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Neoplastic Asbestos-Induced Disease

W. T. ELLIOTT MCCAUGHEY, M.D.

Recognition of the carcinogenic effects of asbestos has evolved slowly over the past 50 years. Lung cancer first came under suspicion in the 1930s and 1940s, and by the 1950s it was well established in Europe as a frequent complication of asbestosis (1, 2). Strong evidence of an association between exposure to asbestos and mesothelioma appeared in 1960 (3), and subsequently the link has been confirmed by many studies. Finally, from 1964 onward evidence has been growing that asbestos may cause cancer in a number of other sites (Table). Cumulatively, these cancers of other sites add significantly to the mortality of asbestos workers (4).

In 1964 and 1965 several important papers concerning asbestos-related cancer came from the Mount Sinai group which included Drs. J. Churg, Selikoff, and Hammond (5–7). These reports described a striking excess of lung cancer and mesothelioma among American insulation workers and a probable excess of gastrointestinal cancer. It thus became obvious that asbestos-induced cancer was an important occupational disease in the United States and was not, as had sometimes been inferred, a disease mainly afflicting Europeans and South Africans. Subsequently, it was shown that many other categories of American asbestos workers were at risk and that paraoccupational neighborhood and domestic exposures to asbestos might also lead to cancer. Moreover, as awareness increased of the widespread contamination of the general environment by asbestos, it became apparent that there was at least a potential risk of asbestos-induced cancer for a large group of people in the general population.

From the Canadian Tumour Reference Centre, University of Ottawa, Ottawa, Ontario, Canada. Address reprint requests to the author there.

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Dr. Churg's special contribution to this unfolding story has come through the leadership and direction he has given to the evolution of objective criteria for the diagnosis of asbestos-related disease, especially mesothelioma. For many years he and his close friend and colleague, the late Dr. Milton Kannerstein, ran the U.S. Mesothelioma Panel and, in a number of important studies during that period, made us all more familiar with the characteristics of mesothelial tumors. The result has been that diagnosis of these controversial neoplasms is now much more objective, and related epidemiologic and clinical observations have become more secure.

Lung Cancer

Though it has been estimated that asbestos may cause some 5% of present-day lung cancers (8), the extent of the contribution of asbestos to the development of lung cancer in an individual patient may be difficult to quantify precisely, especially when the patient has been a cigarette smoker or the evidence of excessive exposure to asbestos is not clear cut. Initially asbestos was thought to cause lung cancer by multiplying the effects of tobacco smoke (9), but subsequently it was observed that asbestos caused lung cancer in nonsmokers (10–12). There is recent evidence that the relative risk of lung cancer in nonsmoking asbestos workers may be as high as or higher than in smoking asbestos workers (11, 12).

All commercial forms of asbestos have caused lung cancer, but some reports suggest that chrysotile, which accounts for more than 90% of the asbestos used in recent decades, is less potent than the two other widely used forms (amosite and crocidolite). However, in one setting (a chrysotile asbestos textile plant) the standard mortality ratio for lung cancer at different levels of exposure has been among the highest reported

TABLE
Neoplastic Effects of Asbestos Exposure in Humans

Definite
Lung
carcinoma
Pleura and peritoneum
diffuse mesothelioma
Gastrointestinal tract
carcinoma
Probable
Ovary
carcinoma
Larynx
carcinoma
Pericardium and tunica vaginalis
diffuse mesothelioma
Probable/possible
Reticuloendothelial system
malignant lymphoma
Breast, kidney, and pancreas
carcinoma

for lung cancer in asbestos workers (13, 14). This may be due to the fact that textile processing produces a greater proportion of the form of asbestos fiber (long and thin) that is particularly carcinogenic. Experimental studies have also shown that fine chrysotile fiber is just as potent as other forms of asbestos in causing lung cancer (15).

The nature of the dose-response relationship between asbestos and lung cancer is particularly important in assessing the effects of low-level exposures. If, as occupational studies suggest, the relationship is linear or almost so (13, 14), very light exposures may proportionately increase the risk. No threshold level of asbestos exposure has been recognized below which no lung cancer risk exists. It is also apparent from dose-response projections that exposures much less than those required to produce asbestosis may cause lung cancer. Asbestos appears to act as a classic promoter in the development of lung cancer, though the pathogenetic mechanisms of asbestos-induced lung cancer are unclear (16). Because asbestos causes lung cancer in nonsmokers and experimental animals, it appears that the fiber may also have an initiating influence.

The frequency of the main cell types in asbestos-induced lung carcinoma appears to be about the same as in the general population. There is evidence, however, that asbestos lung cancers are more likely to be located in the lower lobes than lung cancers in the general population (17). The pathologist's assessment of whether a given lung cancer is related to asbestos exposure must obviously depend on the asbestos content of the lung and the occupational history. Because discrepancies in the two forms of evidence are sometimes marked, both must be taken into account.

Malignant Mesothelioma

Association with Asbestos. Recently, the long controversy over the status and the diagnosis of mesothelioma has been augmented because of certain aspects of its association with asbestos. Though this tumor has undoubtedly been increasing in frequency, it remains rare. Sixteen hundred cases are estimated to have occurred in the United States in 1980 (18). However, the tumor is probably still underdiagnosed in those not uncommon situations in which the behavior or histopathology is not typical or adequate material is not available.

When epidemiologic and lung-asbestos-burden studies are taken into account, it appears that asbestos has caused some 60% to 80% of pleural and peritoneal mesotheliomas. However, the reported extent of the association varies markedly in epidemiologic studies. Thus, in some reports over 80% of patients give an occupational exposure history, whereas in other reports the figure is less than 30% (see ref. 19 for references). One can only speculate on the extent to which these variations reflect varying occupational and environmental conditions in different parts of the world and the enthusiasm and knowledge of the history-taker. Only a small percentage of women with mesothelioma have been occupationally exposed (20, 21).

Quite possibly some people develop mesothelioma as a result of very low level nonoccupational exposure to asbestos. Supporting this possibility are extrapolations based on the dose-response relationship between asbestos and mesothelioma in occupational studies (22) and the fact that in both humans and experimental animals, mesotheliomas have been associated with brief exposures (15, 23). It is also known that nonasbestos forms of mineral fiber with similar physical characteristics (aspect ratio) to those of asbestos fibers may induce mesothelioma in experimental animals and humans. In humans, erionite, a fibrous form of zeolite not related to asbestos, has caused mesotheliomas in Turkey (24).

Much controversy in recent years centers on whether chrysotile asbestos induces mesothelioma. Most observers feel that it is less potent than amosite and crocidolite in this regard. Particularly notable is the fact that peritoneal meso-

theliomas have rarely been observed in persons exposed to chrysotile. Experimentally, some forms of chrysotile have at least the same potential to induce pleural mesothelioma as other forms of asbestos. The role of chrysotile in initiating mesothelioma will have to be further evaluated in light of evidence that the tremolite form of asbestos, which is associated with chrysotile ore, could be a factor in the causation of pleural mesothelioma in chrysotile miners (25).

Other Factors. It is likely that factors or agents other than mineral fiber may be involved in the causation of some mesotheliomas (see ref. 19 for references). Thus, it has been suggested that radiation and chronic inflammation or scarring may have caused occasional mesotheliomas in humans. Genetic predisposition to cancer, as well as shared exposure to asbestos, may operate in the relatively frequent instances of familial occurrence of the neoplasm (26, 27). The list of agents that have caused mesothelioma in experimental animals is a long one (19) and further encourages a critical attitude on the etiology of mesothelioma.

Diagnosis. The pathologist can often diagnose mesothelioma in the early stages given experience, good material, and appropriate laboratory facilities. In several situations, however, considerable potential for misdiagnosis exists.

Cytologists are familiar with the fact that exuberant mesothelial hyperplasia can be readily confused with mesothelioma. Less well appreciated is the extent to which mesothelial hyperplasia may mimic tumor grossly and in biopsies (28). Focal mesothelial hyperplasias on occasion may be so pronounced as to form grossly visible nodules. Mild, and even moderate, cellular atypia may also be present, and—rarely—hyperplastic mesothelium may assume a papillary disposition. Occasionally, hyperplastic mesothelium may invade immediately underlying normal tissue, but necrosis and marked cytologic atypia do not occur in mesothelial proliferations proved to be benign on follow-up (28).

Dr. Churg has pointed out a small group of peritoneal mesotheliomas which run a very slow course and which often begin with what looks like hyperplasia (29). We have encountered occasional patients in whom marked mesothelial hyperplasia has been associated with chronic effusions and after several years of recurrent effusion, the cause of the mesothelial hyperplasia was not clear (28). In these situations the possibility that the hyperplasia is precancerous must be kept in mind.

Another difficult diagnostic problem in small serosal biopsies concerns differentiation of scar tissue from desmoplastic diffuse mesothelioma. This entity was delineated by Kannerstein and Churg some years ago (30). The tumor may contain extensive areas indistinguishable from banal scar tissue which may easily mislead the pathologist in small biopsies (30, 31). Further complicating the interpretation of fibrous serosal lesions is the fact that pleural fibrosis may sometimes be quite cellular and thus resemble fibrous tumor. The degree of nuclear atypia is usually the most critical factor in determining whether the tissue is benign or malignant. As in the case of mesothelial hyperplasia, necrosis favors malignancy (31). A well-developed tissue pattern—storiform or gyriform—also points to mesothelioma (28).

The most common diagnostic problem for the pathologist in biopsy material is differentiation of mesothelioma from metastatic carcinoma. When the tumor has a glandular or tubulopapillary pattern, the differential diagnosis is with adenocarcinoma. Positive staining for mucin with mucicarmine or periodic acid Schiff after diastase is usually considered to be decisive evidence of adenocarcinoma, although I have occasionally seen otherwise typical mesotheliomas with small numbers of tumor cells containing diastase-resistant PAS-positive granules or globules in their cytoplasm (32). Because a small proportion of adenocarcinomas arising in the lung and elsewhere do not secrete mucin, a negative reaction does not help significantly in distinguishing between mesothelioma and adenocarcinoma. Immunostaining for carcinoembryonic antigen is often helpful. Many adenocarcinomas immunostain strongly, but mesotheliomas do not, in our experience. However, mesotheliomas may occasionally react weakly. Though it has been claimed that positive immunostaining for human milk fat globule antigen distinguishes adenocarcinoma from mesothelioma (33), others have reported no discriminatory value (34).

Electron microscopy has been increasingly useful to us in distinguishing between mesothelioma and poorly differentiated carcinoma. In this situation the ultrastructural features (long slender microvilli, cytoplasmic cysternae, distribution of intermediate filaments) that help distinguish classical tubulopapillary mesothelioma and well-differentiated adenocarcinoma (35, 36) are often not helpful. In a recent study of poorly differentiated diffuse epithelial mesotheliomas, we have found that although the classical characteristics of well-differentiated neoplastic mesothelial cells are markedly modified, cytologic

details remain which are useful in distinguishing mesothelioma from carcinoma. These include the presence of cytoplasmic processes lying parallel to the adjacent plasma membranes, abundant cytoplasm with a polar disposition of organelles, and disaggregation of nuclear chromatin (37).

Other Cancers

It seems certain that asbestos causes other cancers (Table), though the strength of the evidence supporting a relationship with individual types of cancer varies. The strongest evidence of an association is with gastrointestinal carcinomas (38) and ovarian cancer (39, 40). In view of the relationship with ovarian cancer, it is of interest that the common ovarian epithelial tumors are believed to be of mesothelial origin and that tumors histologically identical to ovarian serous carcinomas may arise from the peritoneum of females (41, 42). Because asbestos is rapidly transmitted through the wall of the intestine into the lymphatic circulation, there is obviously the potential to initiate cancer in virtually any part of the body.

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