Asbestosis
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dialogue

What is Asbestosis?

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The term asbestosis has been defined as diffuse interstitial fibrosis of the lung parenchyma caused by exposure to asbestos.[1] Controversy has raged over the site of pulmonary fibrosis. Bellis and others[2] have considered the earliest lesion to be in the walls of the respiratory bronchioles and alveolar ducts. Churg[3] and others believe that abnormal respiratory bronchioles and alveolar ducts are a separate and nonspecific reaction to many types of mineral dust exposures and that true asbestosis is a diffuse type of parenchymal fibrosis surrounding the small airways but not just limited to the small airways. Kilburn and Warshaw provide us, in this issue (see page 965), with a provocative study which concludes that small airways disease is present in individuals with asbestos exposure who do not meet the standardized criteria for asbestosis: restrictive lung disease, or reduced diffusion, abnormal gas transport, or ILO x-ray profusion abnormalities of 1/1 or greater that cannot be explained by some coexisting disease process such as diffuse pleural thickening, emphysema, malignancy, or some other disorder. These patients must also fulfill the criteria of having significant exposure to asbestos, as well as having an appropriate latency period since first exposure to asbestos before the diagnosis can be reasonably considered.[3-5]

If Kilburn's hypothesis of a continuum of asbestos-related disease beginning in the small airways and progressing to diffuse interstitial fibrosis is correct, then pathologic proof should be available to support this hypothesis. The studies of Bellis et al[2] have shown a lack of correlation between airway lesions and asbestos body and fiber counts. No correlation with pleural plaques was found. Pathologic examination demonstrates small airways disease in workers with asbestos exposure, with and without asbestosis.[6-8] Data are lacking to establish any relationship between small airways disease and symptoms or functional impairment. Perhaps the most elegant studies published were performed by Begin and co-workers.[9,10] They were able to detect significant small airways impairment only in those patients who had restrictive lung disease, but were unable to detect reduced expiratory rates on the flow volume curves of lifetime non-smokers with asbestosis.

The study of Kilburn and Warshaw makes the common error of using a test with great variability and poor reproducibility to prove a hypothesis, *ie*, the FEF25-75 and FEF75-85.[11,12] The data are further confounded by comparing apples with oranges, or industrial workers with multiple types of heavy dust or fume exposure to a control group from Michigan which consists mostly of rural healthy farmers.

The proposed correlation between pleural plaques and small airways dysfunction will need further confirmation. Pleural plaques occur more frequently in smokers,[13] presumably due to the effect of smoking on mucociliary function. Perhaps welding smoke and other dusts and fumes may also adversely affect mucociliary function and, hence, cause greater fiber retention and a greater frequency to form pleural plaques. If, at a standardized exposure, a population with welding fume and mineral dust exposure has a higher frequency of pleural plaques than the control group, one would anticipate that there might be other asbestos-related disorders also associated with the enhanced fiber retention. While the hypothesis has merit, an epidemiologic study is unlikely to provide an answer. On chest x-ray film, pleural plaques are seen in only approximately 15 percent of patients in whom they are found at autopsy.[14] This means that the majority of patients who have pleural plaques have plaques which are not visible on x-ray examination. There is such great difficulty in finding plaques in a reproducible fashion on chest x-ray examination that any correlation with small airways disease would seem to be spurious. The gold standard is the pathologic correlation between pleural plaques found at autopsy and small airways disease noted in tissue sections. Most recent studies have found no correlation between small airways disease and pleural plaques at autopsy, and therefore, the data of Kilburn et al are interesting, but certainly not convincing of any true association.

The medical/legal implications of the study by Kilburn and Warshaw are enormous if one accepts their hypothesis that small airways disease is the

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earliest stage of asbestosis and that pleural plaques are a radiologic sign of coexisting small airways disease. If this were the case, then all lung cancers occurring in patients with pleural plaques would be considered attributable to asbestos exposure due to underlying early asbestosis. Patients with pleural plaques could seek compensation for "fear of lung cancer," as well as increased risk of lung cancer related to asbestos exposure. Presently, the available data indicate that pleural plaques do not indicate disease, but simply reflect a pleural injury related to asbestos exposure. Exposure may be very remote and very small such as occurring in household contacts of asbestos workers.[15] Pleural plaques are not associated with abnormalities in pulmonary function or exercise impairment[16] unless there is evidence of diffuse pleural thickening. Many other studies have demonstrated small airways disease in asbestos-exposed workers, as well as other types of mineral dust exposure. Abnormalities of small airway function are nonspecific and may be caused by a variety of industrial exposures,[8] as well as being secondary to cigarette smoking. Cigarette smoking may be remote as in household contacts of cigarette smokers.[17] In patients with interstitial pulmonary disease of any type, small airways disease is common,[18] but since it is also commonly found in individuals without interstitial fibrosis, small airways disease means small airways disease and nothing more. There is no pathologic evidence and there is no epidemiologic evidence that small airways disease progresses to asbestosis in man.

The other issue addressed by Kilburn and Warshaw is the possible relationship between pleural disease and lung function impairment. Recently, Schwartz et al[19] also reviewed the correlation between pleural disease and abnormalities in lung function in a similar population of 1,223 sheet-metal workers. They noted an association between circumscribed pleural plaques and a fall in FVC, as well as a slight but significant increase in the FEV_1/FVC ratio. This is the opposite conclusion to that of Kilburn and Warshaw who noted obstructive but not restrictive changes in their cohort. Schwartz and co-workers have also raised the question about the possible association between circumscribed pleural plaques and subclinical alveolitis, not visible on a chest x-ray film, as the possible cause for these restrictive changes. An alternative explanation for these findings would be the coexistence of diffuse pleural disease in patients with circumscribed pleural plaques which spares the costophrenic angle. In my experience, it is not uncommon to find both diffuse pleural thickening and circumscribed pleural plaques occurring simultaneously in patients with asbestos-related pleural disease and unexplained restrictive changes. The ILO Standards require blunting of the costophrenic angle to make a diagnosis of diffuse pleural thickening. This is an arbitrary standard for epidemiologic purposes and is not meant to preclude the possibility of diffuse pleural thickening in the absence of blunting of the costophrenic angle. Hopefully, a perspective study with thin-slice, high resolution CT scanning should further clarify the interrelationship between lung function abnormalities and asbestos related pleural disease.

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Asbestosis 1989

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MEDICAL PROGRESS

ASBESTOS-RELATED DISEASES

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ASBESTOS is a mineral causing much controversy in today's society. Before the passage and enactment of the Occupational Safety and Health Act of 1970, millions of Americans were exposed to relatively high concentrations of airborne asbestos in the workplace. Other citizens — including insulation installers, shipyard workers, and manufacturers of gas masks — encountered asbestos during World Wars I and II, when it was produced at an accelerated rate. Although the importation and use of asbestos have decreased in the United States since 1970, and recently the Environmental Protection Agency (EPA) has proposed a ban on its use, asbestos remains an important product internationally in construction and as a friction material.

The incorporation of asbestos into thousands of U.S. buildings in the past has resulted in the release of asbestos fibers into urban air when those structures are renovated or demolished.[1] Other fibers can become airborne because of the wear of brake linings or roads composed of asbestos ores, as well as through the weathering or erosion of asbestos-containing rock. These phenomena and the documented presence of asbestos fibers in water supplies and food products[2] have fostered concerns about the possible risks of exposure to asbestos outside the working environment. Indeed, the presence of asbestos fibers in the lungs of members of the general population[3] and children[4] suggests that many of us are exposed to asbestos unknowingly and early in life.

The asbestos used in building materials is nonrespirable unless its surfaces become disturbed or worn — a situation that promotes the release of friable asbestos fibers into the atmosphere. The documentation of the presence of airborne asbestos in deteriorating school buildings has caused widespread concern that children will be afflicted with asbestos-related diseases. In response to these fears, Congress recently passed the Asbestos Hazard Emergency Response Act, which requires the EPA to arrange with local education agencies for the inspection of all schools. Legislation is also pending that requires the monitoring, labeling, and management of asbestos in buildings. In addition to the high costs of such surveillance, an estimated $100 billion to $150 billion will be spent for the abatement and removal of the mineral during the next decade.[5]

We address the effects of asbestos on health as documented in occupational cohorts, as well as the advances in the diagnosis and treatment of asbestos-associated diseases. In addition, we describe current basic-science and clinical research in order to elucidate the mechanisms of asbestos-related disease. Finally, we examine the results of several recent epidemiologic studies and risk assessments in order to address the question of whether exposure to asbestos is a health problem outside the working environment. Since it has become increasingly clear that different types of asbestos differ in their pathogenic potential with respect to pleural abnormalities and malignant mesothelioma, we begin by describing the physical and chemical properties of asbestos.

IDENTIFICATION AND TYPES OF ASBESTOS

Asbestos is a family of crystalline hydrated silicates with a fibrous geometry (defined as a ratio of length to diameter, or aspect ratio, of more than 3:1). A commercial designation rather than a mineralogic

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term, the word *asbestos* can be applied to six chemically and physically distinct types of minerals — chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite.

Asbestos is often closely associated with other minerals in ores. For example, iron oxides and quartz are often found with crocidolite and amosite asbestos, whereas chrysotile can be contaminated with forsterite, magnetite, brucite, quartz micas, and feldspar.[6] Tremolite asbestos is a contaminant of some Canadian chrysotile deposits, as well as of industrial talc, vermiculite, sandstone, and other types of asbestos. During processing, asbestos fibers can adsorb both organic solvents, such as oils and hydrocarbons,[7] and inorganic solvents used in the workplace.

The use of asbestos in thousands of manufactured products is dictated by its strength, flexibility, resistance to acid and heat, and durability. Currently, asbestos is incorporated into cement pipes, brake linings, packing and gaskets, thermal and electrical insulation, flooring and roofing products, paper, plastics, and textiles. In the past, asbestos was sprayed onto building surfaces as an insulation material and fire retardant, but this process has been outlawed by the EPA. Although a number of replacements for asbestos have been proposed, none appear to be as attractive and economical or to have as many industrial applications.[8]

Distinguishing various types of asbestos and other fibers is important in the consideration of asbestos-associated diseases. For example, naturally occurring minerals such as palygorskite and zeolites may occur as fibers but are not included under the rubric of asbestos. Chrysotile, which has consistently accounted for 95 percent of the world's production of asbestos, is a member of the serpentine group and consists of pliable, curly fibrils that may occur in bundles (Fig. 1A). Cross sections of the fibers resemble scrolled tubes. In simplistic terms, the macromolecular structure of chrysotile consists of parallel sheets of silica and brucite (magnesium hydroxide) that are stacked with varying degrees of overlap and curvature.[10] The other types of asbestos — crocidolite, amosite, anthophyllite, tremolite, and actinolite — belong to the amphibole group, a family of minerals with characteristic needlelike fibers (Fig. 1B) and a crystalline structure composed of parallel chains of silica tetrahedra. The silicon tetraoxide chains are separated by a band of cations that vary in type, number, and capacity for substitution. As a result, the chemical composition of the amphiboles is complex and may include substantial and variable amounts of monovalent, divalent, and trivalent metals.

The majority of individual asbestos fibers in air and tissues are not visible on light microscopy, although ferruginous bodies (i.e., asbestos bodies) that encapsulate longer asbestos and asbestoslike fibers are often apparent. Chrysotile asbestos can usually be detected with confidence with transmission electron microscopy, but the identification of other fibers requires additional diagnostic tools, including selected-area electron diffraction, a procedure yielding crystallographic data, and x-ray energy dispersive analysis, which provides a blueprint of the chemical composition of fibers.

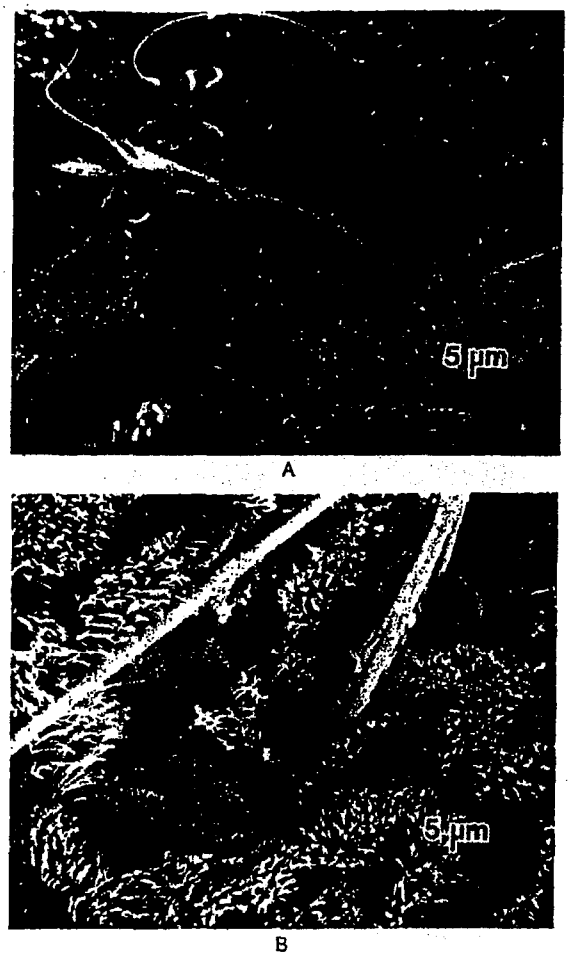

Figure 1. Morphology of the Serpentine and Amphibole Types of Asbestos.

Panel A shows the curly nature of chrysotile, a serpentine type, and Panel B shows the needle-like fibers of crocidolite, an amphibole.

In these scanning electron micrographs, reference samples of asbestos (arrows) from the International Union against Cancer interact with bronchial epithelial cells in organ cultures of human bronchi. (Figure 1A is reprinted from Woodworth et al.[9] with the permission of the publisher.)

The increased pathogenicity of the amphiboles, as compared with chrysotile asbestos, may be ascribed to a difference in the patterns of deposition and clearance of fibers, as well as to their insolubility in lung tissue. The larger fibers of chrysotile tend to occur in bundles and are readily intercepted at airway bifurcations because of their curliness.[11] Alternatively, the straighter amphibole fibers can penetrate deeper into the lung. Over time, the longitudinal fragmentation[12] and leaching[13] of magnesium from chrysotile fibers are ob-

served in the lung. Thus, these phenomena may account for the increased solubility of chrysotile and its less frequent occurrence in the lungs of exposed cohorts, as compared with the amphiboles.

Diseases Associated with Exposure to Asbestos

Since the turn of the century, asbestos has been recognized as an occupational health hazard. Because of the documentation of asbestosis in the workplace in the early 1900s and the subsequent regulation of exposure to asbestos, the disease is less important medically today than lung cancer and mesothelioma.

Mesothelioma

Mesotheliomas arise in the pleura and the peritoneum. Asbestos exposure does not cause localized benign, predominantly fibrous mesothelioma. In contrast, approximately 80 percent of diffuse malignant mesotheliomas occur in men exposed to asbestos in the workplace and sometimes in their family members or in persons who live near mines. The remaining 20 percent of men with malignant mesothelioma have no history of exposure to asbestos, and there is usually no excess of mineral fibers in their lungs. Smoking does not enhance the prevalence of malignant mesothelioma in humans.

Of 17,800 asbestos-insulation workers who have been followed since 1967, 356 have been reported to have died of malignant mesothelioma (pleural or peritoneal).[14] In women who manufactured crocidolite gas masks, all cases of malignant mesothelioma were observed at least five months after initial exposure.[15] These cases involved heavy fiber loads in the lung, as observed at autopsy.[16] In Rochdale, England, textile workers exposed to chrysotile and crocidolite,[17] the risk of contracting malignant mesothelioma was approximately 25 times higher in workers employed for 10 or more years than in those employed for less than 10 years (Liddell FDK: personal communication). A recent study of mortality rates in miners and millers of crocidolite in Western Australia confirms that the development of malignant mesotheliomas after intense exposure is dose-dependent.

Two independent surveys done of the prevalence and geographic pattern of pleural malignant mesothelioma from 1968 to 1984 show that the disease remains extremely uncommon in the United States.[19,20] As compared with mortality due to lung cancer (approximately 130,000 cases per year), an average of 1500 cases of malignant mesothelioma are reported yearly.[21] Whereas the mortality due to mesothelioma in women of all ages and in men under 65 has remained fairly constant or declined slightly, death rates in men 65 or older have increased steadily. There have been excess numbers of cases in several regions where asbestos was manufactured or where there were shipyards in the past, but the high mortality due to the disease in other geographic areas is not related to obvious occupational exposure.

Patients with malignant mesothelioma may be asymptomatic at first, but they often have dyspnea or chest pain with pleural fluid of variable mobility.[22] Pleural thickening or interstitial fibrosis is apparent on chest films in approximately 20 percent of the patients, and CT scans reveal calcifications of the tumor mass in almost half.[23] Since malignant mesotheliomas vary histologically, ranging from epithelial to sarcomatous and mixed forms, diagnosis by microscope is difficult. The tumors may be confused with those of metastatic cancer or, less commonly, with inflammatory or reactive processes, including exuberant mesothelial hyperplasia.[24] When the tumor appears in a glandular or tubulopapillary pattern, it may be misdiagnosed as a metastatic adenocarcinoma.

Advances in histochemistry, immunocytochemistry, and electron microscopy have made possible earlier and more accurate diagnosis of malignant mesothelioma, if sufficient biopsy material is available. Generally, cytologic smears or needle-biopsy specimens do not afford an accurate identification, and only open thoracotomy yields tissue samples adequate for both the diagnosis of malignant mesothelioma and the determination of fiber counts in the lung.[22] When procedures such as periodic acid–Schiff staining (a reaction that stains diastase-resistant vacuoles) are used to detect mucopolysaccharides, positive staining invariably suggests adenocarcinoma. Immunoperoxidase techniques that use antibodies to keratin proteins may identify the keratin-producing cells that are characteristic of malignant mesotheliomas. Alternatively, adenocarcinomas (but not mesotheliomas) react avidly with antibodies to carcinoembryonic antigen. The uniqueness of the fine features of mesothelioma cells — specifically, long microvilli and tonofilaments — can be demonstrated by electron microscopy, a more definitive technique in the diagnosis of most malignant mesotheliomas.[25]

The prognosis of malignant mesothelioma is grim. Most patients survive for less than one year after diagnosis, although untreated persons have survived for as long as three years. A combination of radiation and doxorubicin (Adriamycin) is probably most helpful in prolonging survival,[22] and thoracentesis can minimize dyspnea.

The average latency period between the first exposure to asbestos and the clinical diagnosis of malignant mesothelioma is 35 to 40 years, with most deaths occurring in patients over 60 years of age.[26] In insulators, the incidence of mesothelioma is estimated as proportional to $T^{3.2}$, where T is the time since the initial exposure to asbestos, regardless of age at first exposure.[27] However, the incidence of mesothelioma among factory workers with limited exposure to asbestos is directly related to the time since first exposure, but eventually the incidence tails off.[28]

Several experimental studies give insight into the mechanisms of malignant mesothelioma in association with exposure to asbestos. In a number of experimental systems, carcinogenesis occurs in sequen-

tial stages of initiation and promotion. Whereas initiating substances can interact with the DNA of cells to produce heritable changes in the genetic material, promoters, which favor the proliferation and expansion of the initiated cells in a manner that encourages the development of malignancy, are thought to act epigenetically. According to these definitions, asbestos appears to be a complete carcinogen, possessing both initiating and promoting properties with regard to the induction of mesothelioma in rodents. For example, the intrapleural or intraperitoneal injection of asbestos fibers causes mesotheliomas to develop in a dose-dependent fashion.[29,30]

Lung Cancer

The association between exposure to various types of asbestos and bronchogenic carcinoma has been demonstrated in a number of occupational settings.[31] The average latency period of the disease from the time of first exposure to asbestos ranges from 20 to 30 years. The degree of association varies with the type of asbestos, fiber morphology, concentration, exposure regimen, and such cofactors as smoking habits or the presence of certain other chemicals in the workplace, but there is usually a dose–response relation (fibers per cubic centimeter of air times the number of years of exposure). Cohorts such as textile workers have a higher relative risk of disease than others, such as chrysotile miners and workers in plants that manufacture friction products (Fig. 2).[31]

Lung tumors are rare among asbestos workers who do not smoke. Although early epidemiologic studies indicated that the effects of asbestos and smoking combine in a multiplicative fashion to produce lung cancer,[32] several recent surveys have suggested that this model is inapplicable in some cohorts. For example, there is a weak interaction between the effects of asbestos and smoking in Canadian chrysotile miners and millers, as well as in British factory workers.[33,34]

The risk of lung cancer in nonsmokers with asbestos exposure can be assessed only in a very large cohort, because male asbestos workers are frequently heavy smokers. The inaccurate classification of smokers as nonsmokers may disproportionately inflate the calculated risk of lung cancer among nonsmokers. Workers' estimates of their own cigarette smoking are also questionable, subject to faulty recall, and not always verifiable by independent questioning of friends and relatives. Moreover, a high incidence of passive smoking in the presence of other workers whose smoking rates were higher than those of the general population could enhance the risk among nonsmokers. The data on asbestos workers who are nonsmokers have been summarized recently.[31] But, for the reasons we have mentioned, it remains uncertain whether any type of asbestos acting alone can cause lung cancer in nonsmokers.

Several considerations are relevant to the question of a possible contribution of environmental asbestos to lung cancer among members of the general population. First, the numbers of coated asbestos fibers (ferruginous bodies) in the lungs of persons with and without lung cancer are comparable.[35] Second, the correlation between the incidence of plaques — an indicator of asbestos exposure — and the increased risk of lung cancer is variable, weak, and inconclusive.[36,37] Third, recent epidemiologic studies of persons with low exposure to asbestos either occupationally[38-41] or environmentally[42,43] provide little support for the concept that there is an increased risk of lung cancer when asbestos concentrations are at levels several hundred or thousand times lower than those found in workplace situations in the past. In a recent British paper analyzing two very large cohorts, one working before and the other after the introduction of a new standard of asbestos regulation,[44] the workers studied after the standard was imposed had no clear evidence of increased cases of lung cancer or asbestosis. As the authors point out, however, the follow-up period was short (12 years), and the latency period established for these diseases is far from over.

A current controversy with important medicolegal ramifications concerns the possible causal role of asbestosis in the development of lung cancer. That scar cancers can occur at sites of fibrotic postinflammatory

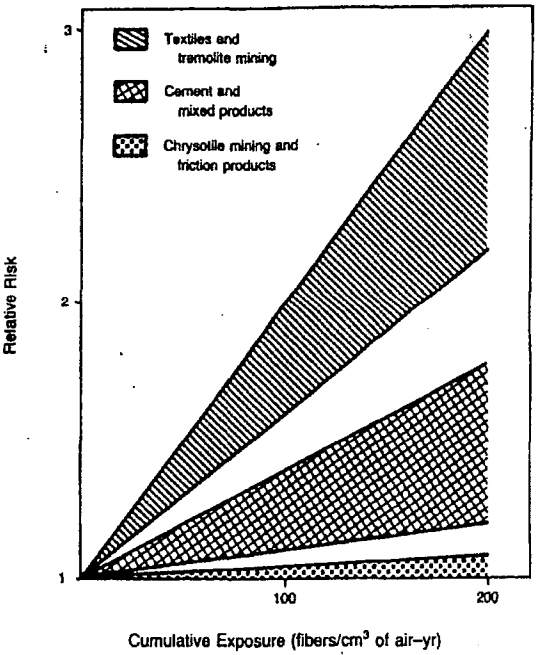

Figure 2. Estimated Risks of Lung Cancer in Various Occupational Cohorts.

The risk gradients for workers exposed to mixed fibers are several times steeper than those for workers in chrysotile mining and manufacture of friction products, but less steep than those for chrysotile textile workers. Exposure is expressed as fibers per cubic centimeter of air times the number of years of exposure. (Reprinted from McDonald and McDonald,[31] with the permission of the publisher.)

disease (e.g., tuberculosis) has long been recognized.[45] There is also evidence for the concurrence of fibrogenicity and tumorigenicity with various fiber types and clinical forms of pulmonary fibrosis in humans.[46] Several difficulties are inherent in dissociating asbestosis from exposure to asbestos without asbestosis as a cause of lung cancer in asbestos workers. First, since the development of both diseases is related to the amount of exposure to asbestos, the appearance together of lung cancer and asbestosis cannot be distinguished directly from the requirement for asbestosis as a precondition for the development of lung cancer. Second, by impairing the lung's ability to clear fibers, smoking may magnify the extent of fibrogenesis due to asbestos. Third, at levels of exposure that cause no detectable fibrosis, the epidemiologic difficulties in detecting small increases in the risk of lung cancer are considerable, particularly when smoking is both prevalent and heavy. A study of Quebec miners and millers suggests that "most, but not necessarily all, [patients with] lung cancer 'attributable' to chrysotile have small (radiologic) parenchymal opacities before death."[47] This study addresses indirectly the issue of distinguishing asbestosis-associated lung cancer from lung cancer in asbestos workers who smoke and who have little or no "clinical" asbestosis.

In West Germany and the United Kingdom,[48] lung cancer is attributed to asbestos if there is evidence of asbestosis on either chest films or pathological examination. Some reports have indicated that adenocarcinomas occur more frequently and more peripherally in patients with lung cancer who have asbestosis.[49] Others stress that the histologic types of the tumors are similar in patients with lung cancer with and without fibrosis.[50] Many asbestos workers with lung cancer[51-53] have histopathological evidence of asbestosis on in-depth examination,[51-53] though some have questioned this view.[54] The diagnosis of asbestosis is made in living patients when radiologic and functional features associated with respiratory symptoms and clinical changes are present. There is no doubt that pathologically evident asbestosis can precede these diagnostic features, as is also true of idiopathic pulmonary fibrosis. Thus, asbestos workers with lung cancer can also have occult minor asbestosis. However, without an autopsy, one must still rely on the clinical evidence of asbestosis in assigning a statistical probability to the relative contribution of asbestos and smoking.

Cancers of the Gastrointestinal Tract and Larynx

Certain cohorts of asbestos workers have been reported to have an increased risk of cancers of the gastrointestinal tract, larynx, kidney, pancreas, ovary, and most recently the eye.[55] An increased risk of lymphoma has also been suggested.[56] Since these risks were first described — in insulation workers in New Jersey who were heavily exposed to asbestos and in a few other cohorts — considerable doubts have arisen, as more cohorts with different exposures in different industries have been followed for longer periods. Recently the subject has been reviewed by Doll and Peto,[56] who generally discount the original concerns about gastrointestinal cancers and those in some other sites. Although those investigators believe that asbestos causes laryngeal cancer, they find the absolute risk to be much lower than that for lung cancer. Since this account, another review has argued that the risk of laryngeal cancer among asbestos workers is insignificant.[57] Indeed, life-style factors, ethanol use, and smoking are clearly much more important. Many available epidemiologic studies are based on death certificates that refer to laryngeal cancer, rather than to actual cases of this far from universally fatal disease.

Whether asbestos causes gastrointestinal cancers is particularly important to the general population, since asbestos-lined cement pipes carry much of the nation's water supply. The magnitudes of the increased standardized mortality ratios (SMRs) originally reported as statistically significant by Selikoff et al.[58] have not been confirmed in studies of more than 30 separate cohorts. When elevated risks were observed for cancers of the gastrointestinal tract or for those of only the colon and rectum, the SMRs were about 2, lower than those in most studies of lung cancer. The majority of cohorts had no significant increase in SMRs.[59]

Asbestosis

The general features of asbestos-induced pulmonary fibrosis are well known. Diagnostic criteria for nonmalignant asbestos-related diseases have been published by the American Thoracic Society,[60] as has a response thereto.[61] Asbestosis is characterized by a history of exposure to asbestos and interstitial pulmonary fibrosis manifested by dyspnea, cough, basal rales, late-stage finger clubbing with cyanosis, and ultimately, right-sided heart failure. Radiologically, the features are those of other interstitial fibroses — namely, fine-to-coarse irregular opacifications that are initially basal, and irregular linear shadows. A formal classification for asbestosis, developed on the basis of the size and profusion of lesions, permits some interobserver standardization.[60] However, lung-function tests remain essential in the detection and assessment of impairment. Diminutions of vital capacity, total lung capacity, residual volume, functional residual capacity, and commonly, low values for diffusing capacity are the general hallmarks of restrictive lung disease. Perturbations of lung function caused by obesity must be considered. The first manifestation of asbestosis may involve either radiologic or functional features, but ultimately both become abnormal, and hypoxemia develops. Frequently, this classical picture is modified by the presence of chronic obstructive pulmonary disease due to smoking. The pathological diagnostic criteria of asbestosis have been reported elsewhere.[62] To date, there is no effective therapy for an established case of the disease.

From the 1930s to the mid-1950s, asbestosis was an occupational disease of overwhelming importance. Now its incidence in the workplace is declining, at least in North America. It is not a threat outside the working environment. In many newly diagnosed cases of asbestosis, the disease is relatively mild and probably will not progress — particularly in cases in which the radiologic indexes of profusion are low.[63] These observations imply that with adherence to good work practices and current standards of hygiene, asbestos workers need not leave their trade. Although workers with seriously restrictive disease probably should not work with asbestos, those with borderline abnormalities in function and low profusion of radiologic abnormalities probably can continue.[57] Though dyspnea is a symptom commonly reported by asbestos workers, an objective assessment is important for both case-management and medicolegal purposes. In one study of 120 asbestos workers seeking compensation, almost half had no ventilatory dysfunction.[64]

Small, irregular opacities seen on radiography, a common and minor feature of asbestosis, are more evident in asbestos workers who smoke.[65] Similar results have been observed in those who work with asbestos insulation.[66] However, since no data on lung function were included, it is unclear whether such changes imply function-reducing asbestosis or radiologic shadow enhancement.

Classical pathology reports show that asbestosis develops in the terminal bronchiolar region.[62] More recent studies have examined the occurrence in asbestosis of small airway disease. Apart from the general difficulties inherent in making this diagnosis, recent data from a sheep model of asbestosis[67] and from asbestos workers[68,69] indicate that small-airway dysfunction that is related to exposure to asbestos as opposed to cigarette smoke is minor and clinically unimportant. A review of airway function in asbestos workers should be consulted for details.[70] Symptoms of obstructive lung disease have been clearly identified with smoking rather than asbestos by Lerman et al.[71]

Some interesting studies have advanced our understanding of the pathogenesis of asbestosis. First, alveolar macrophages obtained from the lungs of asbestos workers by lavage spontaneously hypersecrete tissue-injuring oxidants and macrophage-derived growth factor and fibronectin.[72] The latter two mediators synergistically promote the replication of fibroblasts, a prerequisite for fibrosis. Other studies, most recently from Australia,[73] show a neutrophil–eosinophil alveolitis in patients with asbestosis and elevated numbers of both types of cells in bronchoalveolar-lavage fluid from these patients. The proportion of neutrophils recovered was correlated with the duration of exposure to asbestos. Neutrophils release a collagenase that is not inhibited by α_1-antiprotease and that conceivably induces lung injury.[74] The emphasis on neutrophils and eosinophils, in addition to macrophages, as inflammatory mediators of the fibrosing alveolitis of asbestosis suggests possible therapies. For instance, colchicine decreases the production in macrophages of a fibroblast growth factor in vitro,[75] and quinacrine decreases the flux of neutrophils into alveoli in rats in which silica is instilled.[76] Other studies with bronchoalveolar lavage have indicated variable lymphocytosis in asbestos workers, with a depression of the ratio of helper to suppressor T cells.[77,78] Although lymphocytes produce fibroblast growth factors and have been shown by some studies to be increased in fluid recovered from asbestos workers by bronchoalveolar lavage,[79] these cells have not been demonstrated to be directly involved in asbestos-related fibrogenesis.

Benign Pleural Disorders

Four types of benign pleural disorders are associated with asbestos: benign pleural effusions, pleural plaques, pleural fibrosis, and rounded atelectasis. How fibers are transported to the pleura and how cellular mechanisms contribute to these reactive lesions remain an enigma.[80] Benign pleural effusions occur in a small percentage of asbestos workers, usually less than 20 years after the initial exposure to high concentrations of asbestos.[81] The diagnosis is based on the exposure history and the exclusion of other causes. Only about a third of affected persons are symptomatic and have pleural pain, dyspnea, or both. A few effusions recur, but most resolve spontaneously. The fluid is usually an exudate, occasionally sanguineous. There is no evidence that benign pleural effusions cause pleural plaques, and workers who have only effusions probably do not now need to leave the workplace.

Pleural plaques are currently the most common manifestation of exposure to asbestos. They occur as fibrohyaline nodular lesions, most often on the parietal pleura, but also on the diaphragmatic pleura and less frequently on the pericardium. Their relatively discrete nature and parietal location together account for the virtual absence of decrements in lung function from such plaques. Plaques are best seen on the lower half of the lateral aspects of posteroanterior-view chest films, but lateral- and oblique-projection films may be helpful. Calcification occurs with time, but does not necessarily imply an enlargement of the lesions. Plaques need to be differentiated from fat pads (notably in obese patients), reactions to rib fractures, and in the case of unilateral plaques, other causes of pleural reaction, especially recurrent pneumothoraxes and inflammatory diseases, including tuberculosis. When seen en face in the central portions of the posteroanterior film, they can simulate tumors (when single) or asbestosis lesions (when multiple and small). CT scanning is useful, because it shows more plaques than are revealed by conventional radiography and differentiates them from both fat pads and intrapulmonary lesions. At present, there is little evidence

that pleural plaques on their own carry an increased risk of neoplasia or of the development of "functionally significant asbestosis" — the latter term being reserved by many, including the American Thoracic Society, for parenchymal as opposed to pleural abnormalities.[60]

The prevalence of plaques, particularly with calcification, varies considerably. Plaques are very common in anthophyllite workers in Finland, for instance. Within Quebec, there is at least a twofold variation in the prevalence of plaques between the miners working at Asbestos and those at Thetford Mines,[82] despite apparently similar techniques of mining "similar" chrysotile ores.[82] Geographic variations in pleural changes also occur among persons on a single island, Corsica.[80] These variations are not explicable at present, but they raise the possibility of differential spread of "asbestos" to the pleura or differences in the types of asbestos that cause plaques. These ideas are endorsed by a report suggesting that differences in mica, talc, or breunnerite content may be involved.[83] Sepiolite, a nonasbestos fiber, has been proposed as the cause of pleural calcifications endemic in Bulgaria.[84] Thus, variations in the prevalence of benign pleural reactions may reflect mineralogic or morphologic differences among fibers.

Diffuse pleural fibrosis is a relatively rare manifestation that produces unilateral or bilateral pleural reactions, mostly manifest laterally on posteroanterior chest films. Only rarely can it cause a cuirass effect, with restrictive changes in function that simulate those of asbestosis. Occasionally, the pleural changes encroach on the subjacent lung parenchyma and trap some lung tissue, simulating a tumor. In this event, CT scans suggest the correct diagnosis. Since their histologic appearance is similar, pleural fibrosis and plaques may have a similar pathogenesis.[84]

Characteristics of Asbestos Important in the Causation of Disease

The variable physicochemical features of asbestos complicate attempts to evaluate the effects of different types of fibers on health. Because asbestos workers may be exposed over a lifetime to various concentrations, sizes, aerodynamic features, and admixtures of chrysotile and amphibole fibers, the interpretation of epidemiologic data is sometimes difficult. However, a growing body of information supports the concept that the amphiboles crocidolite, amosite, and tremolite are largely, if not entirely, the cause of malignant mesothelioma in humans. For example, the mortality rate for pleural and peritoneal malignant mesothelioma in male cohorts with occupational exposure to asbestos depends on the types of asbestos handled.[85] Mortality is highest among those who work with the amphiboles alone (10.6 percent), lower among those who work with mixtures (3.6 percent), and lower still among those who work with chrysotile alone (0.2 percent). Asbestos-related peritoneal malignant mesotheliomas are invariably associated with exposure to the amphiboles. The few pleural malignant mesotheliomas that result from the mining and milling of Canadian chrysotile are now attributed to the contamination of Thetford Mines and other Quebec ore with tremolite.[85] Indeed, the relative risk of malignant mesotheliomas among workers handling chrysotile corresponds directly with the ratio of tremolite to chrysotile fibers in the lungs of these persons.[86]

Lung cancer and asbestosis[87] may also be associated more commonly with the amphiboles than with chrysotile. Consistently lower rates of lung cancer occur in occupational cohorts exposed almost exclusively to chrysotile (Fig. 2).[31] In comparison to chrysotile, the amphiboles are associated with a higher risk of disease in miners, millers, and persons who work with building materials. Textile workers exposed to chrysotile have a higher risk gradient than other cohorts, including persons in a textile plant who handle mixed fibers. This high-risk group was exposed to chrysotile from the same source as Quebec miners and millers. Recent analyses of tissues at autopsy show equivalent concentrations and sizes of asbestos fibers, predominantly those of tremolite, in the lungs of persons from these two cohorts, even though the dust levels in the textile plant were an estimated one tenth of those in the mines and mills.[88] Thus, the differences between the types, concentrations, and dimensions of fibers in the lungs of the Quebec miners and millers and those of the textile workers do not account for the extreme differences in the risks of lung cancer between these groups. Under these circumstances, the solvents and oil sprays used in the textile industry seem to be important cocarcinogens.

The concept that fiber size is an extremely important determinant of the pathogenic potential of asbestos was indicated initially in epidemiologic data. Malignant mesotheliomas were first described in the northwestern Cape region of South Africa, where long, thin crocidolite fibers were mined.[89] In contrast, no tumors were observed in the Transvaal district, where workers were exposed to shorter and coarser crocidolite fibers. A number of experimental studies have confirmed these observations. After the intrapleural or intraperitoneal injection of preparations of fibers of a number of sizes, fibers more than 8 μm long and less than 0.25 μm in diameter were found to be most potent in the induction of malignant mesothelioma, regardless of their chemical constitution.[29,30] The intratracheal injection of longer fibers produced asbestosis in rodents, whereas shorter fibers caused no disease.[90] Recently, long-fiber preparations of amosite asbestos were compared with shorter fibers (less than 5 μm) in rats.[91] Widespread asbestosis, pulmonary neoplasms, and malignant mesotheliomas developed only in animals that inhaled long fibers, although significantly more short fibers were retained in the lung over time. Thus, regardless

of the route of administration of asbestos, longer fibers appear to carry greater risks.

Risks of Nonoccupational Exposure to Asbestos and Regulatory Considerations

Expert panels have debated at length the controversial question of whether asbestos is a health risk to the population at large. There have been several well-documented cases of malignant mesothelioma in the vicinity of crocidolite mines and factories, as well as in the families of asbestos workers. An increased prevalence of malignant mesotheliomas and asbestos-related effects have been reported most recently in the residents of certain geologic regions, such as the Anatolian part of Turkey,[92] Cyprus, [93] and northeastern Corsica.[94] However, one would expect from the limited measurements reported that the concentrations of fibers in air in these situations were much higher than those observed in homes and public buildings today.

Lacking direct evidence for the concept that nonoccupational exposure to asbestos poses a risk to the public, governmental agencies and scientists have addressed this question by using the process of risk assessment. From 1983 to 1986, seven estimates of potential lifetime risk of asbestos-induced lung cancer and mesothelioma appeared in the literature.[2,21,95-100] In general, all were calculated according to similar mathematical models, based on extrapolation of mortality data from occupational cohorts down to the theoretical levels of disease occurring at the concentrations of fibers found in public buildings and schools today. The final risk estimates and their degree of uncertainty varied from group to group, because of the selection of occupational cohorts and other variables. One report[95] examined these risk assessments comparatively and attempted to provide a perspective on the estimated lifetime risk of asbestos exposure in schools, as compared with other risks in our society (Table 1). Clearly, the total number of deaths due to asbestos is substantially lower than published risk estimates from common causes.

In the light of current epidemiologic and experimental data, it has become increasingly apparent that estimating the risk due to exposure to asbestos is more complicated than estimating the risk due to soluble chemical carcinogens. The types and sizes of fibers are important variables that must be considered. The linear dose–response model for the prediction of asbestos-induced lung cancer is questionable, because it assumes that any exposure to asbestos will result in some increase in disease — an unproved hypothesis. Moreover, several studies of persons exposed to asbestos show no statistically significant excess cases of lung cancer when concentrations of fibers are low.[38-43]

Risk estimation is the basis of the governmental policies that regulate occupational and environmental carcinogens. However, it is inappropriate to assess the risks of asbestos without regard to the important variables. Despite the questionable assumptions of linearity — the absence of a threshold and unlimited linear extrapolation — the derivation of the risks of exposure to various types of asbestos is possible (as illustrated in Table 2) and should be encouraged. Currently, U.S. regulatory policies do not distinguish between the amphiboles and chrysotile, despite compelling epidemiologic data that show the association of malignant mesotheliomas with the amphiboles rather than chrysotile, which is by far the most common fiber — a point of considerable importance with regard to asbestos exposure in schools. Although there is an occupational standard (0.2 asbestos fiber greater than 5 μm in length per cubic centimeter of air collected over an eight-hour period), the EPA has no standards for action against asbestos in schools or public buildings, where the average airborne fiber counts are generally 1000-fold less.[101] Thus, the decision to remove asbestos is made arbitrarily, often without sufficient information, by private and civic groups. Most alarming are recent publications that show an increase in the asbestos concentrations in the air after fibers are removed from buildings — a phenomenon that is due to disturbance of fibers and improper containment during the removal process.[102,103] Although air monitoring in schools and public buildings has revealed infinitesimal amounts of airborne asbestos in comparison with conditions prevailing in the workplace in the past, governmental agencies, on the general

Table 1. Published Estimates of the Risk of Death in the United States from Various Causes.*

Cause	Annual Mortality Rate
	no. per million
Asbestos in schools	0.02–0.37†
Floods	2
Aircraft accidents (1979)	6
Drowning (ages 5 to 14)	27
Home accidents (ages 1 to 14)	60
Long-term smoking	1200

*Reprinted from Weill and Hughes[95] with the permission of the publisher.

†Data from six published risk estimates were used to estimate the total number of deaths over a lifetime from lung cancer and mesothelioma that were attributable to asbestos exposure per million students exposed in school to 0.001 mixed fiber per milliliter of air for five years, beginning at age 10, and assuming an average life expectancy of 75 years.

Table 2. Risk of Cancer and Exposure to Chrysotile or Mixed Fibers.*

	Lung Cancer	Mesothelioma	Total
	mean estimate (range)		
Chrysotile	0.6 (0.3–1.2)†	0.9 (0.4–1.8)	1.5 (0.7–3.0)
Mixed fibers	0.6 (0.3–1.2)	4.4 (2.2–8.8)	5.0 (2.5–10)
Not related to asbestos	32,000	140	32,140

*Reprinted from Hughes and Weill[21] with the permission of the publisher.

†Estimated number of lifetime deaths attributable to asbestos exposure per million students exposed to 0.001 fiber per milliliter for six years.

grounds of prudence, have advocated visual inspection and massive removal at great expense, instead of operational maintenance.

We suggest that determinations of respirability, the airborne concentrations of fibers, friability, fiber size, and most important, the type of asbestos (particularly when the amphiboles are involved) are the prerequisites for any rational determination of the need for asbestos abatement. In schools, where the risk of malignant mesothelioma may be far more pertinent, focusing on the presence of the amphiboles is critical. For lung cancer, an overall attack on smoking, as advocated by the Surgeon General, will be far more effective than asbestos removal in the reduction of risk. In the absence of epidemiologic data or estimations of risk that indicate that the health risks of environmental exposure to asbestos are large enough to justify high expenditure of public funds, one must question the unprecedented expenses on the order of $100 billion to $150 billion[5] that could result from asbestos abatement.

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