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MEDICAL PROGRESS

THE PATHOGENESIS OF ASBESTOS-ASSOCIATED DISEASES

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ASBESTOS is one of our most useful minerals. Over 3000 manufactured products of contemporary importance contain it. Asbestos is employed in construction materials because it is resistant to thermal and corrosive destruction and increases the tensile strength of the product. These properties are also the basis for the use of the mineral in friction equipment and in a wide variety of consumer items requiring a relatively inexpensive insulation material that is light and subject to molding. Since the turn of the century, about 3×10^7 tons of asbestos have been used in construction and in the fabrication of manufactured goods in the United States. At present, several million Americans are employed in industries that use asbestos products, and countless millions of American citizens are exposed to asbestos cryptically in the course of their daily lives.

Public concern over the effects of asbestos on health is mounting. Although a total ban on its use in this country has been proposed, most would agree that asbestos cannot be replaced expeditiously in many products. Litigation based on personal injury consequent to pulmonary fibrosis and cancer is an increasing problem for companies involved in the manufacture, use, and distribution of asbestos. About 12,000 suits have been brought against 260 companies by workers, their families, and members of the general public.[1,2] The spectrum of liability has now widened to involve the federal government for alleged negligence in establishing adequate environmental standards.

This review summarizes our current knowledge of the adverse effects of asbestos on health and provides a perspective on the pathogenetic mechanisms of the diseases associated with exposure. Since there are several different mineralogic types of asbestos, we will attempt to assess the extent to which findings with one type can be applied to another. Detailed analyses of the issues addressed in this paper have been published elsewhere.[3-6]

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MINERALOGY

Asbestos is not one mineral but a family of fibrous hydrated silicates that are divided on the basis of mineralogic features into two groups: the serpentines and

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the amphiboles (Fig. 1). The term "asbestos" refers to the commercial product after mining and processing and is not a mineralogic designation. Although the length:width ratio of the mineral fiber known as asbestos is by definition ≥3:1, the individual fibers making up the materials used in commerce vary substantially in width and length (Fig. 2).

Chrysotile is the only serpentine of commercial importance. It is composed of pliable, curly fibers made up of fibrillar subunits. These fibrils are arranged in pseudohexagonal arrays composed of silicon oxide sheets formed into scroll-like structures. The magnesium ion, which imparts a strongly positive charge to the fiber, is an integral component of the lattice.

The amphiboles are straight, rodlike fibers consisting of double chains of tetrahedral groups having a basic silicon oxide composition and linked by one or more cations. The amphiboles differ from chrysotile in both physical and chemical makeup. There are several types of amphibole, but crocidolite and amosite are the two minerals of major importance.

Although an asbestos type is classified on the basis of its mineralogic characteristics, the products of different mines are not necessarily the same. Moreover, a commercial type of asbestos is not always mineralogically pure. For example, Canadian chrysotile contains small amounts of an amphibole fiber, tremolite. In addition, industrial grades of asbestos are contaminated with extraneous inorganic and organic substances that are acquired either naturally or during processing.

Deposits of serpentine and amphibole are ubiquitous in the crust of the earth. Outcrops are found in many geologic formations and probably account for the mineral fibers commonly found in surface water. Asbestos is also found with other minerals of commercial importance, such as the iron ore taconite and industrial-grade talc. Canada and South Africa are the major suppliers in the western world, although mines of limited commercial importance are found in many countries. In the United States serpentine and amphibole minerals are distributed widely in geologic strata, but only two relatively small mines in Vermont and California are active. The amount of asbestos produced in the Soviet Union and the People's Republic of China far exceeds that extracted in the West.

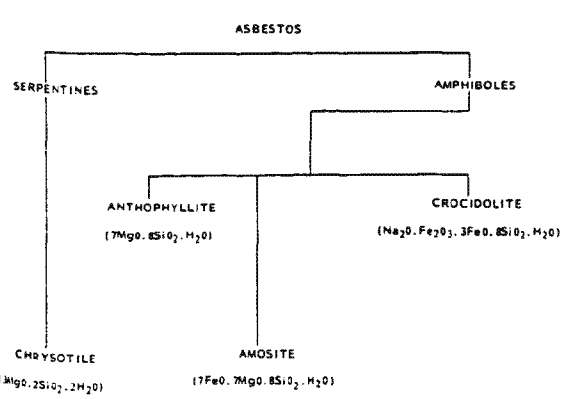

Figure 1. Types of Asbestos of Commercial and Medical Importance and Their Chemical Compositions.

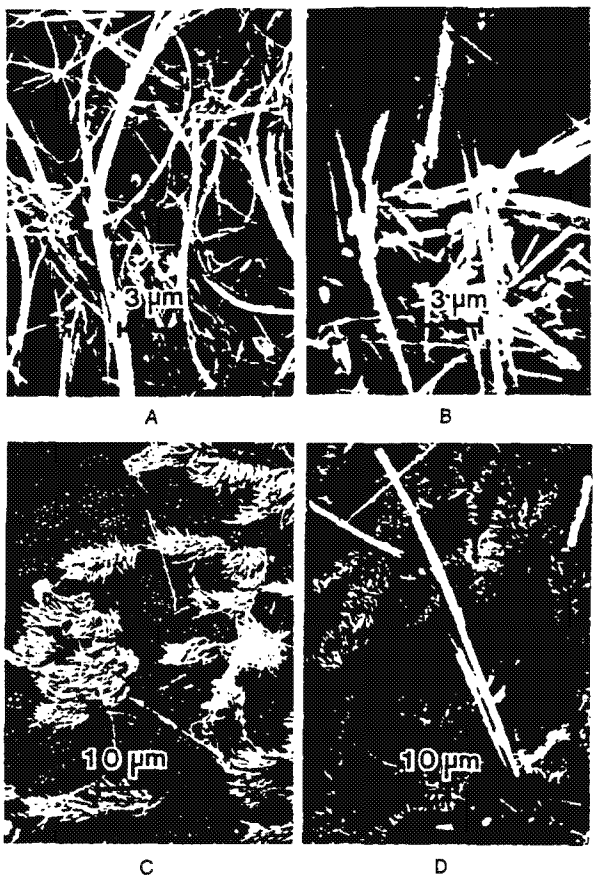

Figure 2. Differing Structural Features of Serpentine (Chrysotile) and Amphibole (Crocidolite) Asbestos.

These scanning electron micrographs of International Union against Cancer reference samples of chrysotile (Panel A) and crocidolite (Panel B) asbestos illustrate the heterogeneity of fibers in both length and diameter. Micrographs of the hamster tracheal epithelium after exposure in vitro to asbestos illustrate the curly, pliable nature of chrysotile (Panel C) and the straight, rod-like form of crocidolite (Panel D). Note the dimensions of the fibers in comparison to the cilia. Photomicrographs were furnished by Mr. Craig Woodworth, Department of Pathology, University of Vermont College of Medicine.

Chrysotile currently accounts for over 90 per cent of the total asbestos marketed in this country and abroad. Crocidolite is the most widely used amphibole, but for reasons considered below, its commercial importance has decreased over the past several decades (Table 1).

Uses of Asbestos

The unique physical properties of asbestos dictate its continued use by industry, despite contemporary concerns about its effects on health. Although various man-made and naturally occurring substances have been developed as substitutes for asbestos, none

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Table 1. Consumption of Different Types of Asbestos in the United States in 1978.*

Use	Type of Asbestos			Total Asbestos
	Chrysotile	Crocidolite	Amosite	
	metric tons			
Asbestos cement pipes	119,700	24,100	200	144,000
Asbestos cement sheeting	7,900	—	—	7,900
Flooring products	90,000	—	200	90,200
Roofing products	26,500	—	—	26,500
Packing and gaskets	12,200	100	—	12,300
Insulation, thermal	6,000	—	—	6,000
Insulation, electrical	2,900	—	—	2,900
Friction products	43,700	—	—	43,700
Coatings and compounds	10,900	—	—	10,900
Plastics	1,200	100	—	1,300
Textiles	1,900	—	—	1,900
Paper	400	100	—	500
Other	9,000	—	1300	10,600
Total	332,300	24,400	1700	358,700

*Modified from the data of Fagan.[7]

matches asbestos in providing tensile strength and moldability as well as resistance to fire, heat, and corrosion. In addition, many of the manufactured substitutes are comparatively expensive.[8]

About 25 per cent of the asbestos consumed in the United States is incorporated into cement piping for water mains and sewage lines. Over 320,000 km of pipe, containing about 10 to 20 per cent asbestos, is believed to be in use in this country. Asbestos-containing cement is employed widely in corrugated and flat sheeting, panels, tiles, and moldings for the construction industry. The mineral is used extensively in roofing and paneling and as a filler in architectural dead spaces. In the past, suspensions of asbestos were sprayed onto the structural steel of buildings to provide insulation and fire protection.

Because of its thermal stability, asbestos is well suited for use in friction material and is applied to molded brake linings. Although substitutes are being increasingly employed in disk brakes, as in the aircraft industry, a drum-brake lining for passenger cars that does not contain asbestos is not available commercially.

Textiles and plastics of a variety of types and applications contain asbestos in various concentrations, since it imparts resistance to fire and corrosion as well as tensile strength without inordinately altering the properties of the product or increasing its weight.

The countless additional industrial uses of asbestos are of concern because they can be overlooked by the manufacturer and unrecognized by the consumer. Although asbestos was known to industry before the turn of the century, its use in the United States increased dramatically during the mobilization that accompanied World War II. Asbestos was employed liberally in the construction and reconditioning of ships and in such diverse war industries as the manufacture of aircraft engines, combat vehicles, and gas masks. Although worldwide production has continued to increase since the war, consumption in this country has dropped substantially during the past decade. This trend can be expected to continue. Since the latency period for the diseases associated with asbestos is usually 20 years or longer, most patients seen today were initially exposed in the 1940s and 1950s, when control measures were often not rigorous.

Diseases of the Respiratory Tract and Thorax

The major pathologic effects of asbestos result from the inhalation of fibers suspended in the ambient air. The occurrence of disease is influenced by the type of mineral and the dimensions of the fibers that constitute it, as well as by the concentration of fibers and the duration of exposure.

Deposition and Transport in the Lungs

Timbrell et al.[9] studied the deposition of fibers of asbestos in the respiratory tract, using a cast of the porcine tracheobronchial tree. The diameter of the individual fibers proved important; length was a less important determinant.[10,11] Fibers with a relatively broad diameter are deposited in the upper respiratory tract, whereas thin fibers are carried peripherally into the parenchyma of the lung, where they lodge in the terminal airways. Bifurcations are common sites for fiber impaction, since patterns of air flow are altered at these sites.

The shape of the fibers also has a role in transport. Aerodynamically, chrysotile has a relatively large theoretical cross-sectional diameter because of its curled configuration. Thus, fibers of this type tend to be deposited more proximally than the needle-like amphiboles, which are transported more readily to the periphery of the lung. These theoretical and experimental considerations have been verified by analyses of the lungs of rodents experimentally exposed to asbestos of different types.[12]

Three biologic mechanisms participate in the clearance of fibers from the lower respiratory tract. By far, the bulk of the dust is removed by the mucociliary escalator of the tracheal bronchial tree, and the material is either expectorated or swallowed.[13-15] In the peripheral airways, short fibers are ingested by macrophages, and at least some of these cells probably migrate across the wall of the bronchioles and acini.[16-18] Asbestos fibers are also taken up by the epithelial cells lining the airways and appear to move between cells of the mucosa.[18-20] This material accumulates in the interstitium and is carried to regional lymph nodes.[17] In general, short fibers are cleared more readily than long fibers,[17] which tend to be retained in the lumens of the respiratory bronchioles and the alveolar ducts.

About a third of the inhaled particles initially lodge in the distal airways. However, only about a quarter of this burden is retained in the respiratory tract one month later.[13] There are two phases of clearance through the tracheobronchial tree. About half the asbestos is removed within a few days. Subsequently,

clearance continues for extended periods. The bulk of this material is excreted in the feces.[15]

A variety of extraneous influences such as cigarette smoke and air pollutants affect the clearance and intrapulmonary deposition of fibers. However, these factors are extraordinarily complex, in part because individuals appear to differ in their responses to inhaled dust.[21-29]

Asbestosis

Diffuse pulmonary fibrosis is the typical lesion associated with prolonged, heavy exposure to asbestos.[30] It develops slowly over a period of years and seems to progress in the absence of continued exposure to asbestos. Initially, fibrosis is found in and around the respiratory bronchioles and alveolar ducts, where relatively long fibers deposit. With time, the fibrotic lesion progresses in a seemingly centrifugal manner, so that increasing numbers of respiratory units are involved. Fibers of asbestos tend to accumulate preferentially in the lower lobes and adjacent to the visceral pleura. Fibrosis is usually prominent in these regions, and the pleural surfaces of these lobes are frequently thickened by a dense layer of fibrous tissue. In advanced asbestosis, the fibrotic pulmonary tissue contracts and is reorganized to form the new air space typical of the honeycomb lung.

Ferruginous bodies are the histologic hallmark of exposure to asbestos.[31-34] They consist of fibers coated by complexes of hemosiderin and glycoproteins and are believed to be formed by macrophages that have phagocytized the particles. Asbestosis can exist when ferruginous bodies are difficult to demonstrate in the lungs by light microscopy. On the other hand, ferruginous bodies can often be found in the absence of serious parenchymal disease.[35,36] Thus, their presence alone is probably not a stimulus for the proliferation of fibrous tissue. Although they have been shown to form from foreign inorganic and organic fibers of many different types,[37] ferruginous bodies in most human lungs have asbestos as a core.[36] For this reason, the structures are commonly known as asbestos bodies.

The number of uncoated fibers in the lung greatly exceeds the number of asbestos bodies in the tissue.[38,39] It is not known why some fibers are coated and form the typical asbestos bodies, whereas others are uncoated. Since uncoated fibers are usually difficult or impossible to demonstrate by light microscopy, lung tissue must be digested and the residue examined by either phase or electron microscopy in order to carry out qualitative and quantitative studies of the fibers. Whereas relatively long fibers (>5 μm) are found by light microscopical techniques, electron microscopy makes it possible to identify very small particles.[40,41] Thus far, attempts to correlate the extent of disease with either the number of asbestos bodies or the overall content of fibers in the lungs have been difficult, although fibrosis is usually evident when 10^6 fibers per gram of lung (wet weight) are present. Quantitative studies pose many problems and are only a crude measure of exposure, partly because many fibers are cleared from the lungs and others fragment to increasingly smaller particles with time.

Macrophages are a key element in the response of the host to asbestos. Whereas these cells phagocytize short fibers and remove them from the airways, they cannot encompass and transport the longer fibers. Although retention of these long fibers in the distal airways appears to be an important consideration in the causation of pulmonary fibrosis,[18,30] the pathogenesis of the lesion is not understood. Incomplete phagocytosis of asbestos fibers in the airways could result in spillage of lysosomal enzymes[42] and release of soluble fibrogenic factors from macrophages.[43] On the other hand, oxygen free radicals liberated by macrophages and other inflammatory cells might also injure lung tissue. This idea is supported by our observations that superoxide dismutase, an inhibitor of biologic oxidants, protects cultured respiratory epithelial cells from the cytotoxic effects of chrysotile (Mossman BT, Landesman JM: unpublished data). Chrysotile is cytotoxic in vitro presumably because the magnesium of the fibers interacts with the plasmalemma and damages it, along with lysosomal membranes of cells.[44,45] It is unclear whether this is an important mechanism of tissue injury, however, since pulmonary macrophages and epithelial cells in the lungs of animals exposed to aerosolized chrysotile fail to reveal ultrastructural evidence of injury.[18,19]

Other biologic phenomena may prove important in the causation of pulmonary fibrosis. Asbestos activates complement by the alternative pathway[46] — a reaction that may be expected to result in the accumulation of leukocytes in the tissue and the release of lysosomal enzymes. This observation is consistent with the finding of an acute inflammatory response in some early lesions.[30,47] Finally, consideration must be given to the possibility that asbestos stimulates the production of collagen by cells. When chrysotile is added to cultures of fibroblasts in vitro, the cells elaborate reticulin and collagen at an accelerated rate.[48,49]

Although the hypothetical mechanisms mentioned above could account for the deposition of fibrous tissue in the lungs, the pathogenesis of asbestosis in human beings remains to be established. The question may be moot, however, since modern environmental controls have dramatically reduced exposure in the work place. The dust concentrations permitted by current regulations will probably not induce substantial pulmonary fibrosis during the lifetime of an industrial worker.

Pleural Lesions

Plaques are curious lesions made up of hyalinized fibrous tissue located on the parietal pleura of the thorax, diaphragm, mediastinum, and pericardium.[50,51] They are usually but not invariably associated with exposure to asbestos.[38] Although the occurrence of plaques correlates with the duration and intensity of exposure, it is common to find lesions in the absence of

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obvious disease of the pulmonary parenchyma. Thus, relatively small amounts of dust can induce the development of plaques. These benign lesions do not appear to develop into malignant mesotheliomas.

Characteristically, plaques are located in the intercostal spaces on the anterior and posterior lateral aspects of the thorax and on the dome of the diaphragm at sites where the visceral and parietal pleuras approximate during respiratory excursions. The configuration of the plaques is highly variable. For example, on the chest wall they usually follow the contour of the rib, whereas on the diaphragm they are customarily either disk-shaped or geometrically shaped and have a nodular surface. Over time the lesions become calcified, permitting easy recognition on x-ray films. Although most of the available epidemiologic information is based on radiologic surveys,[52-55] it is not always clear in published reports whether plaques were differentiated from the fibrous lesions of the visceral pleura that accompany pulmonary asbestosis.

Since plaques are found most often in persons exposed occupationally to asbestos for extended periods,[54-56] their overall prevalence in the United States is low.[57] In Eastern Europe and Asia Minor the lesions are frequently found in older members of the general population who lack documented exposure to asbestos. The presence of fibrous minerals in soil and in local construction materials may account for the common occurrence of pleural plaques in these regions.[58-61]

Malignant mesotheliomas of the pleural and peritoneal cavities are considered pathognomonic of exposure to asbestos, although in many patients a history of contact with the mineral cannot be elicited.[62-64] These rare tumors are of particular concern from a public-health standpoint because they are thought to occur in persons who have had either transient or indirect exposure to asbestos.[65-67] The development of mesotheliomas as a consequence of casual exposure, however, is an uncommon event. On the other hand, the prevalence of the tumor in workers who have had heavy exposure over extended periods is about 2 to 3 per cent and has been reported to approach 10 per cent.[68,69] It is difficult to determine how often mesotheliomas actually occur, because the latency period is usually 20 years or longer and can often be as long as 40 to 50 years. Some suggest that an epidemic of mesotheliomas will appear in the late decades of this century, consequent to the exposure of large numbers of workers during World War II.

The pathogenesis of the pleural lesions associated with exposure to asbestos is not known, but it is a topic of considerable contemporary interest. Fibrosis of the visceral pleura, plaques of the parietal pleura, and mesothelioma probably develop by different mechanisms, although a rigorous defense of this conclusion would be difficult. As mentioned above, asbestos is deposited preferentially in the periphery of the lung after inhalation. It penetrates the visceral pleura and is carried in the pulmonary lymphatics to the pleural surface. One is tempted to attribute the fibrous lesions on the visceral pleura to irritation by the physical presence of fibers on or near the surface. This mechanism might also explain the occurrence of plaques in the parietal pleura. Alternatively, the lesions may represent an organized fibrinous exudate resulting from the physical movement of the lungs against the pleural surface of the thorax.

However, these hypotheses are not fully consistent with the pathological observations. For example, plaques are often found without fibrosis of the visceral pleura or adhesions between the pleural surfaces. In addition, the lesions are localized and do not occur in the apexes or in the costophrenic angles. The pathogenesis of the lesions cannot be defined at present, in part because plaques occur only in human beings and experimental models have not been developed.

Experimental studies by Stanton et al.[70,71] provide an intriguing basis for speculation about the pathogenesis of mesothelioma. The dimensions of the fiber, but not the chemical composition, were found to be the critical determinant affecting the development of tumors in rats. Long, thin fibers of a variety of types proved carcinogenic when introduced into the pleural space, whereas short fibers and those with a relatively broad diameter failed to induce mesotheliomas. These findings are consistent with epidemiologic observations documenting the relatively common occurrence of tumors in populations exposed to grades of crocidolite consisting predominantly of long, thin fibers and the rarity of tumors in persons exposed to the comparatively blunt, shorter fibers of amosite and anthophyllite.[65,72-74] A fibrous zeolite, erionite, has recently been associated with the occurrence of pleural fibrosis and mesothelioma in a rural area of Turkey where commercial mining of asbestos does not occur.[61] Since the fibers of this mineral do not possess the chemical properties of asbestos but are morphologically similar to crocidolite fibers, the observation is consistent with the experimental findings of Stanton and his associates.[70,71]

The basis for the development of mesotheliomas in the peritoneum is uncertain. Presumably, fibers of asbestos in the lungs are transported in lymphatics to the abdomen, where they have been recovered from lymph nodes and other organs.[75,76] Asbestos is also transported across the mucosa of the gut after ingestion.[77,78] Whatever the mechanism for entry of asbestos into the abdomen, it is assumed that the pathogenesis of the tumors in the peritoneal and pleural cavities is similar. Peritoneal mesotheliomas occur only in persons exposed to amphibole asbestos. The gradual disintegration of chrysotile in tissue may account for the relatively uncommon occurrence of mesotheliomas of both the pleural and peritoneal cavities in persons exposed exclusively to chrysotile.[79]

The mechanism of malignant transformation of mesothelial tissues is obscure. Surprisingly little experimental information has accumulated, although there is reason to believe that the lesions may be com-

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parable to the foreign-body sarcomas induced subcutaneously in animals by sheets of plastic, glass, and metal. The cell of origin is not certain, since some tumors are made up of malignant serosal cells, whereas others have the histologic features of fibrosarcoma. Mesothelial cells phagocytize asbestos[80] and proliferate when exposed to asbestos in vitro,[81] but malignant transformation has not been demonstrated after exposure of cultured mesothelial cells to asbestos. Cocarcinogenic substances and cigarette smoke do not appear to be pathogenetic factors in vivo.

Bronchogenic Carcinoma

Epidemiologic studies have documented an association between bronchogenic carcinoma and occupational exposure to asbestos.[82-87] The prevalence of tumors is higher in persons working with the finished products (such as insulators) than in miners and millers. The severity of the pulmonary parenchymal fibrosis correlates with an increase in the number of neoplasms.[88,89] However, the incidence of tumors is also increased in asbestos workers who lack radiologic evidence of asbestosis.

Some controversy exists over the most common histologic type of tumor, but among persons with asbestosis, adenocarcinomas predominate.[90,91] The lesions tend to occur more frequently in the lower lobes in conjunction with severe degrees of fibrosis.[30] Atypical hyperplasia of bronchiolar epithelium and multifocal adenocarcinomas are often found in these sites.

A linear dose-response relation between the cumulative dosage of asbestos and the development of bronchogenic carcinoma has been reported in miners and millers of chrysotile in Canada[85] and factory workers in the United Kingdom.[83] In the former study, those at greatest risk were exposed to concentrations of asbestos in the air that were higher than the current regulations of the United States Occupational Safety and Health Administration permit. A higher carcinogenic potential for crocidolite than for chrysotile has been suggested by studies of occupational groups exposed to either type of asbestos or to the two in combination.[92] Mortality among chrysotile workers is increased 2.4-fold, whereas it is five times higher than normal among miners of both chrysotile and crocidolite.

Surveys of the smoking habits of insulators,[93] factory workers,[94,95] and miners and millers[96] have consistently shown that bronchogenic carcinoma is uncommon in those who do not smoke. Whereas there is only a slight increase in the prevalence of lung cancer among nonsmokers, heavy users of cigarettes (those smoking more than 20 per day) have an 80-fold to 90-fold greater predisposition to cancer of the lung.[93,94] Thus, the combined effects of asbestos and smoking appear to be multiplicative rather than additive.[97]

What is the mechanism of asbestos-induced carcinogenesis in the respiratory tract? A consideration of contemporary concepts of neoplastic transformation is appropriate in developing an answer to this question. As initially recognized by Berenblum, carcinogenesis is a sequence of events that can be divided into steps of initiation and promotion.[98] An initiator interacts with the DNA of the target cell — an event that can result in malignant change. The carcinogen either acts directly with the DNA of the cell or requires metabolic activation by cellular enzymes. A promoter is generally neither mutagenic nor carcinogenic, although it is required if the neoplasm is to develop. For example, if the skin of a mouse is painted with a small amount of a chemical carcinogen, such as a polycyclic aromatic hydrocarbon, tumors fail to develop unless a phorbol ester is subsequently applied to the site. Promoting substances cause cellular division and proliferation as well as biochemical changes in the cell that appear to be essential for neoplastic transformation.[99]

Although epidemiologic data link exposure to asbestos with bronchogenic carcinoma in human beings, the precise role of the mineral in the process has yet to be defined. Since asbestos is not a potent mutagen[100] and inconsistently causes chromosomal aberrations in cells,[101-103] a mode of action comparable to that of a classic chemical carcinogen is unlikely. It therefore seems more plausible to suggest that asbestos increases the susceptibility of epithelial cells of the bronchi and their branches to transformation by carcinogens in the environment.

What biologic mechanisms account for the synergistic carcinogenic effects of asbestos and cigarette smoke in the respiratory tract? A plausible hypothetical construct should be consistent with the apparent lack of a threshold in human beings and the occurrence of neoplasms in the absence of appreciable degrees of pulmonary asbestosis.

Asbestos has many of the properties of classic tumor promoters, such as the phorbol esters.[104] Proliferation and squamous metaplasia are induced in the respiratory mucosa of rodents in vitro.[105] Asbestos interacts with the membranes of cells[106,107] and induces the synthesis of the polyamines that accompany cell division.[108] Since cigarette smoke also contains a host of substances with promoter effects, the inhalants may act in either an additive or a synergistic fashion to enhance the susceptibility of the respiratory mucosa to carcinogens.

However, alternative mechanisms are worthy of consideration. Asbestos can be phagocytized by the bronchial epithelium and can be transported intracellularly both free in the cytoplasm and in phagolysosomes.[20] These fibers may serve as a physical carrier of the carcinogens in cigarette smoke to the basal cell, the presumptive progenitor of the neoplasms. Transfer of polycyclic aromatic hydrocarbons to and through biologic membranes occurs promptly and efficiently when the hydrocarbon is adsorbed to asbestos.[109] Thereafter, the hydrocarbons are converted by microsomal mixed-function oxidases to biologically active epoxides and diolepoxides, which can interact with the DNA of basal cells.[110] Another (but less attractive) hypothesis involves the alveolar macrophage, which phagocytizes asbestos in the airways and possesses the

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enzymatic capacity to convert polycyclic hydrocarbons to active metabolites.[111] At present, the mechanism of asbestos-associated carcinogenesis is unclear, although the mineral appears to act like a classic tumor promoter. The fibrous nature of asbestos is critical, since exposure to nonfibrous oxides of silicon (for example, quartz) and a variety of silicates is not associated with an increased risk of bronchogenic carcinoma in human beings.

Cancers of the Digestive System and Other Organs

Asbestos is implicated in the causation of cancer in the upper and lower gastrointestinal tract and the kidney.[112-115] Oropharyngeal and esophageal tumors occur more frequently in asbestos workers who smoke, whereas a direct relation between smoking and the development of carcinoma of the large intestine and the kidney has not been established.

Selikoff and Hammond[114] and Elmes and Simpson[112] have reported a statistically significant twofold to threefold increase in the prevalence of tumors of the digestive tract in insulators, factory workers, and shipyard employees. Other surveys have either demonstrated a smaller increase or failed to establish an association between exposure to asbestos and neoplasms in this system.[116] We believe that the evidence must be assessed cautiously because the associations thus far reported are relatively weak. Since death certificates are used to obtain data in most studies, it is possible that peritoneal mesotheliomas have been confused with metastatic carcinomas of gastrointestinal-tract origin.

The general population is exposed to small amounts of asbestos in drinking water, beverages, food, drugs, and agricultural products. Potable water often contains mineral fibers that are presumably derived from geologic deposits and refuse dumps. The finding of fibers of amphibole asbestos in the drinking water of Duluth, Minn., resulting from the disposal of taconite tailings into Lake Superior,[117] prompted investigations to determine the concentration and characteristics of mineral fibers in water supplies throughout the United States. Fibers with the properties of both serpentine and amphibole asbestos were found in over half the samples of water studied (Table 2). Thus, many Americans consume water containing asbestos-like minerals.

Table 2. Concentrations of Asbestos-Like Mineral Fibers in the Water Supplies of Selected but Representative Communities in the United States.*

City	Concentration
	no. of fibers >5 μm/liter
Atlanta	5.75
Boston	3.98
Duluth	1.72
Dallas	0
Kansas City, Mo.	0.07
New York	0
Philadelphia	16.95
San Francisco	0.60
Seattle	0.85

*Prepared from Table E-2 in Levine.[3]

Mineral fibers have been detected in the urine of residents of Duluth in numbers corresponding to the concentration of asbestos in drinking water.[118] Interestingly enough, fibers have been found in the glomeruli and tubules of rats exposed in inhalation chambers to synthetic fibers.[119] These observations suggest that asbestos migrates to the kidney after clearance from both the gastrointestinal and respiratory tracts. Whether this has an influence on the occurrence of tumors in the gastrointestinal tract is unknown.

When fed to laboratory animals, asbestos interacts with the mucosa of the gut.[78] Fibers enter cells of the mucosa and prove cytotoxic.[120] The experimental evidence strongly suggests that ingested asbestos is disseminated to abdominal organs by the lymphatics and blood vessels. This conclusion is supported by postmortem studies of occupationally exposed persons; these studies have demonstrated asbestos bodies and uncoated fibers in most major organs.[76]

How does the ingestion of asbestos induce gastrointestinal carcinomas in human beings? In efforts to address this question, rodents were fed large amounts of asbestos over extended periods. With one exception,[121] these studies failed to demonstrate an increase in the prevalence of tumors in the gut.[122-124] The possible synergistic effects of asbestos on the induction of intestinal neoplasms by chemical carcinogens has also been examined.[125] Intragastric administration of asbestos failed to augment tumor development in rodents fed azooxymethane, a recognized intestinal carcinogen.

The carcinogenic potential of asbestos in the gastrointestinal tract appears to be low. The pathogenetic basis for the purported increase in the prevalence of carcinomas in certain occupational groups remains to be established.

Pathogenic Potential of Asbestos Types

As emphasized above, asbestos is not one but a family of fibrous minerals, each of which has distinctive physical and chemical characteristics. Minerals from various parts of the world and geologic formations often have dissimilar physical properties, even though they are classified under a specific mineralogic type. These differences are relevant to our understanding of the effects of asbestos on health, since the characteristics of the fiber have been fully defined in only a few epidemiologic and experimental studies. The problem of evaluating the effects of different types of asbestos on health is compounded by the common practice of custom blending of various minerals for specific industrial applications and the use of one type and then another, depending on availability and conditions of the market.

Since the serpentine chrysotile is used extensively in industry today, it is important to ask whether its pathogenic importance is comparable to that of the amphiboles crocidolite and amosite. These latter minerals are of historical importance, particularly since

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they were used widely during and immediately after World War II and are probably responsible for a substantial proportion of the disease occurring today.

Much current debate centers around the question of whether all types of asbestos possess the capacity to induce mesothelioma. Experiments in animals yield an affirmative answer, but the results of this work may not be applicable to human beings, since pathogenic potential and intrapulmonary transport of fibers are independent considerations. Of all the types, crocidolite is clearly the most strongly associated with the occurrence of the tumor. But there are interesting differences in prevalence, related to the physical character of this fiber type. For example, in Northwest Cape, South Africa, and western Australia, mesotheliomas occur commonly in persons with occupational or casual exposure to crocidolite.[65] The mineral mined in these regions is composed of relatively long, thin fibers. In contrast, mesotheliomas are rare in the Transvaal of South Africa, where the crocidolite fibers are much coarser.

Another amphibole, amosite, is associated sporadically with mesothelioma, whereas the tumor rarely if ever occurs in workers exposed to anthophyllite. Both these latter types are made up of relatively short, blunt fibers. A number of studies have been conducted in miners and millers in Quebec and Italy, where the serpentine chrysotile is extracted.[74,126] Although the results are debated, the bulk of the evidence indicates that chrysotile is not an important cause of mesothelioma in these workers.

However, the data from certain occupational groups, such as workers in the textile industry and insulators who are exposed predominantly but not exclusively to chrysotile, are not as definitive. The risk appears to increase as the mineral is processed or when dust concentrations cannot be evaluated critically. Unfortunately, most epidemiologic studies concerned with this important question are clouded by uncertainty because of the prolonged latency period of mesotheliomas. Considerable effort has focused on determining whether the various types of asbestos differ in their capacity to induce bronchogenic carcinoma and fibrosis of the lung. Unfortunately, there is no good answer to these questions at present, since dose-related differences in the prevalence of disease have not been established.

Regulatory Considerations

No topic is more complex and subject to controversy than the establishment of criteria on which to base standards for air quality in the work place. Regulations are exceptionally difficult to develop, because it is necessary to use data on morbidity and mortality documenting disease retrospectively in members of occupational groups who have had heavy exposure either in the remote past or over a lifetime. The difficulties are compounded by the long latency period of asbestosis and the asbestos-associated cancers.

Although recommendations for levels of asbestos in the air of occupational settings in this country were formulated in the 1940s, it was not until 1970 that federal regulations were promulgated as a result of the passage of the Occupational Safety and Health Act and the Clean Air Act. The initial standard was based on the light microscopical count of fibers of a length of 5 μm, collected by mechanical means. A concentration of five fibers per cubic centimeter of air, averaged over an eight-hour period, was deemed permissible, with stipulations for transient excesses above that concentration. In 1976 the contemporary standard of two fibers per cubic centimeter was established, and more recently a level of 0.5 fiber per cubic centimeter has been proposed.

Is the current limit of two fibers per cubic centimeter sufficiently rigorous to prevent disease in the future? Is it appropriate to base regulation exclusively on determinations of fibers of >5 μm when the bulk of the dust in air consists of fibers of a shorter length? Because standards are based on extrapolations from data accumulated among workers exposed to relatively heavy concentrations of dust in the past, predictions must be based on analyses that assume that there are no thresholds below which the disease fails to occur. Within the ranges usually found in the occupational setting, there appears to be linearity in the dose-response relation, at least with regard to bronchogenic carcinoma. However, the likelihood that cancer will occur is influenced substantially by cigarette smoking, since the risk in the nonsmoker who has heavy exposure to asbestos is increased only a few fold. Thus, the risk for the nonsmoking asbestos worker is substantially lower than the risk for a member of the general population who smokes two or three packs of cigarettes each day.

The conclusion that asbestosis fails to develop below a certain threshold dosage is based on physical examinations and radiologic studies of workers and not on pathological examinations. By these criteria, it is probably impossible to be certain whether a fibrotic lesion in the lung is due to asbestos. With mesothelioma, the data are more controversial. Although a dose-response relation appears to exist, the threshold may be determined by the life span of the person exposed, because the latency period for these tumors is protracted. Since the problem cannot be answered with contemporary epidemiologic and experimental approaches, it must be resolved by practical rather than theoretical considerations.

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