Malignant Mesothelioma

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Advances in Pathogenesis, Diagnosis, and Translational Therapies

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Dedications are insights into the personal lives and motivations of the editors of a book. Because each of us has dedicated so many years of our professional and personal lives to studying and grappling with mesothelioma, we collectively decided to dedicate this book to the amazing and wonderful patients with mesothelioma and their families who have changed each of our lives for the better. Their humanity, compassion, humor, and courage during their unique and heroic battles are beacons that will forever illuminate the path forward.

Personally, we each dedicate the book to special people in our lives:

To Helen, Ally, and Eric Pass, who put up with Poppy becoming completely overwhelmed but still provide him with the love he always needs.

Harvey I. Pass, MD

To my father Reverend Nicholas Vogelzang who at age 85 continues to have intense curiosity, a keen sense of humor, love of family, and dedication to the welfare of others. I love you Dad.

Nicholas J. Vogelzang, MD

To my father, Carmine Carbone, Professor of Orthopedics and sixth generation physician in my family, who inspired and in a way forced me to become the seventh generation physician.

Michele Carbone, MD, PhD

Preface

Malignant mesothelioma remains one of the sentinel malignancies of oncology. It has a breathtakingly rapid natural history with a median survival of 6 to 8 months when untreated, is environmentally related, and has such economic and social impact that attorneys specialize in representing only mesothelioma patients. Expert witnesses devote full time to testifying, and governments are forced to consider not only the banning of the environmental agent but also a reappraisal of the whole tort system for compensation to injured victims. Furthermore, its presence in certain populations has changed the mindset of whole communities, such as Libby, Montana, Cappadocia, Turkey, Sarnia, and Ontario.

Because of its infrequent occurrence, malignant mesothelioma is considered an orphan disease and managed in an anecdotal fashion in most oncologic practices. Yet this disease has set new scientific paradigms—in the clinic, laboratory, and community.

This book has been assembled to correct an information "disconnect" about this orphan disease and to raise awareness among scientists everywhere about new concepts in the molecular genetics, epidemiology, and carcinogenesis of mesothelioma. We, as editors and authors, work to spread knowledge about mesothelioma and reverse the disproportionately low amount of NCI funding committed to the study of this cancer. Furthermore, we believe that study of this fascinating disease, while occurring in the context of litigation concerns, should proceed along the same paths that all science takes, following the trail of discovery. Legal issues should have no influence—but sadly often do have—on the direction taken by science and medicine.

Over the last ten years, data have accumulated indicating that mesothelioma is a cancer caused by the environmental carcinogens asbestos and erionite, which interact with genetic predisposition and viral infection during cardinogenesis. The outcome of these complex interactions determines who among exposed individuals will develop malignancy. Moreover, mesothelioma has become the ideal model to study how genetics and viral infection influence environmental

carcinogenesis, as well as to discover novel targets for early detection and therapy.

Few cancers have caused so much controversy as mesothelioma. For more than 40 years scientists have argued whether chrysotile asbestos does or does not cause mesothelioma. As if the chrysotile controversy was not enough, a new controversy developed in the field of mesothelioma when two of the editors of this book (HP and MC) reported that SV40, a DNA tumor virus that causes mesothelioma in animals, was present in some human mesotheliomas. Besides these important causality issues, conflict exists regarding the best surgical therapy for the disease and the interpretation of novel trials for mesothelioma. All these volatile issues, including the economic, legal, and most important of all, the scientific aspects, are addressed in various chapters in this book. We encourage the reader to not only digest these topics but to follow these controversies in mesothelioma prospectively as new data are introduced.

The proliferation of mesothelioma-specific knowledge has led to an increase in the number of global conferences devoted to mesothelioma, at which scientists present new and exciting findings. A sufficient quantity of mesothelioma-specific research now stands strong and is no longer the stepchild at meetings devoted to lung cancer or sarcoma. Clinicians and scientists alike are being identified as "mesothelioma experts," and their advice in preventing and detecting the disease early, as well as in the treatment of the disease, is being solicited not only by other physicians, but by a growing number of E-mails directly from patients and their families.

The editors envisioned a comprehensive text that described the controversies and facts in order to heighten awareness of the mesothelioma epidemic and to aid both clinicians and bench scientists in their efforts to either treat the disease or design new therapeutic options. The complexity of mesothelioma has only recently been realized, and this complexity demands that the disease "graduate" from being just another chapter in an oncology text. Therefore, this book is intended to be used as an authoritative guide by PhDs, primary care physicians, pulmonologists, medical oncologists, radiation oncologists, and surgical oncologists, as well as by fellows in training in these subspecialties. Moreover, because of the economics and legal impact of mesothelioma, this book will have a significant impact in courts of law.

This was truly an international effort, and the North American, European, Middle Eastern, and Australian perspectives on both the clinical and translational aspects of mesothelioma are represented. This fact, in itself, reinforces the global nature of this smoldering epidemic, and emphasizes that a reference source that can potentially be expanded in future editions should be launched at this time. The editors are grateful to all of the authors who took time from their incredibly busy schedules to contribute to this first effort. Their enthusiasm and patience in providing the most up-to-date information regarding their areas of expertise are reflected in their chapters, and the editors are convinced that their efforts will be rewarded with a newer

generation of oncologists and investigators who will approach mesothelioma with knowledge instead of apathy.

Finally, the editors wish to thank Springer for having the foresight to recognize the void in the literature regarding mesothelioma by publishing this book. When the publishing house was first approached about this project, there was never any hint of too small a market or population to endorse or support the project, and Springer has been a wholehearted working partner in this effort. Special thanks go to Beth Campbell, Stephanie Sakson, Barbara Chernow, Brian Drozda, and Laura Gillan diZerega, all of whom stood by this undertaking with unwavering support.

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Part One

Carcinogenesis

1

The History of Mesothelioma

Dorsett D. Smith

The story of the discovery of this rare tumor and of the subsequent controversies that arose about its causation by specific forms of commercial asbestos is long and complex. It could fill an entire book. This chapter focuses on the early history of the discovery, from 1767 to 1900; on the histologic controversies, from 1900 to 1942; and on the diagnostic controversies and the role of asbestos, from 1943 to 1973 (Table 1.1). The period from 1972 through the 1980s and 1990s could be characterized by advances in the industrial hygiene assessment of exposures, case-control studies, and other major epidemiologic studies concerning health effects in asbestos end-product users, paraoccupational exposures, household exposures, school and building exposures, and the role of specific asbestos fiber types, fiber characteristics, and lung fiber burden analysis. The 1970s to 1990s was also the period when the role of environmental exposure to erionite, tremolite, and ceramic fibers was discovered, and molecular and cellular biology focused on the characteristics of fiber carcinogenicity. In the final period, from the late 1990s to the present, the focus has been on the viral contribution to pathogenesis such as SV40 and human genetics and treatment strategies. The history of the discoveries after 1973 is covered by other authors in other chapters in this book.

Early Discovery, 1767 to 1900

The history of the term *mesothelioma* has entailed more than 100 years of controversy. The earliest mention of a possible tumor of the chest wall was by Joseph Lieutaud (1), generally regarded as the founder of pathologic anatomy in France according to Wolf (2), as quoted by Robertson (3). Lieutaud published a study of 3000 autopsies, among which were two cases of "pleural tumors." The published account mentions a boy who suffered from marked dyspnea following trauma, who at postmortem showed fleshy masses adherent to the pleura and the ribs. Laennec (4) in 1819 is also said by Robertson to have suggested that there was an entity of primary malignancy of the pleura based on

Table 1.1. Important historical events between 1767 and 1972

Year	Researcher	Event
1767	Lietaud	Report of first possible case of pleural mesothelioma
1854	von Rokitansky	First pathologic description of peritoneal mesothelioma
1870	Wagner	First pathologic description of pleural mesothelioma
1890	Biggs	First American case
1920	Du Bray, Rosson	First use of the term *mesothelioma*
1924	Robertson	Best review of literature up to that time
1942	Stout, Murray	Further evidence on histogenesis
1953	Weiss	Association with pleural mesothelioma made in Germany
1954	Leichner	Association of asbestosis with peritoneal mesothelioma
1957	Godwin	Clear pathologic criteria for pleural mesothelioma
1960	Winslow, Taylor	Clear pathologic criteria for peritoneal mesothelioma
1960	Wagner	Mesothelioma associated with northwest Cape crocidolite
1964	Enticknap, Smither	Association of asbestos and peritoneal mesothelioma
1965	Selikoff	New York Academy of Science Symposium, report on U.S. insulators
1969	Wagner	Animal model further perfected
1972	Stanton, Wrench	Stanton hypothesis on the importance of fiber size/length

the epithelial nature of these pleural cells. In 1843, von Rokitansky (5) actively opposed the idea of primary cancer of the pleura, and stated that pleural cancer always was secondary to a primary focus elsewhere. Ironically von Rokitansky in 1854 described what were called primary tumors of the peritoneum, which he called "colloid cancer" and most likely were peritoneal mesotheliomas. This strong opinion on the metastatic origin of pleural mesotheliomas by the German pathologists was to remain the opinion of many pathologists up through the mid-20th century as stated by Willis (6). There were further reports in the early 19th century of what could be considered pleural-based cancers. It was Wagner in 1870 who first described a lesion, which he classified as "Das Tuberkelähnliche Lymphadenom." He felt this was a primary malignancy of the pleura in a 69-year-old woman in whom an epithelial-based malignancy was found. Wagner had described lymph channels filled with tumor. Schultz (7) in 1875 reexamined the preparations of Wagner and emphasized the neoplastic nature of the process and renamed it endothelial cancer. The tumor was thought to arise from the lymph vessels and was commonly called an endothelioma. This was not questioned until 1891, when Engelbach (8) first raised the question of whether these tumors arose from the endothelium of the lymph vessels or from the surrounding serosal surfaces.

During the late 19th century and early 20th century, there was general acceptance that some sarcomas arose from the pleura when there was no evidence of a primary elsewhere, and it was generally accepted that the only tumor that might be primary to the pleura or the subpleura was a primary sarcoma. This was generally the Italian view as summarized by De Renzi (9). In 1890 Biggs (10) was the first American to report two cases of "endothelioma of the pleura" at the New York Pathological Society. Primary fibrous sarcomas of the pleura were generally accepted as arising from the fibroblast but not the pleural tissue itself. The fact that the pleural lining was capable of producing tumors that were both epithelial and of connective tissue origin was first pointed out by Paltauf (11), Borst (12), and Kaufmann (13). By 1909 Patterson (14) found 96 cases in the literature and added two of his own. The disease occurred twice as frequently in men than in women, and the greatest number of cases was found in patients between the ages of 40 and 60 years.

Histologic Controversy, 1900 to 1942

Miller and Wynn (15) were the first to advance the opinion that a peritoneal neoplasm was able to present both epithelial and fibroblastic characteristics because of the embryologic relationship of these cells to the mesoderm. Later, Maximow (16) was able to demonstrate via tissue culture direct transitions from the mesothelioma cell to fibroblast.

In 1924 Robertson's (3) article on endothelioma of the pleura was probably the most thorough review of the literature that had been done up until that time. At the time of that publication, endotheliomas or primary pleural malignancies were certainly rare, in that Clarkson (17) in 1914 stated that out of 10,829 postmortem exams performed in Munich, Germany, there were only two cases of primary endothelioma of the pleura, although he could find records of only 41 cases. Later, Robertson quotes Keilty (18), who reviewed the records of the pathology department at the University of Pennsylvania and found nine cases of primary endothelioma of the pleura in 5000 postmortem examinations.

Bayne-Jones (19) described a 16-year-old boy with a pleural-based malignancy that Bayne-Jones thought was a primary neoplasm of the lining cells of the pleura and an epithelial tumor, which he described as a carcinoma of the pleura. Bayne-Jones thought this tumor was not an endothelioma or it did not arise from the endothelium of the lymphatics but from the mesothelial cells and therefore was an epithelial carcinoma. In 1920 Du Bray and Rosson (20) proposed the term *primary mesothelioma of the pleura*. They thought the term *pleural carcinoma* or *endothelioma* was not appropriate, but that the term *mesothelioma* was most appropriate. In 1921 Eastwood and Martin (21) agreed that the term should be *mesothelioma*. Zeckwer (22) also used the term *mesothelioma* in his report of 1928. The issue as to whether there was such a thing as a primary endothelial malignancy arising from the pleura was carefully discussed by Robertson (3) in his seminal paper, and he

rejected the idea that the epithelial tumors were primary tumors of the mesothelium; he thought that these tumors were most likely metastatic tumors of some other origin. He thought that only sarcomas could be classified as primary malignant tumors, and that all other types of growth were secondary tumors with implementations or metastasis from unrecognized, latent primary malignancies elsewhere.

In 1931 Paul Klemperer and Coleman Rabin (23) published a report of five cases from Mt. Sinai Hospital in New York City, including one case with both epithelial and mesenchymal characteristics. They thought that diffuse neoplasms of the pleura arose from the surface lining cells, the mesothelium, and should be designated mesothelioma as previously suggested by others.

In 1933 S. Roodhouse Gloyne (24) reviewed his series of asbestosis cases and stated, "Of the complications unrelated to the asbestosis the following have been noted: (a) abdominal carcinoma; (b) mitral stenosis; (c) cerebral hemorrhage, and (d) cholelithiasis. There has been one case of squamous carcinoma of the pleura. There is no evidence at the moment that this was in any way related to asbestosis." It is open to speculation as to whether these were the earliest cases of mesotheliomas in asbestos-exposed workers!

Ewing (25) in 1940 raised the question of the influence of chronic irritation or trauma and low grades of inflammation in causing connective tissue changes in the pleura, and wondered if some of the cases of pleural malignancy were connected with tuberculosis. Many of the previously reported cases had evidence of coexistent tuberculosis, in several attacks of pleurisy on the involved side. The trauma and chronic inflammation as a cause of pleural transformation were reviewed by Ewing (25). Ewing's comments were amplified by an excellent review of the literature by Andrea Saccone and Aaron Coblenz (26) from New York City in 1943. The authors were able to identify 41 cases in seven published series between 1910 and 1938 from a total of 46,000 autopsies or 0.09% mesotheliomas. They concluded from their review of the case reports that some of these tumors were misdiagnosed and were metastatic from other sites. Certainly the confusion in making the pathologic diagnosis would continue for many years. From 1960 to 1968 only one half of Canadian mesothelioma cases on death certificates could be confirmed by an expert panel (27).

Further support for the idea that these tumors arose from the mesothelium rather than from the endothelium was provided by Stout and Murray (28) of New York City in 1942. They used their studies on tissue cultures to support the idea that malignant cells arose primarily from the mesothelial cell. Their concept of histogenesis was so controversial at that time that their Department of Pathology chairman required them to publish a statement of his disbelief in their paper. Stout was later to become professor of pathology at Columbia University in New York City. He was able to accumulate pathologic material on 156 mesotheliomas between July 1919 and June 1964. This was the largest series from a single institution in the world as of 1964 and yet Stout (29) later commented that in retrospect he was unaware of a single case associated with asbestosis.

Further support for Stout's theory of histogenesis came from Canada in a paper by Postoloff (30) entitled "Mesothelioma of the Pleura," in which he concluded that, indeed, the mesothelioma is capable of transforming into both an epithelioid malignancy and a sarcomatous malignancy. He emphasized the importance of an osteoid matrix in the histologic features of mesothelioma. He also mentioned that his team found only seven mesotheliomas out of 7878 consecutive autopsies covering a 20-year period between 1923 and 1942.

By 1946 Arnold Piatt (31), a radiologist at the Newark Hospital, reviewed the radiologic aspects of primary mesothelioma or endothelioma of the pleura. By then over 200 authors had discussed and offered opinions on the entity, which at that time was called primary mesothelioma or endothelioma of the pleura. Piatt points out that it was a very difficult diagnostic problem for pathologists, who argued among themselves as to the type and histologic origin of the neoplasm. By then there were as many as 30 different terms used to describe this clinical entity, including *endothelioma*, *mesothelioma*, *endothelial carcinoma*, *pleural carcinoma*, *primary papillary endothelioma of the pleura*, *adenoendothelioma*, *sarcoendothelioma*, *pleural sarcoma*, *round cell sarcoma*, *spindle cell sarcoma*, *angiosarcoma*, *lipomyxosarcoma*, *giant cell sarcoma of the visceral pleura*, *sarcomatous malignancy of the pleura*, *malignant tumor of the pleura*, *mesothelial carcinoma*, *perithelioma*, *endothelioma*, *carcinomatodes*, *lymphangioendothelioma*, *fibroendotheliosis of the pleura*, *lymphangitis proliferans*, *pleuroma*, *abdominal colloid tumor*, and *tubercle-like lymphadenoma* (32).

Definition and Suspicion, 1943 to 1960

In the confusion about whether mesothelioma was truly a separate clinical entity, there were five different opinions as to the source of the tumor: (1) an aberrant nest of lung epithelium became malignant within the lining of the pleura; (2) the endothelial lining of the subpleural lymphatics was the source of the tumor, hence the name endothelioma; (3) the tumor arose from the pleural capillary endothelium or endothelial lining of the subpleural lymphatics, or both; (4) the tumor arose from the mesothelial lining of the pleura itself, or was a mesothelial-derived tumor or a mesothelioma; (5) those tumors of epithelial origin always arose from a primary tumor elsewhere that had metastasized to the pleura. These primary tumors could be so small that they were easily missed on a routine autopsy. A sarcoma was a primary from the subpleural connective tissue. It is because of the differences in opinion about the origin of the tumor that there was such a large number of terms used to describe the same process.

In this setting of confusion, early reports began to filter out that some patients with asbestosis developed an unusual form of pleural malignancy. The first report was by Wedler (33), who reported the results of 30 autopsies on asbestos workers in Germany. He excluded one case, and of the 29 remaining autopsies, four had bronchial cancers, and two others had a malignant pleural growth. He commented about his own

impression that the incidence of cancer, which was 20% for malignant tumors in this population, was much too high to be by chance, and that the lung cancer was due to the asbestos exposure. He reviewed all the known studies at that time, and pointed out that the first mention of a lung cancer associated with asbestosis was made in 1933 by Gloyne (34), who stated, "There has also been one case of squamous cancer of the pleura. There is no evidence at the moment this was in any way related to asbestosis." In 1935 Gloyne (35) was able to report two additional patients with lung cancer and asbestosis. Wedler did not discuss whether the pleural cancers he found were true mesotheliomas or were related to an underlying lung cancer; he simply reported these findings and called them pleural growths of epithelial origin. He stated that lung cancer was the most common complication encountered in cases of asbestosis.

While the report of Wedler was readily accepted in Germany, the information was generally ignored elsewhere. In retrospect, Harrington (36) stated, "Of particular interest is the apparent influence of politics, given that the earliest published accounts emanated from Nazi Germany, thus received less attention and credence than was their due. Furthermore, there was the skepticism—presumably natural rather than biased—on the part of many early scientific observers in both the United States and Britain." In 1947 a patient with a mesothelioma of the pleura and pericardium who worked with asbestos cutting insulation board was reported as chronic pulmonary congestion (CPC) by the Massachusetts General Hospital, but the association with the asbestos exposure was not made (37). In 1952 Cartier (38) reported in a scientific meeting via an abstract of a discussion of a paper by W.E. Smith seven cases of respiratory cancer in 4000 asbestos workers working in the Quebec chrysotile mining and milling industry, and included in the cohort were two cases of pleural mesothelioma. Cartier thought that since the two mesothelioma cases did not have asbestosis, causation from asbestos exposure could not be made. The details of these cases were never published.

A year later, in 1953, Weiss (39) added a third case to the two malignant tumors of the pleura described by Wedler, that of a man with asbestosis and pleural mesothelioma who had done insulation work in a naval dockyard from 1920 until 1935. Weiss believed that the association between asbestosis and pleural mesothelioma was strong, and therefore he recommended that the German government accept this as a work-related condition. Von Rokitansky (40) in 1854 described what were called primary tumors of the peritoneum, which he called "colloid cancer." While this tumor was mentioned in the English literature, first by Miller and Wynn (15) in 1908, the association between peritoneal tumors and possible asbestos exposure was not made until 1954 when another German, Leichner (41), described an autopsy done 2 years earlier on a 53-year-old man who worked in an asbestos factory primarily as a spinner. Leichner reported that the patient had asbestosis and tuberculosis, but had what appeared to be an incidental finding of a peritoneal mesothelioma. Leichner found evidence of asbestos fibers in the tumor, and felt that this peritoneal mesothelioma was

again work related. A short time later, in 1955, Bonser et al (42) reported 72 autopsies of patients with asbestosis in which four were found to have abdominal neoplasms consistent with a peritoneal mesothelioma, but the authors never made the association that these were asbestos-induced peritoneal mesotheliomas.

In 1956 Ackerman (43) wrote that it was the majority opinion that primary mesotheliomas were rare but do exist. A year later, in 1957, Godwin (44) wrote a very important paper that laid down strict diagnostic criteria for the diagnosis of pleural mesotheliomas. In 1958 Van der Schoot (45) reported two mesotheliomas in insulation workers.

In 1958 McCaughey (46) from Belfast, Ireland, reported 11 diffuse and two localized pleural mesotheliomas. He felt there was strong evidence to support the belief that diffuse pleural mesothelioma was a clinical entity in spite of opposition to this idea. He did not make the association in this study to asbestos exposure, but he would do so in retrospect a few years later (47). This paper was a response to an article published by Smart and Hinson (48) of the London Chest Hospital who reported 24 cases of pleural neoplasm and concluded that the occurrence of a true neoplasm of pleura could not really be denied, that the lesion is produced from known primaries, and that there was no need to postulate an origin from that site (49). In 1956 Eisenstadt (50) of Port Arthur, Texas, reported a patient who worked in a refinery who developed what appeared to be a malignant mesothelioma of the pleura. He pointed out that very experienced pathologists denied the existence of such a tumor, but he felt impelled to report the case anyway.

A good example of the confusion about what to do with the diagnosis of mesothelioma is the discussion of the condition by Sir Richard Doll (51) in his classic 1955 study of the association between lung cancer and asbestosis. In Table II of the article he describes 15 patients with asbestosis and some type of lung cancer, but only uses 11 of the 15 in his analysis. Two of the patients are recorded as having either an endothelioma of the pleura or epithelial carcinoma. Three additional patients with lung cancer were found, but they did not have asbestosis. The association between the asbestos exposure and the endothelioma of the pleura was not made, and, evidently, was excluded from this statistical analysis.

The seminal year for making the association between asbestos exposure and mesothelioma is 1960. The seminal paper is that by Wagner et al (52), entitled "Diffuse Pleural Mesothelioma and Asbestos Exposure in the Northwestern Cape Providence." The paper was very controversial because it described 33 cases of diffuse pleural mesothelioma with exposure to only one type of asbestos, so-called Cape Blue asbestos mined in the asbestos hills west of Kimberly in the northwest Cape Providence of South Africa. Wagner et al said the tumor was rarely seen elsewhere in South Africa. This means the tumor seemed to be rather specific to a certain geographic area and a specific type of crocidolite asbestos. The data were considered suspect by many pathologists, in that only four of the patients had full autopsies, the rest having had simple pleural biopsies that were recognized by many as being unreliable in making the diagnosis of mesothelioma. The other

problem was that previously reported patients had heavy industrial exposure and usually asbestosis, and the majority of Wagner et al's cohort did not have asbestosis or heavy industrial exposure. The general consensus at that time was that a true mesothelioma diagnosis could not be made unless there was a complete autopsy excluding some primary tumor elsewhere in the body that had metastasized to the pleura and unless there also was concomitant asbestosis. The initial response was muted, as so eloquently stated by Elliott McCaughey (53) because of "the lack of experimental animal evidence, rejection or lack of knowledge of science conducted outside of the United States, and reluctance of individual writers to change their minds." In an editorial written in South Africa in 1968, the relationship between crocidolite exposure and mesothelioma was still thought to be unproven (54).

In 1960 Eisenstadt and Wilson (55) published a paper describing two patients with pleural mesothelioma. The second patient had a long-term history of exposure to asbestos, and there were asbestos bodies in the lung biopsy specimen. The authors felt there was an association between the asbestos exposure and the subsequent development of this unusual pleural malignancy.

Association and Causation, 1960 to 1973

Also in 1960 Keal (56) reviewed the records of an English hospital and found 23 women with asbestosis. Four had carcinomatosis of the peritoneum without a known primary, one had ovarian cancer, and four others had peritoneal malignancy possibly of ovarian origin. The association with asbestosis is glaring, but the connection between asbestos exposure and peritoneal malignancy was not strongly suggested until 4 years later. Winslow and Taylor (57) published a series of 12 cases of peritoneal mesothelioma in 1960 and reviewed 13 previously reported cases found in the world literature. No association with asbestos exposure was mentioned in their paper. However, the association between asbestos exposure and diffuse abdominal tumors was established in the English literature by the paper of Enticknap and Smither (58) in 1964. Here again, the Germans made the association between asbestos exposure and this rare tumor earlier than other investigators. While attempts to define the tumor mesothelioma were made by earlier investigators such as Klemperer and Rabin (23) in 1931, there was no general agreement among pathologists that such an entity really existed. In 1957 Godwin (44) published strict criteria for the diagnosis of pleural mesotheliomas that placed the pathologic identification on a more firm scientific footing. It was not until 1960 that Winslow and Taylor did the same thing for peritoneal mesothelioma tumors. After Wagner's discovery of the association between Cape Blue crocidolite asbestos and the increased risk of mesothelioma in South Africa, the question arose as to whether this was a unique problem limited to South Africa or whether this was a problem occurring in the United States. The American Medical Association Council on Occupational Health (59) published an article on Pneumoconioses in the *Archives of*