State of the Art

Asbestos-Related Diseases of the Lung and Other Organs: Their Epidemiology and Implications for Clinical Practice[1, 2]

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Contents

Introduction

Although the fire-resistant qualities of asbestos have been recognized since ancient times (1, 2), its commercial exploitation was modest until the latter part of the nineteenth century, when as a result of the industrial revolution, the need arose to develop the means of insulating the steam engine (2). The discovery in 1877 and subsequent development in the 1880s of the extensive chrysotile deposits in eastern Quebec was followed by further exploitation of the already known and extensive deposits in the Ural mountains in Russia and of the more limited deposits in Italy and Cyprus (2, 3). The existence of blue asbestos deposits in the Cape (South Africa) was recorded in the early nine-

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teenth century, but large scale mining only began in the past decade. Amosite, discovered in the Transvaal in 1907, was first commercially extracted in 1908 (2). Milling of the fiber to release it from the ore is usually done at the mine-head, and the fiber is then bagged and exported to the factories of the industrialized world, in particular Britain, other European countries, and the United States.

The world sources of production and use of this mineral are shown in figure 1 in a way that underlines the need for worldwide appreciation of its potential threat to health; figure 2 traces the history of medical recognition of its health effects in relation to the commercial exploitation of the mineral. Thus, adverse effects on health were observed in the early 1900s and first reported in 1907 (1), and it is now recognized that exposure to asbestos may lead to the pathologic conditions listed in table 1. These include fibrosis of varying degrees and virulence of the lungs and pleura; and neoplasms of the lung, pleura, peritoneum, gastrointestinal tract (5–9), and, possibly, the larynx (11–14), ovary (15), and breast (16). Despite legislative action aimed at controlling the health effects in Europe and North America (Gilson, 5, p. 696), deleterious effects on health continued to be reported. Indeed, asbestos-related lung disease has been called "the occupation illness of the 60s," a description that also reflects the extent of current public concern for this health hazard (1).

Although recognition of the association between asbestos exposure and the various health effects listed in table 1 was made initially by shrewd clinical, pathologic, and epidemiologic observation, exploration of the nature of the association with asbestos exposure has subsequently been made by epidemiologic studies. Results of such studies are frequently found in journals of epidemiology, public health, and environmental health, rather than in clinical journals, and in reports of international conferences not covered by the usual clinical reference systems, such as the Cumulative Index (5–9). The published proceedings of these conferences, all internationally supported, in keeping with the international nature of asbestos use, provide excellent source material to which extensive reference is made in this review. For this reason, the proceedings of each conference are cited only once, in references 5 to 9. Individual presentations are subsequently identified in the text by the name of the first author and page number.

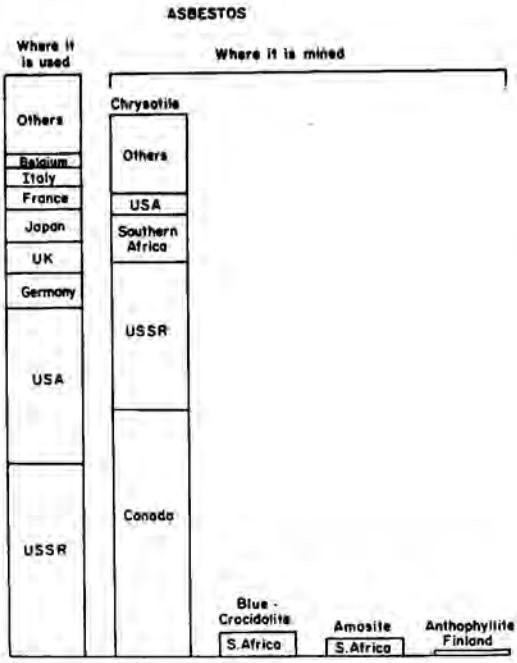

Fig. 1. [From Smither (4); reprinted by permission of publisher.] Asbestos: where it is mined and where it is used. This figure was based on world consumption for 1970, estimated at 3,000,000 tons. The figure for 1974 is estimated at 5,100,000 tons, with Russian production now surpassing the production of the western world.

Nevertheless, the practicing physician is often the first source of medical help for the exposed person whose health is affected, particularly if the exposure is related to the use, rather than production of, asbestos products, or if exposure is nonoccupational, i.e., by neighborhood or household contact.

It has been said by Weiss (17) that "the clinician sees the sick patient against his memories of individuals with a similar constellation of abnormalities half-buried in his apperceptive background and in relation to what he recalls from the literature, usually written by peers with the same small field of vision" and that he "founders into erroneous conclusions because he looks only at the people directly in front of him." By contrast, the epidemiologist sees "the sick patient as an impersonal unit in relation to a populational universe" and "misses a truth because it is buried in a mass of data." Perhaps these remarks apply only to the bad clinician and the bad epidemiologist. Nevertheless, the differences in approach seem to be sufficient to merit a review that attempts to bridge the gap; thus, the

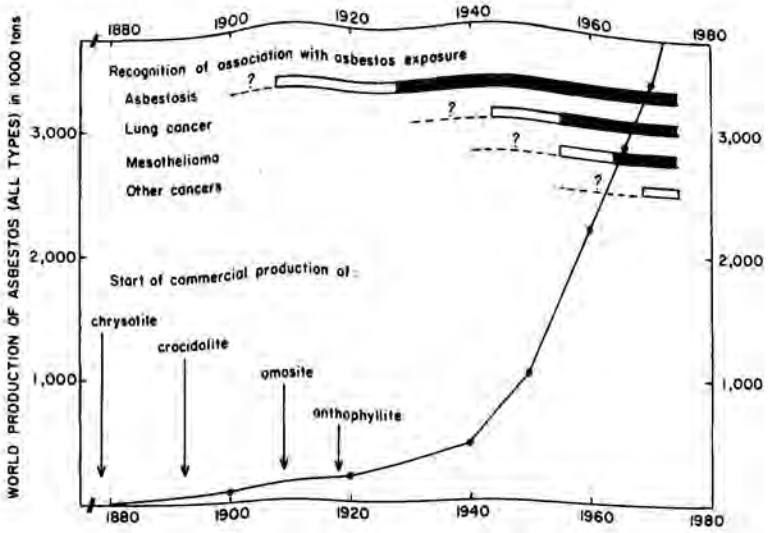

Fig. 2. Diagrammatic representation of the growth of the asbestos industry and the recognition of the associated biologic effects. The following symbols indicate the association with asbestos: ? = suspected; ▭ = probable; ▬ = established.

purpose of the present review is to evaluate current information, particularly that obtained from epidemiologic studies, in light of the implications of this knowledge for clinical practice.

The Asbestos Minerals

Physical Characteristics and Fiber Types

The physician may well question the relevance of the physics and chemistry of the asbestos minerals to the state of his art. The answer is contained in Gilson's summary of the 1964 New York Conference on the "Biological Effects of Asbestos" (5), in which he identified one of the questions requiring further investigation: "Is the type of asbestos an important factor in the risk of asbestosis, bronchial carcinoma, mesothelioma, and other tumors?" Because subsequent observations have suggested that this is so (see later in this review), knowledge of the type of asbestos to which a person has been exposed should guide the practicing physician in establishing a diagnosis and estimating a prognosis.

Asbestos is the general term given to a group of minerals that are fibrous in character and resistant to high temperatures, the two qualities on which their industrial use depends. The most important commercial fibers (shown in table

TABLE 1

PATHOLOGIC EFFECTS OF ASBESTOS EXPOSURE IN MAN

Organ	Effect	Association with Asbestos Exposure*	Reference
Skin	Asbestos corns	Established	5–9
Larynx	Carcinoma	Possible	11–14
Lungs	"Asbestos" bodies and/or fibers	Established	5–9
	Diffuse interstitial fibrosis (asbestosis)	Established	5–9
	Carcinoma (bronchial)	Cofactor with cigarettes	5–9
Pleura	Hyaline plaques and calcification	Established	5–9
	Malignant mesothelioma	Established†	5–9
	Pleural effusion	Possible	10
Peritoneum	Malignant mesothelioma	Established†	5–9
Gastrointestinal tract	Neoplasia	Established	5–9
Ovary	Carcinoma	Remotely possible	15
Breast	Carcinoma	Remotely possible	16

*Association thought to be causal, except where indicated.
†Association, not cause, established.

2) are chrysotile (a white, usually long, silky fiber), crocidolite (a harsher blue fiber), amosite (brown and harsh), and anthophyllite, chiefly mined and used in Finland. In addition, some of these fibrous minerals also occur in the bearer rock of mines developed primarily for the exploitation of other minerals, such as talc, mica (18), and iron, as, for example, in the iron mines at the head of Lake Superior and in Labrador.

Differences in the physical properties of the various fibers determine their particular commercial usefulness. Thus, for example, chrysotile, which consists of long, mainly pliable fibers that split progressively into finer fibrils, lends itself to incorporation into textiles, whereas crocidolite and amosite, which are more acid resistant, are of particular value for marine insulation. Certain asbestos cement products may be made from blends of chrysotile and amosite and/or crocidolite. These differences in the physical properties of the fibers (and in consequence, in their aerodynamic behavior) may account for differences in the health effects of exposure; indeed, it has been argued that "only by relating experimental biologic evidence with the variations in physical size and form . . . can we ultimately arrive at valid medical conclusions" (18). This question is discussed in a later section of the present review.

Uses of Asbestos: Occupations at Risk

World production and use of asbestos have grown greatly since the late nineteenth century; between 1877 and 1967, asbestos production and use increased from 50 tons to 4,000,000 tons per year, an 80,000-fold increase. For industrialized countries, such as Britain and the United States, the increase in asbestos use between 1910 and 1970 was 7-fold (18, 19). This reflects increases in volume of manufactured goods as well as in the variety of uses developed for the material. These are outlined broadly in table 2.

Appreciation of the wide variety of uses of asbestos is important to the physician and serves as an indicator of the many occupations potentially at risk from exposure (table 3). These occupations include asbestos mining, milling, and handling in preparation for its use, either directly (as, for instance, in spraying when mixed with oil) or for its incorporation into the manufacture of a great variety of asbestos-containing products. The latter may be classified broadly into textiles, asbestos cement and other construction products, paper products, friction materials, and insulation products. It is also used in the chemical and plastics industries, where its binding properties (in particular, the positive charge of chrysotile) enhances its union with filler and pigment (Lindell, 7, p. 323).

Once incorporated into manufactured items, the fiber is relatively well bound and is therefore less likely to pose a health hazard to the many workers who use the newly manufactured products (see Secondary Uses, table 2), so long as the product is not sawn, disrupted, or cut in any way; however, asbestos fibers are virtually indestructible. Thompson, 5, p. 196) aptly describes this as a "half-life of an infinity of years." The fibers may be released into the atmosphere again when the original product is removed, replaced, or destroyed, as may occur in the construction and shipbuilding industries, in connection with demolition, repair, and/or refitting. Exposures of this sort, particularly if they occur in a contained environment, such as the hold of a ship undergoing refitting, may involve workers whose primary job has nothing to do with asbestos, e.g., welders or masons. Indeed, failure to appreciate these sources of exposure in both construction and shipbuilding industries (19, 20) probably accounts for the re-emergence of asbestos-related disease in the 1960s. There appears to be no direct information on the numbers of workers at risk in different countries, other than an estimate of 250,000 persons for the United States in 1972 (21).

The reason for including the information on the occupations at risk (table 3) in a clinical review is to offer the physician an overview of the uses of the mineral, so that when faced with an individual with an illness that may be asbestos related, he can formulate a systematic enquiry into the person's occupational history. The physician should thus cover possible exposures in mining, milling, and manufacturing, as well as in the application of manufactured products containing asbestos, directly, or at the time of demolition or replacement (19, 20, 22–26). The physician must not only seek the details of the patient's own jobs, past and present, but must also ascertain whether this work was carried out at the side of other workers whose jobs involved the handling of asbestos products or materials, particularly if in a closed or poorly ventilated environment.

TABLE 2

VARIETIES OF ASBESTOS: PROPERTIES, SOURCES, AND USAGE*

Mineral Type	Serpentine	Amphiboles				
Chemistry, approximate	$Mg_3Si_2O_5(OH)_4$	$X_{2-3}Y_5(Si,Al)_8O_{22}(OH)_2$ with X,Y representing different elements				
Fiber type	Chrysotile (White)	Crocidolite (Blue)	Amosite (Brown)	Anthophyllite	Tremolite	Actinolite
Main elements determining specific composition	Mg	Na, Fe^{2+}, Fe^{3+}	Fe^{2+}, Mg	Similar to amosite, but more Fe^{2+}, less Mg	Ca, Mg	Like tremolite, but contains Fe^{2+}
Physical properties						
Tensile strength, 1,000 psi	350–450	500	175–350	240	< 75	
Flexibility	Very good	Good	Poor	Fair to brittle	Brittle	Brittle
Acid resistance	Poor	Good	Good	Fair to good	Fair	Very good
Texture	Silky to harsh	Harsh	Coarse	Harsh to soft	Harsh to soft	Harsh
Heat resistance	500° C	200° C	200° C	200° C	Fair to good	Very good
Major sources, present and past	Canada (Quebec, B. C., Yukon, Newfoundland, Ontario) Russia (Urals, Siberia) S. Rhodesia Botswana Swaziland Australia (NSW) Cyprus Italy United States (Vt.,† Ariz., Calif.)	S. Africa (N. W. Cape, Transvaal) Bolivia W. Australia†	S. Africa (Tvl)	Finland United States (Georgia† Carolinas)	Italy	Not usually commercially exploited
World use, approximate %	93	3.5	2.5	< 1	< 1	
Industrial uses	Textiles Cement products Friction materials Insulation** "Paper" products	Textiles Pressure pipes Cement products Felts for plastics	Cement Plastic reinforcement Refractory tiles Pressure pipes	Cement (limited) Chemical industry	Chemical industry (as fillers and filters) Talc fillers	

*Information collected by Dr. Graham Gibbs from the following reference sources: Zussman (3), Speil and Leineweber (18), N. W. Hendry, in (5), p. 12; R. Gaze, in (5), p. 23; K. V. Lindell, in (7), p. 323.

†No longer in operation.

**Being phased out.

TABLE 3

OCCUPATIONS AT RISK FOR ASBESTOS EXPOSURE IN MINING, MILLING, MANUFACTURING, AND SECONDARY USES*

Process	Products Made or Used	Jobs Potentially at Risk
Production		
Mining		Rock mining, loading, trucking
Milling		Crushing, milling
Handling		Transport workers, dockers, loaders, those who unpack jute sacks (recently replaced with sacks that do not permit fibers to escape)
Primary uses in		
Spray insulation	Spray of fiber mixed with oil	Spray insulators (construction, shipbuilding)
Filler and grouting		
Manufacturing of		
Textiles	Cloth, curtains, lagging, protective clothing, mailbags, padding, conveyor belts	Blending, carding, spinning, twisting, winding, braiding, weaving, slurry mixing, laminating, moulding, drying
Cement products	Sheets, pipes, roofing shingles, gutters, ventilation shafts, flower pots	Blending, slurry preparation, rolling, pressing, pipe cutting
"Paper" products	Millboard, roofing felt, fine quality electrical papers, flooring felt, fillers	
Friction materials	Automotive products: gaskets, clutch plates, brake linings	
Insulation products	Pipe and boiler insulation, bulkhead linings for ships	
Application		
Construction		
New construction	Boards and tiles; putties, caulk, paints, joint fillers; cement products (tiles, pipes, siding, shingles)	Directly, carpenters, laggers, painters, tile layers, insulation workers, sheet metal and heating equipment workers, masons; indirectly all other workers on construction sites, such as plumbers, welders, electricians
	Insulation materials	
Repair, demolition		Demolition workers for all of these
Shipbuilding		
Construction	Insulation materials (boards, mattresses, cloth) for engines, hull, decks, lagging of ventilation and water pipes, cables	Laggers, refitters, strippers, steam fitters, sailmakers, joiners, shipwrights, engine fitters, masons, painters, welders, caulkers
Repair, refits	Insulation materials, as described for "construction"	Directly, all above jobs on refits, dry dock, and other repairs operations
		Indirectly, maintenance fitters and repair men, electricians, plumbers, welders, carpenters
Automotive industry		
Manufacture	Gaskets, brake linings, undercoating	Installation of brake linings, gaskets, and so on
Repair	Gaskets, brake linings, undercoating	Service men, brake repairmen, body repairmen, auto mechanics

*Information collated by Dr. Graham Gibbs from references 2, 3, 18–20, and 22–26.

Indirect Exposure (Domestic, Neighborhood, Environmental)

Exposure to asbestos fiber is not confined to the place of work (27); the search for exposure in the background of patients with mesothelioma (10, 28–31) has brought to light several forms of indirect nonoccupational exposure. The occurrence of mesothelioma in the family members of asbestos workers led to the recognition of indirect domestic exposure; the source here

is presumed to be the dust brought home in the worker's overalls (10, 31). Likewise, the association between residence near a mine, mill, or factory and the occurrence of mesothelioma brought to light the importance of neighborhood exposures (27). Such neighborhood exposure is also presumed to account for occurrence of pleural plaques and/or calcification in residents of the mining area of Finland (32). Pleural plaques have also been described in agricultural populations (33–35); in some instances, they have been attributed to the working of soil that contains asbestos fibers, e.g., in Bulgaria (33, 34).

The surprisingly high prevalence of asbestos bodies (as evidence of exposure) in routine autopsies indicates an environmental exposure for the residents of most of the larger cities of the world; however, the amounts in the general atmosphere are small (36), and these autopsy findings should probably be regarded more as an index of exposure rather than of disease potential. The Advisory Committee report that followed the Lyon Conference (7) concluded that "there is at present no evidence of lung damage by asbestos to the general public," and "the amount of asbestos in the lungs of members of the general public is very small compared to those occupationally exposed."

Finally, attention has recently been directed toward the widespread occurrence of asbestos fibers in certain natural water sources (37–40). An event that brought this to the notice of the general public was the discharge of mine tailings containing fiber into Lake Superior, a source of drinking water to many cities in the center of the North American continent (38). It is now also recognized that fibers also occur in many natural waters, particularly in mining regions; however, the Advisory Committee report emanating from the Lyon Conference (7) judged there to be no evidence at present of "an increased cancer risk resulting from asbestos fibers present in water, beverages or food or in the fluids used for the administration of drugs." The question must, however, remain under close scrutiny.

The Fate and Biologic Effects of Inhaled Asbestos Particles

Deposition in the Lung

Whether or not inhaled asbestos fibers will be deposited in the lung depends on the aerodynamic behavior of the particles, the dimensions of the respiratory tract they enter, and the pattern of breathing that carries the particles. The aerodynamic behavior of particles is a function mainly of diameter, but also of size, shape, and density. The varying characteristics of commercially used asbestos fibers make it obvious that the environment to which asbestos workers are exposed will contain particles having great variation in size and composition. These include fibers (so-called if their length is at least 3 times their diameter), which may be long (as long as 200 μm) or short. In addition, a working environment is likely to include a range of smaller particles and/or fibers released from the breakdown and disruption of the primary fiber, as well as those due to any other nonasbestos particles added by the mining or industrial process.

Inhaled asbestos particles follow the moving airstreams with each inspiration, and, once they make contact with any part of the surface of the airways or airspaces, are not resuspended in the expiratory airstreams (41, 42). Deposition of the larger inhaled particles (more than 5 μm in diameter) occurs mainly in the nose (assuming nose breathing) and major airways, owing to inertial impaction and sedimentation. Because of Brownian movement, deposition of the smaller particles (less than 1 μm in diameter) occurs mainly in the more peripheral airways and airspaces. This deposition profile is summarized in figure 3.

Deposition patterns can be profoundly modified by breathing patterns; nose breathing causes a high retention rate, even of small fibers, within the nose (41, 42). However, under working conditions, including heat and exertional stress, most workers resort to mouth breathing. Deeper, slower respirations favor a more even distribution of inspired air, and, thus, a more even distribution of inhaled particles. Lung volume also influences distribution and, possibly, retention patterns, particularly if breathing occurs at less than the normal functional residual capacity (FRC) in the range of airway closure (43, p. 98). Likewise, there is some evidence that the state of the airways in smokers is such that inhaled particles will penetrate less deeply into the bronchial tree and thus tend to be deposited more centrally than in nonsmokers (44).

Pulmonary Clearance

Clearance of particles deposited on the mucous blanket is brisk, with half-times of minutes

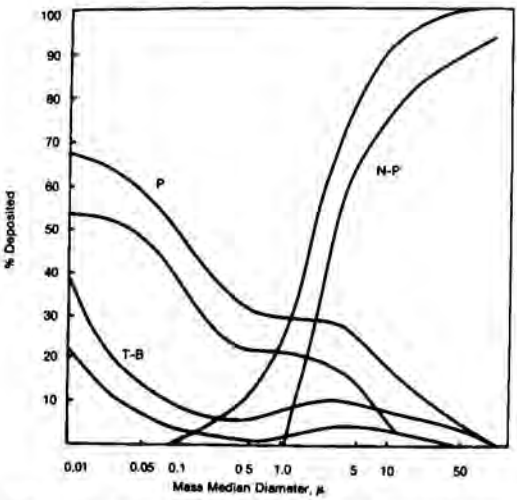

Fig. 3. [From Brain and Valberg (42); reprinted by permission of publisher; copyright 1974, American Medical Association.] Aerosol deposition in respiratory tract. The percentage aerosol deposited was calculated from the assumptions in the model referred to above for a tidal volume of 1,450 ml and a frequency of 15 breaths per min. The profile of deposition of an aerosol is influenced by its effective aerodynamic behavior that (since the distribution of mass for many aerosols is log-normal) may be described by the mass median diameter of the aerosol and its geometric standard deviation. In this figure, per cent aerosol deposited is related directly to the mass median diameter, whereas the 2 lines referring to each lung zone (i.e., N-P, T-B, and P, respectively) indicate the differences in per cent deposition that would result if the geometric standard deviation of the mass median diameter varied from 1.2 to 4.5 μ. N-P = nasopharyngeal surface; T-B = ciliated tracheobronchial surface; P = nonciliated pulmonary surface.

to hours. Mucus and cells from nonciliated airways bearing ingested particles from the major airways are cleared to the pharynx; the material trapped in the nose is also cleared to the pharynx. Here, pulmonary and nasal debris mix with saliva and are swallowed or expectorated (42). This phase of clearance does not appear to be affected by the presence of asbestos lung disease (45) and, under certain circumstances, the effects of smoking in producing bronchitis may even speed this phase of clearance (46, 47).

Particles deposited in the nonciliated regions may be cleared relatively rapidly if they remain on the surface (with a half-time of 24 hours), but once they penetrate fixed tissues, clearance is slowed, with half-times ranging from days to thousands of days (42). It has also been suggested that macrophages decrease the likelihood of fibers penetrating the alveolar walls (42), and that a system of macrophage recruitment meets onslaughts of free fibers and/or particles. Short fibers (< 5 μm) appear to be readily and completely phagocytosed, but long fibers are not, even when attacked by more than one macrophage, which may lead to cell fusion (Allison, 7, p. 89). Clearance of inhaled particles by these mechanisms is believed to be more than 98 per cent effective for most deposited particles (48).

Penetration, Retention, Distribution, and Mobilization of Uncoated Asbestos Particles within the Lung

The use of electron microscopy has revealed the presence of many, many submicroscopic, uncoated asbestos fibers and fibrils in the lung substance of the exposed worker, far more than was ever imagined when the lung fiber population was evaluated by light microscopy alone (49–51). It is also now evident that the proportion of uncoated to coated fibers (i.e., those that form the core of an asbestos body) is very large, of the order of 75 per cent (49), an observation that suggests a very high penetration and retention rate for the submicroscopic particles released into the working environment. Alternatively, these small fibers and/or particles might represent the breakdown products of what were initially larger fibers that had penetrated the alveolar parts of the lung. A second reason for underestimation of the amount of asbestos fiber retained in the lung is the difficulty encountered in its recovery from lungs at autopsy, compared to that of other pneumoconiosis-producing dusts (Nagelschmidt, 5, p. 64). The difficulty in recovery applies more to chrysotile than to other fibers, presumably because of its greater solubility (magnesium, in particular, tends to be leached out) and, hence, its tendency to break down chemically and physically after prolonged residence (51).

Within the lung, there appears to be a tendency for fibers to accumulate in the peripheral regions of the lower zones as indicated by the early appearance of fibrotic reactions in these areas. This distribution has been attributed to posture and gravity effects (Thomson, 9, p. 138).

Most uncoated particles that have penetrated the lung tissue appear likely to remain where they are, particularly if they are intracellular. Some clearance does occur via lymph channels to hilar and mediastinal nodes, where coated and uncoated particles are seen (Hourihane, 5, p. 647), although this appears to be less than

in the case of other fibrogenic dusts, such as silica. This difference in clearance attributed to the greater cytotoxic effect of silica, which tends, therefore, to maintain an extracellular position (50), may explain why hilar node enlargement is a more consistent finding in association with silica exposure than in association with asbestos exposure (52).

Less is known about the penetration of ingested fibers through the wall of the gastrointestinal tract, although animal studies suggest that this does not occur (53), except in the face of a heavy load delivered directly into the stomach (40). What relevance this has to human disease, such as peritoneal mesothelioma, remains to be determined.

Once it has penetrated the lung, the dust appears to remain fixed, but may be remobilized, apparently even from dust macules or scars, the operative mechanism perhaps being episodes of pulmonary edema and/or infection (48). It is believed that such remobilization of dust may result in its excretion, a phenomenon that might explain the rare event of apparent regression of radiologic changes in the worker removed from exposure (Manfreda, Y.: Unpublished data). Alternatively, it may become resequestered and contribute to the extension of disease in the face of no further exposure.

Despite the fact that pleural reactions (effusion, fibrosis, and/or calcification and neoplasm) are common manifestations of asbestos exposure, there is little direct evidence as to how the asbestos gains access to the pleura, which presumably must happen to explain the pleural reactions. Asbestos bodies are rarely seen in the visceral pleura and have never been reported in plaques located in the parietal pleura of exposed persons, even though they may be readily found in the interstitial tissue of the same lung (54). By contrast, asbestos fragments have been found in mesotheliomas even without evidence of asbestosis or coated fibers in the lung (Hourihane, 5, p. 647). This has led to the suggestion that fibers that become coated in the lung are less mobile and less susceptible to lymphatic clearance than uncoated fibers. Thus, electron microscopic studies may reveal many more uncoated fibers in the pleura than anticipated from the scarcity of coated fibers. Alternatively, any fibers that are cleared to subpleural lymphatics may undergo dissolution more readily here than elsewhere in the lung. In any event, information that would shed light on this paradox might well lead to improved understanding of the factors underlying the pathogenesis of mesothelioma.

Coated Asbestos Fibers (Asbestos Bodies)

The coated asbestos fiber was recognized early in the 1900s, because of its characteristic appearance under light microscopy (55). It is usually a rod-shaped structure with clubbed ends, often beaded along its length, is yellow to brown in color, ranges in length from 10 to 30 μm and in thickness from 1 to 6 μm, and has a central, paler core. The coating, consisting of ferritin granules and an amorphous material, probably protein, varies in thickness from very thin to 5 μm (55–57).

On the basis of animal studies, coating is now believed to be an intracellular process and follows the engulfing of particles by macrophages to which they adhere (56). Several macrophages may fuse to engulf large fibers. It is while the fibers are surrounded by partially fused macrophages that coating begins (58). The fiber then becomes incorporated into intracytoplasmic vacuoles, and the first coating material appears to be some form of acid mucopolysaccharide (56). Iron in the form of hemosiderin then accumulates in the cytoplasm of the macrophage. Iron micelles, possibly derived from breakdown of hemoglobin, become subsequently incorporated into the phagosomes, and tend to concentrate around the fiber; eventually, there is clearing of ground substance (57). It is of interest that the process appears to be a progressive one, with the coating increasing with time and uncoated fibers becoming coated months or years after instillation (56); however, because the proportion of uncoated to coated fibers in human lungs appears to remain constant with time (49, 59), there must also be a parallel process of aging and dissolution of the coated fiber. There is some evidence that the coating of a fiber renders it nonfibrogenic. Why some particles become coated and others do not is not understood; however, size may be important, with the typical asbestos body developing only on large particles (greater than 5 μm) that cannot be completely engulfed by one macrophage (58).

It must also be emphasized that not all coated fibers seen in the lung have an asbestos core, and the process of coating is apparently used by the lung in response to a variety of other fibers encountered in the environment. These include glass and cotton fibers, diatomaceous earth, talc, graphite, and carborundum particles (10, 55).

For this reason, the noncommittal term, "ferruginous" body (60), has been suggested as a more exact description in the absence of positive identification of the fiber core. Although accurate identification is now possible using techniques like the electron beam, laser microprobes, ultrasonic disintegration, and mass spectroscopy (55), these techniques are expensive in time and money and will remain research tools for a while (Langer, 7, p. 119). As such, however, they have brought to light certain interesting facts. For instance, it has been shown that although all fiber types may become coated in the laboratory animal (56), in man it is the amphibole fiber that is found more frequently as the core of a ferruginous body than the chrysotile fiber (49, 59), even when both types of uncoated fiber are seen in the lung (Pooley 7, p. 222). The significance of this observation remains to be determined; it may simply represent the relatively high solubility of chrysotile in relation to the other asbestos fibers.

Cellular Effects

Neither the original theory that the fibrogenic effect of asbestos fibers and particles was due to physical irritation nor the solubility theory, attributing their action to leached-out metal ions and/or silicic acid, can satisfactorily explain all of the experimental and clinical observations (Wagner, 5, p. 691). This leads to the hypothesis that host factors, in particular the immune system, might be important, either because of the production or localization of abnormal globulins in alveolar phagocytes or fibroblasts, or because of autoantibodies developing in response to lysis of phagocytes.

The use of tissue and cell culture techniques has further increased understanding of the biologic effects of asbestos at the cellular level (Allison, 7, p. 89). Potential target cells in man are the macrophages (which are responsible for phagocytosis), mesothelial cells, alveolar epithelial cells (which may undergo malignant transformation), and fibroblasts (which participate in the fibrogenic reaction). Two types of cytogenic effects have been detected, an early one attributed to the interaction of asbestos with the cellular membrane, increasing permeability (a reaction that is inhibited by serum and other biologic macromolecules), and a late reaction attributed to inter-reaction of the already ingested particles with the membranes around the secondary lysosomes. Because of the findings of similar direct cytotoxic effects on macrophages and mesothelial cells, but much less often on the fibroblast, it is believed that fibrogenesis may therefore be evoked through the macrophage response. In addition, there are differences between the various asbestos types in their cytotoxic effects, chrysotile showing more potent cytoxicity and capacity for hemolysis than amosite and crocidolite.

Effects at the organ level are presumed to result from the numbers of cells involved, the sites of their accumulation (e.g., the tendency for macrophages to aggregate in peribronchiolar locations), and the cumulative effects of continued assault from inhaled fibers and particles. It is not known whether the development of such changes is determined primarily by the amount of dust accumulated in the lung (to be discussed in detail under Dose Relationship) or whether it depends to an important extent on a person's biologic susceptibility. Experiments in animals and epidemiologic data in man suggest that both are important. The relevant evidence will be considered separately under the various asbestos-related lung diseases.

Dose Relationship of Biological Responses to Asbestos Exposure

The concept of a dose relationship of response to stimulus, already familiar in pharmacology, was introduced by Hatch (61) in an effort to throw light on the nature of the apparent variation in the biologic response to inhaled dust. (Why is one person affected and not the man who works beside him?) Its importance is obvious, not only as a tool for explaining variations in biologic response, but for the very practical reason that inherent in a dose relationship lies the information for a logical and scientific basis on which to establish the criteria for environmental control. Moreover, without such a relationship, the association between dose and response is probably not causal.

Hatch's concept (61), illustrated in figure 4, takes into account the possibility of differences in responsiveness between persons (or between populations) by introducing the third dimension. The implication is that a given dose-response curve can be developed for a given person (or population), but that it will be applicable only to another person (or population) of the same "susceptibility." In this context, susceptibility might be related to any of several biologic characteristics, for instance, the efficiency of clearance mechanisms in the lung, the anatomic characteristics of the lung/airway sys-

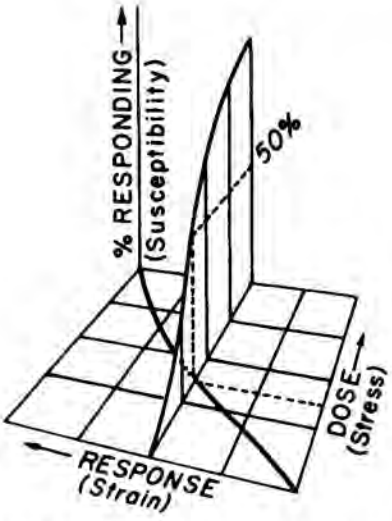

Fig. 4. [Modified from Hatch (61); reprinted by permission of publisher; copyright 1968, American Medical Association.] Dose response for a population. The curve on the horizontal plane portrays the dose-response relationship for a population of susceptibility such that 50 per cent respond to the dose indicated by the dotted line. If only 25 per cent were responsive to that dose, the curve would be proportionately displaced downward toward the dose axis; if 75 per cent were responsive, it would be appropriately displaced upward.

tem, or the physical fitness of the person (less fit persons ventilate more for a given work load). Alternatively, susceptibility might be considered in the immunologic sense.

A major problem, however, in applying the dose-response concept to the study of asbestos-related disease in animals and man lies in the measurement of dose. Presumably, the relevant dose (in Hatch's terms, the dose delivered at the critical site in the body) is the amount of asbestos dust and fiber retained in the lung, i.e., the amount inhaled less the amount exhaled and/or cleared from the lung. Although estimates of the amount inhaled can be derived from direct measurements of dust and fiber in the working environment and from ventilation volume, there is no practical way to measure the amount of dust exhaled and/or cleared from the lung, either in the laboratory animal or in man. Thus, at best, it is possible to measure (or estimate) only the first one half of the dose equation, i.e., the concentration and amount of dust inspired (in Hatch's terms, the magnitude of exposure to external conditions that give rise to stress).

This shortcoming is perhaps less crucial under experimental conditions in which animals can be raised throughout life in environments with different, but known and constant, dust concentrations. Such studies have, in general, shown dose relationships for amount of fibrosis and cancer risk (62). In addition, it seems possible that mathematical computation, taking into account intermittency and pulse exposures (42), may enable future studies to make even better estimates of dose.

In epidemiologic studies, estimates of dose have had to be much more crude, being based on the number of years of service in an industry (63–68); the number of years since first exposure (63, 69, 70); or the total years of exposure, together with an estimate of the dustiness of a worker's job (71–79); or cumulative dust exposure calculated from dust concentrations for given jobs. Doses may be calculated for each individual worker on the basis of his or her work history (80–95), or for groups of workers in given jobs in a given industry (96–98). In all of these studies, there has been the problem of calculating the dose for workers whose exposure usually extended into the remote past, with information about dust concentrations being at best scanty and incomplete and in most instances nonexistent.

Despite the shortcomings of the methods for estimating dose, a relationship of estimated dose to response has, nevertheless, been a consistent finding (table 4). This consistency has been true with exposures encountered in mining, manufacturing, and secondary usage, including removal of old asbestos insulation. Furthermore, it applied to all of the responses examined, i.e., lung fibrosis, as reflected by symptoms (64, 77, 92), lung function (64, 78, 84, 87) and radiographic changes (65, 69, 88, 95), and lung cancer, as reflected in mortality statistics (63, 66–68, 71, 74, 77, 79–83, 85, 93). For mesothelioma, in which much less exposure seems to be capable of producing a response in certain circumstances (see neighborhood and domestic exposure), there is also some evidence for a dose effect using fiber counts in the lungs at autopsy as a measure of exposure. A more complete discussion of dose-response relationships follows in the sections devoted to various asbestos-related lung diseases.

It must be pointed out that although dose-response relationships are evident to a greater or lesser extent for all responses, the degree of correlation is surprisingly low, perhaps because one seldom, if ever, finds more than a 50 per cent

response rate, even in those exposed to the heaviest doses. In addition, the response is usually the result of past, rather than current, exposures. This poor correlation has led to the current interest in "susceptibility," i.e., factors accounting for between-subject differences in response.

The concept of the dose-response relationship, insofar as it applies to exposed workers, can be explored only by studies that use epidemiologic techniques and consider all of those at risk. Of what relevance is the concept of dose-response to a physician dealing with the health problems of an individual patient? In the first place, knowledge of dose-response relationships may provide the answer to why a particular patient was at risk; second, this information may alert the physician to the potential risk to other workers; third, it may have importance in establishing prognosis and determining management. Thus, in the detailed descriptions of the various asbestos-related lung diseases that follow, their relationship to exposure dose, and possible differences in the dose-response relationships of the various fiber types will be discussed and summarized in the final section in terms of the implications to the physician.

Significance of Coated and Uncoated Fibers in Clinical Material

The presence of ferruginous bodies (so called in this section because positive identification of the fiber core has been undertaken in only a few of the more recent studies) or coated fibers in biologic material derived from persons who are occupationally exposed to asbestos has long been recognized as a hallmark of exposure (55). Their presence in routine autopsy material, first reported from Cape Town, South Africa (99), has subsequently been confirmed in many countries, in urban and rural communities, in all parts of the world, in fact, whenever sought (table 5). Prevalence tends to increase with the vigor of the search and depends on the amount

TABLE 4

LISTING OF STUDIES* THAT SHOW A DOSE RELATIONSHIP BETWEEN ESTIMATED EXPOSURE† TO ASBESTOS AND BIOLOGIC RESPONSE

Dose as Measured by \ Response	Fibrosis		Cancer	
	Lung	Pleura	Lung	Pleura
Years of exposure	Bader *et al* (65) Sluis-Cremer (66) Zedda *et al* (72)		Knox *et al* (67) Doll (68) Meurman *et al* (77)	
Years since first exposure	Selikoff *et al* (64) Regan *et al* (70)	Selikoff *et al* (64)	Selikoff *et al* (64) Selikoff *et al* (64)	
Occupation	Harries *et al* (75) Sheers and Templeton (76)	Harries *et al* (75) Sheers and Templeton (76)		
Occupation and duration	Meurman *et al* (77) Balaam and McCullagh (78)		Newhouse *et al* (30) Newhouse (29, 71) Berry *et al* (73) Maneuso and El-Attar (74) Meurman *et al* (77) Enterline and Kendrick (79) Enterline (80) Enterline and Henderson (81)	Newhouse (71)
Cumulative dust exposure	Jodoin *et al* (84) McDonald *et al* (86) Becklake *et al* (87) Rossiter *et al* (88) Weill *et al* (94, 95)	Rossiter *et al* (88)	Enterline *et al* (82, 83) McDonald *et al* (85)	
Fiber count in pathologic material (electron microscopy)				Pooley, F D. (7), p. 222

*Identified by reference number in parentheses.

†Mining (66), mining and milling (84–88, 92), manufacturing (29, 30, 64, 94, 95), and secondary use including removal of old asbestos insulation (64, 65, 75, 76).

TABLE 5

PREVALENCE OF FERRUGINOUS BODIES IN ROUTINE AUTOPSY MATERIAL

Location	No.*	Prevalence (%)	Men/Women	Method	Year†	Reference
Perugia, Italy	109	1.0	1.5	Smears	1969	100
Schwerin, E. Germany	234	9.0	1.4		1971	Quoted in 101
Ann Arbor, USA	100	18.0	1.9		1969	102
Newcastle, England	311	20.3	2.4	Scrapings	1968	103
Glasgow, Scotland	100	23.0	?	Smears	1967	105
Jerusalem, Israel	100	26.0	1.3	Smears	1968	106
Cape Town, S. Africa	500	26.4	1.5	Smears	1963	99
Miami, USA	500	27.2	1.6	Smears	1966	98
London, England	394	36.8	1.4	Sections: left lower lobe	1975	16
Sarajevo, Jugoslavia	100	38.0	2.5	Smears	1971	Quoted in 101
Belfast, N. Ireland	200	40.5	—	Smears	1965	104
Pittsburg, USA	100	41.0	1.4	Smears	1965	107
Dresden, E. Germany	250	43.2	—	Smears	1967	Quoted in 101
Melbourne, Australia	200	43.5	1.0		1969	108
Johannesburg, S. Africa		47.0		Smears, scraping	1965	109
Montreal, Canada	100	48.0	1.7	Scrapings	1966	110
Malmo, Sweden	97	48.4	1.4	Smears	1967	101
Milan, Italy	100	51.0	1.2		—	111
New York, USA	100	53.0	1.2	Ashed sections	1934	9, p. 99
	100	60.0	1.0		1967	9, p. 99
	1,975	47.7	1.3	Smears	1966	9, p. 99
London, England	127	0.0		Sections	1936	112
	100	3.0	4.9	Sections	1946	112
	100	14.0	1.3	Sections	1956	112
	100	20.0	0.8	Sections	1966	112

*Number of autopsies in which a search for ferruginous bodies was made.

†Year of publication was usually within 1 to 2 years of the year in which the study was carried out. Note that for New York and London data at the end of the table, the actual year of the study is given.

of tissue examined (99), or if lung juice is examined, the vigor with which it is extracted. When digested lung tissue is examined, prevalence approaches 100 per cent (113, 114). It is not likely that these figures have been much influenced by the presence of overt asbestos-related lung disease, which was usually specifically excluded from the autopsy series examined (16) or was found to be minimal, perhaps a small single area of basal fibrosis (98, 99).

Despite the fact that ferruginous bodies may not contain an asbestos core, it is probable that most of those found in the lungs of many city dwellers do (Planteydt, 7, p. 80). Thus, prevalence of ferruginous bodies may reasonably be regarded as a reflection of community exposure. In keeping with this is the rural-urban gradient, evident in table 5, which lists the data by increasing prevalence. Thus, rural areas and small cities fall at the beginning of the table; large industrialized urban centers, at the end. A similar rural-urban gradient was seen in another series in which counting methods were standardized (Oldham, 7, p. 231). Prevalence was also consistently higher among men than women. In addition, it increased with age (16, 111), and when within-city distribution was examined, as in the study of London, England, higher prevalences were found among those who lived closest to the docks and/or the industrial heart of east London, among those engaged in heavy manual work, and among those whose occupations were in shipping, transport, and engineering (16). In addition, there is the interesting observation that prevalence increased with time (1936 to 1966) in London, England, but not in New York (see table 5).

Ferruginous bodies have been found on rare occasions in the hilar nodes in persons believed to have been heavily exposed (120), and more rarely, beyond the limits of the thoracic cavity, e.g., in spleen, sinuses; tonsils (54), and hyaline liver plaques (59). Further, in autopsy material obtained from cases with asbestos-related lung disease, fiber count appeared to be some reflection of dose (54, 59, 120).

As already mentioned, the ratio of coated to uncoated fibers within the lung appears to be fairly constant at 10 to 30 per cent (49, 59). Thus, although a count of coated fibers underrepresents the total fiber content of the lung, it should, nevertheless, reflect reasonably accurately trends with respect to age, sex, residence, and occupation.

From the clinician's point of view, this information, based on epidemiologic studies, carries the clear message that the presence of asbestos fibers, coated or uncoated, in biopsy material, autopsy material, or, for that matter, sputum (117–119), which after all, only reflects the lungs' effluent, is an indication of past or current exposure to asbestos (provided the fiber is positively identified). If the fiber is not positively identified, exposure to asbestos remains the likely, but not the only, explanation. Given a history of occupational exposure to asbestos, the physician is unlikely to require positive fiber identification for any clinical purposes. In the absence of history of asbestos exposure, such identification might be useful, but of more importance would be an exhaustive review of all of the patient's previous occupations for however brief a period of time, as well as investigation of the possibility of nonoccupational exposure.

Pleural Plaques, Hyaline or Calcified (Fibrotic Thickening of the Parietal Pleura)

Two types of pleural reaction are seen in association with asbestos exposure: (*1*) an exudative reaction, usually widespread, involving both parietal and visceral pleura and usually, the lung parenchyma, with obliteration of the pleural space; and (*2*) a discrete reaction, involving the parietal pleura, usually in more than one location, and referred to as a pleural plaque (120). The first is associated with symptoms and affects function (121) and will be considered later in this review together with pulmonary fibrosis. The second, usually a radiographic diagnosis in an otherwise healthy person, will be considered in the present section. Both reactions may, of course, occur together in the same person; however, the clinical presentation is likely to be dominated by the extent of the exudative reaction.

Pathology

Macroscopic appearances. Pleural plaques occur as discrete, raised, grey-white lesions on the inner surface of the rib cage and on the diaphragm. In a series of patients who had pleural plaques described at thoracoscopy, Mattson and Ringqvist (121) commented that "despite the confusion of different sizes and shapes, sometimes suggesting an archipelago, the pattern of the plaques is nevertheless monotonous: a flat or slightly uneven surface, white and shiny like synovia or mother-of-pearl, steep edges rising

abruptly from the surrounding normal pleura, here and there rounded mounds with overhanging edges. The consistency was that of cartilage." The distribution of pleural plaques is irregular; they tend to be more marked over the lower ribs, may follow or cross rib lines, may be concentrated in the posterior, lateral, or anterior surfaces, but not the cartilaginous portions (54). The diaphragm is usually involved, frequently in the area of the central tendon (54). They do not occur in the costophrenic angles or over the apices. Mediastinal plaques have not been observed (120), but the pleural surface of the pericardium is not infrequently involved, particularly in the advanced case (54).

Plaque formation appears to occur in areas free of adhesions, and the same person might have unilateral obliteration of the pleura in one hemithorax and abundant plaques in the other, with unfused pleural surfaces (54). Alternatively, plaques might involve one part of the hemithorax; adhesions, another part. Occasionally, plaques are found under adhesions (54). Their thickness varies greatly. Calcification appears to be more common in plaques situated in relation to the anterolateral portion of the upper ribs; it does not appear to relate in any way to the thickness of a plaque (54).

Microscopic appearances. The plaques consist of collagenous connective tissue, cell-poor, with few fibrocytic nuclei, arranged in undulating fashion in a coarse, basket-weave pattern, and containing only few thin-walled capillaries (54, 121). Elastic staining shows intact lamellae beneath the plaque in continuity with the surrounding normal parietal pleural connective tissue, suggesting that plaques are extrapleural and develop between the latter and its covering layer of mesothelial cells (54). Some calcium deposition is present in a high proportion of plaques, and occurs as granules along the course of the collagen fibers, ceasing abruptly where the connective tissue changes into normal pleural tissue (54). Cuboidal mesothelial cells may occur at the edge of the plaque (54), occasionally with metaplastic changes (121, 122). Association with bronchial cancer is discussed subsequently.

Although coated asbestos fibers have not been reported in relation to pleural plaques, even in the extensive series of 172 sections examined by Meurman (54) under polarized light, examination of ashed tissue has revealed the presence of uncoated fibers in many cases (123, 124). With electron microscopy, it is apparent that most plaques contain many small, submicroscopic fibers. It is of interest that these are more concentrated in the calcified zones than in the fibrous zones (Le Bouffant, 7, p. 249).

Epidemiology and Pathogenesis

The association between pleural plaques and asbestos exposure, originally suspected on clinical and epidemiologic grounds, has been amply confirmed by population studies, whether exposure was occupational or nonoccupational. In occupationally exposed groups, such as miners (88) and shipyard workers (75, 76), the prevalence of pleural changes on the chest radiograph has been shown to increase in relation to estimated dose of asbestos, although it is difficult to disentangle age and exposure effects. All varieties of fiber have been implicated, the highest rates occurring with anthophyllite (Jones, 7, p. 243). In addition, factors associated with the site and nature of the deposit appear to be important; for instance, in Quebec, prevalences of calcification differed by as much as 13-fold in 2 adjacent mining areas, working the same fiber in the same geologic deposit (88).

In those not occupationally exposed, particularly in Finland, there is some evidence to suggest that prevalence relates to the proximity of place of residence to mining areas (33, 54). Similarly, there is an increase in the prevalence of pleural changes on the radiograph in some agricultural populations in which the soil contains asbestiform mineral (33, 34).

Given this association between exposure and pleural plaques, however, no satisfactory theory has been developed to explain how parietal pleural reactions develop in response to the inhalation of fibers and particles and their deposition in the lung, which may itself show no reaction to the dust. Furthermore, until recently, the presumed causative agent, namely, the asbestos fiber or particle, had only rarely been detected at the site of the reaction, that is, in the pleural plaque using electron microscopy as indicated above.

One hypothesis is that pleural plaques result from traumatization of the parietal pleura during breathing by sharp asbestos spicules penetrating the pleura. This trauma is believed to produce hemorrhage and subsequent organization of the blood clot in a manner comparable to the process seen in large hemothoraces (33, 123). Against this theory is the failure to dem-

onstrate inflammatory exudates, and the conspicuous absence of adhesions in association with pleural plaques. Also, intracellular transportation via pulmonary lymphatics and then retrograde spread via the chest wall lymphatics due to the massaging action of the respiratory muscles does not seem likely in the absence of hilar and/or mediastinal lymph node enlargement, neither of which has been found in association with pleural plaques (124, 125). The disproportion between the marked parietal pleural response and the small amount of etiologic agent led to speculation about individual sensitivity as a factor, a hypothesis for which there is support in some studies, but not in others. Asbestos-exposed workers with plaques have higher concentrations of gammaglobin (126), but similar concentrations of circulating rheumatoid factor and antinuclear antibodies (127), compared to persons not exposed to asbestos.

Thomson (9, p. 138) suggests the following sequence of events: Fibers, particularly long ones, tend to move toward the lung periphery; some leave the lung and reach the parietal pleura and/or the diaphragm, and those that are held up by the ribs or tendinous part of the diaphragm elicit a reaction in the submesothelial tissues that eventually leads to the formation of a pleural plaque. Calcification, when it occurs, is essentially of a dystrophic type in acellular and degenerated collagen.

It is probably more realistic, however, to accept the conclusion of Jones and Sheers (7, p. 243) that the pathogenesis of pleural plaques that occur in association with asbestos exposure is unknown. For this reason, and because the dose relationship only partly explains the observations, any further light that could be thrown on the pathogenesis of pleural plaques might make an important contribution to the understanding of how asbestos produces its biologic effects, and eventually, how they might be controlled.

Clinical and Radiologic Manifestations

Pleural plaques, hyaline or calcified, in the absence of obliterative pleural lesions and pulmonary fibrosis, are rarely associated with respiratory symptoms, including dyspnea (128). This is in keeping with the fact that their effect on function, although detectable in population studies (128), is modest and is mainly seen as small reductions in lung volumes (129).

By contrast, radiologic changes may be very striking, particularly in the presence of calcification. Hyaline plaques, however, may be difficult to see without special oblique views, and will be detected best by high kV techniques, i.e., 110 to 140 kV, whereas calcified plaques are better demonstrated by lower kV techniques (60 to 80 kV) (Bohlig and Gilson, 7, p. 25).

Calcified plaques are usually seen on the posteroanterior film as irregular outlines of uneven density; they can easily be missed in overpenetrated films, particularly if they overlie the coastal cartilages (10). Noncalcified plaques, usually only seen on the posteroanterior film if they lie in the lateral costal regions, i.e., at right angles to the X-ray beam, appear as ill-defined opacities along the costal margins. Oblique films will be necessary to visualize plaques that are located anteriorly or posteriorly. Routine radiography, however, can apparently detect only a small proportion of plaques identified at autopsy; in one series, only 15 per cent were detected, and detection was confined to the most heavily calcified plaques (124).

The most usual clinical presentation is as an incidental radiologic finding in an asymptomatic patient. This should alert the physician to the possibility of exposure if this is not already known; in the absence of occupational exposure, neighborhood or domestic exposure should be sought.

Although the presence of hyaline pleural plaques alone does not appear to cause symptoms of disability, there is some evidence that they affect prognosis. Thus, in some series (130), they were associated with a higher-than-expected incidence of bronchial carcinoma (Smith, 8, p. 277), whereas in Quebec chrysotile miners and millers, this was not so (92). Malignant mesothelioma has also been reported as developing in the mesothelial cells at the edge of the plaque (122).

Pleural Effusion (Benign)

Exudative pleural reactions, which may occur in association with all of the asbestos-related lung diseases, may also occur as the primary, or at least the most prominent, clinical manifestation (131–135), presenting as an "idiopathic pleural effusion" (131); hence, the justification for considering this diagnosis separately in a clinical review of the asbestos-related lung diseases. The present description is based on the 30 cases so far published (134); however, pleural effusion may well be a more frequent manifestation of asbestos exposure than this modest number suggests, particularly if it were subse-

quently shown to be a phase in the development of other pleural changes.

Pathology. On macroscopic examination at thoracotomy, the pleural surfaces show an active exudative process, characterized by increased vascularity and symphysis. Associated pleural plaques do not appear to be a feature. Microscopic examination shows variable pleural thickening, with "pleural drift of carbon and other dusts and iron-positive granules" (131). Other features include regenerating mesothelium and extensive collateral circulation (131), and there is one report of a granuloma (134). The underlying lung tissue shows varying degrees of interstitial pneumonitis, from mild, low grade inflammation to organized interstitial fibrosis, in which asbestos bodies and fibers are usually, but not invariably, found. Electron microscopic analysis for uncoated fibers has not been reported in this type of case, but it can be assumed that these would be found.

Clinical features. The usual presentation is one of recurring pleural effusion of unknown cause, associated with chest pain (131). The effusion may be unilateral, bilateral, or one side may follow the other in sequence. The presentation may be acute, with fever, leukocytosis, and an increased sedimentation rate, or chronic, with minimal systemic reaction. The pleural fluid is frequently blood stained (red blood cell counts ranging from 5,000 to 50,000 cells per mm^3) and, in most cases, is an exudate. The clinical course varies from that of a benign and self-limiting illness (132, 133) to the development of chronic pleural thickening that requires decortication (131). The patient's association with asbestos may be current, or more often may have been brief and in the remote past (131).

Differential diagnosis. The diagnosis of a benign asbestos pleural effusion should be considered a diagnosis only by exclusion. The chief alternative to be excluded is malignant mesothelioma, one of the manifestations of asbestos exposure that may not develop until many years after the first exposure. The pleural effusions that commonly complicate the latter tumor may precede by months or years the definitive diagnosis of the tumor. Indeed, one could argue against accepting the diagnosis of benign asbestos pleural effusion until all of the present reported cases are followed to death, and death is shown to be attributable neither to carcinoma of the lung nor to mesothelioma. However, as follow-up becomes longer (134), the justification for this diagnosis increases, and asbestos exposure can reasonably be added to the long list of causes of benign, recurrent pleural effusion.

Diffuse Interstitial Pulmonary Fibrosis (Asbestosis)

Definition

Diffuse interstitial fibrosis of the lung associated with asbestos exposure was recognized in the early years of the twentieth century, the first asbestos-related disease to be so recognized (1); however, the term "asbestosis" to describe this pneumoconiosis was not suggested until 1927, when Cooke (136) used it to describe the case of a female asbestos textile worker. It is usual to include fibrosis of the associated visceral pleura under this term, but not that of the parietal pleura (10). There is merit in maintaining this specific usage in line with the widely accepted use of the term pneumoconiosis (137), rather than to use the term "asbestosis" in a generic sense to describe all asbestos-related diseases of the lung and pleura, even neoplasms (10).

Pathology

Macroscopic appearances. The main pathologic features that had been described with care by the 1930s in individual case reports (138, 139) were reviewed by Hourihane and McCaughey (116) in the light of their own pathologic material, based on 69 cases of clinical asbestosis examined at the London Hospital. Macroscopic changes ranged from small areas of basal fibrosis (if sufficiently localized, these may escape recognition by the naked eye) to the fully developed case of a diffuse, fine fibrosis affecting both lungs. Lung size tends to reflect the extent of the fibrosis; when this is diffuse, the lungs tend to be small. Cut surface shows the fine, grey-colored fibrosis that generally appears to affect subpleural areas first, often quite extensively, before advancing into other lobes with the extension of the disease process. Lower lobes tend to be affected first, then middle lobes, and eventually, upper lobes (10, 116, 140). Small honeycomb cysts may be seen, in the lower lobes particularly, and fibrosis and honeycombing also tend to be concentrated subpleurally (140). Emphysema, centrilobular or bullous, is frequently found, with characteristics essentially the same as in emphysema not associated with asbestosis (140, 141). The pleural surface in relation to the fibrosis is invariably involved in

the fibrotic process, either mildly, giving the appearance of a milky covering to the fibrosis, or with widespread fibrosis and symphysis (116, 140). The hilar lymph nodes are not usually enlarged or otherwise affected (10, 142).

Conglomerate lesions of massive fibrosis, comparable to the progressive massive fibrosis of coal workers, occur in the absence of tuberculosis (Gough, 5, p. 368), but are rare, unless the exposure has been to mixed dust including talc (10, 143) or silica (142, 144). In addition, these lesions appear to have a predilection for the lower lobes (142, 144), unlike other forms of progressive massive fibrosis. The occasional solitary fibrotic lesion is seen, for which the term asbestoma has been used (145). Necrobiotic nodules associated with rheumatoid disease (similar to those seen with Caplans' disease in coal workers) are seen (146–149), but only rarely (10).

Microscopic appearances. In animal studies, early dust reactions include a desquamative alveolar response (Webster, 9, p. 117), a reaction that may have its counterpart in man (144, 150). In addition, there is one case report of desquamative interstitial pneumonia with asbestos bodies in the lung (150), and the view has been expressed that this is one end of a spectrum that ends with fibrosing alveolitis (151). An idea of the abnormalities in the early stages of fibrosis comes from examination of biopsy material, usually sought to establish a diagnosis of asbestosis (131, 145). The early reaction in the interstitial tissue resembles that of other forms of interstitial pneumonia, with mixed leukocyte infiltration of the alveolar walls, moderate numbers of phagocytes in the alveoli, and varying degrees of organization with fibrosis (131, 145). In some cases, the early changes are concentrated at the level of the respiratory bronchiole, where reticulin fibers, macrophages, and dust particles collect (10, 116), leading subsequently to what has been termed the basic lesion of asbestosis, namely, a peribronchiolar fibrosis (116). From here, the process extends outward to involve the surrounding alveoli, leading to diffuse alveolar wall thickening, with peribronchiolar and perivascular fibrosis (116). In an occasional case, the fibrosis remains almost exclusively peribronchiolar (144, figure 5), but the more usual picture is that of a diffuse fibrosis, involving the interstitium, frequently associated with areas of solid fibrosis, where laminated collagen may replace the entire parenchyma. Such areas may also show alveolar cell hyperplasia and sclerosis of vessel walls (116). The presence of ferruginous bodies is to be expected, and electron microscopy is likely to reveal very large numbers of uncoated and very fine particles and fibers (152). The pathologic findings in workers exposed to amosite and crocidolite have been shown to be essentially similar to those associated with chrysotile exposure (Wagner, 8, p. 373).

Pathogenesis

Reactions at the cell level have already been discussed, and at the organ level are presumed to relate to the number of cells reacting, which in turn is believed to relate to the retained "dose" of asbestos dust and/or fiber. This appears to be true for mild and moderate fibrosis, respectively, in animals (62) as well as in man, in whom the response has been related to "dose" retained, as reflected by concentration of coated and uncoated particles in the lung tissue at autopsy (49); however, there does not appear to be further progression from moderate to severe fibrosis associated with an increase in dose (49, 62). It is, therefore, postulated that the progression from moderate to severe fibrosis is due to other factors, e.g., nonspecific inflammation, as suggested by Ashcroft and Heppleston (49) or possibly to self-perpetuating host responses, as suggested by Turner-Warwick (144). Thus, based on her observations that non–organic-specific autoantibodies, especially antinuclear antibodies (ANA), occur with only slightly greater frequency in exposed, compared to nonexposed, persons in the general population, and within exposed populations, with greater frequency in those with clinical disease than those without (153–155), Turner-Warwick proposes that ANA acts as an accelerator once the fibrosis has been initiated by a separate agent (Turner-Warwick, 7, p. 258). Such an explanation would fit the clinical observation that asbestosis may appear for the first time and progress long after exposure to dust has ceased. The possibility that genetic factors influence the response to exposure is suggested in one study in which the HL-A B27 occurred with greater frequency in asbestosis cases compared to the general population (156). There is also a progressive decrease in the total lymphocyte count with advancing fibrosis, and the suggestion has been made that the cellular immune mechanism is disturbed in asbestosis (157).

The progression from diffuse interstitial fibrosis to conglomerate fibrosis may, in the past, have been associated with tuberculosis (125),

but this is rare today in the United States (Enterline, 5, p. 156) and in Britain (Smither, 5, p. 166). Nor does such progression appear to relate to a "rheumatoid" diathesis (90). On the other hand, rheumatoid disease developing in the asbestos worker is liable to be associated with the appearance of lung changes of unusual and rather marked character.

The relationship of emphysema to asbestos dust exposure remains to be elucidated. Physiologic studies suggest that airway obstruction is common; in the presence of fibrosis, particularly if this is peribronchiolar in location, it would seem reasonable to ascribe it to the dust load. In the absence of dust fibrosis, and given the importance of the smoking habit, it is more difficult to determine the role of a dust load in the development of emphysema. To date, there has been no systematic autopsy study in which the prevalence of emphysema and/or chronic bronchitis in workers exposed to asbestos was compared with the prevalence in nonexposed persons, such as that of Ryder and associates (158) in coal workers, a study that clearly showed the excess of emphysema in coal miners. An open mind should be kept on the subject until further evidence is available.

Clinical Features

The symptoms and signs of diffuse interstitial fibrosis due to asbestos exposure are no different from those of all other forms of diffuse interstitial fibrosis. Thus, the most prominent symptom is breathlessness, first noted under the stress of effort, then at rest, as the large working reserve of the lung becomes progressively reduced. Cough, either dry or with sputum, not as consistently present as dypsnea, may be severe, with distressing paroxysms (10). Although generally attributed to airway, rather than to interstitial, lung disease, this symptom occurs with greater frequency in the asbestos-exposed worker than in his nonexposed counterpart (96, 97, 118) and often cannot be attributed to differences in smoking habits, suggesting that this symptom also relates to asbestos exposure. Chest pain, not a frequent complaint, has been attributed to muscle aches, because it appears to be present only when dyspnea is severe (10).

The most characteristic physical sign is the presence of crepitations, which are described as having a "crisp, clean, quality" and occurring late in inspiration, usually over the lower or middle lung zones (10). A deep inspiration may be necessary to elicit them. As fibrosis progresses, they become more widespread and occupy a greater part of inspiration. They are attributed to the "sudden opening of airways in deflated territories of the lung" (159), an explanation supported by the fact that they shift to the gravitationally lower lobes with changes in posture (128) and have been shown to be consistently detectable at a given transpulmonary pressure (160). Other adventitious sounds, such as wheezes and rhonchi, are less common. Air entry and chest expansion are likely to be affected in proportion to associated pleural changes.

Clubbing of the fingers and toes is said to be present in most cases (10), although by no means is this always true (161). This sign does not necessarily indicate advanced disease, because it is also reported in men who are still able to work (96, 119). The lack of correlation with severity of fibrosis is seen particularly when the clubbing is evaluated systematically from casts of digits to allow measurement of the hyponychial angle (118, 119) by the method of Regan and associates (162). It is of interest that smoking also appears to play a part in the development of this sign (Harries, 7, p. 19), an association detected in epidemiologic studies, the significance of which is unknown.

Radiographic Changes

In considering the chest radiograph of the individual case for diagnostic purposes (10, 163), evaluation of the pulmonary parenchyma should be based on the following features: small, irregular, and/or round opacities, scored for size or length, profusion, and number of zones affected; hairline ring (honeycomb) shadows; a diffuse haze or ground-glass appearance not obviously due to pleural shadows; short horizontal septal lines or Kerley B-lines, believed to represent lymphatic obstruction (144), and occasional longer hairline shadows. Pleural changes are likely to be present as well (in more than one half of the cases in one series of compensation board material), whereas in 20 per cent of cases, they were present without parenchymal changes (163). Rounded opacities are more evident when the occupational exposure has included silica (95). These findings are in general agreement with previous reports (163–166). Thus, it can be seen that the radiologic features of asbestosis are no different from those of all other forms of interstitial fibrosis, except for the prominence of associated pleural changes, in particular, calcification, which should

always call attention to the possible association with asbestos exposure.

A systematic classification of the radiologic changes associated with asbestos exposure embodying most of the features described, together with the pleural changes, was developed for epidemiologic purposes, first as the UICC/Cincinnati classification (167), later adopted as the ILO U/C classification (168). Its features include a reading sheet, an extended 12-point scale to grade parenchymal changes, and standard films to assist in the evaluation of pleural and parenchymal changes (obtainable from the International Labour Office, Occupational Safety and Health Branch, CH 1211 Geneva 22, Switzerland. Price: Sw Francs 250.–) The use of this classification, by improving precision and probably also comparability between studies, has enhanced the value of the X-ray as an epidemiologic tool (169). Thus, it enables a better placement of the film in the multidimensional "continuum which extends from complete 'normality' at one end to the most severe degree of abnormality at the higher" (Bohlig 7, p. 25). In particular, it has permitted the exploration of the exposure-dose relationships (using the chest radiograph to measure response) in working populations. In addition, this classification has been adopted by compensation boards in several countries to improve consistency in the reading of the chest radiograph and should be used whenever the evaluation of a person's films must be considered relative to those of others. It must be emphasized, however, that this classification is descriptive and not diagnostic; furthermore, although radiologic changes so described relate reasonably well to lung function changes in population studies (87, 95), their relationship to disability, which is likely to vary considerably from subject to subject, has not been widely studied.

Lung Function

Lung function tests have been applied to the study of asbestosis since their general introduction to clinical medicine in the 1940s. In general, there are 4 clinical areas of application (10): first, for diagnosis and assessment of disability; second, for following the evolution of disease with time; third, for the surveillance of healthy workers, with a view to detecting early changes; and fourth, for preemployment examination to screen the "susceptible" person.

In addition, information gained from epidemiologic studies using pulmonary function testing to determine exposure-response relationships has permitted inferences to be drawn about early effects of asbestos on the lung, information that may ultimately have considerable practical value in terms of the worker's health.

Diagnosis. Interstitial fibrosis associated with exposure to asbestos is generally believed to be associated with the restrictive and "alveolar capillary" block patterns of pulmonary function, similar to that seen with the interstitial fibrosis from other causes (Becklake, 7, p. 3). Characteristic features of the established case (with clinical and/or radiographic evidence of disease) are: general restriction of lung volumes, particularly vital capacity (VC), with less effect on residual volume; decrease in flows, such as 1-sec forced expiratory volume (FEV_1), in proportion to the decrease in VC, so that the ratio of FEV_1 to forced vital capacity (FVC) is relatively well preserved; decrease in diffusing capacity, attributable in part to the decreased lung volume (170), although decreased membrane transfer and inhomogeneity of regional ventilation-perfusion relationships within the lung undoubtedly contribute to the impaired gas transfer (43, p. 379). Impairment of gas exchange capability, reflected by arterial desaturation, increased alveolar-arterial Po_2 gradient, and hyperventilation, may at first be evident only under the stress of exercise, but later occurs at rest. The CO_2 exchange is not usually affected, and arterial CO_2 retention is not usually a feature of the established case.

Although there is no evidence to suggest that asbestosis due to chrysotile is any different from that due to other fibers, one epidemiologic study suggests that there may be greater decrease in function for equivalent estimated exposure to crocidolite compared to chrysotile (94), a difference that could be explained by greater retention of crocidolite compared to chrysotile for equivalent estimated exposure; however, in the light of the potential and, indeed, inevitable inaccuracies that beset all efforts to evaluate remote past dust exposure, in amount and/or nature of the fiber, this interesting observation requires further confirmation before it is assumed that different fibers have different fibrogenic potential in man.

It is usually claimed that airway obstruction is not a feature of asbestosis (10, 170–172); however, a review of 375 published cases (173), most with unequivocal parenchymal radiologic changes, indicated that a considerable number of patients had airway obstruction (11 per cent

compared to 39 per cent with a restrictive pattern), whereas in 18 per cent, the function impairment suggested a mixed picture of obstruction and restriction. In addition, scrutiny of epidemiologic studies in working populations (i.e., studies that, by their nature, exclude the disabled and all but a few of those with radiologic disease) invariably shows a sizeable number of persons with evidence of airway obstruction (64, 72, 170, 174–176). However, there is no clear evidence showing an excess of airway obstruction in asbestos-exposed populations compared to those not so exposed (96, 172), and there is no clear evidence that within exposed populations, the prevalence of obstruction increases with increasing exposure (172). The restrictive patterns of lung function also does not show an increased prevalence in relation to exposure (172).

To this time, therefore, epidemiologic studies of lung function have not been able to elucidate the relationship between airway obstruction and asbestos exposure, or the part played by the cigarette habit (additive or synergistic). In consequence, even in the presence of radiologic changes, there is usually hesitation in attributing the obstructive component of a worker's disease to asbestosis, despite the fact that decreased conductance has been shown in other forms of interstitial lung disease (177). Without radiologic changes, there is even greater reluctance to attribute the obstruction to asbestos exposure. Nevertheless, there is enough indirect evidence to suggest that in response to asbestos exposure, the character of the function impairment may be obstructive in a certain number of cases (173); until further evidence is available, an open mind should be kept in this regard.

Assessment of disability. The relationships between *organ malfunction* (as reflected in what may be called descriptive measurements of the lung, i.e., its size or lung volumes, and in the measurements related to its mechanical properties), *organ failure*, generally considered to be present only when gas exchange function is impaired (43, p. 442), and *disability* (diminution of performance as perceived by the subject himself) are not straightforward. Thus, considerable amounts of organ malfunction (i.e., abnormalities of lung function tests) can be present without organ failure (i.e., abnormal blood gases), even under the stress of effort. Likewise, disability in the form of unusual breathlessness may be perceived by the subject early or late in the development of his disease. This discrepancy between function and symptoms is also found in some epidemiologic studies (172, 178, 179), but not others (96, 97). The important conclusion for clinical practice is that in the individual case, disability cannot be predicted with reliability from symptoms, function, or radiographic changes. It should therefore be evaluated by appropriate exercise tests, if necessary at more than one load, for each case individually (Becklake, 7, p. 3).

Evaluation of changes with time. Serial measurements of lung function in individual cases of asbestosis with time suggest that deterioration is most closely reflected in VC (64, 78, 180) and, possibly, maximal voluntary ventilation. The diffusing capacity of the lung for CO (D_{LCO}), originally proposed on theoretic grounds as well as on the basis of some limited observations (176), may not be as useful (128).

Support for these conclusions also comes from epidemiologic studies of exposed working populations in which decrease in VC, in particular the IC component of VC, showed a closer relationship to estimated dust exposure than did D_{LCO}, measured either by the single-breath or the steady-state technique (87, 94). Other tests that showed a relationship to exposure were FEV_1 (87) and maximal mid-expiratory flow (94); however, serial studies of an epidemiologic nature (i.e., following changes in a whole working population, rather than in a few selected subjects) would provide more precise information on this point.

Early detection. This implies detection of dust effects in a person before he or she perceives them as symptoms. Persons showing these early changes are more likely to be found in a working population than in a clinic population, because clinic attendance presupposes symptoms. Furthermore, within a working population, it is reasonable to suppose that symptoms will occur more frequently in those with heavier exposures. In one epidemiologic study confined to exposed persons without clinical or radiologic evidence of disease, and with normal routine lung function, it was possible to detect changes in the lungs' mechanical properties (specifically, a decrease in compliance and an increase in calculated upstream resistance) in those with heavier dust exposure (84). These changes suggesting a dust effect at the small airway level would be compatible with peribronchiolar fibrosis (116). Similar results were obtained in a subsequent study of a larger number of subjects,

reported in preliminary form (181), using the closing volume test. At present, these observations have no practical significance, because it remains to be shown (*1*) that what is detected is, in fact, the beginning of a process that will ultimately lead to asbestosis, and (*2*) that any intervention, such as removal from exposure, would prevent the ultimate development of disease. From what has been said about pathogenesis, however, it appears that in its earlier stages of development, the fibrosis of asbestosis appears to be related to dust accumulated, and therefore, by implication, removal from exposure by preventing further accumulation might slow the process. These findings, therefore, have potential application in the future.

Function versus radiographic methods in the early detection of asbestosis. Several early clinical studies, some based on small numbers of subjects, suggested that in asbestosis changes in function preceded radiographic changes (64, 128, 176). The changes in function identified were in VC (64, 128) and D_{LCO} (176). Subsequent epidemiologic studies suggest that at least as far as these two tests of function were concerned, they were no more sensitive than radiologic changes (87, 94, 95). It must be emphasized that the latter conclusions were based on between-group comparisons of subjects classified by dust exposure, for which identification of appropriate "normal" standards is unnecessary. Detecting abnormality in the individual case with certainty is another matter, because this requires reference to standards of normality, which for both radiographic studies and tests of function have fairly wide ranges. Periodic comparative chest radiographs or function tests, are likely to improve the chance of detecting early abnormalities in a given person. It must be borne in mind, however, that the radiologic changes are invariably of a nonspecific nature, similar to those occurring with aging or the cigarette habit (182); hence, the opinion that in an individual case they reflect early fibrosis should be guarded.

Diagnosis

The criteria for diagnosis of asbestosis depend on the purpose for which diagnosis will be used, and the degree of certainty required. A working clinical diagnosis can be reached on the basis of an exposure history (present, past, or remote past) and the presence of one or more of the following: effort dyspnea, basal crepitations, radiographic changes of parenchymal and/or pleural disease, and lung function impairment of any sort (10, 96, 97, 172). If all 5 criteria are present, the diagnosis would generally be considered established for most compensation boards. With fewer criteria, there is less certainty.

In the absence of an exposure history, or if the exposure history is considered too short to account for the amount of disease present, a tissue diagnosis may be called for, particularly in compensation cases for which attributability is in doubt. In such situations, an open lung biopsy (145) is preferable to a needle biopsy (183), particularly if radiographic changes are minimal. Biopsy material should be critically examined by light microscopy for pathologic features, including presence of coated fibers, and by electron microscopy for the presence of uncoated fibers, using appropriate extraction procedures (Pooley, 7, p. 50). Also, occasionally, the presence of asbestos bodies in the sputum (117–119) may alert the physician to the possibility of exposure and result in an appropriately exhaustive enquiry to reveal the source of exposure. Coated fibers are, of course, commonly found under conditions of heavy and current exposure.

Prognosis, Complications, and Medical Management

The outlook for the person with asbestosis has undoubtedly improved considerably during the past 20 years, both in Europe (67) and in North America (63), with age at death, years of exposure until diagnosis, and years of survival after diagnosis increasing conspicuously in most countries. Also, risk of premature death due to other respiratory diseases seems to be confined to those with high dust exposures (McDonald, 7, pp. 155–179).

Perhaps because of the longer survival period, workers with asbestosis are now surviving into the lung cancer age (63), and deaths from this cause are assuming a much greater importance (McDonald, 7, pp. 189–217). In addition, it should be noted that lung cancer is becoming a more common cause of death in the general population.

Medical management of asbestosis is restricted to the symptomatic care given to subjects with interstitial fibrosis, whatever the cause. The use of corticosteroids is not advocated, because the agent, asbestos, is, as far as is known, fixed in the lung tissue. Appropriate treatment of inter-

current infections may be particularly important in view of the suggestion that nonspecific inflammation may contribute to progression of fibrosis (Ashcroft, 7, p. 236). There is no real evidence to suggest that the only possible effective therapeutic intervention, namely, to remove the person from exposure, has any real influence on the outcome of the case. One assumes that removal might halt further progression, a hypothesis for which there is some evidence (62). It is also known, however, that disease can both appear and progress many years after removal from exposure (63); thus, research should be directed at possible ways of determining what factors determine this future progression and whether it is possible to define the stage or level of exposure at which removal might be an effective preventive measure.

Pre-employment evaluation of lung function to screen out high-risk persons is, in theory, the most important area of future health protection; yet, this is also the area in which there is no systematic evidence to indicate what type of person to screen in or screen out. Attention has been directed toward the pre-employment detection of obstructive lung disease, acute or chronic, on the assumption that such persons are at high-risk of developing asbestosis (Hunt, 5, p. 406). The smoking habit, certainly the greatest risk factor for bronchogenic cancer, does not usually constitute grounds for refusing a recruit. Its role in the development of fibrosis is less clear, there being some evidence to suggest a synergistic effect with dust (185), and some evidence to the contrary.

An interesting possibility, as yet completely unexplored, is that certain physiologic characteristics, for instance, the relative size of airways to air spaces (184), may constitute risk factors and might, for example, be the basis for exclusion of certain types from dust hazard. Finally, it is possible that pre-employment and annual measurements of lung function, particularly FVC, might also prove to be a useful tool in the health care of the worker (87); however, this, too, should be introduced only in a way that permits a critical evaluation of the effectiveness of such a procedure.

Malignant Mesothelioma of the Pleura and Peritoneum

Primary malignant mesotheliomas arise from the pluripotential mesothelial cells (of the pleura, peritoneum, and pericardium) and in consequence, may present with widely varying histologic features. Nevertheless, they have been considered a pathologic entity (10, 185), albeit rare, for some time; their association with asbestos exposure was mentioned as early as 1946 in an individual case report (10). This association was dramatically brought to the attention of the medical public by Wagner and colleagues (27) in a report of 33 cases with occupational and/or environmental and/or domestic exposure in the crocidolite mining area of the Northwest Cape, South Africa. The association with asbestos exposure has now been confirmed from many parts of the world (table 6).

Pathology

A characteristic feature of the macroscopic appearance of the malignant variety is the tendency to spread along serosal membranes (186), encasing the lung by a bulky, lobulated mass that usually invades the fissures. Areas of necrosis within the tumor may give rise to cystic spaces filled with glutinous fluid, a distinctive feature of this tumor, although not necessarily a specific one, because it is also seen in adenocarcinoma (10). Local metastases to chest wall, mediastinum, and pericardium, rather than remote metastases, declare malignancy of the tumor; however, metastases to hilar and abdominal lymph nodes are not uncommon, and, occasionally, more distant sites, such as liver, thyroid, adrenals, bone, and brain are involved (10, 186). It has been emphasized, however, that the diagnosis is one of exclusion, and that all potential sites for primary growth (particularly lung, pancreas, intestine, and ovary) must be examined; consideration must also be given to the possibility that the primary tumor has already been removed (McCaughey, 5, p. 603). The peritoneal tumors present a similar appearance, but do not tend to engulf the abdominal organs to the same extent as the pleural tumors. Glutinous ascitic fluid, however, is a common feature (10). Primary pericardial tumors do not appear to be associated with asbestos exposure.

Microscopically, 4 varieties are recognized according to the dominant cell types (186, 187). *Epithelial,* or tubulopapillary, tumors are characterized by branching acini, lined by columnar or cuboidal cells, often containing mucin and having a tendency to spread. *Mesenchymal,* or sarcomatous, tumors range in appearance from cellular fasciculated fibrosarcoma to myxoma, with the amount of associated collagen in the tumor varying considerably. The *undifferen-*

TABLE 6

ASSOCIATION BETWEEN MESOTHELIOMA* AND ASBESTOS EXPOSURE†

Country	Years Reviewed	Cases of Mesothelioma		Control Subjects		Main Source of Exposure, Occupation, and/or Fiber	Reference
		No.	Per Cent Exposed	No.	Per Cent Exposed		
Uncontrolled case studies							
South Africa	1956–1960	33	97			Crocidolite mining	Wagner *et al* (27)
	1956–1971	252	82			area in N-W Cape	Webster** (8, p. 195)
UK: Liverpool	1955–1970	52	80			Shipyard occupations	Whitwell and Rawcliffe (187)
France: Rouen, LeHavre	?	14***	86			Textile manufacture	Fondimare *et al*†† (188)
Germany: Hamburg	1958–1968	98	58			Shipyard and manufacture	Bohlig *et al* (189)
Holland: Walcheren	1962–1968	25	88			Shipyard occupations	Stumphius (117)
USA: Harrisburg, Pa.	1958–1963	42	74			Textile insulation manufacture	Lieben and Pistawka (190)
Chicago, Ill.	c. 1969	77	86			Various industrial exposures	Godwin and Jagatic (191)
Somerville, N.J.	1948–1970	72	83			Mainly chrysotile textiles	Borow *et al* (192)
Australia: Victoria	1962–1968	15	87			Crocidolite or mixed	Milne (193)
Case-control studies							
UK: London	1917–1967	76	53	76	12	Factory processing crocidolite	Newhouse and Thompson††† (28)
Scotland	1950–1967	80	67	80	32	Shipyard occupations	McEwen *et al*†† (194)
Belfast	1950–1964	42***	76	42	21	Shipyard occupations and insulation	Elmes *et al* (195)
Newcastle	1948–1969	41	95	56	41	Shipyard occupations	Ashcroft (196)
Italy: Piedmont	1960–1970	50	18	50	2	Various manufacturing processes	Rubino *et al* (197)
Sweden: Malmo	1957–1966	34	53	34	12	Textiles, insulation, shipyards	Hägerstrand *et al* (198)
Germany: Hamburg	1958–1968	150	71	104	24	Shipyard and manufacture	Hain *et al* (199)
Holland: Walcheren	Not stated	67	72	67	18	Shipyard occupations	Zielhaus *et al* (200)
Canada: all provinces	1960–1972	190	26	182	7	Production more than mining	McDonald†††(201)
USA: all states	1972	99	48	86	20	Production and manufacturing	McDonald†††(201)

*Usual source was hospital autopsy records; pleural and peritoneal included, except for references 195 and 201.

†Exposure was established by interview, except where stated; includes occupational and domestic exposures, possible as well as definite.

**Includes Wagner's cases.

††Exposure deduced from presence of coated or uncoated fibers.

***Pleural tumors only.

†††Men only.

tiated, or polygonal, type is usually composed of solid sheets of cells with abundant eosinophilic cytoplasm, which may look remarkably benign. The *mixed* type comprises all of the characteristics previously described. Some believe that all tumors would turn out to be of the mixed variety if a sufficient number of sections were taken (Planteydt, 5, p. 80). A surprising and not uncommon finding is the presence of only one tumor element in the metastases (10).

Although ferruginous bodies are usually found in the lungs in cases of asbestos-associated mesothelioma (Hourihane, 5, p. 647), it is unusual to find parenchymal fibrosis (i.e., asbestosis) of any degree when the tumor arises in the pleura; on the other hand, in peritoneal tumors, pulmonary fibrosis may be a prominent feature, giving rise to the hypothesis of obstruction to the thoracic lymphatic drainage and retrograde lymphatic spread of the asbestos fiber to the abdominal lymphatic system. Peritoneal tumors, representing perhaps 10 per cent of cases, appear to occur more frequently in some series (30) than in others (201), and one study shows a sex difference in the preponderant tumor site, peritoneal tumors being more frequent in women (30); however, peritoneal tumors predominate in some all-male series (Selikoff, 7, p. 209).

Epidemiology: Association with Asbestos Exposure

Despite their being rare tumors, estimated to have an incidence of the order of 1 per 1,000,000 per annum in the general population, the association of mesothelioma with asbestos exposure has been consistent in all parts of the world (table 6). Although all commercial fibers except anthophyllite (77), but including talc, have been implicated, there are important between-fiber differences in mesothelioma risk, being greatest with crocidolite, less with amosite, and apparently even less with chrysotile. With amosite and chrysotile, there appears to be a higher risk in manufacturing than in mining and milling. These were the conclusions reached by the Advisory Committee on Asbestos Cancers at the Lyon meeting (7, p. 341) and are based on published epidemiologic studies, including prospective and retrospective mortality studies. In addition, mesothelioma rates seem, in general, to be increased in cities that have ship building or ship repair industries (202), and in some working populations may approach 10 per cent, particularly if exposed to crocidolite (Newhouse, M. L.: Personal communication). Unlike bronchial cancer, smoking does not play a synergistic role in the development of mesotheliomas.

The most disconcerting aspect of the relationship between malignant mesothelioma and asbestos exposure is its documented association with apparently low levels of exposure, for relatively brief periods in the remote past from neighborhood or domestic sources described (27, 30, 31). The commonest documented neighborhood exposure is that of children playing in the streets within one-half mile of a factory or mine, usually for several years in early childhood, although one cannot usually be certain that they did not also play in the waste and/or the tailings. However, neighborhood exposures seem certain to have been less than those to which workers themselves were exposed, implying lack of a dose relationship to exposure. On the other hand, in certain other occupational groups, such as the workers in the London asbestos textile factory studied by Newhouse and associates (30), a dose effect on risk can be discerned. Furthermore, when dose is measured by number of asbestos bodies and/or fibers in pathologic material (187, 188, 197), this is found to be higher than in the general population, although lower than usually seen in relation to pulmonary fibrosis.

Pathogenesis

Animal experiments indicate that, when given intrapleurally, all types of asbestos fiber, as well as certain types of glass fiber, are capable of producing malignant mesothelial tumors, and risk appears to increase with dose (Wagner, 7, p. 285). Inhalation experiments, on the other hand, tend to produce cancers. This has led to the hypothesis that all types of fiber, once they reach the pleura, exercise "biologic activity." There is some evidence, however, that this activity is size dependent, fibers less than 2.5 μm in diameter or between 10 and 80 μm in length being particularly effective at inciting mesothelial growths (Stanton, 7, p. 289). For these reasons, opinion is moving away from the view that the gradient of biologic activity shown in man, at least with regard to risk of developing mesothelial tumors, is due to chemical differences between fibers, and toward the view that it is due to physical differences between fibers. Thus, it is believed that the determinants of pathogenicity of a fiber are the degree to which it penetrates and settles in deep lung spaces, and

this, in turn, is controlled by its aerodynamic properties (Timbrell, 7, p. 295).

In addition, it must be pointed out that malignant mesothelioma is not uniquely associated with asbestos exposure, and a small number of cases without such a history are seen in all series; this proportion is usually small, but has reached over 80 per cent (197). Mesothelial tumors arising in the pericardium have not been linked to asbestos.

Despite the now accepted association of malignant mesothelioma with asbestos exposure in man, the pathogenesis of this tumor is far from clear. Presumably, it is only by sustained research, using animal models, and looking for risk factors in exposed populations, that an understanding will eventually be reached of the mechanisms underlying its development. Indeed, some believe elucidation of the relationship of this tumor to exposure to be the most important area for future research, and the key to understanding the mechanism by which exposure to asbestos produces its effects in man (202).

Clinical Features

Pleural tumors invariably present with dull chest or shoulder pain, of insidious onset, but slowly becoming persistent enough to interfere with sleep (Elmes, 7, p. 267). In some cases, however, the pain may be severe and pleuritic. Breathlessness, usually related to accumulation of pleural fluid, weight loss, tiredness, and cough follow. As mentioned previously, there may also be a history of previous pleural effusions (203). The presumed sequence of events is as follows: serous effusion, perhaps developing in association with plaques, possibly clearing later, to recur with blood staining, increasing in amount as the tumor develops; invasion and thickening of parietal and visceral pleura, eventually leading to the lung's becoming imprisoned, with retraction and immobilization of the chest cage on the affected side (117). The presenting symptom of a peritoneal tumor is also usually dull pain, later followed by swelling and weight loss.

The physical signs will depend on the stage at which the patient first presents; usually, pain precedes systemic symptoms and the presence of clear physical signs by weeks or months. Apart from the clinical signs of the effusion and/or pleural invasion, clubbing of the fingers is common; acute arthropathy which may also be a feature of associated asbestosis (204) has been reported, with regression and reappearance, after surgical removal and recurrence of the tumor, respectively (Elmes, 7, p. 267). There is only one report of hypoglycemia in association with pleural mesothelioma (204); the association may therefore be taken as incidental. The presenting signs of abdominal tumors are invariably fluid and swelling; complications include partial or complete intestinal obstruction.

The clinical course is usually one of rapid progression; for pleural tumors, the average survival time from onset of symptoms is approximately 6 months; for peritoneal tumors, 13 to 14 months. This varies, however, and in one series, 17 per cent were alive after 3 years (187). Nevertheless, the more benign the course, the more likely that the pathologic classification should be revised to benign mesothelioma (205).

Diagnosis and Treatment

The diagnosis can be definitely made only by tissue examination. There are a number of reasons why it is difficult to make a positive diagnosis of this tumor during life, even when adequate biopsy material is available. These include the wide variety of cell types within a single tumor, especially those of the mixed type, and the need to exclude primary tumors elsewhere. Nevertheless, it is claimed that diagnosis on biopsy material can be accurate in most cases (Hourihane, 5, p. 647). In addition, there is the difficulty of obtaining agreement between pathologists on histologic characteristics (McCaughey, 7, p. 58), a difficulty reflected by the relatively modest number of cases, less than 50 per cent in some series (206), subsequently confirmed by mesothelioma review panels. This difficulty may be less important in clinical medicine, in which the important distinction is between a benign and a malignant tumor, than in epidemiologic studies that seek to investigate the association with a history of asbestos exposure, in which consistency of diagnostic criteria in exposed and unexposed groups is all important.

Because of the between-tumor and within-tumor histologic variation mentioned previously, and the not infrequent development of the growth in the track of the biopsy needle, other methods of examination have been used to increase the certainty of diagnosis. Thus, the presence of hyaluronic acid in the pleural fluid (207) or its demonstration in tumor tissue by histochemical techniques (208) may be of some value in distinguishing between mesothelioma and secondary carcinoma, but is not the definitive test it was originally believed to be (207). Cytologic examination of pleural fluids, by light

and electron microscopy, may offer useful contributory evidence. A series of papers under the general title "Assessment of Methods Used in the Studies of the Biological Effect of Asbestos to Pathology" (7, pp. 58–81) provides a most convenient and up-to-date summary of these methods, their precision, and general applicability.

The radiologic appearances vary according to the stage to which the disease has progressed. Common features are the presence of a pleural effusion, lobulated tumor masses that may be visible only after removal of the pleural fluid, chest wall masses, satellite lung lesions, and, occasionally, hydropneumothorax (209).

In a review of treatments (13, p. 277) Elmes pointed out that there is no effective curative treatment, although surgical excision, local and/or systemic cytotoxic therapy, and radiotherapy have all been tried. He also pointed out several features that suggest a considerable contribution of the body's defense mechanism, both in the formation of abnormal tissue and in the shaping of its clinical course. Relative to the first point is the apparently low dose of exposure capable of eliciting a response; relative to the second is the not infrequent occurrence of chest injuries and/or infections at the onset of the clinical course, and the sometimes rapid dissemination, apparently provoked by treatments, such as radiation or cytotoxic drugs. For these reasons, he believes that this tumor may eventually turn out to be controllable through improving body defenses. Thus, it is not surprising that the use of BCG vaccine in treatment is a matter of great current interest, with, as yet, no definitive evidence on which to base clinical action.

Meanwhile, therapy is symptomatic, and diagnostic measures should be kept to a minimum. Removal of fluid for diagnostic examination and to relieve breathlessness should be done as infrequently as possible. Indeed, as Elmes notes, the establishment of a precise diagnosis in life, given the absence of a potentially curative treatment, is an academic, rather than a clinically useful, exercise.

Carcinoma of the Lung Associated with Asbestos Exposure

An association between asbestosis and bronchial carcinoma, suspected in the 1930s on the basis of individual case reports (210), was subsequently confirmed in two British reports, one by the Chief Inspector of Factories, issued in 1947, and the second, an analysis of autopsy material from more than 1,000 cases of pneumoconiosis published in 1951 (211). From these, it appeared that asbestosis was associated with a much higher lung cancer risk than other pneumoconiosis, with 15 to 20 per cent of men recorded as having asbestosis dying from this cause. This risk was reported to have further increased considerably in Britain by 1963 (10), and a similar increase in lung cancer risk during the same decades has been reported from Germany (Jacob, 5, p. 536). The emergence of lung cancer as an important threat to the health of asbestos workers is attributed to the improvement in dust conditions, with less mortality from asbestosis occurring after longer periods of exposure and, therefore, survival of workers through the long latent period of lung cancer (63).

Subsequent epidemiologic studies have amply confirmed the association between asbestos exposure and lung cancer, mortality experience being the chief method of study (63, 67, 82); however, table 7 indicates that despite the consistently increased relative risk in these reports, there are considerable between-study differences as to its degree. Some of these differences must certainly be ascribed to between-study differences in the methods used to calculate risk (217), particularly in such factors as composition of the risk group (in terms of age, years of exposure, and length of follow-up), and the nature of the control or reference group, which could be either a low-exposure group within the working population, or an appropriate reference population derived from national statistics. In addition, most studies deal with relatively small numbers of deaths (less than 100 in all but 2 of the studies), so that calculation would inevitably be influenced by the addition or loss of one case. Finally, differences in exposure dose and smoking habits are other relevant factors for which standardization is seldom possible. As Wagner and associates point out, however, "an additional lesson to be learnt from the apparent conflict of evidence is the need to pay more attention to the type of asbestos and to the physical state of the respirable faction of the dust" (218), and the evidence that there are real differences in risk associated with the different fiber types, as well as the different types of exposure to the same fiber, is becoming more convincing. Such differences, however, have a greater significance in the field of environmental control and safety standards than in the practice of clinical medicine.

The interaction of cigarettes and asbestos exposure as risk factors, clarified to some extent by

epidemiologic studies, is, however, of very real importance in clinical practice. Carcinoma of the lung appears to develop only very rarely in the nonsmoker exposed to asbestos (63, 73) whereas the risk associated with exposure to both is considerably more than additive, and probably multiplicative (63, 73, 219).

It was originally believed that the tumor was a scar cancer, because of its common location in the lower lobes, where fibrosis tends to be most marked (220). Animal experiments support this hypothesis (62). However, although usually found in lungs, which are the seat of fibrosis (67, 221), this is not always so (220). Cases have also been reported in association with relatively mild fibrosis, and occasionally in the absence of fibrosis (220). Similarly, although cases occur almost exclusively in smokers (63, 219), there is some evidence to suggest that the distribution of cell types is different from that seen in smokers without exposure, namely, a greater preponderance of adenocarcinoma (222). This has led to the hypothesis that the carcinogens in cigarette smoke may have been delivered to the more peripheral regions of the bronchial tree by the fibers and dust particles (222). Not all series show this greater preponderance of adenocarcinoma, however, and the question remains open. In one series, the presence of pleural plaques appeared to be associated with a higher risk for developing cancer (130), but it also seems possible that the presence of plaques may also merely reflect a higher exposure dose. Multiple primary tumors, sometimes of different cell types, have also been described in relation to asbestos exposure (223).

The clinical picture, prognosis, and treatment are no different from those seen in the person not exposed to asbestos, except that the associated fibrosis may limit the treatment options. Advice to, and help in, quitting smoking are clearly even more important for the worker exposed to asbestos than his or her unexposed companion, and a concerted effort at worker education might prove worthwhile.

Another practical problem concerns compensation, in particular, the question of attributability of lung cancer to exposure in the absence of significant fibrosis. Some compensation boards, acting on the dose-relationship information, award the benefit of the doubt if exposure has been considerable in a nonsmoker.

Finally, as has been emphasized elsewhere (220, 223), the "occupational history may not seem important in patients with carcinoma and is often not diligently pursued." The epidemiologic evidence summarized here underlines the importance of establishing this association.

Other Asbestos-Related Cancers

In most mortality studies of asbestos workers, there is a greater-than-expected risk for all cancers (table 7). Lung cancer shows the greatest relative risk, followed by cancers of the gastrointestinal tract. The excess of gastrointestinal cancers is evident in all series, whatever the reference population used to calculate expected number of deaths, with one exception, namely, workers exposed in anthophyllite mining (77). This presumably is further evidence of the difference in the biologic effects of the different fiber types. There is also some evidence to suggest that environmental exposures may be of importance in gastrointestinal cancer (16).

In addition to lung cancer, there is increasing evidence that asbestos exposure is associated with cancer of the larynx (11–14). Like lung cancer, this cancer also has a long latent period (13), and cigarette smoking is a well-recognized associated risk factor. Indeed, it is surprising that its association with asbestos has only recently been recognized, but this is perhaps because it is less common than lung cancer.

An association between asbestos exposure and ovarian cancer, suggested originally on the basis of both clinical (10) and animal studies (15), has not, in the view of the Advisory Committee on Asbestos Cancers (7, p. 342), been confirmed in the first large mortality survey of women asbestos workers (7, p. 203). It is believed that the clinical cases originally believed to be ovarian tumors were malignant mesothelioma of the peritoneum (10, 186).

An association of asbestos exposure (as reflected in the lung count of asbestos bodies) and carcinoma of the breast in women has been reported in one study from London, England (16), a study that, paradoxically, did not show the same thing for carcinoma of the bronchus. Other cancers with suspected, but unsubstantiated, associations with asbestos exposure are leukemia, multiple myeloma, and Waldenström's macroglobulinemia (10). They are mentioned here, not to alarm physicians or their patients, but to underline the strength of the association between asbestos and many human cancers. For certain cancers this association calls for clinical action, even though it remains to be proved whether asbestos itself is the

TABLE 7

RELATIVE RISK OF CANCER FOR MALE ASBESTOS WORKERS

Occupation and Country	Fiber	Population Studied: No.	Population Studied: Minimal Exposure	Population Studied: Years of Follow-Up	Deaths: Total No.	Deaths: No. Due to Lung Cancer	Relative Risk of Cancer*: All Others	Relative Risk of Cancer*: Lung	Relative Risk of Cancer*: G-I	Reference
Mining and milling										
Canada	Chrysotile	5,958	5 years	6	187	12	–	1.5	–	Braun and Trauen (212)
	Chrysotile	9,692	1 month	ave., 25	3,270	135	–	1.4	–	McDonald (7, p. 155)
	Chrysotile		1 month	ave., 25	3,270	134	1.4†	3.1†	1.6†	McDonald (7, p. 155)**
Finland	Anthophyllite	1,041	3 months	2–33	248	21	–	1.6	0.5	Meurman *et al* (77)
	Anthophyllite	?	10 years	2–33				3.3	0.9	Meurman *et al* (77)
Production: Secondary use										
UK										
Textiles	Mainly chrysotile	113	20 years (pre 1933)	≥ 20	39	11	4.8	13.7	1.7	Doll (68)
Textiles	Mainly chrysotile	674	10 years (post 1933)	ave., 17	69	8	0.6	1.0	–	Knox *et al* (67)
Insulation production	Mainly chrysotile	1,024	6 months	15	133	7	1.1	2.3	–	Elwood and Cochrane (213)
Mainly textiles	Mainly crocidolite	1,834	1 month	1	180	46	–	4.8	–	Berry *et al* (73)
	Mainly crocidolite	1,304	2 years	10–25	114	36	3.6	5.6	–	Newhouse (71)
Insulators; pipecovers	Chrysotile, crocidolite, amosite	165	Not stated	26	98	28††	6.7	17.6	–	Elmes and Simpson (214)
USA										
All types of production	Not stated	529	Not stated	3	41	10	1.4	3.2	–	Dunn and Weir (215)
All types of production	Not stated	1,265	Not stated	20	330	35	3.1†	3.3†	3.1†	Mancuso and El-Atar (74)
All types of production	Little amosite or crocidolite	1,026	3 years	Retirees from age 65 on	568	29	1.2	1.7	1.1	Enterline *et al* (83)
Maintenance	Includes amosite and crocidolite	438	3 years	Retirees from age 65 on	254	30	2.1	4.3	1.7	Enterline *et al* (83)
Insulation production	Amosite	933	1 year	ave., 26	484	73	5.1	6.4	2.0	Selikoff *et al* (216)
Insulation workers***	Mainly chrysotile	623	20 years†††	28	421	84	4.0	8.3	3.1	Selikoff (7, p. 209)
Insluation workers***		5,118	20 years†††	4	881	191	3.5	5.1	2.1	Selikoff (7, p. 209)

*Comparisons were made with appropriate national statistics, except where indicated. Relative risk = observed/expected number of deaths.
†Internal comparison of low- and high-exposure groups.
**Best estimate of relative risk for lung cancer was 5.0 using other methods.
††Includes cancer of the pleura and larynx.
***Engaged in a wide variety of jobs.
†††Years since first exposure.

human carcinogen, or a cocarcinogen, and/or potentiator of cigarette smoke and/or other factors.

The Influence of Fiber Type and the Nature of Exposure on Biological Response

After the 1964 New York Conference (5), the UICC working group on cancer urged study of "the relationship of dust dosage (including concentration and duration of exposure) and the composition and physical state of the dust to the incidence of asbestosis, carcinoma of the lung, mesothelioma and other cancers." In other words, 2 areas were identified for urgent future research: (*1*) to establish whether dose-response relationships exist between exposure and biologic response, and (*2*) to establish whether the composition and physical state of the dust affects these dose-response relationships.

In the ensuing 11 years, health scientists throughout the world have gathered data in support of the first hypothesis, namely, that a dose-response relationship exists for all of the responses listed (asbestosis, carcinoma of the lung, other cancers, and, probably, mesothelioma). Furthermore, this holds for all types of fiber and for all types of exposure investigated. The evidence has been already summarized in table 4.

It has proved more difficult to investigate the second hypothesis, that composition and physical state of the dust influence the responses, because this requires the comparison of dose-response curves for different fibers, or for the same fiber under different exposure conditions, e.g., mining and milling compared to manufacturing. Even animal studies in which exposure can be relatively well controlled are inconclusive about the relative fibrogenicity of different fiber types (62, 224) although differences in carcinogenic potential have been shown (224). Epidemiologic studies in man in different occupationally exposed groups suggest differences between fibers, and between exposures, in terms of their carcinogenic potential both for lung cancer (table 6) and for mesothelioma (224); however, it is usually impossible to establish to what extent these can be explained by differences in exposure levels and associated factors, such as cigarettes and other co-carcinogens. Furthermore, exposures to one fiber type only are rare (usually in mining), and most production workers have mixed exposures (224). For instance, table 8 summarizes data collected in Quebec asbestos workers, exposed only to chrysotile fibers. Even in these results, which show a dose effect for all responses, there are between-area differences, particularly for radiologic changes, for men of the same stock and working the same geologic deposit, and with exposure calculated using the same type of index. Given these between-area differences, to what extent, if any, are these dose-response curves applicable to other working populations?

Criteria for comparability require that both the dose and the response be measured in a similar fashion and that the populations compared have equivalent susceptibility. Enough has already been said to indicate that even if the first 2 criteria were met, virtually nothing is known about the factors accounting for susceptibility, much less whether it is possible to measure them in practice. The only comparison attempted was inconclusive, because mortality was assessed by fundamentally different techniques (figure 5). Thus, it is not possible to deduce from this comparison whether, indeed, there is greater risk for production workers compared to miners (figure 5, upper panel) attributable to differences in the nature of the exposure, an interpretation for which there is little scientific justification, or whether the risk is comparable for both groups, but the scaling (figure 5, lower panel) requires appropriate adjustment.

Despite the difficulties in making between-study comparisons, a consensus has emerged, outlined in a carefully reasoned paper by Kleinfeld (224), and in the conclusion of the Advisory Committee on Asbestos Cancers (7, p. 341). It is believed that there are gradients in the mesothelioma-producing potential, related to fiber type (greatest with crocidolite, less with amosite and with chrysotile, least with anthophyllite) and to occupation (e.g., for amosite, greatest in insulation workers compared to miners). Gradients in fibrogenic capability of the different fibers, less clear, may also be present, with crocidolite leading chrysotile, whereas gradients in lung cancer risk may be more closely related to the nature of the exposure, with production leading mining, at least for chrysotile.

To date, the best explanation of these gradients in biologic potential is that developed by Timbrell (7, p. 295), namely, that biologic activity relates to the degree of penetration and deposition in the lung (see also figure 6). Thus, the greater mesothelioma potential of crocidolite compared to amosite, anthophyllite, and chrysotile, could be due to its smaller fiber size and its other aerodynamic properties, which permit greater penetration and deposition. Similar-

TABLE 8

EXPOSURE-RESPONSE RELATIONSHIPS IN QUEBEC CHRYSOTILE ASBESTOS MINERS AND MILLERS

Dust Index*	<10	10–	100–	200–	400–	800–	Source	Reference
Death rate/1,000 persons† from								
Respiratory cancer	10	13	13	16	21	32	Cohort of	85, 92
Pneumoconiosis	2	2	1	5	5	24	11,107	
Abdominal cancer	18	14	19	12	26	29	men born	
Other respiratory causes	12	18	24	19	16	25	1891–1920)	
Circulatory causes	123	119	118	116	118	135		
Prevalence of radiologic changes								
in men 56–65 years, %**								
Small, irregular opacities (1/0 or +)							Study of chest	88, 92
Thetford area	–	7	10	13	21	34	radiographs of	
Asbestos area	10	6	17	23	15	20	13,021 past	
Any pleural changes							and present	
Thetford area	23	20	33	29	34	39	employees	
Asbestos area	5	15	18	14	15	24		
Prevalence, %††								
Dyspnea	7	18	23	26	30	37	(1,015 current workers)	86, 92
Decrease in lung function, %***								
VC	0	–4	–9	–11	–14	–15	(1,015 current	87, 92
FEV_1	0	–4	–7	–10	–13	–14	workers)	
Steady-state DL_{CO}, at rest	0	–3	–6	–5	–9	–11		

*Million particles per foot^3 per year (91).
†Age corrected; followed up to 1969.
**Standardized for age and years of employment.
††Age standardized.
***Age and height standardized.

ly, the greater mesothelioma and, possibly, cancer potential of amosite in manufacturing processes, compared to mining, could be attributed to the smaller particle size for the fiber released in a production plant compared to that at the mine head.

At the practical level of environmental control, regulations proposed for chrysotile in 1968 (225) by the British Occupational Hygiene Society were at a level (2 fibers per cm³ averaged over 3 months) that, it was hoped, would allow no more than 1 per cent risk of disease (specifically, asbestosis) in a 50-year working life. Evidence suggests that this would also reduce risk of bronchogenic cancer. At the time, the British Occupational Hygiene Society was uncertain that standards for other fibers should follow "by analogy." They subsequently proposed the same standards for amosite (226), but a standard 10 times more stringent for crocidolite (227) was promulgated by government regulation. Furthermore, because all standards should be regarded as no more than an expression of the "best available hypothesis" of levels adequate to protect human health, they should always be reviewed in the light of subsequent evidence. This was done in 1973 for chrysotile, and no change was recommended (228). In the United States, the Occupational Health and Safety Administration (OSHA) promulgated a standard of 5 fibers per cm³ in 1972, to be reduced to 2 fibers per cm³ in 1976 (229), and there was a recent proposal to lower further the standard to 0.5 fibers per cm³ (230). These standards apply to all fiber types.

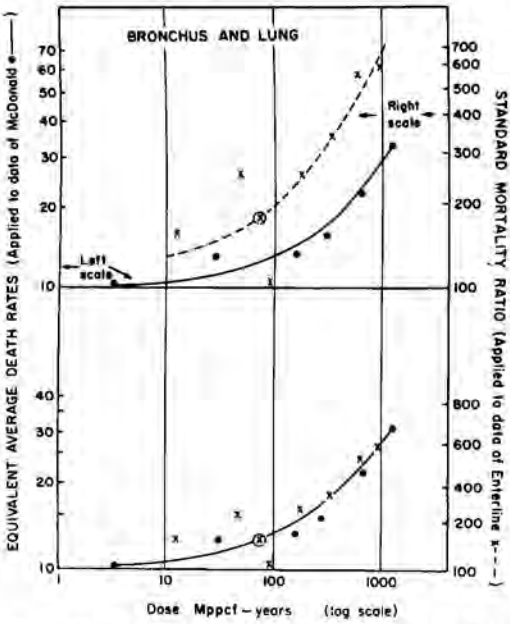

Fig. 5. [From Schneiderman (93); reprinted by permission of publisher.] Dose-response relationship for cancer of the bronchus and lung. The data shown are those of McDonald (7, p. 189), describing chrysotile asbestos miners (*left* scale), and those of Enterline and associates (82, 83), describing production workers (*right* scale). In McDonald's data, mortality was expressed as equivalent average death rates (85, 92) to enable a within-population comparison between men with low and higher dust exposure. The data of Enterline and associates were reported as standardized mortality ratios, which used for comparison the most appropriate general population statistics. Dust exposure in both studies was calculated in similar fashion and expressed in million particles per foot³-years (82, 83, 91). The vertical scales are drawn so that an equivalent average death rate of 20 is equated with a standardized mortality ratio of 200 in the top panel and 400 in the bottom panel, which results in both sets of data falling on the same curve.

Research should continue in an attempt to identify more precisely the reasons for between-fiber differences in biologic effect, because a better understanding of what determines the biologic responses of this mineral can only result in its human use being conducted under conditions that more effectively protect the health of the exposed worker.

Clinical Implications of the Epidemiologic Findings

Faced with a patient in whom the diagnosis of one of the described diseases has been made, i.e., fibrosis of the lungs and/or pleura, or cancer of the lungs and/or pleura, it may be important to establish whether, in this particular case, the disease is asbestos related. If the patient is currently known to be exposed, this rarely presents a problem. If not, a systematic history is called for, and should include all his or her previous occupations (including short-term jobs, summer jobs, and so on), as well as those of his or her work colleagues and family members. In addition, places of residence should be noted, particularly if the diagnosis is mesothelioma and/or pleural plaques. The discovery of asbestos fibers, coated or uncoated, in biologic material (sputum or biopsy or surgical material) requires explanation, if not already evident from the history. Establishment of an association with asbestos has importance if attributability is questioned (in cases of compensation), as well as for other workers if the risk had not previously been recognized.

The dose relationship, particularly of fibrosis,

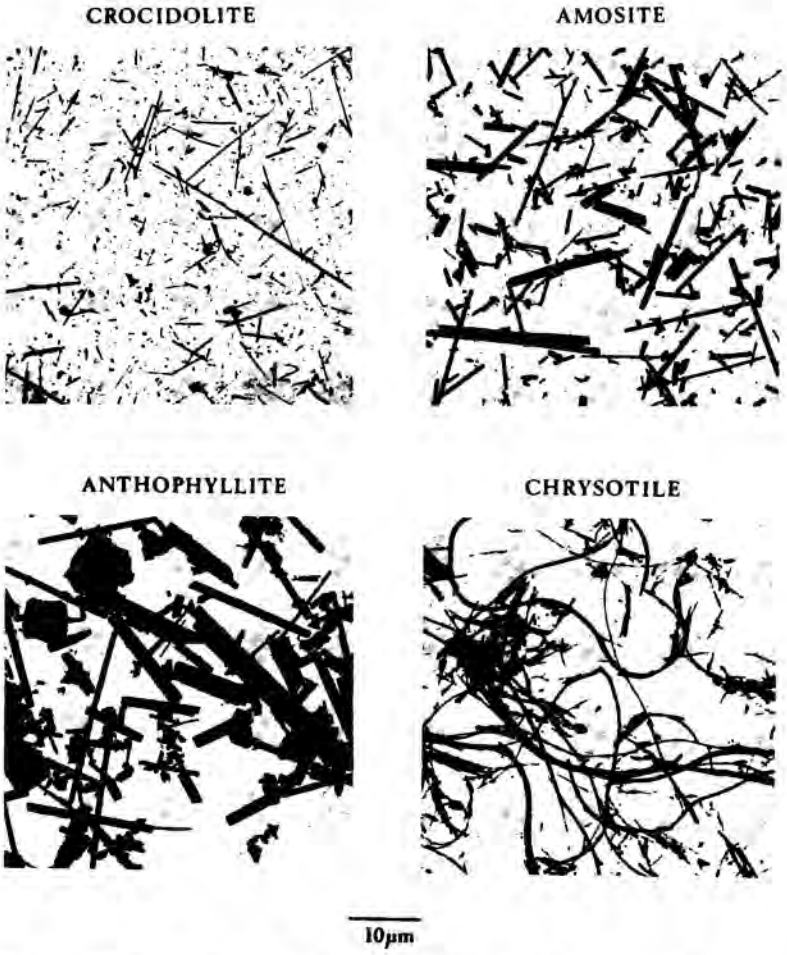

Fig. 6. [From Timbrell, V.: Physical factors as, etiologic mechanisms, in *Biological Effects of Asbestos,* IARC Scientific Publication No. 8, Lyon, 1973, p. 295; reprinted by permission of publisher.] Electron micrographs of crocidolite (north-western Cape Province), amosite (Transvaal), anthophyllite (Finland), chrysotile (Canada) at the same magnification (× 1700). Features to note are (*1*) the rectilinear shape of the amphibole fibers compared with the curved and twisted morphology of chrysotile fibers; (*2*) the order of the diameters of the amphibole fibers, suggested by numerous electron micrographic examinations of these fibers from the 3 geographical areas, crocidolite < amosite < anthophyllite; (*3*) the longitudinal fragmentation of the chrysotile fibers and the small diameter (about 0.03 μm) of the ultimate fibrils.

to exposure should always be borne in mind, and the patient in whom disease develops after a relatively short period (for example, less than 25 years) must be taken as an indicator of unsatisfactory past and/or present working conditions, requiring forceful corrective action. The same attitude should be taken toward the person in whom fibrosis is believed to be present in its early stages or development, either on clinical, radiologic, or functional evidence. Any claim that this is not so because the "environmental levels" to which the person was exposed were "safe" is incorrect; levels were clearly not "safe" for the particular person concerned, either because of greater-than-suspected dose, or greater-than-average susceptibility.

It must be emphasized that the clinician's job is not only to recognize the case of asbestos-related disease, but also to see that it is brought to the attention of the appropriate executive authority (in many areas, the Workmen's Compensation Committee, which informs the company concerned). This recognition and referral has social implications at 2 levels. For the person, the implication is appropriate compensation, society's fumbling best to make up for his

or her loss of health. At the second level the occurrence of an asbestos-related illness is approached as a failure of control measures, and one seeks to identify the point of failure so that appropriate action can be taken to protect the health of the new generation of workers (the children and younger colleagues of today's victims), who may be currently entering the industry.

Nowhere is this more evident than with the finding of a patient with malignant mesothelioma whose only possible contact with asbestos is indirect, through neighborhood and/or domestic exposure. Given a history of neighborhood exposure, should one advise the family to move for the sake of its other members? Probably not, because the long time lag of this tumor makes it most likely that they have already received any exposure relevant to the future development of mesothelioma. Should new families moving into the district be advised against this, unless there has been appropriate action for environmental control over the previous years? An unanswerable question. Given a history of domestic exposure, the clinician should at least be able to assure the new families that work practice codes now insist that dusty work clothes are not taken home to be cleaned.

Faced with a person with a known exposure risk, what medical measures can be taken to protect his or her health? Sadly, it must be admitted that there are none, because effective health protection lies in effective environmental control, and medical surveillance is, probably correctly, considered a form of biologic monitoring supplementary to environmental monitoring (231). Thus, good work practices and quitting or refraining from smoking are the best "medical measures" for the individual worker; however, the examination implied by medical surveillance can provide other services, including case detection and other forms of health care. As knowledge improves, it is possible that medical surveillance will be able to fulfill its hoped-for role, namely, the detection of health effects in a person at a stage when some action (for instance, removal from exposure) might prevent eventual disablement.

Given the "imperfect" state of the art, it is, at present, believed that medical surveillance should include a clinical examination (emphasis on basal crepitations), an annual chest radiograph, and a measurement of lung function, probably the most useful being the forced expiratory volume test, and possibly the diffusing capacity. At what point in time changes in one or more of these methods of examination call for action remains to be established.

For the currently exposed worker, research in this area certainly has the most relevance, in particular, methods of identifying the persons in whom the disease will progress, whether or not exposure continues. Animal work suggests that withdrawal from exposure may slow progression (62), and in the absence of definitive data, this must also be assumed to occur in man. With regard to the future worker, it remains to be determined whether the person at high risk can be identified before entry into the industry. Meanwhile, there seems to be merit in deploying energy into maintaining currently proposed standards. Three times in the twentieth century, levels have been set, because the asbestos worker's health became a matter of public concern. Had the standards been more systematically adhered to, it is likely that the asbestos-related diseases would not have re-emerged as the "occupational illness of the 60s," a testimony to the working conditions of the previous decade. It is to be hoped that current concern is translated into effective action for the workforce currently entering the industry.

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