The Epidemiology and Pathogenesis of Malignant Mesothelioma*

John E. Craighead, M.D.

Malignant mesotheliomas of the pleural and peritoneal cavity have long been recognized as tumors unique in man. They were first described before the turn of the century, although their causation at that time was totally obscure. Now, we are aware that a substantial proportion of the mesotheliomas occurring in the Western world result from exposure to amphibole asbestos. In this brief survey, I will attempt to define the general epidemiologic features of the malignant mesothelioma and summarize our understanding of the mechanisms whereby these tumors develop.

Malignant mesotheliomas develop sporadically in members of the general population. A variety of chemical and physical agents has been implicated in their causation from time to time, but aside from therapeutic irradiation, no specific causative factor other than amphibole asbestos has been established. In the late 1800s, the amphibole asbestos types crocidolite and amosite were first mined and milled in South Africa. In the early decades of this century, increasing numbers of this asbestos type were imported into Europe and North America. However, malignant mesotheliomas did not become an important occupationally associated neoplasm until after WWII. Apparently, the first reports of an association between asbestos and mesotheliomas emanated from Germany during WWII, but these sporadic reports did not come to the attention of the world medical community until years after the cessation of hostilities. The first association of malignant mesothelioma with amphibole asbestos exposure was documented by Wagner and colleagues during an investigation of an outbreak of these tumors in the so-called Blue Hills region of the Northwest Cape territory of South Africa. This study was exceptional for its time inasmuch as it demonstrated not only the occurrence of mesotheliomas in miners but also cases among nonoccupationally exposed persons living in geographic proximity to the mines. Wagner et al suggested at this time that the physical characteristics of the asbestos fiber may be important in determining whether mesotheliomas occur in exposed populations, an observation substantiated by Stanton and Wench some years later.

After the end of the WWII, mesothelioma began to appear in the UK. In 1964 Whitwell and Rawcliffe documented the occurrences of large numbers of cases in Liverpool, where shipbuilding and repair was concentrated during the war. Subsequently, cases of mesothelioma became evident in shipyard communities throughout the Western world. These same tumors also were found among workers in heavy industry and in the insulation trade. The association of mesotheliomas with a broad cross-section of occupations first came to public attention at the symposium of the New York Academy of Sciences in 1964. An epidemic of malignant mesotheliomas is now a reality in most industrialized countries, and there is every reason to believe that excessive numbers of cases will continue to occur into the next century.

I have emphasized the important role of amphibole asbestos in the genesis of malignant mesotheliomas. Considerable debate now centers around the possible role of chrysotile asbestos in the causation of these tumors. Since chrysotile has been widely used for the past half century in manufacturing and construction of all types, it is critical to ask whether it is etiologically associated with malignant mesothelioma. Almost all knowledgeable epidemiologists now agree that if chrysotile is a cause of mesothelioma, an event of this type is found with exceeding rarity. The question is confused by the rare occurrence of mesotheliomas among miners and millers in Canada who have been heavily exposed to the chrysotile ore products. Clearly, mesotheliomas develop sporadically in this specific population of workers (fewer than 100 cases have been reported), but there is no good evidence that the "pure" mineral chrysotile specifically causes the tumor. Many authorities suggest that tremolite contaminants in the ore product may be responsible. There is lingering concern that residual crocidolite and amosite in the lungs of many Canadian miners and millers could be a cause due to the importation of amphibole into Canada decades ago. In any event, aside from these rare and sporadic cases, among worker groups exposed to processed chrysotile, mesotheliomas do not appear to occur as a result of exposure to processed chrysotile in excess of what might be expected in the general population. Thus, whatever factors are responsible for the genesis of these tumors in Canadian miners and millers, they do not cause disease in workers exposed exclusively to chrysotile after it has been purified by the milling process. This conclusion has enormous public health implications with specific regard to the removal of chrysotile-containing insulation and building materials from public buildings in the United States.

What pathogenetic mechanisms play a key role in the genesis of tumors caused by amphiboles? The question can be addressed from several perspectives. First, animal studies have shown that a variety of nonasbestiform fibrous particles induce the development of mesotheliomas in rats after intrapleural and intraperitoneal inoculation. Thus, the tumors would appear to develop in response to the long-term presence of fibrous foreign bodies in proximity to mesothelial surfaces. Stanton and Wench showed that the length and breadth of the fibrous material most probably is critical in the induction of the disease.

Epidemiologic studies have shown that amphibole is responsible for almost all, if not all, of the mesotheliomas attributable to asbestos. These fibers are retained in the lungs of occupationally exposed individuals after inhalation, presumably for a lifetime. Under these circumstances, the fibers would appear to be phagocytized by macrophages. And, there is reason to believe that the phagocytized fibers result in 2 pathogenetic events in the pleural tissue: macrophages that have phagocytized asbestos generate oxygen radicals and growth substances which doubtless have effects on adjacent cells and tissues. Exposure of this type has been shown to result in DNA damage which at times is

*From the Department of Pathology, University of Vermont College of Medicine, Burlington. Reprint requests: Dr. Craighead, Department of Pathology, University of Vermont, Burlington 05405

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associated with either karyotypic alterations or minor mutational changes in the cell genetic makeup. Given the concurrent occurrence of mutations and the production of growth substances in a localized area of the pleura, one might envision a multistage series of events whereby genetically damaged cells are stimulated to proliferate. Were this process to continue over an extended time, neoplastic transformation could occur in the mesothelial progenitor cells in the lining layers of the peritoneal and pleural cavities. Although this hypothesis most probably cannot be proved definitively, it is a plausible explanation for carcinogenesis consistent with all of the experimental and epidemiologic evidence existing today.

Accepting the validity of this notion, we might then consider the epidemiologic evidence further. As indicated above, amphibole asbestos types are retained in the lungs for indefinite periods and tend to accumulate adjacent to and in the pleural tissue. In contrast, chrysotile fibers break down into subfibers in lung tissue due to the leaching effect of body fluids. These subfibers deteriorate or dissolve further and are then eliminated by the lymphatic system of the lungs and the mucociliary escalator system of the airways. A number of studies of human lungs have shown that chrysotile does not accumulate in inordinate quantities in the lungs of occupationally exposed individuals.

Epidemiologic evidence suggests that the likelihood of an individual’s developing a mesothelioma relates proportionately to the length of their life. One might speculate that an individual encumbered by a burden of amphibole asbestos might invariably develop a mesothelioma were he to live long enough. This is, of course, a hypothesis that cannot be proved, but it argues strongly for the initiation of deliberate efforts to develop prophylactic approaches to reverse the course of the neoplastic events which might invariably occur in amphibole-exposed individuals. Clearly, therapeutic research efforts and interventions in the future might reasonably focus on means whereby the macrophage and its products might be altered in such a way that the mesothelioma would not be inevitable.

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Natural History and Staging of Malignant Mesothelioma

Karen H. Antman, M.D.*

NATURAL HISTORY

Patients with malignant pleural mesothelioma, characteristically aged 50 to 80 years (median 60), first seek medical attention for dyspnea, nonpleuritic chest wall pain, or both. The ratio of men to women is 2:5:1, presumably

*Associate Professor of Medicine, Dana-Farber Cancer Institute, Harvard Medical School, Boston.