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The History of Mesothelioma

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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*

Environmental Health in 1963, in which there is a section on asbestosis. The panel of experts concluded:

> The relationship between cancer of the lung and asbestosis constitutes a problem of great current interest. There is no doubt that the two diseases appear in the same lung. Whether that occurrence is one of mere coincidence, or of direct cause–effect, the relationship cannot be resolved on the basis of a single case. The total body of evidence favors a relationship, especially as it involves certain kinds of asbestos and possibly only those that contain specific chemical substances have the capacity to cause cancer. Attention is invited to experiences in the union of South Africa where pleural mesotheliomas have been discovered in appreciable numbers of persons exposed to the inhalation of crocidolite-amosite asbestos. Certainly detailed epidemiologic clinical and experimental studies are required for the ultimate resolution of the problem. [p. 37]

In 1962 Wagner (60) was able to produce mesothelial tumors of the pleura by direct implantation of asbestos dusts in laboratory animals. In 1963 Wagner reported at the 14th International Congress of Occupational Health on 120 cases of mesothelioma, but curiously less than one half of the patients directly worked with asbestos; they just lived in the area where there was environmental exposure. The question at that time was whether this was a localized group of mesothelioma patients or the forerunner of an international epidemic. This question was answered at the International Meeting on Biological Effects of Asbestos held at the New York Academy of Sciences in New York City in October 1964 but not published until December 31, 1965 (61). Reports at the New York meeting from Newhouse and Thompson in London, Elmes and Wade in Ireland, Jacob and Anspach in Germany, Hammond, Selikoff, and Churg in the United States, and Viliani and coworkers in Italy confirmed the global extent of the problem.

Selikoff et al (62) reported their working experience with the relationship between asbestos exposure and mesothelioma in the *New England Journal of Medicine* in 1965, further cementing the relationship between asbestos exposure and mesothelioma and raising the question of whether others types of asbestos might also cause mesotheliomas. The authors did not believe that American workers had significant exposure to crocidolite. They thought that the emergence of mesotheliomas in their cohort of asbestos insulators represented mainly exposure to chrysotile and amosite. All patients had heavy exposure and asbestosis. This article was followed by an editorial in the *New England Journal of Medicine* on March 18, 1965 (63). The editorial mentions that amosite, the third commercially used form of asbestos, has yet to be incriminated, but there are no definitive studies to date to confirm or deny such a connection.

Sluis-Cremer (64) of the Miner's Medical Bureau in Johannesburg, South Africa, gave a report to the New York Academy of Science in 1965. Sluis-Cremer in his discussion of mesotheliomas pointed out that his epidemiologic studies found mesotheliomas only in the northwest cape area of South Africa. The Transvaal amosite deposits had been actively developed for longer than this period, and he mentioned that

in the 1940s amosite was produced in three times the amount of the northwest crocidolite, yet no mesotheliomas were seen in the northwest area related to amosite exposure.

Of particular interest was the case control study of Newhouse and Thompson (65). They diagnosed 83 patients, 41 men and 43 women, with mesothelioma in association with a Cape Blue asbestos factory that opened in London in 1913. There were 27 peritoneal tumors and 56 pleural tumors. The factory used Cape crocidolite exclusively until 1926, when small amounts of amosite and chrysotile were added. Eighteen patients were employed in the asbestos factory and eight as insulators and laggers. An additional nine patients lived in the same house as an asbestos worker. Particularly distressing was the discovery of 36 patients with no known work or domestic exposure to asbestos. Eleven of these patients lived within one-half mile of the asbestos factory, suggesting neighborhood exposure. This case-control study and one by Elmes et al (66) were the first two case-control studies to confirm the earlier report of Wagner from South Africa. The concern about neighborhood exposure was echoed by Lieben and Pistawka (67) of the Pennsylvania Health Department, who reported that of 42 patients with mesothelioma only 20 had occupational exposure, eight lived within the vicinity of an asbestos plant, and three had family exposure.

The general medical community had believed that if asbestosis could be avoided by reducing exposure to friable asbestos, then asbestos-related malignancy would also be avoided. The early mesothelioma cases were generally heavily exposed in the early 1900s prior to the promulgation of dust control measures. Selikoff (68) stated in 1969, "I have yet to see a mesothelioma in a man who began work after 1930 or a case of lung cancer in an asbestos worker who had worked in that industry less than twenty years." However, the data of Wagner, Newhouse and Thompson, Lieben, and others challenged this. Thompson (69,70) reported in 1963 asbestos bodies in the lungs of people who were not asbestos workers and called it a modern urban hazard.

In 1968 Utidjian et al (71) reported that almost 100% of urban dwellers had asbestos bodies in their lungs. By 1970 Thompson's original observations were widely confirmed in Montreal, Milan, London, Newcastle, Glasgow, Belfast, Dresden, Pittsburgh, Miami, and New York (68). A paradigm shift had occurred; by 1970 it was generally accepted that low-level exposure to northwest Cape Blue crocidolite was capable of causing mesothelioma. By 1966 the importation of crocidolite asbestos had been voluntarily abandoned in England, and new asbestos regulations accepting the relationship between asbestos and mesothelioma were adopted in 1969. The standard for asbestos exposure in England was set at 0.2 f/mL (F is the degree of fineness of abrasive particles) for crocidolite or one-tenth the acceptable level of exposure to other forms of commercial asbestos at 2 f/mL (72). The question remained how much exposure was too much. The next 30 years would be focused on the role of other types of commercial asbestos and noncommercial asbestiform materials. Wagner and Berry (73) by 1969 had perfected an animal model that would help answer

many of these questions. Stanton and Wrench (74) had demonstrated in 1972 that the carcinogenic potential of asbestos was related to its diameter and length.

In 1965 Sir Bradford Hill (75) proposed criteria for assessing causation in chronic diseases. His seminal paper presented at the Royal Society of Medicine provided a systematic approach to evaluate the association between asbestos exposure and mesothelioma. The main requirements were strength of association, consistency of association, dose-response relationship, and biologic plausibility. The acceptance of new ideas moves slowly. Biologic plausibility of carcinogenesis is meant primarily to be based on animal and cell tissue modeling or by analogy to other human tumors. Unfortunately, biologic plausibility for many in the 1960s and early 1970s meant that if I can't understand it, I don't believe it.

The Doubters and the Role of Other Forms of Asbestos

It seems that every advance in science has its naysayers who are pulled along screaming and kicking. Garrett Schepers (76), then working as an American pathologist, was originally from South Africa. He related his own experience at the New York Academy of Sciences meeting:

> As a boy, I lived not far from Kuruman for a number of years. One could not imagine a more healthy territory. However, there is a particular irritating type of grass in the area (Klitsgras), whose seeds burrow into every garment they cling to, as these seeds are armed with fine barbs. Surely, when the wind blows, as often it does in Kuruman, some of these minute barbs may be inhaled. I wonder whether some of these fiber structures reported in the lungs of persons in that area may not represent reactions to grass barbules. I offer this Klitsgras theory of Kuruman mesotheliomatosis in order to clear the hurdle created by the discovery of this rare disease in such abundance in persons with such little meaningful exposure to asbestos. Perhaps the South African pathologists will now have their turn to make mincemeat of my theory. [p. 599]

Also at that meeting Schepers stated:

> My first impression is that there is now less certainty that asbestos inhalation is associated with pulmonary neoplasia than there was 10 or 20 years ago. Perhaps this is due to greatly reduced dust exposures. Asbestos may after all prove to be carcinogenic only in overwhelming dosage. Thus, the high prevalence of neoplasia which was reported several decades ago may be a function of the severity of exposure rather than an indication of high carcinogenic potency. I suspect that in the final analysis the carcinogenicity of asbestos will be rated as of low order. Perhaps carcinogenicity will prove to be a correlate of asbestosis rather than a specific biological function of the mineral asbestos. This may be the crux of the matter. In all cases of asbestos-associated lung cancer that I have personally studied (the number now exceeds two dozen), there invariably was well-established asbestosis. Not only was the asbestosis of marked degree in the areas where the cancer arose, but there generally was evidence from serial chest x-rays that asbestosis had been present in the lungs for a protracted period. [p. 595]

Ian Webster (77), who was J.C. Wagner's brother-in-law and a well-respected pulmonary pathologist, still stated that there were unsolved problems in the relationship between asbestos and malignancy in a paper he published in February 1973 in the *South African Medical Journal*. Webster remained skeptical as to why this previously rare tumor seemed to be found primarily only in direct relationship to crocidolite exposure. Webster suggested that some other factor, possibly mineral, must be present to explain the high incidence of mesothelioma in a very localized area of South Africa. He looked at exposure to asbestos and the association with 232 cases of pleural mesothelioma. Almost all the individuals had been exposed to Cape Blue asbestos and only two miners had been exposed to amosite as far as could be discerned. Thirty-two cases occurred where there was no evidence of any asbestos exposure, presumably having environmental exposure. There were only two cases related to exposure to amosite out of 232 confirmed cases of mesotheliomas. He stated, "Furthermore, it is difficult to conceive of amosite in the intermediate group of asbestos fibers causing malignancy, as suggested by Wagner et al when there are so few cases in the employees of the amosite mines." He goes on to say, "The production of amosite far exceeded that of Cape Blue asbestos. It is suggested that more attention should be paid to the determination of the nature of the substance of the Cape Blue areas and not in the Transvaal Blue, and apparently limited to the areas where amosite is mined." The same opinion had been offered earlier, in 1969, by George Wright (78), one of America's most respected investigators in occupational pulmonary disease, who in his review, "Asbestos and Health in 1969," stated, "That something other than, or in addition to, asbestos plays a role in mesothelioma formation seems inescapable." Wright accepted asbestos as a cause of mesothelioma but felt there was a "tolerable level of airborne asbestos fiber which does not cause an undue risk of development of mesothelioma." He later states that "the tolerable level was substantial."

The Role of Amosite and Chrysotile

In 1965 the polarization of expert opinion began between Irving Selikoff and his Mount Sinai co-investigators, and the British and largely European view on the role of chrysotile asbestos in causation of mesothelioma versus crocidolite asbestos. Selikoff et al (62) stated,

> American asbestos utilization differed to some extent from British and South African experience in at least one important respect. Crocidolite is a relative newcomer to the American asbestos-industry scheme. Thus American imports of crocidolite (none mined here) were less than 500 tons in 1935 and reached a level of only 20,000 tons even in 1962. In contrast, chrysotile, the type of asbestos fiber widely used in the American asbestos industry, was imported at a level of 165,000 tons in 1935 and 650,000 tons in 1962.

Later the authors stated, "If mesothelioma could be found with increased frequency in association with asbestos in this country, it would demonstrate that this tumor was another neoplastic hazard of

asbestos exposure in general and not limited to one area or to one type of asbestos." How much of the incidence of mesothelioma in America was due to amosite was unclear.

J.S. Harington (79) wrote a chapter on mesothelioma in the book *The Prevention of Cancer*, edited by Raven and Rowe in 1967. He stated, "The results of animal experimentation so far available suggests that crocidolite and chrysotile may be more active in inducing mesotheliomas than amosite. If the present trend is confirmed, substitution in mining and industry of amosite (for example, for the more dangerous types of asbestos where they cannot be safely used) may be a practical and important preventative measure."

In an unsigned editorial in *Lancet* published on March 5, 1966, the author stated, "A possible important clue to prevention was just uncovered by Wagner in South Africa, where after showing association between mesothelial tumors and exposure to the crocidolite form of asbestos, he and his colleagues were unable to find any tumors in those exposed only to the amosite or chrysotile-types of fiber. The position in South Africa remains the same, despite the continuing intensive search in the amosite and chrysotile mining areas." He goes on to say, "Mesothelioma tumors have been seen in a few individuals apparently exposed only to chrysotile in the United States and Canada, and other populations, either industrial or residential, exposed only to one type of fiber must now be investigated. This can be achieved only by international cooperation, because such exposures are almost entirely limited to those engaged in mining and milling of the fiber, which is done in the countries where the different types of asbestos are found." Selikoff et al (80) reviewed the results of a study of an asbestos insulation manufacturing plant in Paterson, New Jersey, and published their results in the *Archives of Environmental Health* in September 1972. In this paper the authors pointed out "few data exist concerning the comparative neoplastic potential in man of the several kinds of asbestos, and particularly there has been no evidence concerning whether amosite variety is carcinogenic. . . . Whether or not amosite is carcinogenic is of some practical importance. Because this variety of asbestos has not been reported to cause cancer, there has been a tendency in Great Britain, for example, to substitute it for other types of asbestos, especially crocidolite." Selikoff and coworkers went on to report an increased incidence of lung cancer and mesothelioma in this plant, where it was thought to be just a pure exposure to amosite asbestos. While it was generally accepted in the United States that pure amosite caused a high incidence of mesotheliomas and lung cancers, the paper by Selikoff and coworkers was not well accepted abroad. McCullagh (81) published a paper in the *Journal of the Society of Occupational Medicine* in 1980, "Amosite as a Cause of Lung Cancer and Mesothelioma in Humans." He pointed out that many of the Paterson, New Jersey, cohorts studied by Selikoff had previous exposure to asbestos. He felt that rather than one fiftieth of the group, it seemed more likely that one third of the group or 300 members of the Paterson cohort had been occupationally exposed to asbestos before entering the cohort. This is of import since crocidolite was being used in large quantities in

asbestos factories in the same area. Selikoff had felt that very little crocidolite had been used in the shipyards and in the United States, and therefore, if a mesothelioma developed, it was most likely related to amosite since there was very little crocidolite exposure. In fact the monthly trade journal *Asbestos* mentioned the use of crocidolite and amosite asbestos in July 1919.

John Harington and Neil McGlashan (82) reviewed the destination of South African exports of crocidolite and amosite asbestos as well as chrysotile from 1959 until 1993, and the studies indicate that the United States received a considerable amount of crocidolite asbestos up until 1992. This study and others have suggested there was more crocidolite asbestos used in the United States than had been previously recognized, and that the use of crocidolite asbestos is a major reason why there was an increased risk of mesothelioma.

J.C. Wagner recapitulated his overview of the association between blue asbestos and mesotheliomas in an article published in the *British Journal of Industrial Medicine* in 1991. He reviewed his story of the discovery of the association between asbestos and mesothelioma, and concluded that there was evidence that all types of commercial asbestos except anthophyllite may be responsible for a mesothelioma. He went on to state, "The risk is greatest with crocidolite, less with amosite, and apparently less with chrysotile. With amosite and chrysotile there appears to be a higher risk in the manufacturing than in mining and milling. . . . There is overwhelming evidence that crocidolite is a main fiber associated with mesotheliomas." This has primarily been the British view, and Raymond Parkes (83), in his classic book *Occupational Lung Disorders*, 2nd edition, published in 1982, stated about mesothelioma causation, "On present evidence its occurrence appears to be closely, but not uniquely, related to crocidolite alone or a mixture of fiber types in the distant past" (p. 276).

The most recent article relating to the historical crocidolite exposure issue in the United States was by Langer and Nolan (84) entitled, "Asbestos in the Lungs of Persons Exposed in the USA" and published in *Monaldi Archives of Chest Disease* in 1998. In their appendix of crocidolite consumption in the United States, they pointed out that blue asbestos for boiler and steam covering for locomotives was advertised in trade journals, such as *Engine*, as early as 1897. The data from the U.S. Department of Commerce reveals significant crocidolite importation in the 1920s and 1930s, and it included the spraying of crocidolite in the form of Limpet up until 1966. The paper goes on to mention that all three major fiber types were permanently used on ships, and crocidolite was extensively applied in warships in the United Kingdom. International investigators outside the United States have interpreted this to mean that crocidolite was also used aboard American ships, and if mesotheliomas occurred among American insulation workers who worked in military shipyards, this was indirect evidence of crocidolite exposure. The authors went on to state, "Still other investigators suggested that British ships were re-outfitted in U.S.A. ports during the war, and they have been the source of crocidolite exposure to

American shipyard workers. This most certainly occurred and citations in the literature support this."

It seems ironic that 100 years earlier in 1870 the distinct pathologic entity of pleural mesothelioma was postulated by one Wagner, and then greatly advanced 100 years later by another physician named Wagner whose contributions have propelled science into the next millennium.

Selikoff in hindsight also reviewed the literature on mesothelioma and stated, "During the 1950s there were several reports of deaths in asbestos workers caused by these diffuse tumors of the mesothelial surfaces. These isolated cases would have received little notice had it not been for the fact that the tumor has always been considered extraordinarily rare. It is no longer rare amongst asbestos workers. Indeed, it is so common a cause of death amongst them now. While still rare amongst individuals not known to be exposed to asbestos—it almost constituted tumor specific to asbestos exposure." Furthermore, writing in 1988, Dr. Selikoff and coworkers (85) stated, "Nevertheless only in the past 25 years has malignant mesothelioma been widely accepted as an independent diagnostic entity." These workers found 175 deaths from mesothelioma occurred among 2221 men who died between 1967 and 1976, and 181 more deaths in the next 8 years for a total of 356 deaths from mesothelioma out a total of 3500 deaths from all causes by 1984; 134 of these were pleural and 222 were peritoneal mesotheliomas.

The history of the early years of mesothelioma discovery are an example of how slowly the medical community accepts new discoveries. Acceptance was in part slowed by the lack of specific mesothelial cell markers such as are available today to assure proper diagnosis; experts disagreed among themselves as to the proper classification of these tumors. As the frequency of these tumors increased, pathologists made the diagnosis with more confidence and, as noted by Selikoff, there was general acceptance of not only the criteria for diagnosis but also the clear association with asbestos exposure by 1973. The role of specific fiber types would have to await the results of further studies, particularly lung fiber analysis by electron microscopy over the next 30 years.

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