia affecting mesothelial cells may be reflected by aneuploidy detected in pleural fluid examined by flow cytometry.[28] The serous fluid in sarcoidosis and peritoneal dialysis shows no evidence of mesothelial hyperplasia.[29,30]

The greatest challenge in interpreting pleural biopsies derives from trapped mesothelial cells cut off from the surface. These trapped nests of mesothelial cells occur near the surface and may simulate deep invasion below the natural, sharply demarcated lower limit of the pleura. In reactive mesothelial hyperplasia, the degree of cytologic atypia may be extremely worrisome, particularly in cytologic preparations. Certain guidelines have been developed for differentiating atypical mesothelial hyperplasia from malignancy in biopsy specimens, but they may not be applicable to every case (Table 57-2).

Mesothelioma *in situ* is seldom seen outside the setting of thoracoscopic biopsies performed in the follow-up of high-risk populations, such as workers heavily exposed to asbestos.[31] Whitaker and colleagues accumulated the greatest experience with mesothelioma *in situ*.[20] The neoplastic cells in mesothelioma *in situ* show obvious cytologic features of malignancy without a tendency toward local invasion or distant metastasis. Mesothelial cells in these lesions may arrange themselves as skip or continuous monolayers of atypical dome-shaped cells; small papillary excrescences with or without a core of connective tissue; or tubulopapillary loops with bridging and cribriform formation. The papillary projections eventually coalesce into bulkier tumor masses or invade the underlying tissues (Fig. 57-2).

Nonepithelial Abnormalities

Only a few forms of injury, such as blunt trauma and ultrasound blasting, affect the submesothelial layers without affecting the surface mesothelial cells. Consequently, little is known about the early stages of submesothelial response to injury. Indirect evidence of a specialized response occurs in the form of metaplastic changes, including fibroblastic and myogenous metaplasia, that are sometimes seen in pleural biopsies.[32] In mesothelioma, the pathologist may see areas of desmoplastic, rhabdomyoblastic, angiosarcomatous, osteosarcomatous, and chondrosarcomatous differentiation.[12,17,33-35] These features indicate the potential of subserosal cells to respond independently from their surface counterparts and seek a direction of differentiation of their own.

MALIGNANT MESOTHELIOMA

Etiology

The evidence implicating asbestos in the development of mesothelioma is no longer challenged after extensive clinical, epidemiologic, and pathologic investigations. A well-substantiated diagnosis of mesothelioma is taken as *prima facie* evidence of causation by asbestos.[36] Clinically, history of exposure and pleural plaques are commonly seen, but they are not mandatory requirements for the diagnosis of mesothelioma.[37] The plaques are seen in fewer than one fifth of the patients with mesothelioma.[37] The presence of asbestos bodies in the lungs of patients with mesothelioma has been documented in routine hematoxylin and eosin—stained sections and in sections stained by Prussian blue.[38,39] Evidence of an

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TABLE 57-2
Comparison of Atypical Mesothelial Hyperplasia and Mesothelioma

Hyperplasia	Mesothelioma
Cell balls without vascular cores	Distinct papillary growth pattern
Mesothelial cells displaced by biopsy may appear atypical	Truly invasive spread of malignant cells
Tangential cut across folds of serous membrane may simulate invasion	Spread noted along a broad surface, indicating invasion
Pseudoinvasion restricted to area of subserosal repair	Invasion beyond elastic lamina into fat and skeletal muscle
Sequestered benign mesothelium accompanied by inflammatory reaction	Minimal or absent inflammatory component around invading nests of cells
Mesothelial proliferation and inflammatory reactions greater toward the pleural surface	Proliferation without preferred distribution
Trapped mesothelium forms regular, discrete pseudoacini	Invading cells arranged as irregular and elongated tubules or prongs
Immunohistochemistry: negative or weakly positive for EMA; negative for S-100 protein	Immunohistochemistry: positive for EMA (strong thick-membrane pattern); may be positive for S-100 protein
Higher Ag NOR counts	Lower Ag NOR counts

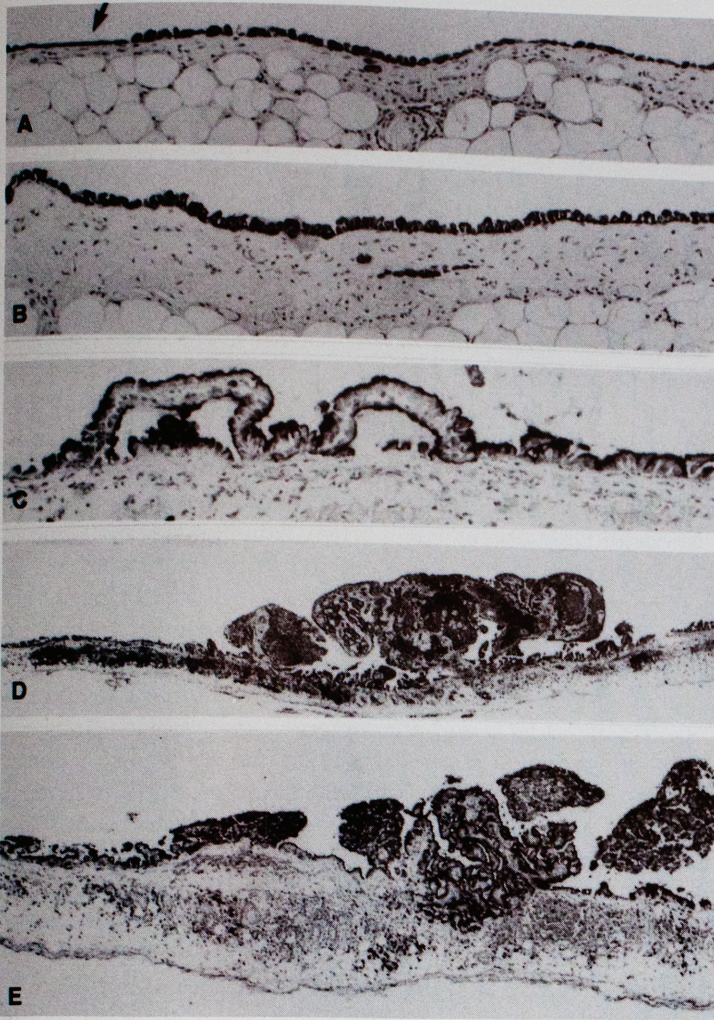*Ag NOR, Nucleolar organizing region of the nucleus by silver impregnation.*

FIGURE 57-2. Mesothelioma *in situ*. (**A**) Monolayered *in situ* proliferation has a skip area of normal, flattened mesothelium (*arrows*). (**B**) The *in situ* neoplastic growth covers the entire pleural surface. (**C**) Surface growth with tubular loops. (**D**) Papillary surface excrescences do not involve the submesothelial layer. (**E**) Mesothelioma presents as confluent nodules with early invasion. Papanicolaou stain; low magnification(s); courtesy of D. Whitaker, M.D., Perth, Australia.)

boles and is found in smaller concentrations. This peculiarity of a fiber that dissolves over a period of time has generated considerable debate but does not exonerate chrysotile from its carcinogenic role if inhaled years earlier.[46] Workers who handled chrysotile exclusively were not immune to the development of mesothelioma.[47]

Epidemiology

Malignant mesotheliomas occur three times more frequently in men than in women.[48] The tumor affects patients in their fifth and sixth decades who have had exposure to asbestos in the workplace.[49] Even though the relation between mesothelioma and asbestos exposure is well documented, mesotheliomas may rarely originate in old scars after radiation exposure or as a result of plombage of the pleural space.[50-52]

There are some peculiarities in the geographic distribution of mesotheliomas unrelated to asbestos exposure in the workplace. For instance, in the Anatolian plateau, villagers who use zeolite-rich tuffa rocks in house construction frequently develop mesothelioma.[53] In Denmark, a cluster of mesothelioma cases developed around persons who mixed asbestos-containing cement in their own houses, and in India, mesothelioma has been linked to organic fibers derived from sugar cane.[54,55]

Clinical Features and Prognosis

The average latency period for the development of mesothelioma after documented asbestos exposure ranges from 10 to 70 years with an average of 30 to 40 years. Exposure can be heavy or absolutely minimal or unnoticed until a careful history is obtained. Because the treatment of mesothelioma is ineffective, the diagnosis is tantamount to a sentence of death. The average interval between onset of symptoms and death is at most 18 months, although some longer survivals have been observed.[56]

Few factors affect prognosis, but an epithelioid rather than a biphasic or a sarcomatous histologic subtype appears to have a slightly better prognosis.[49] Mesotheliomas rarely present as a widespread malignancy, but late in the course of the disease, there is spread to intrathoracic (*e.g.*, contralateral lung, pericardium) and extrathoracic organs (*e.g.*, peritoneum, bone, distant organs).

The tumors start as small, raised areas on the surface of the mesothelium and progress to coalescent nodules that eventually form pleural masses (Color Fig. 57-2). Tumors with large amounts of collagen infiltrating the pleura appear as a thick rind encasing the lung (Color Fig. 57-3). Fleshy tumors that invade the underlying lung parenchyma may be difficult to differentiate from adenocarcinomas with a pseudomesotheliomatous pattern of growth.

There are three major histologic appearances of mesothelioma: epithelioid, sarcomatoid, and biphasic or mixed (Table 57-3). Each of these blend into one another, and the pathologist often speaks of a predominant histologic type rather than a pure histologic variant. The distribution of mesothelial subtypes varies somewhat in the literature. In my experience, 64% of mesotheliomas are the epithelial type, 27% are biphasic, and only 9% are predominantly sarcomatoid. Most epithelial mesotheliomas display epithelial cells arranged as cords, nests, acini, cell balls, and papillary formations. Individual malignant cells are mostly polygonal with abundant cytoplasm and bland nuclei. Appreciation of the densely eosinophilic cytoplasm in the tumor cells facilitates the diagnosis of mesothelioma. Within the neoplasm, it is possible to

increased asbestos burden in mesothelioma has been provided by phase-contrast light microscopy and by coated and uncoated fiber counts by scanning and transmission electron microscopy.[40-42]

Even with these sophisticated techniques, as many as 28% of mesothelial patients show an asbestos body count within the normal range.[43] Many of these patients give a history of exposure to asbestos, lending weight to the idea that clearance of asbestos particles varies among persons and according to the type of asbestos fiber inhaled.[44]

Asbestos is not a single mineral but a family of fibrous silicates, classified according to the shape of their fibers into serpentine (*i.e.*, curved and short) and amphibole (*i.e.*, straight and long). Chrysotile is the only serpentine fiber of commercial importance. There are several amphiboles, including amosite and crocidolite, with important industrial applications. Another three amphiboles, tremolite, actinolite, and anthophyllite, may appear as contaminants in a variety of commercial products.

All types of asbestos have been implicated in mesothelioma and have been consistently isolated from the lungs of patients with this tumor.[45] Chrysotile disappears more quickly than the amphi-

TABLE 57-3
Histologic Patterns and Differential Diagnosis
of Mesotheliomas

Histologic Pattern	Differential Diagnosis
EPITHELIOID MESOTHELIOMA	
Tubulopapillary	Papillary adenocarcinoma (*e.g.*, lung, ovary, thyroid)
Solid	Amelanotic melanoma
Pseudoglandular	Mucin-secreting adenocarcinoma (*e.g.*, GI, pancreas)
Clear cell	Renal cell carcinoma
Cribriform or microcystic	Carcinoma of the breast
Lymphohistiocytoid	Large cell lymphoma
BIPHASIC MESOTHELIOMA	
Spindle and epithelial components (*e.g*, papillary, acinar, solid)	Synovial sarcoma
SARCOMATOID MESOTHELIOMA	
Patternless	Fibrosarcoma
Storiform	Malignant fibrous histiocytoma
Vascular	Hemangiopericytoma, angiofibroma
Palisading	Neurofibroma
Giant cells	Liposarcoma, osteosarcoma
Desmoplastic	Fibromatoses

identify a predominantly tubular or a papillary pattern, or both may be intermixed (Color Fig. 57-4; Figs. 57-3 and 57-4).

A tubulopapillary configuration is seen at least focally in as many as 90% of all epithelial mesotheliomas. Other patterns are possible, but there is no prognostic significance attached to these histopathologic variants (Table 57-4). Poorly differentiated epithelial mesotheliomas with a predominantly solid pattern must be differentiated from metastatic carcinomas arising in a number of sites and from melanotic melanoma. Melanoma is positive for S-100 and HMB-45, but mesothelioma is not. Mesotheliomas may have a predominantly clear cell pattern and must be differentiated from renal cell carcinoma. A spindle cell component is of no help, because both tumors may demonstrate it; the same applies to glycogen and lipid. Invariably, renal cell carcinoma must be separated on clinical grounds or by ultrastructure, because mesothelioma and renal cell carcinoma lack a reliably positive immunocytochemical marker. Poorly differentiated or anaplastic forms of epithelial mesotheliomas may mimic metastatic sarcomas. Some tumors may display a microcystic pattern resembling breast carcinoma. Epithelioid mesotheliomas uncommonly display foci of necrosis, but these are not as extensive as in carcinomas of comparable size. The tumors may also show foci of inflammatory cells, predominantly lymphocytes, or lymphocytes may overwhelm the histologic picture rendering a subtype known as lymphohistiocytoid mesothelioma.[57] When lymphocytes are admixed with nests of epithelioid cells, thymoma has to be ruled out.[58]

Approximately 10% to 15% of mesotheliomas belong to the sarcomatoid variant, which has a prognosis similar to that for biphasic mesotheliomas but worse than that for epithelioid neoplasms.[59] Most sarcomatoid mesotheliomas display a fibrosarcomalike appearance and are composed of cells with elongated cytoplasm, arranged in parallel bundles (Color Fig. 57-5). Nuclei are fusiform or oval but occasionally appear rounded. In general, sarcomatoid mesotheliomas show greater pleomorphism and more mitosis than their epithelioid counterparts. The stroma of sarcomatoid mesotheliomas can be rather hyalinized or scant with formation of a storiform, whorl, or herringbone pattern. Sarcomatoid mesotheliomas with abundant collagen in between the cells are designated "desmoplastic".[60,61] Cell atypia may be overlooked in these tumors, but foci of necrosis, a storiform appearance, and focal infiltration of adipose tissue and skeletal muscle aid in their recognition. Desmoplastic mesotheliomas should be differentiated from the fibromatoses, solitary fibrous tumors (SFTs) of the pleura, and submesothelial hyperplasia.[62] Occasionally, sarcomatoid mesotheliomas acquire a malignant fibrous histiocytomalike, hemangiopericytomalike, fibrosarcomalike, or neurofibrosarcomalike pattern. Nuclear pleomorphism, frequent mitosis, and giant cell formation may render the tumor difficult to
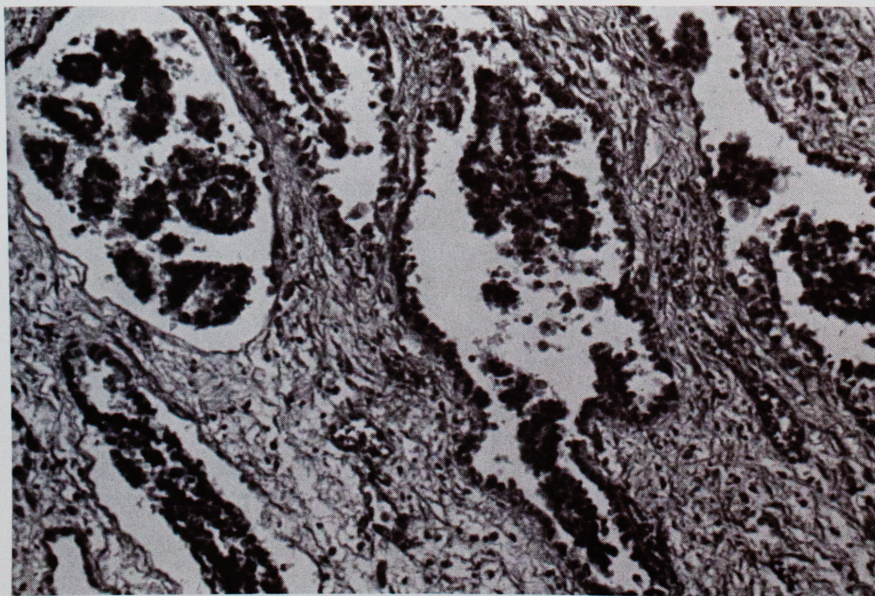

FIGURE 57-3. A histologic section from the tumor in Color Figure. 57-3 shows the characteristic features of tubulopapillary mesothelioma. (H & E stain; low magnification; contributed by the editor.)
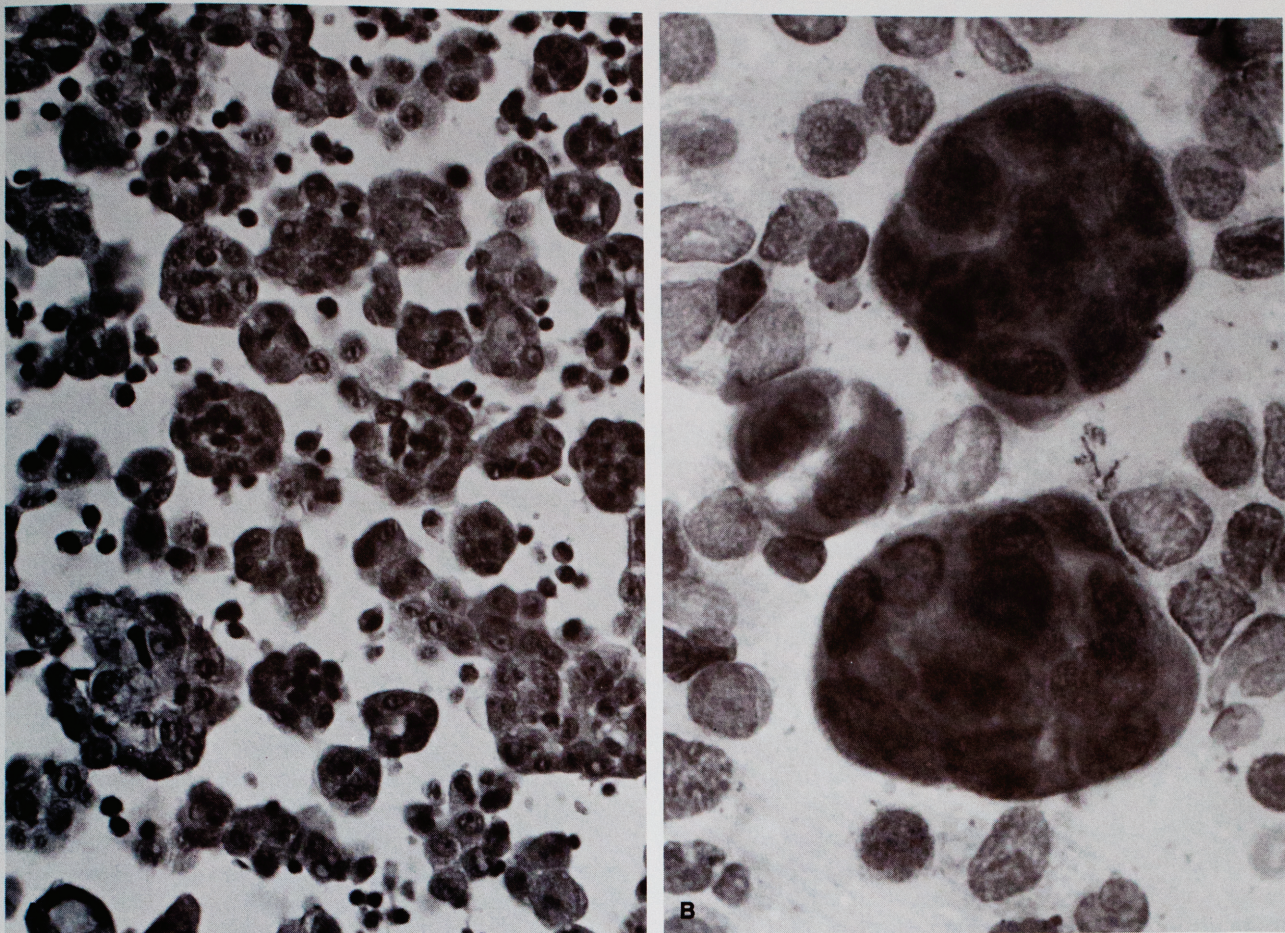
FIGURE 57-4. Cytologic examination of pleural fluid from the patient in Color Figures 57-2 and 57-3 and in Figure 57-3. (**A**) Low-power view shows numerous papillary structures. The specimen was negative for mucicarmine. (Mucicarmine stain; intermediate magnification.) (**B**) Higher magnification shows two cell balls in the same fluid sample. (Papanicolaou stain; high magnification; contributed by the editor.)

differentiate from a pleomorphic, high-grade sarcoma involving the pleura.

Biphasic mesotheliomas are composed of various mixtures of epithelioid and sarcomatoid cells (Color Fig. 57-6). They account for about 25% to 30% of all mesotheliomas, and their biologic behavior is the same as that in sarcomatoid tumors. Less commonly, a mesothelioma may be poorly differentiated and show bizarre areas of spindle cells intermixed with giant cells and only rudimentary attempts at epithelioid differentiation.

Diagnosis

There are considerable difficulties in the histologic evaluation of mesothelioma. The first problem is the distinction between an early mesothelioma and a florid reactive hyperplasia (see Table 57-2). With immunocytochemistry methods, several features have been claimed to assist in this differential.[63-67] Reactive mesothelial cells are negative or only weakly positive for epithelial membrane antigen (EMA), but mesothelioma cells give a strong thick mem-

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TABLE 57-4
Electron Microscopic Findings in the Differential Diagnosis of Malignant Mesothelioma

Diagnosis	Microvilli	Cell Junctions	Intermediate Filaments	Cytoplasmic Content
Mesothelioma	Bushy, slender, and long	Rather long desmosomes	Concentric around nucleus	Paucity of organelles; no secretory granules
Mucinous adenocarcinoma	Short or absent	Junctional complexes	No preferential pattern	Fluffy, electron-dense mucosubstance
Clara cell adenocarcinoma	Short, slender	As above	As above	Clara cell granules
Carcinoma of type II cells	Short, stubby	As above	As above	Lamellar bodies
Renal cell carcinoma	Short, slender	As above	As above	Lipid droplets, glycogen accumulation
Carcinoma of breast	Short or absent	Short desmosomes	Large amount	Sparse secretory granules

brane pattern of immunopositivity along the entire perimeter of the cells. Reactive mesothelial cells are considerably less endowed with microvilli compared with cells deriving from mesothelioma. Reactive mesothelial cells are consistently negative for S-100 protein, but mesotheliomas may be positive. Another approach is to stain the nucleolar-organizing region of the nucleus by silver impregnation (i.e., AgNOR method).[68] In one such study, the AgNOR count in malignant mesothelioma was considerably higher than in mesothelial hyperplasia.[69]

Another important tool that should not be neglected in favor of immunocytochemistry are histochemical special stains. There are four histochemical procedures that are useful in the differential diagnosis between mesothelioma and adenocarcinoma: periodic acid-Schiff with diastase (PAS-D), mucicarmine, Alcian blue, and colloidal iron. The PAS-D method is the most reliable for this purpose. Glycogen in mesotheliomas appears as punctate areas of bright red PAS-positive material and is removed by diastase digestion. A semilunar, peripheral distribution of PAS-positive material is characteristic of mesothelial cells.

Neutral mucins of adenocarcinomas lack the punctate distribution of glycogen. More importantly, this type of positivity is not removable by diastase digestion. Strong, unequivocal, positivity with the PAS-D stain excludes mesothelioma as a diagnosis. A negative result, however, does not exclude adenocarcinoma, because this tumor is positive for PAS-D only in 40% to 50% of the cases.

Alcian blue stains hyaluronic acid positively in mesothelioma; this dull bluish positivity can be removed by hyaluronidase digestion. The reactions with colloidal iron are essentially similar, except that the positive material appears green. Acid mucopolysaccharides are elaborated in the cytoplasm but easily ooze out into the surrounding extracellular space. Hyaluronic acid can be identified infrequently in mesothelioma as inspissated secretions within lumina in tumor cells. Acid mucosubstances are not stable and tend to leech out of tumors left in fixative for extended periods. Alcian blue and colloidal iron may give a positive reaction in adenocarcinomas that contain weakly acidic or neutral mucosubstances, and hyaluronidase pretreatment would not affect the degree of positivity.

Mucicarmine identifies neutral and weakly acidic mucosubstances such as those secreted by adenocarcinoma. This stain is consistently negative in mesothelioma specimens, although nonspecific haloing of luminal spaces may be misinterpreted as a false-positive result. As with PAS-D, a negative result does not rule out an adenocarcinoma because only 50% of these tumors are mucicarmine positive. Moreover, many primary sites, such as the kidney, adrenal, liver, and thyroid, are consistently mucicarmine negative. The positivity for mucicarmine in adenocarcinoma is seen primarily in the cytoplasm of cells or in the lumens of acini and glands. However, mucicarmine occasionally cross-reacts with hyaluronic acid, and borderline results should be weighed against other stains used in the individual case.

Immunohistochemistry has been extensively applied to differentiating mesothelioma from carcinoma, but no substance secreted exclusively by mesothelioma has emerged as a positive marker. The diagnosis relies heavily on negative markers. Most often, this is accomplished by testing for carcinoembryonic antigen (CEA), a complex glycoprotein located in the plasma membrane and the glycocalyx, characteristic of adenocarcinoma. Early studies demonstrated high sensitivity and specificity of CEA for excluding mesothelioma.[70,71] However, a few investigators have found mesotheliomas showing focal areas of positivity for CEA.[72,73] In my experience, no mesothelioma ever exhibits a reliable pattern of positivity when stained for CEA. The pathologist should be aware of areas of necrosis and macrophage accumulation that may spuriously take up the immunostain due to nonspecific peroxidase activity.

Because the diagnosis of mesothelioma depends heavily on the negativity of immunocytochemical reactions, it is wise to use more than one marker. Many have been tried, but I have found CEA, LeuM1, Ber Ep4, and B72.3 to be the most reliable.[74–74b] Glycoprotein constituents of cell membranes are responsible for the immunopositivity for LeuM1, B72.3, and Ber Ep4 in adenocarcinomas. There have been a few reports of mesotheliomas showing focal immunostaining for LeuM1.[75] I have seen the same phenomenon with B72.3 and Ber Ep4 but believe this finding is inconsequential if the pathologist understands that no immunocytochemical result should be interpreted by itself. The marker results must be interpreted in light of the histopathologic features and clinical findings.

Positive reactions in mesothelioma are observed in the cytoskeleton (e.g., keratin, vimentin) and on the surface of tumor cells (e.g., EMA, HMFG-2). However, mesothelioma and adenocarcinoma are frequently positive for keratin, and keratin immunopositivity fails to discriminate between mesothelioma and adenocarcinoma.[76] Mesothelioma is positive for various antibodies that recognize low- and high-molecular-weight keratin, and adenocarcinoma is positive only for low-molecular-weight keratin. The concentric, perinuclear distribution of the intermediate filaments is responsible for the strong perinuclear or rim-pattern immunopositivity for keratin in mesothelioma.[76] This contrasts with the weakly or moderately diffuse arborizing pattern of keratin immunopositivity of adenocarcinoma.

Vimentin is variably expressed in epithelioid mesothelioma, but it is commonly coexpressed with keratin by the spindle component of biphasic and sarcomatoid mesotheliomas.[63,77,78] Because various epithelial neoplasms, including lung carcinomas, may express vimentin, this marker is of little assistance in the differential diagnosis between mesothelioma and adenocarcinoma.[79,80] Vimentin positivity fails to discriminate between sarcomatoid mesothelioma and various sarcomas because most of them express vimentin. Coexpression of vimentin and keratin is more discriminatory, with exceptions represented by epithelioid sarcoma, synovial sarcoma, and a small fraction of leiomyosarcomas.

EMA is consistently and strongly expressed in mesothelioma. In mesothelial hyperplasia and adenocarcinoma, only a few cells stain for EMA.[81] The staining of hyperplastic mesothelial cells is diffuse and weak, without any resemblance to the strong subplasmalemmal positivity expressed by mesothelioma.[82] In interpreting immunocytochemical results, it is important to make a distinction between the thick cell membrane pattern and a linear enhancement of immunostaining along the periphery of the cell. The latter occurs with CEA and other antibodies that recognize glycocalyx and may result from the edge effect of immunoperoxidase reactions. However, no antigen other than EMA gives the consistently thick, spiked, and intense reaction characteristic of the thick cell membrane pattern (Fig. 57-5).[82] The florid microvilli on the mesothelial cell surface is the basis for the thick cell membrane pattern seen in mesotheliomas stained for EMA. A similar distribution but less-intense reaction is observed with HMFG-1 and
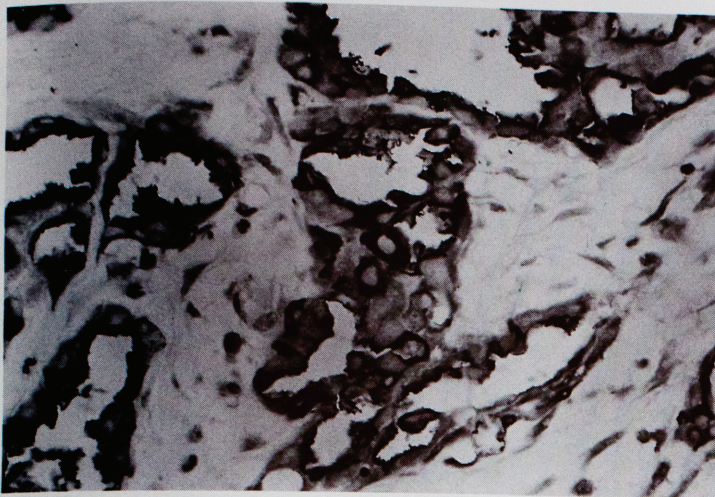
FIGURE 57-5. Epithelioid mesothelioma stained for epithelial membrane antigen. The immunostain outlines irregular, pseudoglandular slits. Notice the thick rim of positivity around the cell borders. (Immunoperoxidase stain; intermediate magnification.)

HMFG-2, two antibodies against milk fat globule proteins. The diffuse pattern of immunopositivity of EMA and CEA observed in adenocarcinoma corresponds to the presence of these antigens in the membranes of endoplasmic reticulum.[83]

Electron microscopy is my method of choice for the diagnosis of mesothelioma. Ultrastructural interpretation is based on objective criteria and is not plagued by the instability of antigen preservation or the inherent subjectivity of interpreting immunocytochemical reactions. The diagnostic ultrastructural clues are preserved even in suboptimally fixed tissues. No artifacts affect the distribution and dimensions of intermediate filaments or microvilli to cause diagnostic difficulties. Because secretory granules cannot be artificially created by any biologic or artificial process, their presence is extremely reliable in the diagnosis for adenocarcinoma.

The ultrastructural features of mesothelioma in biopsy and effusion specimens have been well described (Fig. 57-6).[84,85] The dominant feature is a combination of profuse surface microvilli in the absence of secretory granules in the cytoplasm (Fig. 57-7). Mesothelioma may contain glycogen lakes resembling a large secretory vacuole, but the lack of a limiting membrane and the punctate rather than flocculent appearance permit their identification.

The length and diameter of microvilli enable differentiation between mesothelial and adenocarcinoma (Figs. 57-8 and 57-9). In general, the ratio of the length to the diameter is greater than 15 in mesothelioma and less than 15 in adenocarcinoma. However, this figure is not absolute when applied to a single electron micrograph, because some overlap does occur. Correlation with the histologic picture and examination of several areas of the tumor alleviate most diagnostic problems. Ovarian carcinomas may present with microvilli as long as those of mesotheliomas, but they are distributed around the entire perimeter of the cell. Anemone tumors present with microvilli that may be even longer than mesothelioma, but these tumors are of obvious lymphohistiocytic origin.[86]

In mesothelioma, the microvilli may come into contact with the surrounding stroma, a phenomenon not demonstrated by adenocarcinomas. Microvilli may project into intracellular lumina and extracellular hollow spaces. Difficulties may arise in differentiating poorly differentiated mesotheliomas from adenocarcinomas that lack secretory granules and may have microvilli longer than usual. In these neoplasms, other ultrastructural differences may be of assistance; for instance, the desmosomes are considerably longer in mesothelioma than in adenocarcinoma.[87]

Sarcomatoid mesotheliomas are characterized ultrastructurally by spindle cells loosely separated by a stroma containing proteoglycans and collagen fibrils.[88] Each cell has an elongated nucleus, with blunted ends, prominent rough endoplasmic reticulum, scattered glycogen particles, inconspicuous Golgi zones, and an absent basal lamina. The cytoplasm contains abundant intermediate filaments, and the surrounding stroma shows collagen and an amorphous matrix. This ultrastructural appearance corresponds well with the immunocytochemical observation of
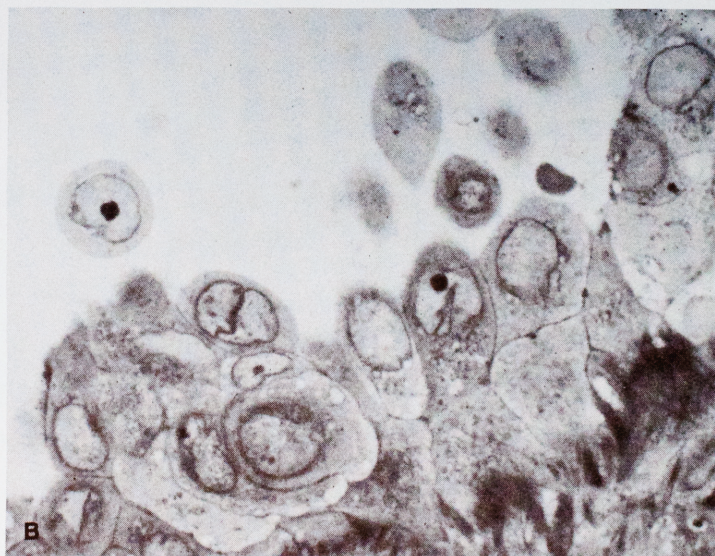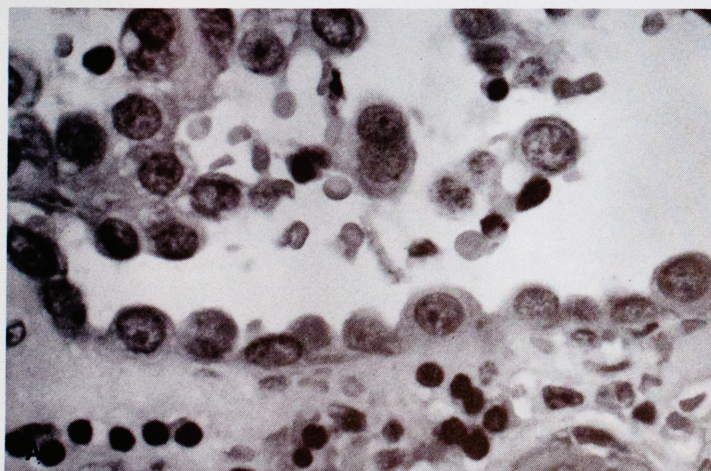

FIGURE 57-6. Mesothelioma in an open biopsy specimen. (**A**) Paraffin-embedded material shows malignant nuclei. (H & E stain; high magnification.) (**B**) Thin section from plastic-embedded tissue demonstrates cells clasping one another in crisp architectural detail. (Toluidine blue stain; high magnification; courtesy of E. Hoffman, M.D., New Orleans, LA.)
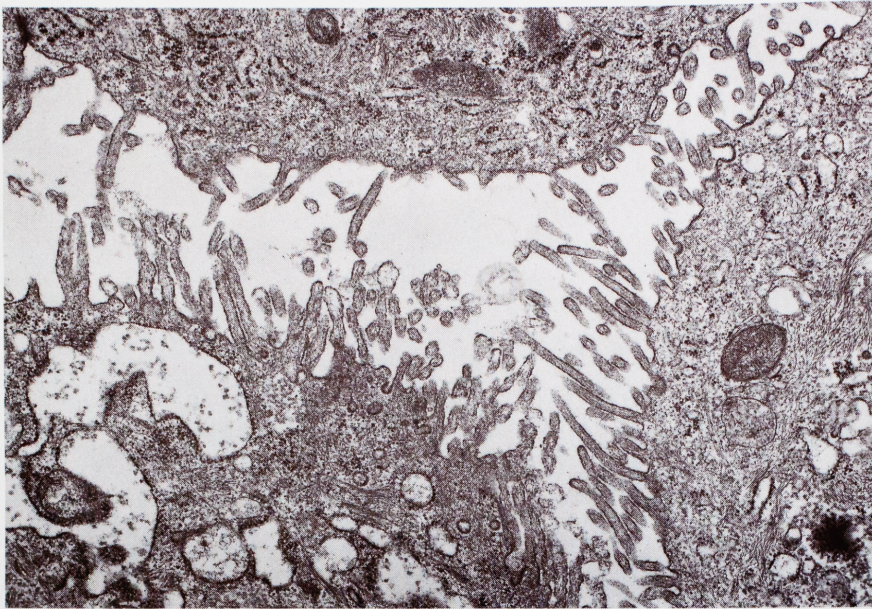
FIGURE 57-7. Ultrastructure of mesothelioma. The space between several cells contains tall, slender microvilli. The cytoplasm shows intermediate filaments and glycogen, but no secretory granules. (Original magnification × 6000.)

keratin- or vimentin-positive cells separated by amorphous, nonreactive intercellular substance. Sarcomatoid mesothelial cells may have intertwined cytoplasmic processes, rudimentary desmosomes, or sprouting microvilli.

BENIGN MESOTHELIOMAS

Malignant mesotheliomas affect extensive areas of the serous surfaces, hence the designation "diffuse." This has led to the concept that a correspondingly benign lesion should exist and that the lesion would be localized. The reality is that a truly benign epithelial mesothelioma has never been described in the pleura, even though benign tumors composed of epithelial cells do occur in the peritoneum. Benign localized tumors composed of fibroblastlike cells are not common in the peritoneum but are found with certain frequency in the pleura. Because many of these cases were described before the introduction of immunohistochemistry, controversy surrounds their cell of origin and the direction of their differentiation, but this controversy is not as important as recognizing these lesions as benign conditions with a malignant potential and excluding malignant mesothelioma and metastatic neoplasms in their differential diagnosis.[89]

Solitary Fibrous Tumor

This distinct category of tumors seems to arise directly from the subserosal multipotential mesothelial cells. Previously known as localized pleural mesothelioma, a solitary fibrous tumor (SFT) of the pleura is uncommon and occurs most frequently between the fifth and seventh decades of life.[90] The tumor has a slight female preponderance and is rare in children. Most patients are asymptomatic, but nonspecific complaints of chest pains, dyspnea, arthralgia, and fever have been reported. The masses range from 1 to
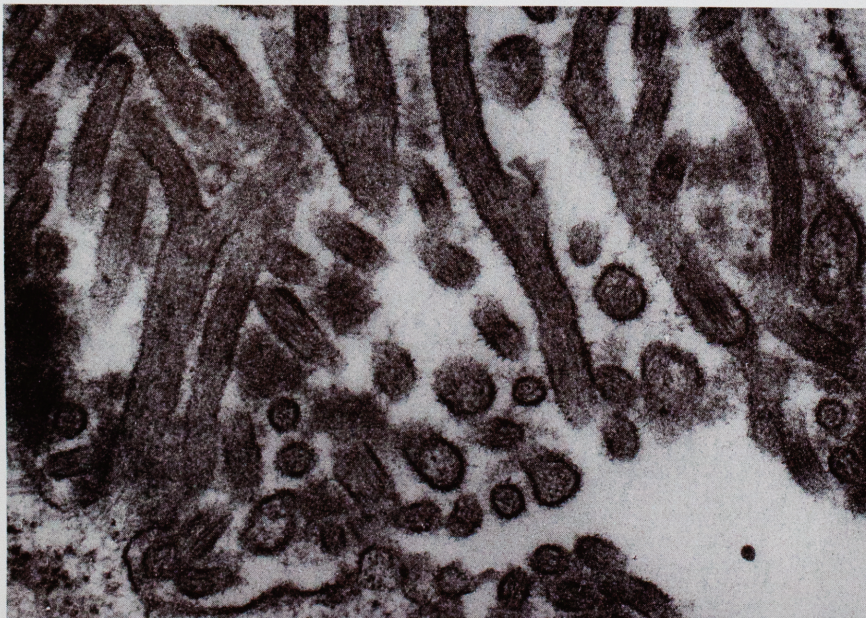

FIGURE 57-8. Microvilli in mesothelioma. Complex, intertwined microvilli show actin filaments cut longitudinally and transversely. (Original magnification × 24,500.)
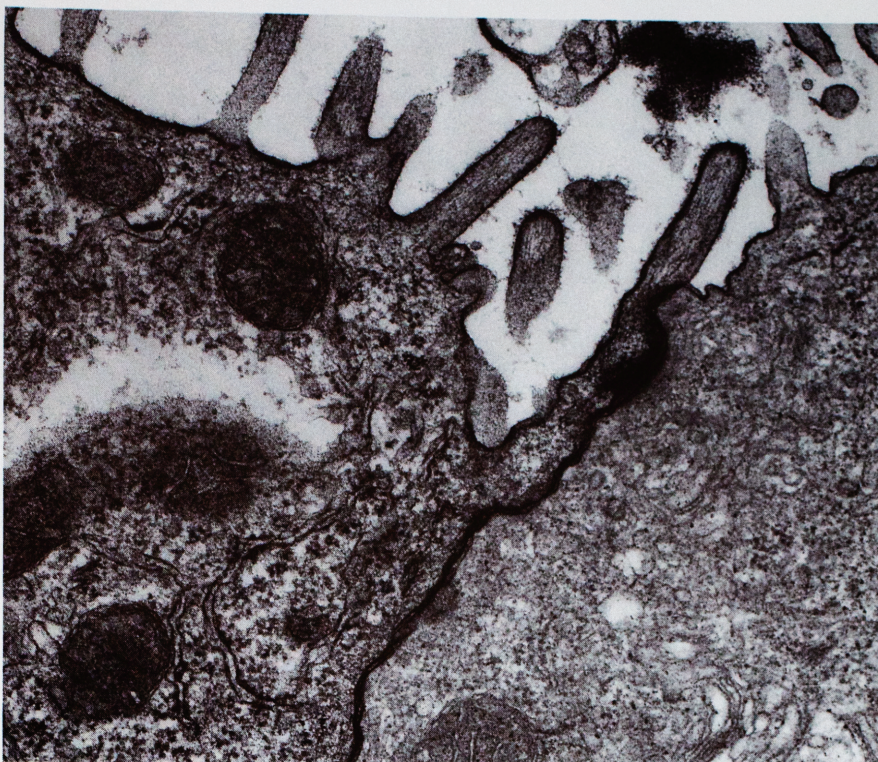
FIGURE 57-9. Adenocarcinoma shows short and less numerous microvilli and a sinuous terminal bar. Antennular glycocalyx coats the surface of the microvilli. (Original magnification × 36,000.)

36 cm in their greatest diameter, and some have weighed as much as 5 kg. Approximately 5% of SFTs of the pleura have been associated with hypoglycemia, the mechanism for which is poorly understood.[91]

SFTs are sessile or pedunculated masses, attached to the parietal or visceral pleura. The tumors compress the lung and may mimic a pleural-based parenchymal mass on the chest roentgenogram. SFTs are rubbery, firm textured like a smooth muscle neoplasm, and covered by a thin, shiny pleura. The pedicle of some of the tumors may contain large, engorged feeding vessels (Fig. 57-10).

Microscopically, fascicles of bland spindle cells with elongated nuclei are oriented in parallel bundles. There is a small amount of amorphous matrix in the intercellular spaces but no inflammatory response, a feature helpful in differentiating the lesion from pleural fibrosis in small biopsies. Occasionally, foci of myxoid change, hemorrhage, cyst formation, or necrosis may occur in large tumors. Although a fascicular pattern is observed, the random pattern predominates (Fig. 57-11).

SFTs may entrap epithelial cells of the lung, which should not be confused with the epithelial component of a biphasic mesothelioma. Unlike pleural plaques composed of collagenous tissue in an almost mummified, basket-weave fashion, SFTs contain active fibroblasts in between hyalinized fibrous bands and tracts. Occasionally, a storiform or a palisading pattern can be observed. Cell atypia and mitosis are not common, even though occasional hyperchromatic nuclei may be observed.

These tumors usually follow an indolent course, but local recurrence is seen in some cases. According to England and Hochholzer, malignant forms represent 29% of these tumors.[92] They are recognizable by histologic features such as hypercellularity, pleomorphism, necrosis, and more than four mitoses per 10 high-power fields. They have the potential to recur and produce local and distant metastasis (Fig. 57-12 and 57-13).

The histogenesis of SFTs of the pleura is controversial. Although most investigators think it is a submesothelial proliferation of fibroblasts, others support the concept that they are true mesotheliomas. Most immunocytochemical studies show a tendency toward nonmesothelial, fibroblastic differentiation in which vimentin is positive but keratin is not.[93] In my experience, all of these lesions have been positive for vimentin but negative for keratin, favoring a fibromatous differentiation.

Our ultrastructural studies support a fibromatous differentiation without excluding a submesothelial cell derivation. The pre-
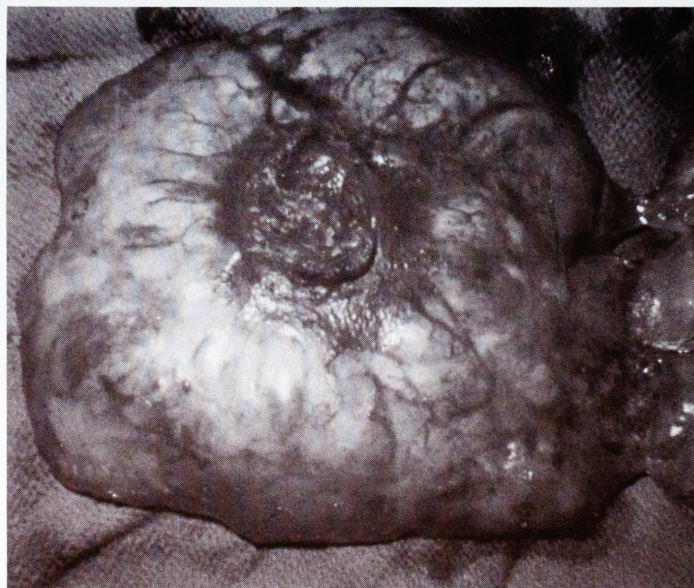

FIGURE 57-10. This benign localized fibrous tumor of pleura grew attached to the visceral pleura by a pedicle containing large, engorged vessels. (Contributed by the editor.)
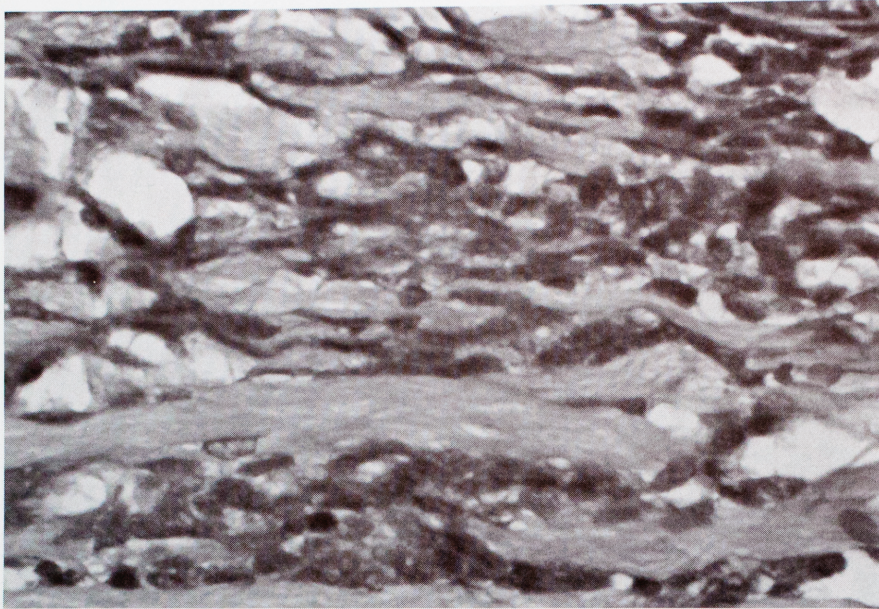
FIGURE 57-11. Microscopy of the tumor in Figure 57-10 shows the random pattern of growth with elongated fibroblastlike cells and intervening collagenous bands. (H & E stain; high magnification; contributed by the editor.)

vious studies showing epithelial differentiation probably reflected trapped mesothelial cells in the vicinity of the pleura. Tumor cells display prominent endoplasmic reticulum and abundant intermediate filaments. Occasionally, rudimentary epitheliallike features are seen in the cells, perhaps reflecting an origin from submesothelial totipotential cells.

Benign Extrapleural Neoplasms

SFTs are not restricted to the pleura; similar neoplasms have been described in the lungs, mediastinum, peritoneum, liver, and sinonasal and scrotal areas.[94–99] They should not be called fibrous mesothelioma, unless their constituent cells show evidence of mesothelial differentiation.

Unlike localized fibrous proliferations, benign multifocal accumulations of epithelioid mesothelial cells have been reported almost exclusively in the peritoneum. Some of these lesions have been interpreted as well-differentiated papillary mesotheliomas.

Most of them occur in females, and a peritoneal implant from an ovarian tumor is the obvious differential diagnosis. Papillary mesothelial tumors have been described in the pericardium but not in the pleura.[100]

Papillary mesothelioma may be multifocal, represented by numerous lesions that stud the peritoneal surfaces. Microscopically, the papillary projections contain a fibrovascular core surrounded by a single layer of bland cuboidal mesothelial cells. These cells usually reveal epithelioid mesothelial differentiation, including a brush border and long microvilli.

Another benign condition affecting the peritoneum is a multicystic neoplasm known as benign cystic mesothelioma.[101] This lesion is more common in females, but approximately 17% of them occur in men.[102] Benign cystic mesotheliomas are composed of mesothelial cells that are detected ultrastructurally and with immunocytochemistry methods. Some of these are virtually noncystic and may appear undistinguishable from adenomatoid tumors of the epididymis, the testicles, and the spermatic cord in
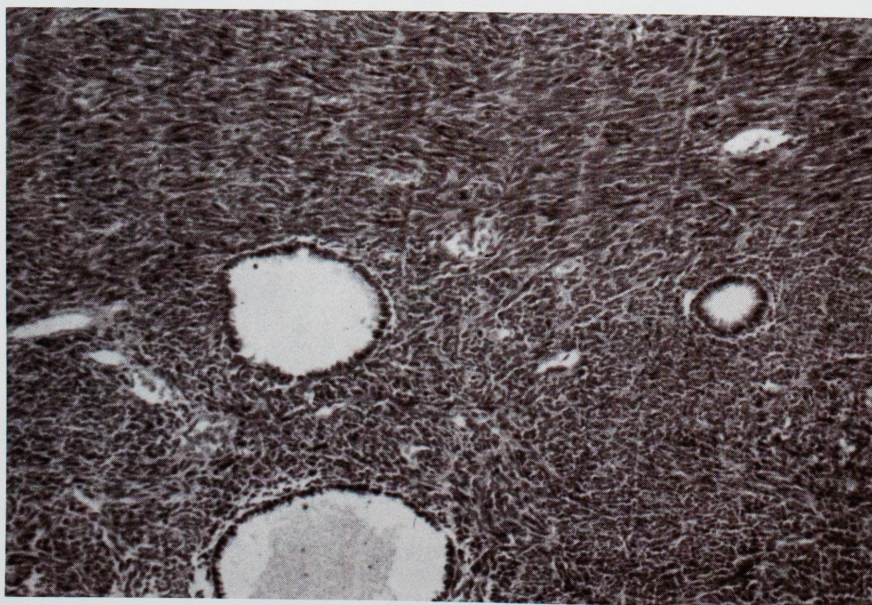

FIGURE 57-12. This malignant form of localized fibrous tumor of the pleura recurred locally three times after surgical excision. Note the high cellularity and entrapment of small airways by the tumor. (H & E stain; low magnification; contributed by the editor.)
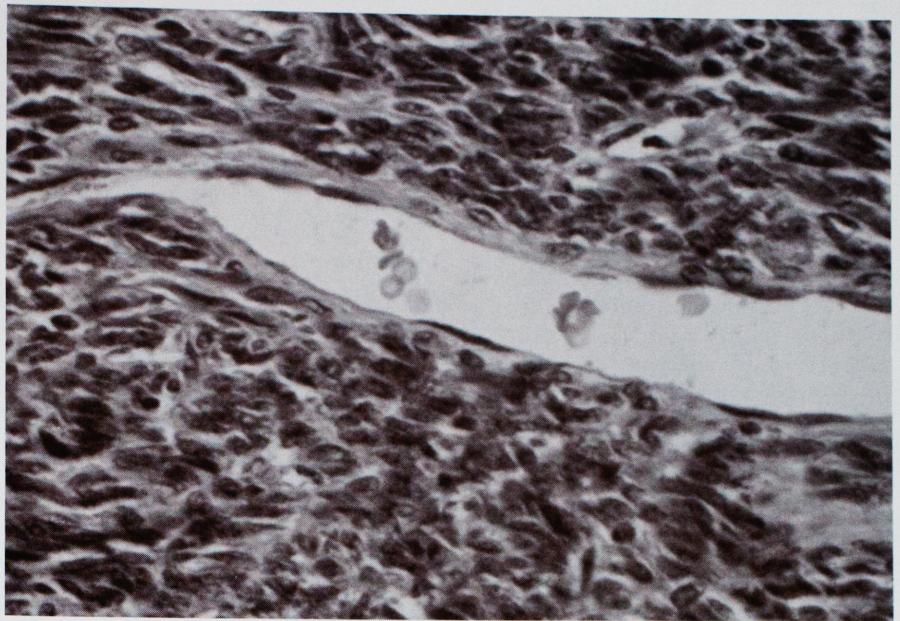
FIGURE 57-13. On closer examination, the same tumor as that in Figure 57-12 shows hypercellularity, cell pleomorphism, and frequent mitosis. (H & E stain; high magnification; contributed by the editor.)

men and of the fallopian tubes, the broad ligament, the hilus of the ovary, and uterus in women.

An adenomatoid tumor occurring in pelvic or extrapelvic peritoneum must be differentiated from cystic peritoneal mesothelioma and from metastatic foci, a task compounded by the fact that cystic, papillary, and adenomatoid patterns may be combined in the same lesion. Rarely, solid localized collections of mesothelial cells have been found within the parenchyma of certain organs, including the lungs. These are bland lesions composed of nondescript cuboidal mesothelial cells that are not arranged in any particular pattern. Ultrastructural and immunocytochemical examination of these cellular collections have demonstrated their mesothelial features.

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