Epidemiology of Mesothelioma and Historical Background

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Abstract Mesothelioma is a "new" malignant disease strongly associated with exposure to amphibole asbestos exposure (amosite and crocidolite) environmentally and in the work place. Nonetheless, in recent years, we have learned that many cases of mesothelioma are idiopathic, while some are caused by therapeutic irradiation or chronic inflammation in body cavities. This paper reviews the key epidemiological features of the malignancy in the context of the biological and mineralogical factors that influence mesothelioma development. These tumors challenge the diagnostic pathologist's acumen, the epidemiologist's skill in devising meaningful and definitive studies, the industrial hygienist's knowledge of environmental hazards in diverse occupational settings, and the clinician's skill in managing an intrepid and uniformly fatal malignancy.

Many, if not most, of the major life-threatening diseases afflicting humankind were recognized well before the Christian era. In that context, malignant mesothelioma is a "new" disease with its diagnostic features and natural history having been known to medical science for less than a century. It is my charge in this brief overview to trace the development of our knowledge of mesotheliomas as clinical and pathological entities, relating the occurrence of this malignancy to exposure to a unique family of fibrous minerals that gives rise to the majority of cases of mesothelioma. In doing so, we now are obliged to recognize the occasional patient with idiopathic disease and as of yet unidentified genetic or environmental parameters of disease susceptibility as mesotheliomas are studied critically.

As I sat at the breakfast table this morning, the now inevitable television advertisement appeared announcing the availability of skilled litigants in nationally prominent law firms who will make themselves available to asbestos "victims" whose suffering, they argue, deserves a substantial monetary award. Similarly, vivid advertisements soliciting the afflicted are plastered on the sides of municipal buses and in subways in major cities in America. Clearly, the search for the rare unfortunate few who suffer from mesothelioma has become big business for lawyers in the USA. The ultimate outcome is ligation that has already bankrupted countless

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American businesses as plaintiffs seek redress for the presumptive, subtle injury patients unknowingly suffered as a result of the supposed callous disregard of insensitive industrialists. Will advertisement focused on the general public bring to the attention of medical science "new" etiologies for these unique cancers? Or, will these cases redefine the epidemiological features of the disease and its etiological relationship to low-dose asbestos exposure? Can subtle unrecognized exposures result in the malignant disease? Only time will tell. Unfortunately today's juries, rather than scientists, are obliged to draw conclusions based on incomplete evidence presented by advocates in the courtroom.

It is difficult to be certain when mesothelioma became a recognizable clinical and pathological entity, given its rarity in the general population and the ability of these tumors to mimic common neoplasms involving the pleural and peritoneal cavities [54]. E. Wagner [79], a German pathologist, is generally accorded credit for the initial description of a tumor believed to be the prototype of the modern day mesothelioma. In the past, these malignant lesions often simulated the clinical picture of pleural tuberculosis, a condition that was not uncommon centuries ago. Sensitive diagnostic tools, electron microscopy [22, 75], and immunocytochemistry [18], now make it possible for the pathologist to recognize these tumors with a high degree of certainty when, so often, skilled clinicians demure. It has only been during the last 3 decades that newer diagnostic tools have allowed the epidemiologist the luxury of carrying out analyses using dependable patient data.

Even the term mesothelioma has been a matter of uncertainty for those who seek an orderly nomenclature. Thus, in the first few decades of the last century some 30 different names were used when referring to tumors having at least some of the morphological features of the malignant lesions now recognized as mesotheliomas, the most common of which was "endothelioma," a convenient designation attesting to the vague resemblance of the tumor cells to vascular endothelial cells. Finally, in the early 1930s, Klemperer and Rabin [41] proposed the designation "mesothelioma" in describing a clinical/pathological entity that commonly exhibited both sarcomatous and carcinomatous histological features, either exclusively or as a random mixture of the two. But even as late 1957, an occasional "doubting Thomas" questioned the existence of such tumors. For example, in a case report published in the widely read *New England Journal of Medicine*, the renowned diagnostic pathologist and Harvard professor Benjamin Castleman announced to the medical community that a case under discussion in a clinical/pathological conference was the first mesothelioma he had been comfortable in diagnosing.

This was merely 2 years before Christopher Wagner (a pathologist) and his colleagues, the tuberculosis specialist Kit Sleggs and Paul Marchand [81], a chest physician, described in a landmark publication an epidemic of mesothelioma consequent to environmental exposure to crocidolite asbestos. It was Sleggs who prophetically identified a cadre of unique patients believed to have tuberculous pleuritis but who failed to respond to the customarily effective management of tuberculosis at the time. It was Marchand [48] who helped recognize the common occurrence of this disease among members of the indigenous population who were believed to have a most unusual form of lung cancer. However, at the time, senior South African pathologists, including Ian Webster [82], had little difficulty diagnosing the unique tumors which Wagner (at the time a junior level pathologist) brought to their attention, for they were already aware of similar lesions occurring elsewhere in the amphibole asbestos mining districts of South Africa [80]. But who among the pathologists in the Northern Hemisphere paid much heed to an apparent epidemic of an unheard of malignancy occurring in the native population of an obscure corner of southern Africa, particularly when the mining industry

was more than anxious to suppress knowledge of a suspect industry-associated cancer? At the time, everyone knew that, in general, cancer was a sporadically occurring condition, not one that manifested itself as an epidemic in both women and men, and on occasion, teenagers. To me, as a practicing pathologist in a major Boston teaching hospital in the early 1960s, mesothelioma was rarely a consideration in the differential diagnosis of a chest tumor.

Diagnostic uncertainty, nonetheless, continued to plague the histopathologist for years thereafter when these rare entities came to their attention. Recognizing this conundrum in the mid-1960s, leaders in the world community of pathology established review panels in Europe and North America to evaluate pathological material from individual suspect cases [39]. These experts then tendered a specific diagnosis or arbitrarily expressed either uncertainty or frank disagreement as to the identity of the tumor among the members of the assembled panel. Clearly, clinical case surveys and epidemiological studies would have proven fruitless in the absence of a concrete diagnostic identification of the tumors. But, improvements in the tools available to the pathologist were forthcoming. As noted above, it was not until the 1970s that electron microscopy was introduced, imperfect as it was, and in the 1980s immunohistochemistry came into vogue as a diagnostic crutch. To this date, new markers of malignant mesothelial cells continue to be introduced in an effort to confront the ambiguities of diagnostic pathology, allowing a more precise diagnosis. Nonetheless, an occasional case generates controversy even among experienced pathologists.

Prior to the 1960s, a case of mesothelioma was a "rare bird" perhaps coming to the attention of the hospital pathologist once or twice in a professional lifetime. Often as a sporadic malignancy of childhood and adolescence, they were idiopathic curiosities too uncommon to warrant serious research (asbestos-related mesotheliomas have not been found to develop in those younger than 35 years despite an occasional claim to the contrary) [33]. There is every reason to believe that many obscure thoracic neoplasms of unknown etiology in women were either classified in the past as breast cancer believed to have metastasized to the pleura, or ovarian cancer spreading unabated throughout the abdominal cavity, implanting on the peritoneal wall. And then there are the anatomic variants, some simulating sarcomas or a complex obscure tumor such as a synovial sarcoma [40]. All too often, mesotheliomas mimicked adenocarcinomas of bronchogenic origin developing at the periphery of the lung and invading the pleural cavity, the so-called pseudomesotheliomatous adenocarcinoma.

Although asbestosis as a clinical and pathological entity among textile workers was recognized in the UK and the USA and was considered a potential cause of lung disease before 1900 [57], many millers died of asbestosis after a period of dust exposure of no longer than a decade. Accordingly, because of its relatively long latency period, it is the writer's belief that mesotheliomas failed to appear before patients had died because of asbestosis or left the work force. It was not until after the First World War that public health authorities recognized what was believed to be an increase in lung cancer among tradesmen without clinical evidence of asbestosis, but a history of work in an industry where asbestos was liberally used [25, 57]. Most probably, some of these cases were mesotheliomas, but who would know in the absence of autopsies and a clear idea of the diverse pathological features of these tumors? Who could imagine sarcomas developing in anatomic concert with malignant epithelial cells (the so-called biphasic tumors)? It was not until the Second World War that industry-related mesotheliomas were recognized to be occurring in Europe. Alas, these early cases were reported in the wartime German literature as "pleural cancer" in publications [83, 84], out of the reach of most American and British physicians at the

Fig. 2.1 Examples of promotional advertisements published in trade journals in the past

time (but apparently known and ignored by the Allied intelligence community).

Prior to that time, more specifically in 1934, the passenger vessel *SS Morro Castle* was destroyed at sea by fire, a tragedy that prompted an inquiry by the US Congress into the apparent ineffectual fireproofing of American registered ships including naval vessels. It was already known that amosite asbestos was resistant to the degrading effects of sea water and could provide excellent insulation protection per unit of weight. Accordingly, by 1940 the US Navy specifications for new ships and those undergoing reconditioning and repair dictated the routine insulation of a vessel's interior with amosite and to a variable extent, chrysotile. Most commercial shippers (i.e., the merchant marine) soon abided by these regulatory criteria, precautions that no doubt saved ships and the lives of many sailors during the war, but has resulted in much suffering thereafter. With the mobilization for the Second World War, amosite was routinely incorporated into the insulation of some 3,000 newly launched merchant vessels and navy warships, resulting in the gross contamination of a vessel's interior compartments, particularly the engine rooms (Fig. 2.1). For example, a recent evaluation of a mothballed World War II Navy destroyer demonstrated roughly 25 t of asbestos insulation still intact in the bowels of the vessel.

It would be rank speculation to attempt to estimate the numbers of Navy personnel and merchant mariners who were heavily exposed aboard ship while serving their country, and to the best of the writer's knowledge, no serious attempt has ever been made by governments in Europe or North America to estimate the exposures sustained by wartime servicemen and the outcome in the form of disease. Not surprisingly, shipyards were also heavily contaminated by friable asbestos and millions (because of a high turnover rate of shipyard workers in the Allied countries and occupied Europe) were heavily exposed to crocidolite and amosite as well as large amounts of chrysotile asbestos during the late 1930s and 1940s. Who knows how they fared.

Responsibly, the US Navy commissioned a study during the waning years of the Second World War to assess the possible adverse effects of asbestos on personnel, focusing on the disease asbestosis [30]. Unfortunately, the observation

period was much too short because the latency of asbestosis is variable but often a matter of decades, even with heavy exposure, and mesothelioma rarely becomes evident before an elapsed period of some 20 years from the time of initial exposure. Drs. Fleisher and Drinker, who conducted the above study, may have been competent in their trade but they failed as historians. Either they ignored or were not aware of the European experience with asbestos malignancies. Importation of crocidolite and amosite into Germany and Britain began in the early 1900s. Clearly, mesotheliomas were erupting among industrial workers and naval personnel throughout the 1920s and 1930s. But, alas, at the time many mesotheliomas were believed to be traditional lung cancers [67].

A recently completed, unpublished evaluation of case material in my laboratory strongly suggests that exposures in the 1940s during the war may give rise to mesotheliomas diagnosed some 40–60 years later (the duration of latency is thought by many authorities to be inversely related to the intensity of exposure). However, since the latency period of most mesotheliomas ranges from 20 to 40 years, it was not until the 1960s that mesotheliomas attributable to wartime exposure began to appear in large numbers in Great Britain [26, 34, 68, 74, 85] and Germany [9]. Soon, an increasingly large number of cases were diagnosed among American shipyard workers who were then engaged in other forms of employment [76]. But as noted above, it was not until 1960 that the first compelling report relating environmental crocidolite exposure to mesothelioma was published, and it was 1971 when amosite was also considered a likely cause, if not the major culprit, in industrialized societies by knowledgeable members of the public health community. In the USA, credit must be accorded Dr. Irving Selikoff, a chest physician, who recognized the impending disaster as mesotheliomas came to his attention among workers at the Union Asbestos and Rubber Company (UNARCO) in New Jersey where Unibestos amosite insulation for newly constructed ships was manufactured. Interestingly enough, the initial cases identified by Dr. Selikoff were peritoneal mesotheliomas, attesting to the heavy exposures these workers had sustained.

It was then that the pathfinding physicians, Drs. Irving Selikoff and Christopher Wagner organized a landmark conference under the auspices of the New York Academy of Sciences to consider the accumulating scientific observations associating asbestos exposure with malignant and nonmalignant diseases, including the common types of lung cancer and both peritoneal and pleural mesotheliomas.

At this juncture, a pause seems appropriate to summarize briefly what clinicians and epidemiologists have learned over the past half century regarding this fascinating malignancy and its relationship to asbestos exposure. As we all know, mesotheliomas usually develop unilaterally in the pleural cavities, and to a more limited extent in the abdomen. But they also develop on rare occasions in the pericardium, the spermatic cords, and both the male and female gonads. Because these highly malignant lesions are shrouded in body cavities, they generally are widespread and incurable when clinicians finally are obliged to search for the cause of subtle chest or abdominal discomfort accompanied by a unilateral pleural effusion or ascites. Despite the current availability of potent chemotherapy (as discussed elsewhere in this symposium) and the increasingly common extrapleural pneumonectomies (carried out by intrepid thoracic surgeons in an all too often futile attempt to eliminate or control the spread of the neoplasm) the prognosis is grim and most patients are dead within a period of 3 years from the time of diagnosis. As noted above, the vast majority of mesotheliomas develop in the chest cavities where they gradually invade the chest wall and mediastinum and not infrequently metastasize to the contralateral lung, the spinal vertebrae, and the peritoneal cavity. In the abdomen they trigger the accumulation of massive

ascites while spreading widely to implant on the surfaces of the peritoneal wall and major organs, only occasionally metastasizing to the chest.

The pathogenesis of mesotheliomas in a population of occupationally exposed men or women is largely dependent upon mineralogical type and the fiber dimension as well as the severity of exposure. On occasion, the incidence of abdominal tumors is as great as 20% of a heavily exposed worker population whereas in most situations it is lower. However, in Great Britain, Coggon et al. [16] discovered a greater than sixfold occurrence of peritoneal tumors in comparison to pleural malignant lesions among construction workers. Carpenters seem to be at exceptional risk for mesotheliomas in the UK, most probably because of the widespread use of composition asbestos boards in the past.

As noted above, the latency of these lesions from the time of first exposure until the onset of symptoms is unpredictable. Almost invariably, it is greater than 20 years but at times it can be as long as 50 or 60 years. Who knows what disease processes lurk in body cavities before the malignancy is sufficiently large to cause symptoms? Of interest has been the reported substantially shorter latency period among a few environmentally exposed patients in the crocidolite mining district of Western Australia [2, 3]. It is generally agreed that peritoneal mesotheliomas develop as a result of heavier and more prolonged exposures, but comparative quantitative thresholds have never been established for any asbestos type because of the profound difficulties of conducting comprehensive long-term studies on a rare disease sometimes caused by exceedingly low dosages of a toxic substance. But the lack of evidence is not evidence for a lack of a threshold since many members of the general population have asbestos particles in their lungs in the absence of disease [23]. The classical nonmalignant stigmata of exposure, that is, pleural plaques, bilaterally symmetrical pleural thickening, and asbestosis are surrogate measures of relatively heavy exposure to an amphibole. They occur more frequently in those with peritoneal rather than pleural malignant disease, suggesting that a heavier exposure is required to initiate these lesions in the abdominal cavity. Too little epidemiological information on spermatic cord and gonadal lesions exists to allow conclusions regarding causation and latency since it is likely that many of these tumors are idiopathic and not caused by asbestos exposure. It has been the author's experience that some peritoneal mesotheliomas present clinically for the first time as tumorous masses in the spermatic cord simulating hernias. Anecdotally, it has been hypothesized that talc particles and asbestos accumulations on or around ovaries may play a causative role in the genesis of ovarian mesothelioma, a hypothesis that now dictates the nonuse of talc on surgical gloves.

Are all mesotheliomas caused by exposure to asbestos? Of course not! According to the comprehensive studies of Spirtas et al. [70], overall the attributable risk for exposure to asbestos is 88% for men, but in only 58% of male cases could asbestos exposure be implicated in a patient's abdominal tumor. In women, the attributable risk proved to be 23% for pleural and peritoneal mesotheliomas combined. (Unfortunately, these epidemiologists were dealing with numbers and not detailed case information; thus, it is impossible to determine the validity of a claim of asbestos exposure, and the type(s) involved). But as William Blake has told us: "to generalize is to be an idiot!" Overstated? Yes, since all too often subtle, brief but heavy exposures to asbestos in a patient's distant past can on occasion be linked causatively to the disease. The writer is aware of several cases of mesotheliomas in white collar, middle aged men whose only known exposure was summertime employment in industry while attending college.

To an extent, the information briefly summarized above represents events occurring in another time frame of history when preliminary information on environmental asbestos exposure was

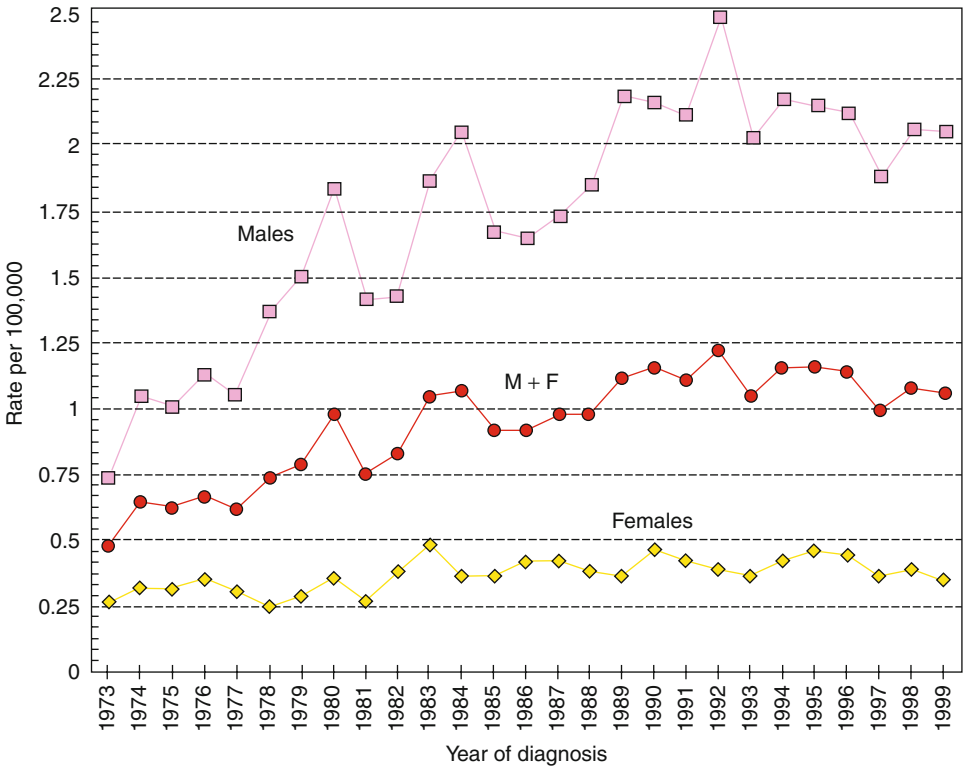

Fig. 2.2 Age-adjusted incidence of mesothelioma in the USA from 1973 to 1999 (Data from the Surveillance Epidemiology and End Results registry [SEER])

accumulating and risks were poorly defined. More recently, accumulating data suggests the likelihood of a new pattern of disease in younger members of the population, more specifically, men and women entering the workforce since the 1980s. The writer has evaluated the occupational background of some 35 men younger than 45 years who suffered from abdominal mesotheliomas but had no known history of vocational or avocational exposure to asbestos. Similarly, countless numbers of idiopathic thoracic mesotheliomas are now being diagnosed in the USA. These patients display none of the traditional markers of exposure and have no compelling history of exposure. Burdorf et al. [14] noted in the Netherlands and Sweden a consistent low incidence of mesotheliomas among women, an observation that has also been documented in the USA (Fig. 2.2). If there truly exists a background incidence of mesotheliomas that are not caused by asbestos, pathologists have yet to recognize unique morphological features of the disease that would allow the identification of idiopathic mesotheliomas. There may be exceptions to this claim, however, that is, the so-called well-differentiated papillary mesothelioma, which occurs on rare occasions in the abdominal cavity of young women who have no history of exposure to asbestos. These tumors fail to exhibit invasive characteristics and on occasion resolve without treatment. And, the writer has observed only glandulopapillary features in the idiopathic

abdominal mesotheliomas he has discovered in young men.

Indirect passive exposures of spouses and children in the household to the clothes of asbestos workers were believed in the past to occasionally result in pleural plaques and/or mesothelioma, but all too often the conclusions were anecdotal and presumptive rather than based on proof. Only a limited number of fiber burden analyses have been carried out on the lung tissue of household members of an asbestos worker substantiating the claim of indirect, inadvertent exposure. Hillerdal [36] has reported the development of mesothelioma in a housewife believed to have been exposed to approximately 1 fiber/mL for 2 h, once per week for a period of 5 years. Ferrante and his colleagues [28] documented 18 cases of mesothelioma in homemakers who laundered the work clothes of their husbands, all cement factory workers, over a 20 year period [60].

Exposures of residents in a community surrounding an industrial source of asbestos were recently alleged by Maule and her colleagues [50]. Those living near an asbestos cement plant had a relative risk of 10.5. In Japan, Kurumatani and Kumagai [42] documented a standardized mortality rate of 14 among men and 41 for women who occupied homes located within a radius of 300 m of an asbestos cement pipe plant that used both chrysotile and crocidolite. In an unpublished report, public health epidemiologists, in the state of New Jersey, reported an odds ratio of 31.7 in the community of Manville located near a large asbestos manufacturing plant that is no longer operative.

By the mid-1960s the news was "out of the bag" and investigators on several continents scurried to gather experimental and epidemiological evidence, which would elucidate the enormous gaps in our knowledge. A flurry of laboratory studies soon demonstrated that asbestos causes neoplasm to develop in rodents and subhuman primates when massive amounts of the fibrous minerals are injected by artificial means into the animals' pleural and peritoneal cavities [19]. Insightful experimental work by Stanton and Wrench [71] using a modification of this approach showed that relatively long, thin fibers triggered the development of malignant mesotheliomas in rodents, a concept now found to be relevant to human disease based on epidemiological studies. These studies have distinct limitations because of their artificiality, particularly the introduction of asbestos directly into the body cavity, thus bypassing the cleansing apparatus of the respiratory tract. Inhalation studies using rats have yielded quite different results (Table 2.1).

Of note are the studies [8, 10, 13] which showed that smooth-surfaced materials such as plastic sheets of various configurations induce sarcomas in rats when implanted subcutaneously, an observation suggesting a possible model for asbestos-induced mesothelioma in which the vast surface area of long and thin fibers (surface area = $\pi r^2 \times$ length), such as with crocidolite, triggers malignant transformation by mechanisms discussed in more detail below.

Experimental modeling in animals and casts of the human respiratory tract by Timbrell [77]

Table 2.1 Summary data for inhalation experiments in rats conducted by Davis and Coworkers (Adapted from [6])

Fiber type	Description	Dosage[a]	# Tumors/ # tested
Chrysotile	UICC-A	0.4	1/42
Chrysotile	UICC-A	2.0	0/42
Chrysotile	Long	5.5	3/40
Chrysotile	Short	1.2	1/40
Amosite	Long	2.1	3/40
Amosite	Short	0.07	1/42
Crocidolite	UICC	0.4	1/43
Crocidolite	UICC	0.9	0/40
Tremolite	Korean	1.6	2/39
Control		0	0/228

PCM Phase contrast microscopy: fibers/mL $\times 10^3$
[a]Exposure 7 h/day, 5 days/week for 1 year

showed that the depth of a fiber's penetration into the lung is roughly the inverse of its diameter. Fiber length does not prove to be an impediment to the transport of a thin fiber down the branching tubular network of the tracheobronchial tree to finally deposit it at the level of the pleura. Importantly, fiber length is most probably a critical factor in arousing a luxuriant alveolar macrophage response near the mesothelial cells of the pleura, where oxidant chemicals and proteases are generated as a product of the scavenger cells that attempt to imbibe the long indigestible fibers, an event that is most probably catalyzed by the amphibole fiber's iron concentration. Additionally, biochemical and molecular studies have provided plausible insights into the mechanisms of carcinogenesis, work that strongly implicated oxygen and nitrogen free radicals generated by macrophages in mutagenesis by means of direct DNA damage [35, 58]. Other studies have explored the possible effects of factors generated by experimentally exposed cells in vitro on the growth of tumors in vivo [12, 20, 21].

Alas, there still remain gaps in our knowledge of the biological basis for the diverse morphological features of mesotheliomas and their constituent cells. However, we might reflect on the original findings of the renowned experimental histologist Maximow [52, 53], who demonstrated in vitro spontaneous transformation of one cell type to another, quite independent of asbestos or other foreign materials, an observation expanded upon more recently by Stout and Murray [73]. Among the products that might be elicited by mesothelioma cells are cell differentiation factors that could account for the morphological variability in individual tumors and between tumors in different cases. We might also consider the relevance of our rapidly evolving knowledge of the pluripotential properties of newly discovered lines of stem cell that have the capacity to differentiate into a variety of cell types when experimentally introduced into host animals. In a recent report, McQualter et al. [55] described a population of multipotential epithelial stem/progenitor cells in the mouse lung, which they claimed have the capacity for self-renewal and possibly remodeling as well as regeneration and repair. At this time we have no compelling experimental or epidemiological evidence to account for the various routes of differentiation manifest by mesothelial cells as they undergo malignant transformation. More simply stated, why are some tumors sarcomatoid and others epitheloid and still others a mixture of the two? [45].

Quite independent of the experimental work concerned with mechanism of tumorigenesis, epidemiological studies during the past 50 years have provided science with a vast body of meaningful insights which have helped dictate the scope of governmental regulations designed to control exposure and the uses of asbestos by industry. It has now been clearly shown that friable amphiboles (crocidolite, amosite, and tremolite) are the major cause of mesothelioma worldwide, with crocidolite being the most potent carcinogen (most probably because the fibers tend to be exceptionally long and thin) but amosite by far the commonest cause worldwide. This is not startling new information for it emanates from work accomplished before the1970s, but despite much effort we have yet to establish scientifically defensible threshold levels for regulatory purposes. It is clear that these three types of amphiboles are biologically similar, only differing in relative pathogenicity, whereas the orphan anthophyllite (comprised of relatively thick and blunt fibers) either lacks the capacity to cause mesotheliomas or does so rarely, even though anthophyllite induces the formation of pleural plaques in humans with alacrity [6]. Unfortunately, chrysotile, which worldwide was the major commercially used asbestos in the past, has yielded the most vexing epidemiological data and considerable regulatory controversy. Indeed, there have been countless opinions published which allude to the possibility, rather than the probability, that chrysotile causes mesothelioma while many other

carefully conducted and comprehensive epidemiological surveys in Canada indicate that pure, friable chrysotile is blameless [5, 15, 17, 37, 54, 67]. Indeed, the most recently acquired information from studies of South African miner populations [61] supports the notion that the relatively obscure contaminant, tremolite, is causatively responsible for the occasional mesothelioma developing in Canadian miners and millers of crude chrysotile ore. Hodgson and Darnton [38] recently supplemented their 2000 report referenced above with an evaluation of a comparative meta-analysis conducted by Loomis et al. [44] which shows different mesothelioma rates for chrysotile miners and textile millers. The data further supports the evidence exonerating chrysotile as a cause of this neoplasm.

Of major concern and a subject of controversy is the capacity of asbestos to cause mesotheliomas in the family members of asbestos workers [27, 32]. Anecdotal observations convincingly argue that such cases occur as a result of indirect exposure, but again there is insufficient data to calculate a threshold. Obviously, the definition of a threshold for those indirectly exposed in the home due to the laundering of a family member's work clothes or re-entrainment of subtle asbestos accumulations in the home setting is beyond the capabilities of modern epidemiology. Despite arguments to the contrary, the most obvious occurrences of this type have been in households where a family member has worked in a shipyard, an asbestos production plant, or as a plumber/pipefitter. Roggli et al. [65] has published some of the more detailed information on this topic including the results of fiber burden analyses on lung tissue of diseased family members. Interestingly enough, 9 of the 34 homemakers in his study had pleural plaques and three had abdominal mesotheliomas, an incidence approaching ten percent! As might be expected, a substantial proportion of these patients had increased concentrations of amphiboles in their lung tissue.

Environmental exposures (occurring outside of the occupational setting and the home) resulting in mesotheliomas are also an issue [29, 60]. There is now abundant evidence to indicate that crocidolite causes malignant disease in the community setting with "outbreaks" documented in residents of North America, Africa, Australia, and Asia [2, 3, 18, 43]. But what about members of the general public? Environmental monitoring of urban air (and potable water) has shown that the ambient air in major cities contains minute amounts of asbestos, primarily chrysotile fibers. Some would argue that cases of idiopathic mesothelioma are, in fact, a reflection of lifelong low-level exposures to ambient asbestos even though evidence supporting such conjecture is limited. Recently, Goldberg et al. [31] published data suggesting that the distribution of cases of mesotheliomas believed to be "idiopathic" in French communities was similar to the geographic distribution of patients with asbestos-related tumors, suggesting that subtle asbestos exposure was also the cause of these so-called idiopathic cases.

Why is mesothelioma such a relatively rare neoplasm, even among workers heavily exposed to asbestos? Certainly, the prolonged latency periods of this malignancy influences the outcome, since many potential "victims" fail to live long enough to develop a mesothelioma, succumbing to other more common diseases unrelated to asbestos exposure. But the answer could also lie in the crypts of our individual genetic makeup. Thus, the occurrence of the malignancy might well be based on biological factors that predispose to susceptibility (or resistance) to the carcinogenic effects of asbestos [11]. In experimental studies, we found differences in the incidence of malignant disease in mice of several different inbred strains after intraperitoneal introduction of asbestos, an observation suggesting genetic influences on latency and overall susceptibility [20, 21]. Rare, sporadic, "family" outbreaks of mesotheliomas are consistent with this observation [7, 46, 49, 64]. And, in the genetically mediated

disease of humans known as Mediterranean Fever, the characteristic chronic serositis, which occurs in the body cavities of these patients, is associated with the sporadic, uncommon appearance of mesothelioma in mid-life [43, 63]. Perhaps this is a reflection of the apparent role of smoldering inflammation in the pathogenesis of mesothelioma, as has been proposed for the infrequent development of mesotheliomas in those afflicted with chronic tuberculosis [57, 66]. In Turkey, the relatively common appearance of mesotheliomas among members of isolated population groups who are exposed to erionite, a volcanic fibrous zeolite mineral, has again raised the possible role of genetic factors in carcinogenesis for consideration [4, 24]. Could inheritance be responsible for the development of mesothelioma in patients years after they received therapeutic irradiation for neoplastic disease [1, 51, 72]? Clearly, we are only now acquiring insights into possible predisposing factors that might ultimately influence the development of this unique malignancy. The interplay between environmental and host factors, to a large extent, remains to be defined [76].

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