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5. Natta C. Failure of the α -thalassaemia gene to decrease the severity of sickle cell anemia. *Blood*. 1978; 51:1163-8.
6. Huisman THJ. Sickle cell anemia as a syndrome: a review of diagnostic features. *Am J Hematol*. 1979; 6:173-84.
7. Felice AE, Webber B, Miller A, et al. The association of sickle cell anemia with heterozygous and homozygous α -thalassaemia-2: in vitro HB chain synthesis. *Am J Hematol*. 1979; 6:91-106.
8. Powars DR, Schroeder WA, Weiss JN, Chan LS, Azen SP. Lack of influence of fetal hemoglobin levels or erythrocyte indices on the severity of sickle cell anemia. *J Clin Invest*. 1980; 65:732-40.
9. Altay C, Gravely ME, Joseph BR, Williams DF. Alpha-thalassaemia-2 and the variability of hematological values in children with sickle cell anemia. *Pediatr Res*. 1981; 15:1093-6.
10. Embury SH, Duzy AM, Miller J, et al. Concurrent sickle-cell anemia and α -thalassaemia: effect on severity of anemia. *N Engl J Med*. 1982; 306:270-4.
11. Higgs DR, Pressley L, Serjeant GR, Clegg JB, Weatherall DJ. The genetics and molecular basis of alpha thalassaemia in association with Hb S in Jamaican Negroes. *Br J Haematol*. 1981; 47:43-56.
12. Serjeant GR, Serjeant BE, Milner PF. The irreversibly sickled cell: a determinant of haemolysis in sickle cell anemia. *Br J Haematol*. 1969; 17:527-33.
13. Lathé GH, Ruthven CRJ. Factors affecting the rate of coupling of bilirubin and conjugated bilirubin in the van den Berg reaction. *J Clin Pathol*. 1958; 11:155-61.
14. Millard DP, Mason K, Serjeant BE, Serjeant GR. Comparison of haematological features of the β^0 and β^+ thalassaemia traits in Jamaican Negroes. *Br J Haematol*. 1977; 36:161-70.
15. Betke K, Marti HR, Schlicht I. Estimation of small percentages of foetal haemoglobin. *Nature*. 1959; 184:1877-8.
16. Serjeant GR, Higgs DR, Aldridge B, Hayes RJ, Weatherall DJ. Alpha thalassaemia and homozygous sickle cell disease. In: Brewer GJ, ed. *The red cell*. New York: Alan R Liss, 1980:781-6.
17. Sewell A, Millard D, Serjeant GR. The interaction of alpha thalassaemia with SS disease. In: Brewer GJ, ed. *The red cell*. New York: Alan R Liss, 1978:93-102.
18. Breslow NE, Day NE. Statistical methods of cancer research. Vol. 1. Lyon: International Agency for Research on Cancer, 1980:162-76.
19. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and the stages of puberty. *Arch Dis Child*. 1976; 51:170-9.
20. Higgs DR, Pressley L, Clegg JB, et al. Detection of alpha thalassaemia in Negro infants. *Br J Haematol*. 1980; 46:39-46.
21. Noguchi CT, Schechter AN. The intracellular polymerization of sickle hemoglobin and its relevance to sickle cell disease. *Blood*. 1981; 58:1057-66.
22. Seakins M, Gibbs WN, Milner PF, Bertles JF. Erythrocyte Hb-S concentration: an important factor in the low oxygen affinity of blood in sickle cell anemia. *J Clin Invest*. 1973; 52:422-32.
23. May A, Huchins ER. The concentration dependence of the oxygen affinity of haemoglobin S. *Br J Haematol*. 1975; 30:317-35.
24. Dover GJ, Boyer SH, Charache S, Hiestand K. Individual variation in the production and survival of F cells in sickle-cell disease. *N Engl J Med*. 1978; 299:1428-35.
25. Pembrey ME, Wood WG, Weatherall DJ, Farine RP. Fetal haemoglobin production and the sickle gene in the cases of eastern Saudi Arabia. *Br J Haematol*. 1978; 40:415-29.
26. Serjeant GR. Fetal haemoglobin in homozygous sickle cell disease. *Clin Haematol*. 1975; 4:109-22.
27. Serjeant GR, Sommers A, Stevenson M, Mason K, Serjeant BE. Comparison of sickle cell- β^0 thalassaemia with homozygous sickle cell disease. *Br J Haematol*. 1979; 41:83-93.
28. Hayes RJ, Condon PI, Serjeant GR. Haematological factors associated with proliferative retinopathy in homozygous sickle cell disease. *Br J Ophthalmol*. 1981; 65:29-35.
29. Hawker H, Neilson H, Hayes RJ, Serjeant GR. Haematological factors associated with avascular necrosis of the femoral head in homozygous sickle cell disease. *Br J Haematol*. 1982; 50:29-34.

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

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 $\geq 3:1$, 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 pseudo-hexagonal 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

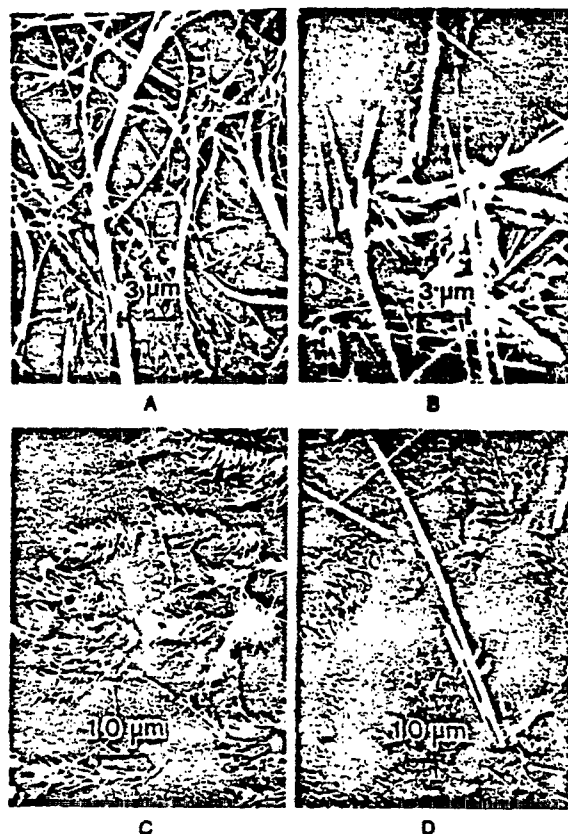


Figure 2. Differing Structural Features of Serpentine (Chrysotile) and Amphibole (Crocidolite) Asbestos.

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.

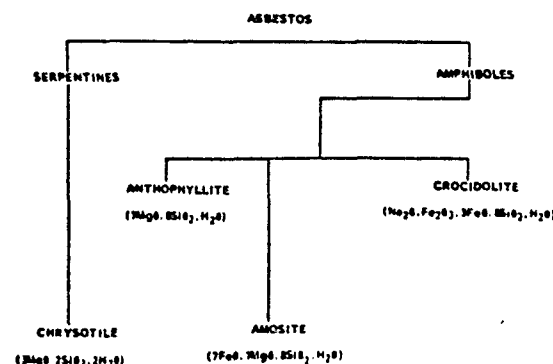


Figure 1. Types of Asbestos of Commercial and Medical Importance and Their Chemical Compositions.

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.

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	AMPHIBOLE	
	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,

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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 ($>5 \mu\text{m}$) 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 enzymes⁴² 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 pathway⁴⁶ — 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.^{58,59}

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 zolite, 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-

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 asbestos⁸⁰ 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.⁹⁰ 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 Canada⁸⁵ 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 millers⁹⁶ 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 mutagen¹⁰⁰ 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

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 Hammond¹¹⁴ and Elmes and Simpson¹¹² 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,

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 $\geq 5 \mu\text{m/liter}$	
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 L-2 in Levine.¹

many Americans consume water containing asbestos-like minerals.

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 post-mortem 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 azoxymethane, 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 $>5 \mu\text{m}$ 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.

REFERENCES

1. Feder BJ. Asbestos injury suits mount with broad business impact. *The New York Times*. 1981 July 3:1.
2. Warning: asbestosis may cost you more than money. *Economist*. 1981; 280:83-4.
3. Levine RV, ed. Asbestos: an information resource. Washington, D.C.: U.S. Government Printing Office, 1978. (DHEW (NIH) Publication no. 78-1681).
4. Simpson W, ed. Asbestos: final reports of the advisory committee on asbestos. London: Her Majesty's Stationery Office, 1980.
5. Selikoff IJ, Lee DHK. Asbestos and disease. New York: Academic Press, 1978.

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6. Selikoff IJ, Hammond EC, eds. Health hazards of asbestos exposure. *Ann NY Acad Sci.* 1979; Vol. 330.
7. Asbestos. 1982; 63:10.
8. Background information on substitutes for asbestos. Washington, D.C.: United States Environmental Protection Agency, Office of Toxic Substances, 1980.
9. Timbrell V, Bevan NE, Davies AS, Munday DE. Hollow casts of lungs for experimental purposes. *Nature.* 1970; 225:97-8.
10. Timbrell V. The inhalation of fibrous dusts. *Ann NY Acad Sci.* 1965; 132:255-73.
11. Harris RL Jr, Timbrell V. The influence of fibre shape in lung deposition — mathematical estimates. In: Walton WH, ed. *Inhaled particles IV.* Part 1. Oxford: Pergamon Press, 1977:75-89.
12. Wagner JC, Berry G, Skidmore JW, Timbrell V. The effects of the inhalation of asbestos in rats. *Br J Cancer.* 1974; 29:253-69.
13. Evans JC, Evans RJ, Holmes A, et al. Studies on the deposition of inhaled fibrous materials in the respiratory tract of the rat and its subsequent clearance using radioactive tracer techniques. 1. UICC crocidolite asbestos. *Environ Res.* 1973; 6:180-201.
14. Morgan A, Evans JC, Holmes A. Deposition and clearance of inhaled fibrous minerals in the rat. Studies using radioactive tracer techniques. In: Walton WH, ed. *Inhaled particles IV.* Part 1. Oxford: Pergamon Press, 1977:259-74.
15. Muggenburg BA, Boecker BB, Diel JH, Snipes MB. Observations on the lung retention of inhaled, relatively insoluble, environmentally-related particles. *Chest.* 1981; 80:195-205.
16. Kanazawa K, Birbeck MSC, Carter RL, Roe FJC. Migration of asbestos fibres from injection sites in mice. *Br J Cancer.* 1970; 24:96-106.
17. Lee KP, Barras CE, Griffith FD, Waritz RD. Pulmonary response and transmigration of inorganic fibers by inhalation exposure. *Am J Pathol.* 1981; 102:314-23.
18. Brody AR, Hill LH, Adkins B Jr, O'Connor RW. Chrysotile asbestos inhalation in rats: deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. *Am Rev Respir Dis.* 1981; 123:670-9.
19. Suzuki Y, Churg J, Ono T. Phagocytic activity of the alveolar epithelial cells in pulmonary asbestosis. *Am J Pathol.* 1972; 69:373-88.
20. Mossman BT, Kessler JB, Ley BW, Craighead JE. Interaction of crocidolite asbestos with hamster respiratory mucosa in organ culture. *Lab Invest.* 1977; 36:131-9.
21. Lippman M, Albert RE, Peterson HT Jr. The regional deposition of inhaled aerosols in man. In: Walton WH, ed. *Inhaled Particles III.* Surrey, England: Unwin Brothers Limited, 1971:105-22.
22. Auerbach O, Hammond EC, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking, 1955-1960 vs. 1970-1977. *N Engl J Med.* 1979; 300:381-6.
23. Newwoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. *N Engl J Med.* 1974; 291:755-8.
24. Lamb D, Reid L. Mitotic rates, goblet cell increase and histochemical changes in mucus in rat bronchial epithelium during exposure to sulphur dioxide. *J Pathol Bacteriol.* 1968; 96:97-111.
25. Dowell AR, Kilburn KH, Pratt PC. Short-term exposure to nitrogen dioxide: effects on pulmonary ultrastructure, compliance, and the surfactant system. *Arch Intern Med.* 1971; 128:74-80.
26. Evans MJ, Cabral LJ, Stephens RJ, Freeman G. Renewal of alveolar epithelium in the rat following exposure to NO₂. *Am J Pathol.* 1973; 70:175-98.
27. Freeman G, Juhas LT, Fariosi NJ, Mussenden R, Stephens RJ, Evans MJ. Pathology of pulmonary disease from exposure to interdependent ambient gases (nitrogen dioxide and ozone). *Arch Environ Health.* 1974; 29:203-210.
28. Warr GA, Martin RR. Histochemical staining and *in vitro* spreading of human pulmonary alveolar macrophages: variability with cigarette smoking status. *J Reticuloendothel Soc.* 1978; 23:53-62.
29. Brody AR, Craighead JE. Cytoplasmic inclusions in pulmonary macrophages of cigarette smokers. *Lab Invest.* 1975; 32:125-32.
30. Craighead JE, Abraham JL, Churg A, et al. The pathology of asbestos-associated diseases of the lungs and pleural cavities. *Arch Pathol Lab Med* (in press).
31. Gloyne SR. The formation of the asbestosis body in the lung. *Tubercle.* 1931; 12:399-401.
32. Suzuki Y, Churg J. Structure and development of the asbestosis body. *Am J Pathol.* 1969; 55:79-107.
33. Gaensler EA, Addington WW. Asbestos or ferruginous bodies. *N Engl J Med.* 1969; 280:488-92.
34. Davis JMG. Further observations on the ultrastructure and chemistry of the formation of asbestos bodies. *Exp Mol Pathol.* 1970; 13:346-58.
35. Bignon J, Gomi J, Bonnaud G, Jaurand MC, Dufour G, Pinelion MC. Incidence of pulmonary ferruginous bodies in France. *Environ Res.* 1970; 3:430-42.
36. Churg AM, Warnock ML. Asbestos and other ferruginous bodies: their formation and clinical significance. *Am J Pathol.* 1981; 102:447-56.
37. Gross P, Cralliey LJ, deTreville RTP. "Asbestos" bodies: their nonspecificity. *Am Ind Hyg Assoc J.* 1962; 23:541-2.
38. Churg A. Pulmonary asbestos burden in patients with pleural plaques. *Am Rev Respir Dis.* 1981; 123: Suppl: 135, abstract.
39. Sebastian P, Fondimare A, Bignon J, Monchaux G, Desbordes J, Bonnaud G. Topographic distribution of asbestos fibres in human lung in relation to occupational and non-occupational exposure. In: Walton WH, ed. *Inhaled particles IV.* Part 2. Oxford: Pergamon Press, 1977:435-46.
40. Miller A, Teirstein AS, Langer AM, Selikoff IJ. Submicroscopical asbestos fibers and disease. *N Engl J Med.* 1975; 292:1195.
41. Hardy HL. Submicroscopical asbestos fibers and disease. *N Engl J Med.* 1975; 292:1194.
42. Davies P, Allison AC, Ackerman J, Butterfield A, Williams S. Asbestos induces selective release of lysosomal enzymes from mononuclear phagocytes. *Nature.* 1974; 251:423-5.
43. Heppleston AG, Styles JA. Activity of a macrophage factor in collagen formation by silica. *Nature.* 1967; 214:521-2.
44. Craighead JE, Bradley BJ, Mossman BT. Comparative studies on the cytotoxicity of amphibole and serpentine asbestos. *Environ Health Perspect.* 1980; 34:37-46.
45. Harington JS, Allison AC, Badami DV. Mineral fibers: chemical, physicochemical and biological properties. *Adv Pharmacol Chemother.* 1975; 12:291-402.
46. Wilson MR, Gaumer HR, Salvaggio JE. Activation of the alternative complement pathway and generation of chemotactic factors by asbestos. *J Allergy Clin Immunol.* 1977; 60:218-22.
47. Dodson RF, Williams MG Jr, Hurst GA. Early response of free airway cells to "amosite": a correlated study using electron microscopy and energy dispersive x-ray analysis. *Lung.* 1980; 157:143-54.
48. Hext PM, Richards RJ. Biochemical effects of asbestiform minerals on lung fibroblast cultures. *Br J Exp Pathol.* 1976; 57:281-5.
49. Richards RJ, Jacoby F. Light microscope studies on the effects of chrysotile asbestos and fiber glass on the morphology and reticulin formation of cultured lung fibroblasts. *Environ Res.* 1976; 11:112-21.
50. Meurman LO. Asbestos bodies and pleural plaques in a Finnish series of autopsy cases. *Acta Pathol Microbiol Scand.* 1966; Suppl 181:1-107.
51. Roberts GH. The pathology of parietal pleural plaques. *J Clin Pathol.* 1971; 24:348-53.
52. Meurman LO. Pleural fibrocalcific plaques and asbestos exposure. *Environ Res.* 1968; 2:30-46.
53. Mattson S-B, Ringqvist T. Pleural plaques and exposure to asbestos. *Scand J Respir Dis [Suppl].* 1970; 75:1-41.
54. Gibbs GW. Etiology of pleural calcification: a study of Quebec chrysotile asbestos miners and millers. *Arch Environ Health.* 1979; 34:76-83.
55. Hillerdal G, Lindgren A. Pleural plaques: correlation of autopsy findings to radiographic findings and occupational history. *Eur J Respir Dis.* 1980; 61:315-9.
56. Hourihane DO'B, Lessof L, Richardson PC. Hyaline and calcific pleural plaques as an index of exposure to asbestos: a study of radiological and pathological features of 100 cases with a consideration of epidemiology. *Br Med J.* 1966; 1:1069-74.
57. Robinson JJ. Pleural plaques and splenic capsular sclerosis in adult male autopsies. *Arch Pathol.* 1972; 93:118-22.
58. Hromek J. Large scale incidence of characteristic pleural changes in citizens of the western section of the former Jihlava region. *Rozhl Tuberk Nemucech Plen.* 1962; 22:405-9.
59. Navrátil M, Trnppé F. Prevalence of pleural calcification in persons exposed to asbestos dust, and in the general population in the same district. *Environ Res.* 1972; 5:210-6.
60. Burlikov T, Michailova L. Asbestos content of the soil and endemic pleural asbestosis. *Environ Res.* 1970; 3:443-51.
61. Arvinli M, Bary YI. Malignant mesotheliomas in a small village in the Anatolian region of Turkey: an epidemiologic study. *J Natl Cancer Inst.* 1979; 63:17-22.
62. Godwin MC, Jagatic J. Asbestos and mesotheliomas. *Environ Res.* 1970; 3:391-416.
63. Acheson ED, Gardner MJ. Mesothelioma and exposure to mixtures of chrysotile and amphibole asbestos. *Arch Environ Health.* 1979; 34:240-2.
64. Elmes PC. Mesotheliomas, minerals, and man-made mineral fibres. *Thorax.* 1980; 35:561-3.
65. Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in North Western Cape Province. *Br J Ind Med.* 1960; 17:260-71.
66. Whitwell F, Scott J, Grimshaw M. Relationship between occupations and asbestos-fibre content of the lungs in patients with pleural mesothelioma, lung cancer, and other diseases. *Thorax.* 1977; 32:377-86.
67. Epler GR, Fitz Gerald MX, Gaensler EA, Carrington CB. Asbestos-related disease from household exposure. *Respiration.* 1980; 39:229-40.
68. Selikoff IJ, Lillis R, Nicholson WJ. Asbestos disease in United States shipyards. In: pp. 295-311.

69. Newhouse ML, Berry G. Predictions of mortality from mesothelial tumors in asbestos factory workers. *Br J Ind Med*. 1976; 33:147-51.
70. Stanton MF, Wrench C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst*. 1972; 48:797-821.
71. Stanton MF, Layard M, Tegeris A, Miller E, May M, Kent E. Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension. *J Natl Cancer Inst*. 1977; 58:587-603.
72. Meurman LO, Kiviluoto R, Hakama M. Mortality and morbidity among the working population of anthophyllite asbestos miners in Finland. *Br J Ind Med*. 1974; 31:105-12.
73. McDonald AD, McDonald JC. Mesothelioma after crocidolite exposure during gas mask manufacture. *Environ Res*. 1978; 17:340-6.
74. McDonald AD, McDonald JC. Malignant mesothelioma in North America. *Cancer*. 1980; 46:1650-6.
75. Lippmann M, Yeates DB, Albert RE. Deposition, retention, and clearance of inhaled particles. *Br J Ind Med*. 1980; 37:337-62.
76. Auerbach O, Conston AS, Garfinkel L, Parks VR, Kaslow HD, Hammond EC. Presence of asbestos bodies in organs other than the lung. *Chest*. 1980; 77:133-7.
77. Sebastian P, Masse R, Bignon J. Recovery of ingested asbestos fibers from the gastrointestinal lymph in rats. *Environ Res*. 1980; 22:201-16.
78. Westlake GE, Spjut HA, Smith MN. Penetration of colonic mucosa by asbestos particles. *Lab Invest*. 1965; 14:2029-33.
79. Jaurand MC, Bignon J, Sebastian P, Goni J. Leaching of chrysotile asbestos in human beings: correlation with *in vitro* studies using rabbit alveolar macrophages. *Environ Res*. 1977; 14:245-54.
80. Jaurand M-C, Kaplan A, Thiollet J, Pinchon M-C, Bernaudin J-F, Bignon J. Phagocytosis of chrysotile fibers by pleural mesothelial cells in culture. *Am J Pathol*. 1979; 94:529-38.
81. Rajan KT, Wagner JC, Evans PH. The response of human pleura in organ culture to asbestos. *Nature*. 1972; 238:346-7.
82. Doll R. Mortality from lung cancer in asbestos workers. *Br J Ind Med*. 1955; 12:81-6.
83. Enterline P, de Couffe P, Henderson V. Respiratory cancer in relation to occupational exposures among retired asbestos workers. *Br J Ind Med*. 1973; 30:162-6.
84. Selikoff IJ, Hammond EC, Churg J. Carcinogenicity of amosite asbestos. *Arch Environ Health*. 1972; 25:183-6.
85. McDonald JC, Liddell FDK, Gibbs GW, Eysen GE, McDonald AD. Dust exposure and mortality in chrysotile mining, 1910-75. *Br J Ind Med*. 1980; 37:11-24.
86. Selikoff IJ, Hammond EC, Seidman H. Latency of asbestos disease among insulation workers in the United States and Canada. *Cancer*. 1980; 46:2736-40.
87. Blot WJ, Harrington JM, Toledo A, Hoover R, Heath CW Jr, Fraumeni JF Jr. Lung cancer after employment in shipyards during World War II. *N Engl J Med*. 1978; 299:620-4.
88. Cremer-Stuif GK. The relationship between asbestosis and bronchial cancer. *Chest*. 1980; 78:380-1.
89. Selikoff IJ, Bader RA, Bader ME, Churg J, Hammond EC. Asbestosis and neoplasia. *Am J Med*. 1967; 42:487-96.
90. Kannerstein M, Churg J. Pathology of carcinoma of the lung associated with asbestos exposure. *Cancer*. 1972; 30:14-21.
91. Whitwell F, Newhouse ML, Bennett DR. A study of the histological cell types of lung cancer in workers suffering from asbestosis in the United Kingdom. *Br J Ind Med*. 1974; 31:298-303.
92. Enterline PE, Henderson V. Type of asbestos and respiratory cancer in the asbestos industry. *Arch Environ Health*. 1973; 27:312-7.
93. Selikoff IJ, Hammond EC, Churg J. Asbestos exposure, smoking, and neoplasia. *JAMA*. 1968; 204:104-10.
94. Selikoff IJ, Seidman H, Hammond EC. Mortality effects of cigarette smoking among amosite asbestos factory workers. *J Natl Cancer Inst*. 1980; 65:507-13.
95. Berry G, Newhouse ML, Turok M. Combined effects of asbestos exposure and smoking on mortality from lung cancer in factory workers. *Lancet*. 1972; 2:476-9.
96. Meurman LO, Kiviluoto R, Hakama M. Combined effect of asbestos exposure and tobacco smoking on Finnish anthophyllite miners and millers. *Int J*. pp. 491-6.
97. Saracci R. Asbestos and lung cancer: an analysis of the epidemiological evidence on the asbestos-smoking interaction. *Int J Cancer*. 1977; 20:323-31.
98. Berenblum I. Irritation and carcinogenesis. *Arch Pathol*. 1944; 38:233-44.
99. Marx JL. Tumor promoters: carcinogenesis gets more complicated. *Science*. 1978; 201:515-8.
100. Chamberlain M, Turney EM. Asbestos and glass fibers in bacterial mutation tests. *Mutat Res*. 1977; 43:159-64.
101. Huang SL. Amosite, chrysotile and crocidolite asbestos are mutagenic in Chinese hamster lung cells. *Mutat Res*. 1979; 68:265-74.
102. Price-Jones MJ, Gubbings G, Chamberlain M. The genetic effects of crocidolite asbestos: comparison of chromosome abnormalities and sister-chromatid exchanges. *Mutat Res*. 1980; 79:331-6.
103. Sincok A, Seabright M. Induction of chromosome changes in Chinese hamster cells by exposure to asbestos fibres. *Nature*. 1975; 257:56-8.
104. Mossman BT, Landesman JM, Craighead JE. Asbestos exhibits properties of a classical tumor promoter on hamster tracheal epithelial cells. *Proc Am Assoc Cancer Res Am Soc Clin Oncol*. 1981; 22:129. abstract.
105. Mossman BT, Craighead JE, MacPherson BV. Asbestos-induced epithelial changes in organ cultures of hamster trachea; inhibition by retinyl methyl ether. *Science*. 1980; 207:311-3.
106. Woodworth CW, Mossman BT, Craighead JE. Comparative effects of fibrous and nonfibrous minerals on cells and liposomes. *Environ Res*. (in press).
107. Mossman BT, Halleron PA, Craighead JE. Stimulation of Na⁺-K⁺ ATPase activity in tracheal epithelial cells after exposure to crocidolite asbestos. *J Cell Biol*. 1979; 83: Suppl. 284a. abstract.
108. Mossman BT, Landesman JM, Craighead JE. Asbestos stimulates ornithine decarboxylase (ODC) activity in hamster tracheal epithelial cells. *J Cell Biol*. 1980; 87: Suppl. 307a. abstract.
109. Lakowicz JR, Bevan DR. Benzo[a]pyrene uptake into rat liver microsomes: effects of adsorption of benzo[a]pyrene to asbestos and non-fibrous mineral particulates. *Chem Biol Interact*. 1980; 29:129-38.
110. Mossman BT, Craighead JE. Mechanisms of asbestos carcinogenesis. *Environ Res*. 1981; 25:269-80.
111. Autrup H, Harris CC, Stoner GD, Selkirk JK, Schafer PW, Trump BF. Metabolism of [³H]benzo[a]pyrene by cultured human bronchus and cultured human pulmonary alveolar macrophages. *Lab Invest*. 1978; 38:217-24.
112. Elmes PC, Simpson MJC. Insulation workers in Belfast. 3. Mortality 1940-66. *Br J Ind Med*. 1971; 28:226-36.
113. Hammond EC, Selikoff IJ, Churg J. Neoplasia among insulation workers in the United States with special reference to intra-abdominal neoplasia. *Ann NY Acad Sci*. 1965; 132:519-25.
114. Selikoff IJ, Hammond EC. Multiple risk factors in etiology of environmental cancer. In: Fraumeni JF, ed. *Persons at high risk of cancer: an approach to cancer etiology and control*. New York: Academic Press, 1975:467-83.
115. Selikoff IJ, Hammond EC, Seidman H. Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Int J*. pp. 91-116.
116. Miller AB. Asbestos fibre dust and gastro-intestinal malignancies. Review of literature with regard to a cause/effect relationship. *J Chronic Dis*. 1978; 31:23-33.
117. Cook PM, Glass GE, Tucker JH. Asbestiform amphibole minerals: detection and measurement of high concentrations in municipal water supplies. *Science*. 1974; 185:853-5.
118. Cook PM, Olson GF. Ingested mineral fibers: elimination in human urine. *Science*. 1979; 204:195-198.
119. Cunningham HM, Moodie CA, Lawrence GA, Pontefract RD. Chronic effects of ingested asbestos in rats. *Arch Environ Contam Toxicol*. 1977; 6:507-13.
120. Jacobs R, Humphrys J, Dodgson KS, Richards RJ. Light and electron microscope studies of the rat digestive tract following prolonged and short-term ingestion of chrysotile asbestos. *Br J Exp Pathol*. 1978; 59:443-53.
121. Gibel W, Lohs Kh, Horn K-H, Wildner GP, Hoffmann F. Tierexperimentelle Untersuchungen über eine kanzerogene Wirkung von Asbestfiltermaterial nach oraler Aufnahme. *Arch Geschwulstforsch*. 1976; 46:437-42.
122. Gross P, Harley RA, Swinburne LM, Davis JMG, Greene WB. Ingested mineral fibres: do they penetrate tissue or cause cancer? *Arch Environ Health*. 1974; 29:341-7.
123. Smith WE, Hubert DD, Sobel HJ, Peters ET, Doerfler TE. Health of experimental animals drinking water with and without amosite asbestos and other mineral particles. *J Environ Pathol Toxicol*. 1980; 3(5&6): 277-300.
124. Smith WE, Miller L, Elsassner RE, Hubert DD. Tests for carcinogenicity of asbestos. *Ann NY Acad Sci*. 1965; 132:456-88.
125. Ward JM, Frank AL, Wenk M, Devor D, Tarone RE. Ingested asbestos and intestinal carcinogenesis in F344 rats. *J Environ Pathol Toxicol*. 1980; 3(5&6):301-12.
126. Rubino GF, Piolatto G, Newhouse ML, Scansetti G, Aresini GA, Murray R. Mortality of chrysotile asbestos workers at the Balangero Mine. No. Italy. *Br J Ind Med*. 1979; 36:187-94.



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CC: B. W. Karrh, M.D./
J. C. Bonnett, M.D.

FILE

EMPLOYEE RELATIONS DEPARTMENT

July 12, 1982

TO: PAUL WYCHE, PUBLIC AFFAIRS DEPT.
D-8078

FROM: BURFORD W. CULPEPPER, M.D. *BWC*

MEMO FOR RECORD

Tom Heinz, Asst. to Jeremy Main of Fortune Magazine, called me on 8 July 1982 requesting confirmation on statements to be made in the magazine article concerning:

- asbestos latency period (15-40 years)
- lead, fibers, silica, asbestos, etc., as old hazards in industry
- N-hexane, polyvinyl chloride, benzene, carbamates, some sulfa compounds as new hazards.

A question of teratogenicity was raised concerning the new hazard chemicals and I suggested that the significant toxic property of those chemicals was not teratogenicity. However, I would review it and call him back.

A second call was made to me on 9 July 1982. I confirmed that teratogenicity was not the most significant hazard of the chemicals listed; ref. "Patty's Industrial Hygiene and Toxicology" and "Chemical Hazards In The Workplace."

The chemicals were described to him as follows:

- N-hexane - solvent industrial glue. Neurotoxic hazard.
- Polyvinyl chloride - basic material for synthetic resins. Has been associated with increased incidence of tumors.
- Benzene - industrial solvent and byproduct in many processes. Associated with blood diseases.
- Carbamates - fungicides, rubber accelerator, etc. Some evidence for teratogenicity in animals; i.e., rats and mice at high doses.
- Sulfa compounds - a large category of chemicals, including many compounds that cannot be specifically categorized as a group.

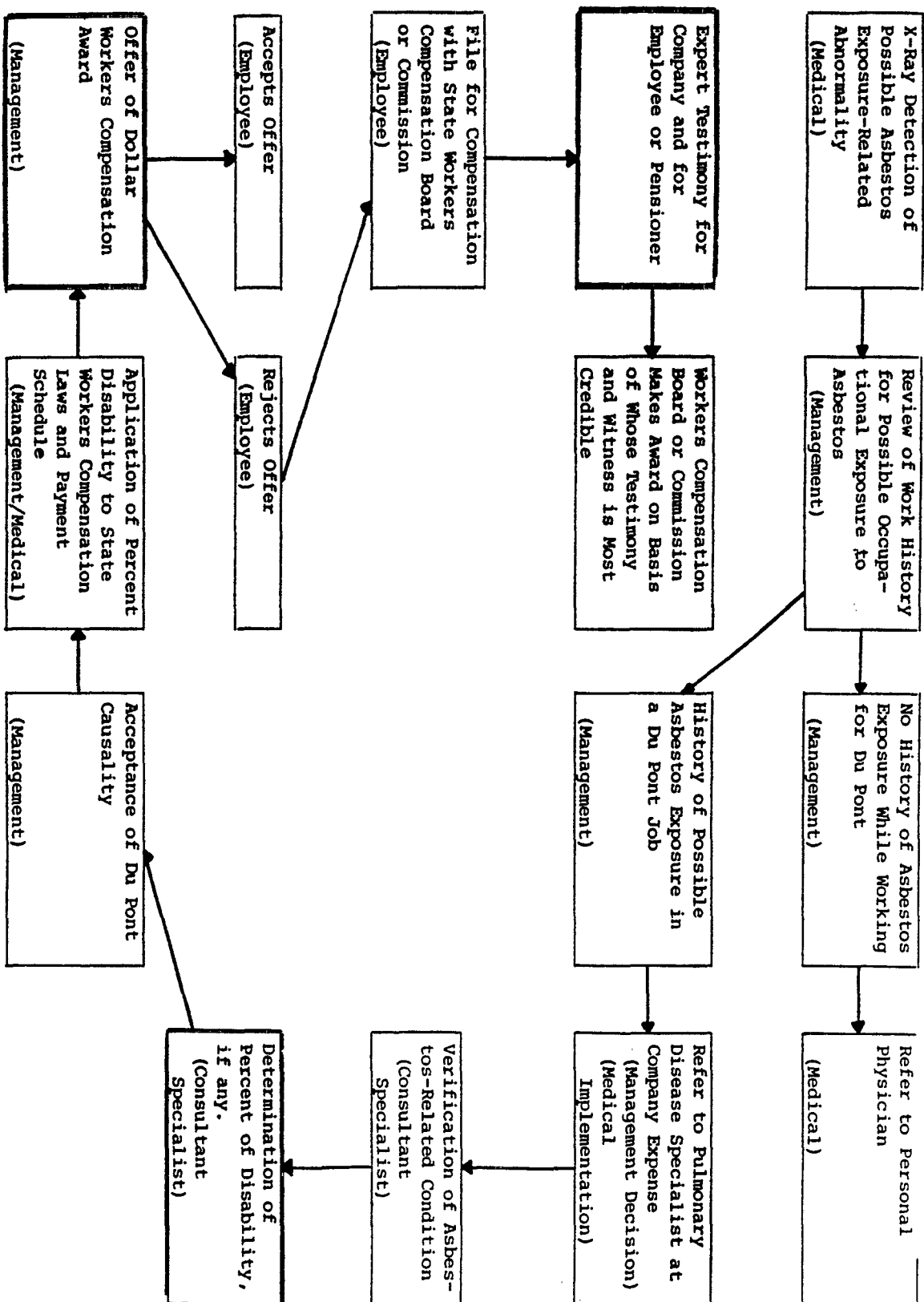
He appreciated the help and did not seem to know much about the chemicals, the properties of the chemicals, or the pronunciations.

BWC/mch

DUP 0947263

DU 038557

DUP 0947264



DU 038558

Harold G. Jacobson, MD Section Editor
E. Robert Heitzman, MD, Section Coordinator

Radiology of Asbestos Disease

Lawrence R. Goodman, MD

ALTHOUGH the hazards of asbestos exposure were first reported in the early 1900s, the full extent of its effects is still being evaluated. Persons with occupational exposure to asbestos have a higher incidence of pulmonary fibrosis (asbestosis), various pleural disorders (plaque, thickening, and effusion), and neoplasms (lung, pleura, and gastrointestinal). In recent years, attention has turned to asbestos as an environmental pollutant. Household contacts of asbestos workers, persons living near asbestos plants, and urban dwellers frequently have asbestos fibers in the lungs at autopsy.

The chest roentgenogram often offers the first evidence of asbestos exposure, because a history of asbestos exposure is difficult to obtain or is not sought. Therefore, it is important for both the radiologist and clinician to understand both the radiological findings of asbestos exposure and the significance of each change.

The final diagnosis of asbestosis (pulmonary fibrosis) rests on a combination of pulmonary lesions on the roentgenogram, bibasilar rales, and reduced lung function in a patient with the appropriate exposure history. Microscopic verification is usually not obtained.^{1,2} The diagnosis of asbestos-related pleural disease relies more heavily on the radiological changes (see below). Roentgenograms demonstrating the typical lateral pleural changes in the absence of old trauma or empyema have a 0.81 correlation with prior exposure to asbestos.³

A rough correlation exists between the degree of asbestos exposure and the type of disease produced. Pulmonary fibrosis (asbestosis) and malignant neoplasms of the lung and gas-

trointestinal tract are most likely to develop in those individuals with the heaviest exposure. Those persons with mild to moderate exposure are more likely to contract benign or malignant pleural disease. These relationships are complex and depend on the type of fiber, pattern of exposure, and time since initial exposure. Usually, a 15- to 20-year latency period occurs between the initial exposure and the first radiological or clinical evidence of disease. Cigarette smoking potentiates both the fibrogenic and carcinogenic effects of asbestos.⁴

For both epidemiologic studies and the individual patient, good-quality 120-kV posteroanterior and lateral roentgenograms usually provide the necessary radiological information. Oblique roentgenograms may accentuate questionable pleural changes. Although computed tomography (CT) will demonstrate lesser degrees of fibrosis, pleural plaques, and pleural calcification, routine use of it hardly seems justified. The major value of CT appears to be in distinguishing focal plaques (benign) from intraparenchymal nodules (presumably cancer) and determining whether large lesions are lung masses, solid pleural lesions (presumably mesotheliomas), or focal pleural fluid collections. In patients with proven lung cancer and mesothelioma, CT is a valuable aid in determining the extent of the lesion both for planning of treatment and determining prognosis.

Asbestosis (Pulmonary Fibrosis)

The radiological changes of pulmonary fibrosis may precede, be associated with, or follow the onset of pulmonary symptoms. Unlike most other pneumoconioses (with the exception of talcosis), the predominant radiological lesions involve the lower half of the lungs. These are usually small, irregular, poorly defined linear opacities. Pinpoint opacities, thickened septal lines, gross linear stranding, and honeycombing are less fre-



Fig 1.—In this posteroanterior film of right hemithorax, reticular nodular interstitial infiltrate is present throughout lungs (asbestosis) in this patient with emphysema. Observe mild pleural thickening along lateral chest wall and minor fissure. Small calcified plaque is noted as well (black arrow). Spheroid, pleural-based mass (white arrow) was not present on previous films, proving at surgery to be adenocarcinoma involving lung, pleura, and chest wall.

quent (Figs 1 and 2, left). (Their severity is scored on a 12-point scale adopted by the International Labor Office.) Lung volumes tend to be normal or diminished. Associated obstructive lung disease is more likely caused by smoking than by asbestos. Conglomerate masses (progressive massive fibrosis), a well-known complication of silicosis and coal workers pneumoconiosis, are extremely rare in asbestosis. When it does occur in asbestosis, it tends to be in the lower lobes, the area of predominant pulmonary fibrosis. Therefore, any focal lung density appearing in a patient with exposure to asbestos should suggest a carcinoma rather than a conglomerate mass.^{1,4}

A recently recognized entity that may mimic lung cancer or the rare

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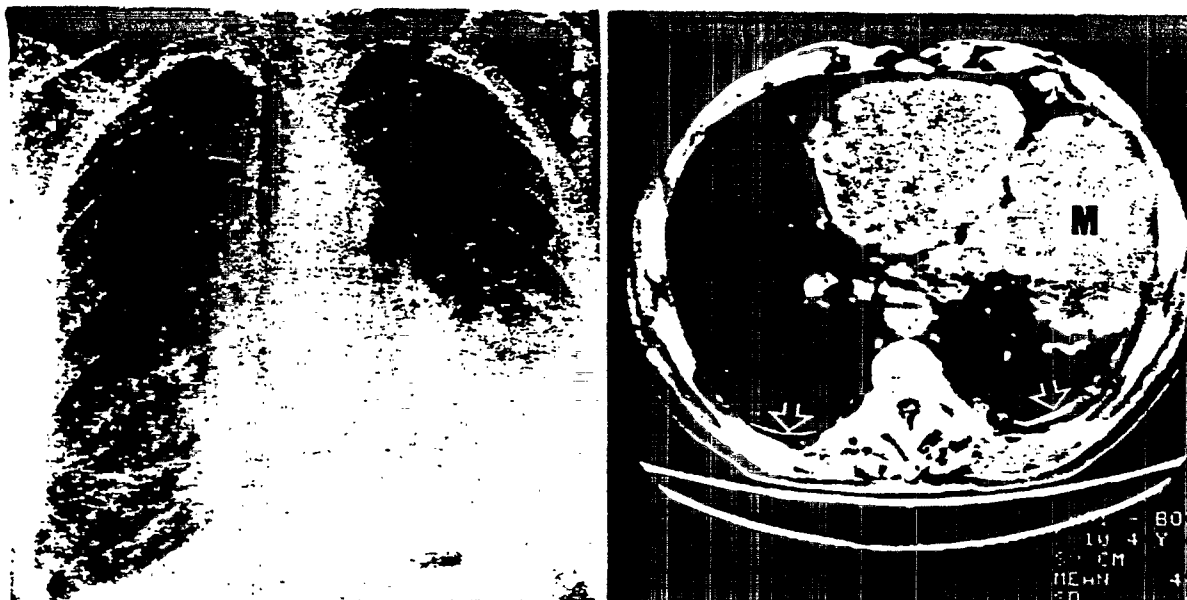


Fig 2.—Left, in this posteroanterior roentgenogram of chest, considerable dense, linear, interstitial thickening is noted in lower half of right lung (asbestosis). Costophrenic angle is blunted and pleura is thickened to level of posterior segment of third rib. On left side, upper lobe nodule as well as homogeneous opacification of lung base is present. Differential diagnosis included loculated effusion, mesothelioma, and lung cancer. Right, Computed tomographic scan through lung base demonstrates large, left lower lobe lung mass (M), bilateral pleural thickening, and calcification (arrows) (oat cell carcinoma, left lower lobe).

lower lobe progressive massive fibrosis is the pulmonary pseudotumor (rounded atelectasis). This is usually a swirl of atelectatic parenchyma adjacent to thickened pleura. Tomograms or oblique films may demonstrate a "tail" to the medial aspect of the mass, and CT may show clearly the atelectatic nature of the lesion. Thus, one can often distinguish between round atelectasis and a tumor.¹³

Lung Cancer

Asbestos and cigarette smoking are cocarcinogens. Lung cancer is 70 times more likely to develop in a smoking asbestos worker than in a nonsmoker without asbestos exposure. The malignant neoplasms are most frequently peripheral and at the bases of the lungs as opposed to the more frequent upper lobe predominance. The tumor frequently arises in a background of interstitial fibrosis or pleural disease, making detection of a small neoplasm difficult (Fig 1). Any change identified on serial films should be viewed with great suspicion, because fibrosis and plaques often take years to demonstrate radiological progression. Tomograms or CT may be helpful in distinguishing overlapping shadows, a lung nodule, or a pleural mass¹³ (Fig 2).

Benign Pleural Disease

Pleural disease may take several guises. Asymptomatic, focal, bilateral pleural thickening along the midlateral thoracic wall are characteristic of pleural plaque due to moderate asbestos exposure. Plaques may also be discerned along the mediastinal pleura, the pericardium, and the diaphragm. They tend to spare the lung apexes and costophrenic angles. The majority are not calcified, and most are noted in the absence of pulmonary fibrosis. When calcification occurs, it is in the parietal pleura in a characteristic distribution along the surface of the diaphragm and the lateral chest wall (Figs 1 and 3). Plaques do not undergo malignant degeneration, but are an indicator of significant asbestos exposure. When these characteristic plaques are present, the vast majority of patients have a history of asbestos exposure.¹ Asbestos workers with pleural plaques, but no fibrosis, have a 2½-fold increase in lung cancer.¹⁴

Diffuse pleural thickening with involvement from the apex to the base may also be due to asbestos exposure. Unlike pleural plaques, this radiological appearance may be observed in a variety of diseases (Fig 2, left).

Pleural effusions are frequently harbingers of pleural or pulmonary malignant neoplasms. Any patient with a notable asbestos history and at least ten years since initial exposure should be presumed to have a malignant neoplasm until proved otherwise. However, effusions may be benign in nature. Epler et al¹⁵ have recently shown that benign effusion was the most common asbestos-related abnormality during the first twenty years after exposure.

Mesothelioma

Mesothelioma is approximately three to five times more frequent in asbestos workers than in nonasbestos workers. Because it is a relatively rare tumor, however, its incidence is considerably less than lung cancer. Exposure to asbestos is often mild to moderate, and frequently a 30- to 40-year latency period ensues between initial exposure and development of the mesothelioma.^{1,2}

Mesotheliomas may arise from any mesothelial surface, but the vast majority are located in the pleura or pericardium. Symptoms include the insidious onset of pain, dyspnea, and weight loss. The most frequent radiological manifestation is that of pleural effusion. The effusion is often large and may obscure the pleural



Fig 3.—Posteroanterior chest roentgenogram shows lobular pleural plaques along each lateral chest wall (arrows). Lung apices and costophrenic angles are spared. Calcified pleural plaque is noted on left diaphragm (arrowhead). Little or no interstitial fibrosis is present (asbestosis-pleural plaques).

Fig 4.—In this posteroanterior roentgenogram of chest, large right pleural effusion obscures extensive malignant mesothelioma. Lateral portion of right third rib (upper arrows) is destroyed, and upper segment of trachea is deviated to left. Two nodules observed over left upper lobe represent calcified pleural plaques en face. Diaphragmatic, mediastinal pleura and lateral pleural calcifications are also present (lower arrows).



tumor. Large effusions may cause the mediastinum to shift to the contralateral side or mediastinal pleural involvement may "freeze" the mediastinum and prevent mediastinal shift (Fig 4).

When the mesothelioma is visible, it usually appears as a lobular mass between the lung and the chest wall. It may be localized in a small area or may encase a large portion of the lung. The volume of the involved hemithorax may be diminished. Secondary invasion of the chest wall, lung invasion, or lung metastasis are frequently observed late in the course of the disease (Fig 4). Computed tomographic examination frequently discloses the tumor to be more extensive than initially appreciated. Mediastinal invasion and contralateral or subdiaphragmatic spread are frequently demonstrated by CT examination.

Nonoccupational Lung Disease

Concern for the effects of asbestos on the general population arises from multiple sources. Families of asbestos workers have a higher incidence of asbestos-related lung disease. The air in most urban areas contains small numbers of asbestos particles. Autopsies of adults in urban centers frequently show asbestos bodies in the lung, although at a much lower concentration than in asbestos workers.¹ The disease-producing potential of inhalation of asbestos in a low concentration in the general population is still unknown. It has been suggested that the lateral pleural thickening occasionally observed in nonasbestos workers may be related to low levels of asbestos exposure.²

References

1. Preger L: *Asbestos-Related Disease*. New York, Grune & Stratton Inc, 1978.
2. Becklake ME: Asbestos-related diseases of the lung and other organs: Their epidemiology and implications for clinical practice. *Am Rev Respir Dis* 1976;114:187-227.
3. Albelda SM, Epstein DM, Gefter WB, et al: Pleural thickening: Its significance and relationship to asbestos dust exposure. *Am Rev Respir Dis* 1982;126:621-624.
4. Souter CA, Simon G, Turner-Warwick M: The radiology of asbestos-induced disease of the lungs. *Br J Dis Chest* 1974;68:235-252.
5. Mintzer RA, Cugell DW: The association of asbestos-induced pleural disease and rounded atelectasis. *Chest* 1982;81:457-460.
6. Epler GR, McLoud TC, Gaensler EA: Prevalence and incidence of benign asbestos pleural effusion in a working population. *JAMA* 1982;247:617-622.
7. Ochs CW, Smith JP: Chronic pleural thickening: Some observations on cause and pathogenesis. *Military Med* 1976;141:77-81.

PERMISSIBLE REUSABLE RESPIRATOR FOR DUSTS AND MISTS



MINE SAFETY AND HEALTH ADMINISTRATION
NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH

APPROVAL NO. TC-21C-170

ISSUED TO

NORTON COMPANY, SAFETY PRODUCTS DIVISION
CRANSTON, RHODE ISLAND, U.S.A.

LIMITATIONS

Approved for respiratory protection against dusts and mists having a time-weighted average not less than 0.05 milligram per cubic meter or 2 million particles per cubic foot. Not for use in atmospheres containing toxic gases or vapors or in atmospheres containing less than 19.5 percent oxygen.

CAUTION

Clean respirator filter in accordance with manufacturer's instructions. This respirator shall be selected, fitted, used, and maintained in accordance with Mine Safety and Health Administration, Occupational Safety and Health Administration, and other applicable regulations.

MSHA — NIOSH Approval TC-21C-170

Issued to Norton Company, Safety Products Division, December 1, 1976. The approved assembly consists of the following Norton part number 7170 respirator.

PERMISSIBLE RESPIRATOR FOR DUSTS AND MISTS



MINE SAFETY AND HEALTH ADMINISTRATION
NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH

APPROVAL NO. TC-21C-170A

ISSUED TO

NORTON COMPANY, SAFETY PRODUCTS DIVISION
CRANSTON, RHODE ISLAND, U.S.A.

LIMITATIONS

Approved for respiratory protection against pneumoconiosis and fibrosis producing dusts and mists. Not for use in atmospheres containing less than 19.5 percent oxygen or in atmospheres containing toxic gases or vapors.

CAUTION

This respirator shall be selected, fitted, used, and maintained in accordance with Mine Safety and Health Administration, Occupational Safety and Health Administration, and other applicable regulations. Follow manufacturer's instructions for fitting the respirator to the face. Discard and replace the respirator if it becomes damaged or breathing resistance is excessive.

MSHA — NIOSH Approval TC-21C-170A

Norton Company, Safety Products Division, December 1, 1976. The approved assembly consists of the following Norton part number 7170 respirator.



Dust Respirator

Disposable and Reusable

Model No. 7170

MSHA/NIOSH APPROVAL TC-21C-170 AND TC-21C-170A

WARRANTIES — Our commercial non-consumer products are warranted to be free from defects. Our only obligation to the commercial user will be at our option, to replace any portion proving defective or to refund the purchase price thereof. The commercial user assumes all other risk, if any. We make this warranty to the commercial user in lieu of the warranties of merchantability, fitness for particular purpose and all other warranties, express or implied. No deviation is authorized. Norton Company consumer products are sold only with warranties implied by law.



DUP 0947268

DU 038562

RESPIRATOR APPLICATIONS

Disposable Respirator ... Approved for respiratory protection against pneumoconiosis-producing and fibrosis-producing dusts and mists. This respirator is approved for use in atmospheres containing asbestos dusts and mists.

Reusable Respirator ... Approved for respiratory protection against toxic dusts and mists, including systemic poison dusts and mists, having a permissible time-weighted average (TWA) concentration not less than 0.05 milligram particulate matter per cubic meter of air or not less than 2 million particles per cubic foot of air.

RESPIRATOR DESCRIPTION

The Norton Model 7170 Respirator is a compact, lightweight, particulate-filtering respirator which protects against inhalation of dusts and mists. It is designed for application both as a Disposable Respirator and as a Reusable Respirator.

RESPIRATOR INSPECTION

1. Inspect respirator thoroughly before use to insure that it is in satisfactory operating condition. Discard respirator if damaged or if parts are missing.



DONNING, FITTING, AND WEARING RESPIRATOR

1. Remove respirator from plastic film bag and examine it to insure that it has not been damaged. Save bag for reuse.
2. Position respirator on face so that wide portion of facepiece is over chin and narrow portion of facepiece is over nose.
3. Place lower headband straps around head below ears and fasten hook and catch together.
4. Place upper headband straps around head above ears and fasten hook and catch together.
5. Adjust tension in headband straps to provide tight seal of facepiece to face and yet allowing comfortable wearing of respirator.
 - a. Tension in straps may be increased while wearing respirator by grasping ends of headband straps between thumbs and forefingers and pulling on straps or by holding hook or catch with thumb and forefinger of one hand and pulling strap through hook or catch with thumb and forefinger of other hand.
 - b. Tension in straps may be decreased while wearing respirator by holding hook or catch with thumb and forefinger of one hand and pulling strap through hook or catch with thumb and forefinger of other hand.

6. Use finger tips to form adjustable metal strip to shape this section of facepiece to fit nose.

7. Check for tightness of seal of facepiece to face by inserting tip of small finger through circular hole in respirator valve guard and pushing exhalation valve flap against exhalation valve seat. Exhale gently while keeping exhalation valve closed. If leakage of exhaled air is detected to be passing between facepiece and face, readjust position of facepiece on face, reform shape of adjustable metal strip, and/or readjust tension of headband straps, and then retest for tightness of seal of facepiece to face. Repeat procedures until seal of facepiece to face is adequate.

8. Periodically check tightness of seal of facepiece to face while wearing respirator and make adjustments if necessary.

CLEANING AND SANITIZING RESPIRATOR

1. Clean and sanitize respirator after each day of use.
2. Remove deposits of dust or mist particulate matter from outer surface of respirator filter by brushing off particulate deposit (clean paint brush is suitable). Carry out brushing operation inside ventilated hood to prevent inhalation of dust or mist particulate matter.
3. Use clean, non-linting cloth wetted with Norton Cleaner-Sanitizer or any suitable cleaner-sanitizer solution to clean and sanitize respirator. Use wetted cloth to wipe surfaces of respirator facepiece, adjustable metal strip, headbands, exhalation valve guard, exhalation valve, and inhalation valve by wiping. Do not wipe surface of filter.
4. Use clean, non-linting cloth wetted with clean water (preferably distilled or demineralized water) to rinse surfaces of respirator facepiece, adjustable metal strip, headbands, exhalation valve guard, exhalation valve, and inhalation valve. Do not rinse surface of filter.
5. Allow respirator to dry in clean air at normal room temperature.

STORING RESPIRATOR AFTER CLEANING AND SANITIZING

1. Place cleaned and sanitized respirator into plastic film bag.
2. Store respirator so that it is protected against dust, chemicals, moisture, excessive heat, and physical damage. Prevent distortion of respirator during storage.

RESPIRATOR REPLACEMENT

Discard respirator and replace it with new respirator if breathing becomes difficult due to plugging of filter by retained dust or mist particulate matter.

WARNING

This respirator must not be used in atmospheres containing oxygen at a partial pressure less than 148.2 mm mercury (19.5% by volume oxygen at sea level). This respirator should not be used in atmospheres which contain harmful vapors or gases or for protection against volatile dusts which emit vapors or gases. It must not be used in poorly ventilated areas, in enclosed spaces, for abrasive blasting, or for fire fighting. This respirator is approved for use in atmospheres containing asbestos under TC-21C-170A. No non-powered air-purifying respirator totally eliminates asbestos fibers from the breathing zone. Better protection against asbestos is provided by high-efficiency filters used with elastomeric facepieces such as the Norton #7580 or equivalent.

Norton Company, Safety Products Division, Cranston, R.I. 02920 U.S.A.

Made in USA

40-700208 REV. E

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