Pathology of Malignant Mesothelioma

Françoise Galateau-Sallé

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With 169 Figures, 158 in Full Color

International Mesothelioma Panel
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Preface

The Urgency of Improving and Standardizing Diagnostic Methods for Mesothelioma

Recent decades have seen substantially increased worldwide incidence and mortality rates for mesothelioma. Studies in many countries have confirmed its association with asbestos exposure. Nonetheless, important scientific and public health questions still need answers.

What morphologic and chemical characteristics of these fibers explain their carcinogenic effects? Is there a threshold below which asbestos exposure would be harmless? What risks are associated with the current conditions of occupational exposure—which are much shorter and much less intense than those observed in the historical cohorts that enabled identification of the risks associated with this material? Does spending time in buildings with asbestos have carcinogenic effects when the asbestos fibers are observed at levels substantially lower than those associated with occupational exposure? What about environmental exposures from either natural (fibers in the soil) or industrial (asbestos mines, asbestos processing plants) sources? Can asbestos induce primary pleural tumors of a histologic type other than mesothelioma? Are the man-made mineral fibers used as asbestos substitutes likely to induce mesothelioma? Are there other agents capable of such an effect? How will the mesothelioma epidemic develop in the decades to come in different countries?

Quantification of the risks associated with asbestos is also a major scientific and public health issue. Controversy surrounds the models currently used, which postulate a linear no-threshold relation, and the parameters that characterize the dose–risk curve. Risk assessments based on these models play a determinant role in forecasting incidence trends and estimating the scale of asbestos impact on populations, and they have various concrete consequences, including financial.

These questions are therefore not at all academic: They are important when determining prevention policies and financial compensation. An international mobilization of biologic, experimental, clinical, and epidemi-

ologic research has sought to improve our understanding of these questions.

One of the most important pathways to a better understanding of all these questions involves the improvement and standardization of diagnostic methods for mesothelioma.

Scientists face many difficulties in understanding the mechanisms of this cancer's development, the role of the several varieties of asbestos and of a wide range of other factors, and the extent of the consequences of asbestos exposure. More problems come when interpreting past incidence trends and when forecasting future trends. Many of these issues are related to limitations in our capacity to diagnose mesothelioma and in the difficulty pathologists face in finding methods that are sensitive, specific, and reproducible from an international perspective. The subsequent failure to identify cases and the inaccurate diagnoses of metastases and other forms of pleura-based tumors such as mesotheliomas cause individual harm; bias epidemiologic surveys, mesothelioma incidence estimates, and international comparisons; and impede the study of changes in this cancer's incidence over time. These factors have led to important scientific (and legal) debates in a variety of circumstances.

Publication of this work by the International Mesothelioma Panel is therefore particularly welcome. It provides information about recent advances—some quite spectacular—in methods for diagnosing mesothelioma. Let us hope that this volume will promote diffusion of the most effective of these methods to the vast number of pathologists who are not specialized in this domain but who must occasionally examine this tumor.

Mesothelioma is still a complex scientific and public health problem, and all the forecasts indicate that it will remain with us for at least several more decades. Constant improvement of diagnostic methods is urgently needed to improve our understanding and management of it. Future work by the International Mesothelioma Panel to improve early detection through the new tools now available to pathologists (e.g., molecular biology, immunohistochemistry) will help with the international resolution of this question, a resolution today still in its first stages.

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I dedicate this book to our readers, hoping they will find in this monograph assistance and answers to their questions.

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Epidemiology of Mesothelioma

Malignant mesothelioma has risen from obscurity and rarity during the first half of the twentieth century to become a major occupational and public health problem late in the latter half of that century and the beginning of the twenty-first century. The nexus between asbestos exposure and subsequent development of mesothelioma was established definitively in 1960 by Wagner et al. [1] in South Africa. By the late 1990s, the incidence of mesothelioma in some industrialized nations was roughly comparable to that of cancer of the larynx [2], and the mortality rate was similar to that for renal cell carcinoma in men and for uterine cancer in women [2–4]. Apart from lung cancer, mesothelioma constitutes the most important occupational cancer among industrial workers.

Most mesotheliomas encountered during the early twenty-first century are a consequence of prior occupational exposure to asbestos from the 1940s through the 1970s, including end-use and bystander exposures [5, 6]. The relation between inhalation of asbestos fibers—especially one or more of the amphibole varieties—and mesothelioma is accepted by almost all authorities as causal; because of the consistency and specificity of the asbestos-mesothelioma relation, the incidence of mesothelioma is usually considered to be an index of societies' past usage of asbestos (Table 1.1) [7–10].

Recent incidence rates for mesothelioma in various countries are listed in Table 1.1 and are generally in the range of 14 to 30 cases per million persons per year (>15 years of age) [9, 10]. The highest incidence is found in Australia, where the rate in 1997 was 29.8/million persons/year (50.6/million/year for males and 9.0/million/year for females, standardized to the world population >20 years of age, whereas the corresponding crude rates in 1997 for Australia were 59.8/million for males and 10.9/million for females) [4]. In the United States, the current rate for the sexes combined is 10.0/million/year [11].

It has been estimated that about 10,000 mesotheliomas occur annually throughout North America, Australia, and seven nations in western Europe and Scandinavia [9]. Peto et al. [5] predicted about 190,000 mesothelioma

Table 1.1. Mesothelioma incidence across nations relative to historical use of asbestos*

Nation	Mesothelioma incidence (cases/million/year)	Use of asbestos (kg/capita/year)
Australia (1995)	33	4.4 (1968)
The Netherlands (1995)	27	3.4 (1976)
United Kingdom (1991)	23	2.7 (1970)
Italy (1993)	22	2.5 (1975)
France (1996)	17	2.6 (1970)
Finland (1995)	15	2.2 (1970)
Germany (1997)	15	3.0 (1975)
Sweden (1995)	15	2.4 (1970)
United States (1999)	10	2.3 (1975)
Norway (1995)	14	1.9 (1970)

Modified from Tossavainen [9].

deaths across six nations in western Europe (Britain, France, Germany, Italy, The Netherlands, and Switzerland) over the 35-year period dating from 1999. Modeling of data for France indicates that mortality from mesothelioma among French men aged 50 to 79 will continue to increase, reaching a peak of 1140 deaths in 2030 (optimistic forecast) to 1300 deaths in 2040 (pessimistic prediction), and no preventive measures implemented at this time can affect this trend [12]. In Australia, the incidence of mesothelioma is expected to peak in about 2020 (approximately 18,000 cases for the period 1945–2020) [4]. In the United States, the peak incidence was predicted to occur by the year 2000, with a slow decline thereafter [7]. In the United Kingdom, the rate of increase in mesothelioma-related deaths slowed slightly in 1997, when there were 1330 deaths, but the rate increased thereafter, with 1535 deaths in 1998 and 1595 in 1999 [13]; the crude death rate for mesothelioma in Great Britain rose from 29.57 per million for males during 1989–1991 to 40.93 during 1995–1997, and for the same periods the equivalent death rate in females rose from 4.67 to 5.77 [14]. The Health and Safety Executive [15] estimated that deaths from mesothelioma in men in the United Kingdom "may peak around the year 2011, at about 1700 deaths per year," whereas mesothelioma-related deaths in women "are running at about one-sixth of the level in men." In this respect, mesothelioma incidence rates have increased about fourfold or fivefold in Australia over a period of almost 20 years, and the rate in females has also increased about threefold; however, the male incidence is more than five times that in females [4]. In some nations, the time trend of increasing incidence after 1986 is restricted largely to those aged over 50 years, suggesting that controls on occupational exposures introduced from the 1970s have been effective [4]. However, this is not the case for all industrialized countries. In France, for instance, the relative risk of developing a pleural mesothelioma among men is 1.83 for the youngest

generation (men born in 1953) compared to the 1928 generation [16], whereas the maximum risk for males occurs for the 1925–1929 birth cohort in the United States [17]. These contrasting findings show that awareness about the danger of asbestos exposure effects was not the same in all countries.

Asbestos Exposure and Mesothelioma

In national registries, about 90% of male mesothelioma patients have a history of asbestos exposure, especially those with pleural mesotheliomas, with a somewhat smaller percentage for patients with peritoneal mesothelioma (about 60%) [4, 18]. The proportion of asbestos-associated mesotheliomas is lower in females and varies among countries, ranging from 25% in the United States to as much as 70% in Australia [4, 18]. In some series a small number of the exposures are occupational, so nonoccupational exposures comprise a much larger proportion of mesothelioma cases among women [19]. Roggli et al. [19] found that the lung tissue asbestos burden was elevated in 70% of a series of female mesothelioma patients in the United States: the main fiber type was amosite, followed by tremolite.

The occupations producing the greatest number of mesotheliomas have changed over the years from miners/millers and those involved in product manufacture and insulation work to other end-users of asbestos-containing products, most notably persons in building construction and demolition industries and in shipyards [6–8, 13, 20], in part because working conditions in the building industry in particular have been poorly regulated. Individual life-time risks of mesothelioma are highest among crocidolite miners/millers, power station workers, railways laborers, and naval, merchant naval, and shipyard personnel [4]. However, the number of personnel employed in each of the last-cited occupations are smaller than in the building construction industry, so carpenters/joiners, for example, contribute greater absolute numbers to national mesothelioma tolls, although the individual risk is less [4]. Substantial numbers of mesotheliomas are now seen as a consequence of nonoccupational exposures, including occasional "handyman"-type exposure, domestic exposure (e.g., from laundering asbestos-contaminated work clothes), and other types of occasional or nonoccupational exposures [4, 6, 21, 22]. Mesothelioma has been reported to occur after brief low-level or indirect exposure [23].

The risk or incidence of mesothelioma shows a dose-response relation to cumulative asbestos exposure, so the risk is greatest with heavy exposures [24, 25], and peritoneal mesotheliomas [26] are usually related to heavier cumulative exposures than pleural mesotheliomas. In general, the incidence of mesothelioma in asbestos-exposed cohorts reflects the fiber type or types, cumulative exposure, and the time following exposure so remote exposures

are more significant for mesothelioma induction than recent exposures, other factors being equal [24].

Asbestos occurs in two major mineralogic groups: the amphiboles (of which amosite and crocidolite constitute the major commercial forms) and chrysotile [27]. Over recent decades, chrysotile comprised about 95% of world asbestos production, most originating from Canada and Russia [6]. Fibrous tremolite, anthophyllite, and actinolite constitute other forms of amphibole asbestos. Production of these minerals, however, was restricted to only a few mines or industries, although small amounts of fibrous tremolite occur in Canadian chrysotile (usually about 1% or less), and tremolite was used in certain regions (e.g., as a whitewash in Greece and Cyprus and in New Caledonia) [6]. Although it has been claimed that all varieties of commercial asbestos have the capacity for mesothelioma induction, there is general agreement that crocidolite is the most potent type of asbestos for mesothelioma induction, followed by amosite and then chrysotile [6, 28]. There is much debate regarding the ability of chrysotile to cause mesothelioma. Some of the differences relate to interpretation of the epidemiologic data, but at the heart of the controversy lie the differing views on the importance of biopersistence in carcinogenesis and the significance of chrysotile contamination by tremolite. The association between mesothelioma and chrysotile exposure is largely based on studies of the Quebec chrysotile miners and millers, a situation where tremolite contamination of the chrysotile ore is well recognized [29, 30]. It is outside the scope of this volume to debate this issue, and the reader is referred elsewhere [28–38]. The greater potency of the amphiboles for mesothelioma induction compared to that of chrysotile is thought to be related to the fiber characteristics and to the greater biopersistence of amphibole fibers in lung tissue than chrysotile (which fragments or dissolves more rapidly), so the half-life of chrysotile (weeks to months) in lung parenchyma is much shorter than the half-life for the amphiboles (years to decades) [6, 38]. The factors influencing fiber clearance from the lung were well summarized by Roggli and Brody [39].

Fiber dimensions are also thought to be important for mesothelioma induction, so short-length fibers have little carcinogenic activity in comparison to long-length fibers (>5 μm in length and especially >8–10 μm in length) [6, 40]. Boutin et al. [41] demonstrated asbestos fibers concentrated in parietal pleural "black spots" in exposed subjects. Amphiboles outnumbered chrysotile in all samples: 22.5% of fibers were 5 μm or longer in the black spots. The black spots were histologically similar to milky spots as seen by conventional and electron microscopy. These findings may well explain why the parietal pleura is the target organ for mesothelioma and plaques.

Most mesotheliomas now encountered among the populations of Europe, North America, and Australaia occur in individuals with a history of mixed asbestos inhalation (e.g., chrysotile plus amosite fibers released by

operations on insulation materials or high-density asbestos-cement building products) [6].

It should be remembered that a history of exposure to asbestos or the lack thereof is important when assigning causation to a malignant mesothelioma. However, a history of exposure to asbestos should play no role in the diagnosis; diagnosis depends on the gross, microscopic and special-technique observations, as it does with any other tumor.

Latency

There is characteristically a prolonged time interval (i.e., latency) between the first inhalation of asbestos and the subsequent diagnosis of mesothelioma, generally in the range of 20 to 40 years [37]. For most mesotheliomas, the latency is more than 20 years, with 15 years or less for only about 1% of mesotheliomas [13, 42–44]; some authorities delineate a minimum lag-time of 15 years from exposure and others 10 years [43]. When the latency is less than 10 to 15 years, it is likely that the proximate exposure was coincidental and that there were one or more unrecognized exposures more remote in time [38].

Other Factors Implicated in the Induction of Mesothelioma

Despite strong association with past asbestos exposure, there are other mesotheliomas for which the cause is unknown [45].

Erionite is a naturally occurring fibrous zeolite and is known to induce mesothelioma among the inhabitants of certain villages in the Cappadocian region of Turkey [46–48]. Erionite has fiber dimensions and properties similar to those of amphibole forms of asbestos.

There are anecdotal reports of mesothelioma following *irradiation*, including radiotherapy for childhood cancers such as Wilms' tumor; cases of mesothelioma have also been reported following injection of radioactive thorium dioxide (Thorotrast) for radiologic investigations (for references, see elsewhere [22–49]). However, a retrospective cohort study on a large group of women with breast cancer and patients with Hodgkin's disease—many of whom had been treated by radiotherapy—found no significant increase in the relative risk of mesothelioma [50]. In addition, coexisting asbestos exposure represents a confounding factor for some cases associated with irradiation: In one report on mortality among plutonium workers, all the mesotheliomas occurred in patients who had also sustained asbestos exposure [51]. The incidence of mesothelioma was not increased (as a second malignancy) in one study of patients with prior radiation therapy [52].

Prior Inflammatory Disorders Affecting Serosal Membranes

Mesotheliomas have occurred years after chronic inflammatory lesions of the pleura (e.g., chronic empyema or packing of the pleural cavity with lucite spheres as treatment for tuberculosis (plombage therapy)), and there are a few reports (about eight 8 cases) of an association with familial Mediterranean fever (FMF), possibly related to recurrent FMF serositis [53]. However, cases of this type are exceptional. For example, in relation to FMF, cases of mesothelioma have been reported in the Mediterranean region after white-washing homes with tremolite-containing material [54, 55]. Most cases of "postinflammatory" mesothelioma with a short interval between inflammation and tumor are probably mesotheliomas that presented with a burst of inflammatory activity followed by a period of quiescence [56].

Simian Virus 40 and Mesothelioma

A voluminous literature has grown rapidly on the detection of simian virus 40 (SV40) DNA in up to 60% of human mesotheliomas (see Chapter 2). These reports followed an initial observation that SV40 induces mesothelioma in experimental animals when injected into the pleural cavity [57]. For humans, early poliomyelitis vaccines contaminated with SV40 were a potential source for the SV40 DNA. However, the evidence in favor of SV40 as a cofactor for mesothelioma induction is still inconclusive, and a recent position statement from the British Thoracic Society evaluated the evidence for this relation as "weak" [58].

Familial Factors

The clustering of mesothelioma within families has been reported in several articles, which has suggested a genetic susceptibility to the tumor [59]. Some have occurred in the apparent absence of asbestos exposure, whereas others have also been associated with asbestos exposure. However, the genetic and biologic differences between asbestos-related and non-asbestos-related tumors are unclear [60]. A recent report described a family of three sisters who developed mesothelioma in association with environmental-residential exposure to asbestos; in two of the cases, comparative genomic hybridization showed a loss only at 9p; and it was suggested that this region might be a site of one or more oncosuppressor genes, which might be related to increased genetic susceptibility to the carcinogenetic effects of asbestos [61].

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2
Molecular Biology

The 20- to 40-year latency for the development of mesothelioma suggests that multiple genetic alterations are required for tumorigenic conversion of a normal to a malignant mesothelial cell. Although the lung fiber burden depends on the particular fiber type and the extent of exposure [1], the biopersistence of the more carcinogenic amphibole fibers is significantly higher than that of the serpentine-type fibers, as shown by rat lung inhalation studies [2, 3]. The long latency from the time of initial asbestos exposure to diagnosis [4] and the early recognition of recurrent chromosomal abnormalities in malignant mesothelioma provide early support for multiple clonal chromosomal abnormalities and multistep carcinogenesis in the development of mesothelioma. This chapter reviews the mechanisms of asbestos-induced oncogenesis, the abnormal expression of oncogenes and growth factors induced by fibers, the chromosomal damage induced by asbestos and observed in malignant mesothelioma including chromosomal deletion and chromosomal polysomy, both reflecting genomic instability, and the role of well identified tumor suppressor genes such as *p16*^{INK4}*, p53*, and *NF2* and of two mechanisms of inactivation of tumor suppressor genes, MDM2 and SV40, in malignant mesothelioma.

Mechanisms of Asbestos-induced Oncogenesis

There are presently several indications that asbestos may act directly at a mitotic level and indirectly via induction of reactive oxygen and nitrogen species and growth factors. Experimental evidence shows asbestos in tissue culture can interfere with normal chromosomal segregation (mis-segregation of chromosomes) by interacting with the mitotic apparatus, leading to aneuploidy [5]. In vitro experiments have also shown that human mesothelial cells acquire extensive numerical and structural chromosomal abnormalities shortly after exposure to a low concentration of asbestos fibers [6]. Some of the most frequent numerical changes observed in vitro are identical to those commonly reported in malignant mesothelioma. These