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REVIEW ARTICLE

Asbestosis: A Reassessment of the Overall Problem

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Keyphrases □ Asbestosis—review of chemistry, industrial hygiene, animal and human toxicology, and carcinogenic aspects □ Toxicology, asbestos—review of chemistry, industrial exposure, carcinogenic aspects in animals and humans □ Carcinogenicity, asbestos—review of chemistry, industrial hygiene, animal and human toxicology □ Mesothelioma, asbestos induced—review of asbestos chemistry, industrial exposure, animal and human toxicology, and carcinogenic aspects

It has been established that occupational exposure to asbestos fibers induces mesothelioma of the pleura and peritoneum and carcinoma of the lungs, esophagus, and stomach after a latent period varying from 20 to 40 years (1). The daily dumping, since 1955, of 67,000 short tons of taconite tailings containing amosite asbestos fibers into Lake Superior, the potable water supply for Duluth, has raised the issue of the possibility of an increased cancer risk for the inhabitants of the area. Air pollution by the same type of fibers adds an additional risk. However, legal action against the polluter resulted in the decision that there was no demonstrable hazard from asbestos dumping and that therefore it could be continued (2). At this point in time, it has not been established, either experimentally or in humans, that ingestion of asbestos fibers causes cancer of the GI tract.

The wide use of asbestos and the observation of asbestos bodies in sputum specimens from individuals with no known exposure call for a review and reassessment of the overall problem of asbestosis. It is also essential that problem areas be discussed and that solutions be suggested.

SOURCES AND USES

The generic term "asbestos" describes naturally occurring incombustible mineral silicates that are separated into filaments. The varieties are actinolite [$CaO{\cdot}3(MgFe)O{\cdot}4SiO_2$], amosite [$(FeMg)SiO_3$], anthophyllite [$(MgFe)_7Si_8O_{22}(OH)_2$], chrysotile ($3MgO{\cdot}25{:}O_2{\cdot}2H_2O$), crocidolite [$NaFe(SiO)_2{\cdot}FeSiO_3{\cdot}H_2O$], and tremolite [$Ca_2Mg_2Si_8O_{22}(OH)_2$] (3).

Smither (4) tabulated the amounts and sources of asbestos in current use throughout the world for 1969 (Table I). Asbestos is used in the construction industry, floor tiles, asbestos cements, roofing felts, shingles, insulation materials, cement powders, acoustical products, textiles, brake linings, clutch facings, paper, paints, roof coatings, plastics, and miscellaneous other products. Asbestos filter pads are used in the beverage industry, in processing blood and its fractions, and in clarifying intravenous fluids.

Each and every one of these uses has exposed various segments of the population to the threat of asbestosis; the extent of exposure will be explored industry by industry. It must also be remembered that primary exposure in the insulation industry results in secondary exposure to between 3 and 5 million workers in the construction and shipyard industries (5).

ANALYTICAL CHEMISTRY

The chemical composition of the various forms of asbestos presents a difficult problem of analysis, particularly in cases of asbestosis where the amount of

Table I—Annual World Production of Asbestos (3,000,000 Tons)

Type	Percent Production	Amount[a] and Location
Amosite	3.0	90,000, South Africa
Anthophyllite	0.5	10,000, Finland
Chrysotile	93.0	1,250,000, Canada
		750,000, USSR
		250,000, South Africa
		100,000, United States
		100,000, Europe
		350,000, Others
Crocidolite	3.5	110,000, South Africa

[a] In tons.

offending chemical is small. The situation with air or water samples is much less complicated. Another complication is the contamination of amosite and crocidolite asbestos with benzo[*a*]pyrene and oils (6). Blood serum can elute benzo[*a*]pyrene from crocidolite fibers, but oil is far less efficiently removed (7). Canadian chrysotile asbestos has a very low content of polycyclic aromatic hydrocarbons but becomes contaminated with C_{14}–C_{35} *n*-alkanes during the milling process (8). Storage of the fibers in polyethylene bags results in a reaction which produces a yellow oil with strong absorption at 421 nm. The material has been identified as 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone and is absent from fibers stored in glass (9).

Various asbestos fiber types can be identified with the polarizing microscope using specific refractive index media if the fibers are thicker than 0.5 μm (Table II). Smaller fibers can be identified with the transmission electron microscope, and selected area electron diffraction is more dependable than elemental analysis with the scanning electron microscope (3).

X-ray diffraction has been used for the quantitative determination of amosite, chrysotile, and crocidolite samples by measuring the area under the major diffraction peak and comparing it with a standard. The method is applicable to amosite and crocidolite in the 1–8-mg range and to chrysotile in the 1–10-mg range (10). This method has been applied to bulk and settled dust samples, but they must contain at least 5% chrysotile before the method is usable and more than 20% for accurate results (11). Similar analyses have been made of amosite and crocidolite (12).

X-ray diffraction analysis has been utilized for the accurate analysis of asbestos in lung tissue (13). The technique can be applied to related occupational lung diseases and can quantitatively differentiate between causative agents (14). When amosite, chrysotile, crocidolite, and tremolite are reduced to particles under 10 μm in size by cutting, the accuracy of the X-ray diffraction method decreases and the background increases. Impact reduction does not decrease the fine fibers, and accurate quantitative results are obtained (15).

IR spectrophotometry has been used in the determination of chrysotile asbestos, but difficulties are encountered in preparing disks with a chrysotile content <100 μg. Moreover, at the 2.7-μm absorption band, other serpentine minerals present can invalidate the results (16). A similar situation exists for the other forms of asbestos in that their IR spectra are almost identical. Other problems include reproducible particle size, uniform mixing of the fibers and halide matrix, chemical exchange in the fiber matrix, and chemical alteration of the sample during grinding (17).

The use of atomic absorption spectrophotometric methods in the analysis of asbestos fibers has been confined to the determination of nickel, chromium, cobalt, and manganese, which apparently contaminate the fibers during processing. The actual fibers are destroyed by treatment with hydrofluoric acid; thus atomic absorption spectrophotometric procedures at present cannot directly determine the asbestos content of bulk or environmental samples (18). However, it has been suggested that these trace metals may be associated with the carcinogenic process and that all experimental animal studies should have the asbestos monitored for trace metals (19). Similar studies should be undertaken in industry, *e.g.*, asbestos textiles, because trace metals have been associated with the etiology of asbestosis (20).

It has been suggested that electromotive phenomena are involved in the unexplained exacerbations of asbestos carcinogenesis and that unless trace metal determinations are made the results obtained may exclude important data (21). Neutron activation analysis has been employed to determine the iron, chromium, cobalt, nickel, and scandium content of amosite, anthophyllite, chrysotile, and crocidolite. Milling apparently did not significantly change the trace metal content. The difficulty with the method is the prolonged irradiation time, the time for decay for the short-lived nuclides, and the necessity for chemical separation to improve the accuracy of detection of individual radionuclides (22).

The difficulties in the determination of bulk asbestos is compounded when body tissues are analyzed for their asbestos fiber content. Normal mineral extraction methods including acid, alkali, or peroxide digestion destroy the asbestos fibers, so fiber recovery depends on the fiber type involved and the use of milder methods for tissue destruction. Analysis for tissue fiber types by X-ray diffractometry is of limit-

Table II—Crystallographic Properties and Refractive Indexes of Asbestos

Type	Crystal System	Specific Gravity	Refractive Index	Dispersion Staining Color	
				Parallel	Perpendicular
Amosite	Monoclinic	2.6–3.0	1.66–1.70	Red magenta	Golden yellow
Anthophyllite	Orthorhombic	2.85–3.5	1.60–1.66	Blue green	Golden yellow
Chrysotile	Monoclinic	2.36–2.5	1.49–1.57	Light blue	Magenta
Crocidolite	Monoclinic	3.0–3.45	1.69–1.71	Magenta	Blue magenta

Table III—Dust Limit Values for Asbestos[a]

Country	Mass Concentration	Particle Concentration	
		Limit Value	Measuring Instrument
England	0.24 mg/m³ asbestos, respirable	4 fibers/cm³ > 5 μm (25 years exposure)	Membrane filter
United States	—	12 fibers/cm³ > 5 μm 7.0 particles/cm³	Membrane filter Impinger
USSR and CSSR	2.0 mg/m³ total dust	—	—
East Germany	—	100 particles/cm³ (A > 40 wt. %), 250 particles/cm³ (A > 40 wt. %)	Konimeter
West Germany	Total dust: 1.0 mg/m³ (A^b = 50 wt. %), 1.5 mg/m³ (A = 10–50 wt. %), 2.0 mg/m³ (A = 10 wt. %)	fibers = $\frac{C_s \cdot C_f}{100} \leq 20$ fibers = 20 $C_{max} = \frac{450}{VA_T}$ particles/cm³	Konimeter

[a] Reference 35. [b] A = asbestos component in wt. %; A_T = asbestos component in particle percent.

ed value. The same is true for the IR spectrophotometric method.

Differential thermal analysis also fails as a procedure because residual organic phases produce a series of strong exothermic reactions in the same range as asbestos. Electron beam instruments are the best for identification of asbestos fibers in tissue and allow long-term examination without physical or chemical artifacts interfering (23).

BIOCHEMICAL ASPECTS

Earlier studies suggested that the protein coating of asbestos bodies was collagen or a collagen-like substance (24). It has also been suggested that such bodies adsorb ferritin or a preformed iron–protein complex or that the protein and iron are adsorbed separately to build up the total complex. Histological evidence indicates that the alveolar macrophage cytoplasm contributes to the coating, with the iron being derived from phagocytized erythrocytes (25).

Newer studies on asbestos body coating indicate that the protein is not collagen based upon its hydroxyproline, glycine, leucine, and phenylalanine content (26). A histochemical study suggests that acid mucopolysaccharides are present in asbestos bodies and that such material acts as a matrix for iron deposition (27). This study supports the view that colloidal iron deposits on the acid polysaccharides during the formation of these bodies (28). The iron involved may be derived from hemolyzed erythrocytes (29).

Asbestos also can cause pleural calcification without fibrosis, but the biochemical mechanisms involved have not been elucidated (30). It has been reported that total and free serum amino acids, total protein, and globulins are higher in asbestos workers than in a control population (31). Asbestos workers also show a decrease in prealbumin and albumin and an increase in α-glycoprotein, α_2-lipoprotein, and transferrin and in serum IgG, IgM, and IgA fractions. There was no correlation between the length of asbestos exposure or the degree of asbestosis (32). There was an increase in the antinuclear antibody related to these parameters, but other immunological tests were negative (33).

INDUSTRIAL HYGIENIC ASPECTS

Dust Measurement—Such measurements have been highly controversial, because the instrumentation produced artifacts in the collected particles. Past standards for asbestos dust in the United States were based upon dust collection with an impinger, which collected few fibers and many grains. Moreover, it was not amenable to long personnel sampling, even though such sampling actually best approximated actual worker exposure (34). Therefore, more precise measurements were sought utilizing better instrumentation.

Table III gives the results of such investigations with different types of instruments and the dust limits obtained (35). These values are subject to change as new instrumentation is available and better correlation with epidemiological studies is obtained. It is now possible to evaluate each method in light of its good and bad points.

The British have checked many methods of dust estimation and found that the Owens jet counter is of value for taking snap samples but that efficiency decreases with increasing particle size and increasing air sampled. The konimeter suffers from the same defects and, in addition, the glycerin or petroleum coverslips cannot be ignited to remove combustible contaminants. The thermal precipitator is generally used in the United Kingdom and Europe, but its efficiency decreases for long fibers. The impinger is useful for particles 1 μm and larger but gives low values for asbestos.

The membrane filter method is good for 1-μm and larger fibers. It is consistent and covers the sampling rate between 10 and 500 cc/min. Moreover, samples can be taken for short or long periods, and the apparatus operates either electrically or by hand pump, is

robust, and can be used as a personnel monitor. The gravimetric method is in wide use in the United Kingdom but gives no indication of particle-size or fiber-size distribution. Tyndallometric methods (light scattering) count particles equal to spheres from 0.3 to 10 μm in 15 size ranges covering several counting rates but give a 25% lower value than a membrane filter with 5-μm and larger fibers. Moreover, it is doubtful that light scattering will work with all asbestos fiber types. Other limitations include counting all particles passing the light beam, the large size of equipment, and the necessity of checking by the membrane filter technique (36).

The U.S. Public Health Service has developed a more sophisticated membrane filter technique using counting under phase contrast microscopy and data reduction and statistical analysis by computer. The method is highly suitable for developing basic data for delineating the limits for airborne asbestos dust more accurately (34). Other investigators compared the membrane filter and electrostatic collector methods and found that the former gave excellent results but that the latter was inaccurate in measuring high concentrations of coarse particles because of short circuits and dust adherence to the discharge electrodes (37).

A comparison between the impinger and the membrane filter instruments revealed that the latter was probably better for the evaluation of fibers related to disease induction and, therefore, was more relevant to setting hygienic criteria (38). For measurement of total dust in a given environment or working area, the high volume sampler gives good results but does not, in general, give a direct measurement of individual exposure to dust and fibers. Such fixed-site samplers are used to obtain data on the efficiency of operation of dust control equipment (39).

Specifications for the evaluation of asbestos exposures in the working environment were defined by an international committee (40). Recently, these hygienic standards were extended to include amosite asbestos (41). Plant safety is only one aspect of the problem, because without effluent controls the outside environment can become contaminated and expose nonasbestos workers to the health threat of asbestosis. Moreover, it has been shown that such atmospheric contamination varies with the season, being greater during the winter months (42). The threshold limit for asbestos, 5 million particles/ft^3, or the German MAK value of fibers of 5 μm or more/cm^3 covers only inhalation and not ingestion; ingestion also must be addressed if the total environmental exposure to asbestos is to be realistically assessed (43, 44). Moreover, the threshold limit and MAK values must be modified as better measuring equipment becomes available. The fiberglass industry has recently been evaluated to determine its possible contribution to pneumoconiosis, and the survey indicated that the industry should not be put in the hazardous occupation category (45).

Protective Equipment—Dust in the work environment carries a certain risk, large or small, to health. There is no known absolute zero response because individual responses vary from one person to another and there is often a long latent period in the final development in the disease state (46). Methods for worker protection from airborne dust include: (*a*) enclosed working areas with or without a local exhaust system, (*b*) general room ventilation with large quantities of air, (*c*) water spraying to moisten dust, (*d*) use of a separate building, (*e*) local exhaust system over the work area, (*f*) work during evenings or on weekends to reduce the number of workers exposed, and (*g*) respiratory equipment (47).

All of these methods are used in prevention of asbestos exposure, but only the last, respiratory equipment, is useful in preventing individual exposure to the fibers. Continuous evaluation is necessary to develop performance characteristics of new and, perhaps better, dust respirators for fibrous dusts (48). Spray operators should be protected with a self-powered supplied air respirator or a constant-flow airline respirator with a belt control assembly and a quick-release coupling. For those not subjected to high asbestos dust concentrations, regular approved asbestos dust respirators can be used. All users should be instructed in the proper care and use of the respirator, particularly the necessity of changing filters (49).

The types of respirators required in the United Kingdom for protection against various concentrations of three types of asbestos are listed in Table IV (50). Table V indicates the magnitude of the problem in the English asbestos textile industry and the fact that particles did not include the fibers between 5 and 100 μm. A comparison of the data for 1952 and 1960 shows that the introduction of better hygienic practices reduced the dust exposure in various operations (51). In the dockyard, positive pressure power respirators are used and showering and changing from work clothes have reduced asbestosis cases and prevented further asbestos contamination of the environment (52). Spraying fibrous insulation can produce concentrations with fiber counts of 100 F/cc, requiring the use of air-supplied respirators because conventional filter-type respirators do not provide adequate protection (53). It has been shown that breakdown of the sealant covering sprayed asbestos insulation can introduce potential health hazards to occupants of such areas (54).

From the foregoing review of the industrial hygienic aspects of the asbestos problem, it is evident that

Table IV—Respiratory Protection against Asbestos Dust[a]

Concentration of Chrysotile or Amosite Asbestos, Fibers/cc Air	Concentration of Crocidolite Asbestos, Fibers/cc Air	Respirator
Up to 40	Up to 4	Dust respirator
Up to 200	Up to 20	Positive-pressure dust respirator
Up to 800	Up to 80	Ultrahigh-efficiency dust respirator
Greater than 800	Greater than 80	Positive-pressure airline breathing apparatus

[a] Reference 50.

Table V—Dust Levels at Various Textile Processes, 1952–1966[a]

Department	Process	Yearly Mean Dust Levels: T.P.[b], Particles/cm³ 1952	T.P.[b], Particles/cm³ 1960	LRTP[c] and Membrane, Fibers/cm³ 1961	LRTP[c] and Membrane, Fibers/cm³ 1966
Fiberizing	Mixing floor	500	—	—	—
	Opening	440	Now totally enclosed		
	Bag slitting	—	110	4.5	4
	Mechanical bagging	—	120	4	4.5
Carding	Fine cards	200	200	5.5	5.5
	Medium cards	810	400	7.5	8
	Coarse cards	1140	420	7	7.5
	Electrical sliver cards	490	260	5	2
Spinning	Fine spinning	170	110	4	3.5
	Roving frames	510	150	5.5	5.5
	Intermediate frames	530	100	5.5	5.5
Weaving	Beaming	190	220	8	3.5
	Pirn winding	350	130	3	2.5
	Cloth weaving	180	140	3	2
	Listing weaving	130	110	2	1
Plaiting	Medium plaiting	140	80	4	4

[a] Reference 51. [b] TP = thermal precipitator. [c] LRTP = long-running thermal precipitator.

progress in worker protection has occurred but that problems will constantly arise in other areas.

ANIMAL TOXICOLOGY AND CARCINOGENESIS

All forms of asbestos have been administered to many animal species by various routes except orally.

Intraperitoneal—Heating asbestos powder for 3 hr at 1000° and then cooling produced forsterite (Mg_2SiO_4) and enstatite ($MgSiO_3$) which, when administered intraperitoneally to CF-1 mice, killed 30 of 50 animals within 48 hr. Unheated asbestos did not have this effect. In another experiment with CF-1 mice, intraperitoneal injection of 0.5 ml of a 50% suspension of asbestos and serial sacrifice of the animals over 343 days gave evidence of a progressive, proliferative, granulomatous, invasive fibrosis histologically similar to mesothelioma (55).

Administration of five doses of 20 mg of amosite, anthophyllite, and crocidolite asbestos to female Wistar strain rats showed that the abdominal granulomas produced and the lymph nodes contained fibers of various lengths. Short fibers were intracellular while long fibers were not. Transport of fibers from the site of injection depends upon the length and begins with those measuring 20 μm and increases with decreasing length (56). Injection of chrysotile asbestos in fiber lengths of <5 and <3 μm produced the same percentage of tumors, but the time to tumor was prolonged with the smaller size fibers. The critical size for tumor induction appears to be longer than 2–3 μm. The addition of benzo[a]pyrene did not distinctly influence tumor induction (57).

Intratracheal—When 3.5 mg/ml of an aqueous suspension of chrysotile was administered to rats in total doses of 10.5–14 mg in 3–4 days and the animals were sacrificed at 4 days, the lungs showed a proliferative inflammation of the smaller bronchi and bronchioles. There were polypoid processes of avascular fibroblastic tissue originating from ulcerated areas in the mucosa and bronchial lumen. With time, 12–24 months, this inflammatory tissue converted to collagenous scars, which caused permanent deformities of the bronchi and bronchioles. There was also a macrophage reaction with a minimal stromal participation. It was suggested that the polypoid lesions were artifactual and related to the mode of administration because they did not occur in inhalation studies (58).

Russian chrysotile induced pulmonary carcinomas, sarcomas, premesotheliomas, and mesotheliomas in rats when 2 mg was injected three times monthly. Fiber sizes varied from 5 to 15 μm. When benzo[a]pyrene, 0.14 mg, was adsorbed on the asbestos, the number of lesions increased over the 9–28-month observation period. Moreover, asbestos alone had no effect during the first 6 weeks, but the addition of benzo[a]pyrene produced definite lesions in that time interval (59).

A study of asbestosis in guinea pigs showed that only crystalline chrysotile produced lung lesions. The dose instilled was 60 mg of fibers, 5 and 10 μm in length. The collagen content of the lungs was significantly increased (60). Other studies employing rabbits instilled with 2.5- or 15-μm fibers at a total dose of 100 mg at monthly intervals of 2–19 months showed foreign body reactions in the lungs, nodular reticulinosis, and diffuse interstitial reticulinosis (61).

Intrapleural—Injection of 10 mg of a saline suspension of chrysotile asbestos into the lower right pleural cavity of mice, with sacrifice intervals varying from 1 week to 6 months, resulted in pleural granulomas containing asbestos bodies in 2 weeks. The fibers were coated with acid mucopolysaccharide impregnated with ferritin or hemosiderin. Similar results were obtained with rats injected with a dose of 25 mg of the fibers (62).

Injection of 0.05 ml of a 50% lanolin suspension of asbestos into the right pleural cavity of female Osborne–Mendel rats monthly for 6 months did not produce any neoplasms in the lungs, pleurae, mediastium, or thoracic wall. This lack of carcinogenesis may have been due to the vehicle used, because saline suspensions do induce neoplasms (63). Administration of 20 mg of amosite, chrysotile, crocidolite, or extracted crocidolite intrapleurally in SPF or standard Wistar strain rats of both sexes produced a rapid onset of mesotheliomas. The time to onset was dependent on the type of asbestos, being longer for amosite than for the other varieties, although the fiber lengths (<2–200 μm) were the same. Solvent extraction of the crocidolite did not influence the results (64). A mathematical model was developed to describe the times to occurrence of the mesotheliomas (65).

In another study employing female Sprague–Dawley rats, injection with 66.7 mg of the three asbestos varieties produced mesotheliomas of the pleura and undifferentiated lung carcinomas (66). It has been shown that the carcinogenicity of amosite, chrysotile, and crocidolite asbestos fibers is related to structural

shape rather than to physicochemical properties. In contrast to a previous investigation (64), this study showed that amosite produced a more rapid onset of mesotheliomas (67). Injection of 20 mg of Russian chrysotile produced premesotheliomas and 42.26% mesotheliomas in the animals after 8 months (68).

Because the amount of asbestos required for the induction of mesotheliomas is small, it has been suggested that trace metal contamination may be involved (69). Neutron activation of chrysotile asbestos indicated that trace amounts of scandium, chromium, iron, and cobalt were present and were leached out and excreted and that 90% of the radionuclides were at the injection site at sacrifice. These findings indicate that fiber translocation is a slow process and that trace metal may not be involved in the neoplasm induction (70). Intrapleural injection of 25 mg of chrysotile asbestos into guinea pigs induced pleural granulomas in 14 days (62). This observation was confirmed (71).

Inhalation—Rats were exposed to chrysotile dust (quantity and fiber size not specified) for 18 hr/day for 50 days. The dust was found in the alveolar macrophages, which underwent changes to fibroblasts. There were also small nodular giant cell lesions. Changes occurred in the basement membrane with numerous impocketings in the cytoplasm of both epithelial and endothelial cells (72). Inhalation by rats of chrysotile dust (size range of <1–>20 μm) for 100 hr over 1 month showed that particles <3 μm rapidly produced fibrotic lesions in the lungs. Phagocytic ingestion is required to produce the lesion (73).

Inhalation of 86 mg/m^3 of chrysotile dust by rats for 2 years resulted in lung cancer. The incidence was greater in animals subjected to the additional insult of intratracheal instillation of 0.05 ml of 5% aqueous sodium hydroxide. It was suggested that traces of nickel, cobalt, and chromium might be involved in cancer induction (74). Another study showed that particles <20 μm long were fibrogenic, with this activity limited to groups of alveoli (75). Exposure of guinea pigs to amosite, chrysotile, and impure crocidolite dusts with particle sizes ranging from <0.3 to 2.2 μm produced asbestos bodies and diffuse interstitial fibrosis. Cuboidal metaplasia of the epithelium of the alveoli was also observed, and it had a pseudoadenomatous appearance at the 7th month. Amosite dust induced the asbestosis more rapidly than the other forms of asbestos. The lesions from chrysotile dust were severe and the impure crocidolite caused respiratory infection in the guinea pigs (76). These observations were confirmed for chrysotile fibers (72).

Peribronchiolar fibrosis of the rabbit lung was produced by inhalation of the various types of asbestos fibers (77). Lung lesions appeared earlier and were more severe in rabbits inhaling amosite fibers than in those exposed to chrysotile fibers (76). Rabbits inhaling fibers of amosite (3–5 and 0.2–0.5 μm), chrysotile (6–15 and 0.2 μm), and crocidolite (3–6 and 0.5 μm) in concentrations of 48.2 ± 1.4, 47.4 ± 1.7, and 48.7 ± 2.4 mg/m^3, respectively, developed a pulmonary fibrosis (78).

The selection of the animal species for asbestosis studies is critical because of the differences in the respiratory tract. When asbestos-exposed rats are maintained for more than a year, there is a considerable reduction in the lung dust burden because the alveolar clearance mechanism is more efficient than that of hamsters and guinea pigs (79). Vervet monkeys exposed to amosite, chrysotile, and crocidolite fibers developed the usual signs and symptoms of asbestosis and succumbed more readily to respiratory tract infections (76). Focal areas of interstitial fibrosis were found in a donkey that worked in an amosite mine, in a baboon living in the vicinity, and in rats *(Rattus namaquensis)* whose burrows were near an asbestos mill (80).

Other Routes of Administration—Injection of 58 mg of asbestos in lanolin into the marrow cavity of rats and rabbits resulted in oligocellular lesion but no tumors. Injection of asbestos into the paranasal sinuses of Osborne–Mendel rats gave similar negative results (63). Injection of chrysotile asbestos into the stomachs of rats indicated migration of the fibers *via* the bloodstream into the spleen, omentum, heart, brain, and lungs (81). However, it has been suggested that this mode of administration could have torn stomach blood vessels and that the asbestos suspension under pressure directly entered the bloodstream (82).

***In Vitro* Studies**—Tissue culture studies with guinea pig macrophages and mouse L line fibroblasts in the presence of chrysotile fibers (20–30 or 300 μm long or 10–20 or 100 μm long) were not lethal to, and did not impair glycolytic activity of, the former. The mice fibroblasts were not killed but did produce more collagen than the controls (83). Further studies of guinea pig macrophages indicated that both chrysotile and crocidolite fibers were cytotoxic because there was decreased lactic acid production, a loss of fluorochromasia by the cells, and a marked release of lactate dehydrogenase into the medium. Crocidolite was more toxic than chrysotile and pretreatment of the fibers with chelating agents, edetic acid (EDTA) and polyvinylpyrrolidone *N*-oxide, did not reduce the cytotoxic effect, indicating that the phenomenon was connected with physical and not chemical characteristics of the fibers (84).

Incubation of rat macrophages with amosite, chrysotile, and crocidolite dusts resulted in cell toxicity as measured by changes in acid phosphatase activity, 2,3,5-triphenyl-2*H*-tetrazolium chloride reducing power, and lactic acid production. Acid phosphatase activity was increased by chrysotile but not affected by the others. Chrysotile also slightly decreased the 2,3,5-triphenyl-2*H*-tetrazolium chloride reducing power and inhibited lactic acid production. Only chrysotile hemolyzed rat erythrocytes, and this action was prevented by polyvinylpyrrolidine *N*-oxide (85).

Increased lactic dehydrogenase activity and cell membrane permeability were seen after exposure of guinea pig alveolar and peritoneal macrophages to chrysotile fibers (86). Chrysotile asbestos has a high hemolytic activity whereas amosite, crocidolite, and anthophyllite lack this activity or are only weakly

lytic. This effect was attributed to the adsorptive capacity of chrysotile dust for erythrocyte membrane components (87). Comparison of the hemolytic activity of heated and unheated chrysotile fibers showed that the lytic properties were not identical because the lytic effect of the former was antagonized by carboxymethylcellulose and the latter by polyvinylpyrrolidone *N*-oxide (88). Chrysotile fibers adsorb globulins, and the adsorption bond strength was related to their fibrogenic activity (89).

It was demonstrated that amosite, anthophyllite, chrysotile, and crocidolite dusts absorb both serum IgG and rheumatoid factor, and it was suggested that the amount of the latter in asbestos workers correlated with the intensity of exposure (90). Stimulation of collagen synthesis by crocidolite fibers first elevates and then depresses proline hydroxylase activity; the latter effect occurs as the fibrotic lesion develops (91). Chrysotile produced a marked increase in tritiated thymidine uptake in the rat pleural mesothelium as early as 5–7 days after treatment, indicating a high degree of sensitivity to chrysotile. There was a rapid loss of the label after 7 days (92).

HUMAN TOXICOLOGY AND CARCINOGENESIS

The first case involving asbestos and human disease was recorded in 1907; the first case in the United States was reported in 1930. However, protective standards were not adopted until 1972. The extent of occupational and nonoccupational exposure is unknown, but the use of asbestos in the manufacture of cement pipes, sheets, shingles, floor tiles, millboard, roofing felts, pipe covering, insulation paper, flooring felts, friction and packing material, paints, roof coatings, caulks, sealants, safety clothing, curtains, brake linings, clutch facings, spray insulation, asphalt paving, welding rod coatings, and filter mediums in the pharmaceutical and beverage industries results in widespread exposure of the entire population (93). Such exposures have resulted in lung and pleural carcinoma and mesothelioma (94, 95). To understand the asbestos problem more fully, we shall discuss it industry by industry and point out the salient features of asbestosis from a clinical viewpoint.

Diagnosis—One preliminary sign of exposure to asbestos is the finding of asbestos bodies or asbestos fibers in sputum specimens (96, 97), but this sign does not indicate the presence nor the extent of disease or disability (98). Clinical observation of progressive dyspnea out of proportion to radiological changes in the lung and finger clubbing is indicative of asbestosis. The progression of the disease includes nonspecific interstitial fibrosis of the perihilar region, granular ground-glass-type infiltration, fibrosis extending throughout both lungs and pleura, marked emphysema with blebs and bulba, pleural diaphramatic plaques, and, finally, carcinoma and mesothelioma of the lungs, pleura, and peritoneum (99). Calcification of the parietal pleura and pleural plaques are distinct signs of asbestosis (100).

Definitive diagnosis of asbestosis requires the finding of asbestos fibers or asbestos bodies in affected tissue; but unless a biopsy is performed, such findings usually occur only at necropsy (101). The following diagnostic tests are also useful: a chest X-ray, vital capacity, 1-sec vital capacity, and lung compliance. The latter two tests progressively decrease during asbestos exposure, and the frequency of dyspnea is related to the decreased vital capacity (102).

Pleural calcifications by themselves are of little diagnostic significance (103) but can be helpful when a biopsy specimen shows asbestos bodies (104). "Asbestos pleural effusion" recently were added to the diagnostic signs of asbestosis (105). It also has been suggested that the ventilation perfusion ratio and the determination of blood gases should be included in asbestosis evaluation (106) because this condition is a restrictive disease with decreased diffusion capacity (107). This idea has been disputed, and it has been suggested that radiological changes in the lung coupled with measurements of forced vital capacity and 1-sec forced expiratory volume give a better assessment of the patient's condition (108). Whole body plethysmography and spirography have proven useful in following the progression of asbestosis, but chronic bronchitis can complicate the diagnosis (109).

Major clinical signs of asbestosis include diminished breath sounds, basilar crepitations, limited chest expansion, clubbing, and cyanosis. The latter two signs occur in advanced stages of the disease. Chronic bronchitis and a localized emphysema as well as right ventricular cardiac enlargement are seen. Cor pulmonale is the major complication and cause of death in asbestosis. Pulmonary endarteritis with intimal hyperplasia consistent with pulmonary hypertension and bronchioelectasia are present.

Measurement of pulmonary function is vital for a good diagnosis, because a chest roentgenogram can resemble the picture seen in viral pneumonia, lymphangtic carcinoma, Haman-Rich syndrome, and other diseases (110). Although there is a mixed impairment of the gas transport mechanisms in asbestosis, there is no relation between physical performance or radiological findings and diffusing capacity (111). Examination of 1069 men in the asbestos industry showed that only vital capacity and forced vital capacity could indicate the beginning phases of asbestosis (112).

In asbestosis, pleural reactions may occur in conjunction with mixed fibrotic reactions, making radiographic interpretation difficult. Moreover, the histological changes do not always correlate with the radiological pattern (113). In asbestos workers, vital capacity reduction precedes radiological changes by 10–15 years; the latter occurs after 20 years of exposure. After 30 years of exposure, the incidence of functional and radiographic abnormalities is the same (114). Difficulties in interpretation of radiographic changes in the various pneumoconioses have resulted in an international standard for rating the various degrees of pulmonary damage from dust exposure (115).

Radiocardiographic examination of eight patients with pulmonary asbestosis showed a reduction in

mean pulmonary circulation time and pulmonary blood flow and an increase in total blood volume, right ventricular telediastolic volume, and right ventricular postsystolic residual volume, indicative of a reduced pulmonary vascular bed (116). ECG changes consisting of left axis deviation, partial or complete bundle branch block, and right ventricular hypertrophy correlated with radiological findings in 29 cases of asbestosis (117).

Pulmonary radiological changes in asbestos workers have been related to age and years of employment (118). Examination by radioiodinated albumin scintography of 20 patients with asbestosis revealed pulmonary changes characteristic of fibrosis, with reduced radioelement in the peripheral lung field (119). Mucociliary function, as measured by inhalation and pulmonary clearance of ^{51}Cr or ^{99m}Tc microspheres, was normal in asbestosis (120). Severe asbestosis symptoms can be confused with mitral insufficiency, even when ECG and pulmonary function studies and occupation indicated asbestos was the agent involved in the residual function deficit (121).

From a diagnostic viewpoint, it is necessary not only to define the degree of cardiopulmonary impairment in obstructive pulmonary disease but to do a retrospective analysis of the patient's employment record to arrive at a positive diagnosis of asbestosis.

Pathology—The pathological changes occurring during the development of, and death from exposure to, asbestos have been well documented. It was shown that "folded lung," an extremely rare form of lung pathology, occurs in asbestosis. Folding occurred due to a fibrous membrane on the costal surface of the visceral pleural of the lower lobe. No adhesions were observed (122).

Pathological changes in the lungs in asbestosis include diffuse interstitial fibrosis with collagenization, ground-glass appearance of the parenchymal tissue, thickening of the pleura with calcified plaques, thickening of the alveolar walls and intraalveolar septa, alterations in the capillary network, macrophages containing asbestos fibers, and alveolar dilation with cuboidal metaplasia (123–127).

Asbestos does induce squamous cell carcinoma and adenocarcinomas in the lungs, and cigarette smoking increased the incidence by 8.05 times. Moreover, lung carcinoma exceeded mesothelioma by five to six times (128). In asbestosis, squamous cell carcinoma is usually in the lower lobes where the greatest number of fibers are found (129). Another complication of asbestosis is mesothelioma of the lungs and pleura. One serosal cavity is usually involved, but the underlying viscera are rarely involved. Spread is *via* the local lymph nodes with direct extension to the chest wall and spine. Distant metastases are rare (130). The latent period is usually 20 or more years.

The malignant elements are of both epithelial and mesenchymal character, with a tubular or tubo-papillary pattern containing cuboidal or flattened cells and masses of collagen. Hyaluronic acid is often present (131). The disease is rapidly progressive, averaging 2 years from onset to death (132). Microscopic examination of the malignant mesothelioma cell reveals an epithelial cell, which is large and polygonal with amphophilic cytoplasm and a clear cytoplasmic membrane. The round nucleus occupies one-third of the cell and has a loose vesicular chromatin. There are a large round eosinophilic nucleolus and multiple nucleoli. The nuclear membrane is folded or crenated, and there are many small intracytoplasmic vacuoles. Mitoses are uncommon, but multinucleated tumor cells are seen (133).

Mesotheliomas can be confused with other metastatic tumors if diagnosis is made on histological evidence alone (134). Some confusion has arisen as to the significance of pleural calcification in the development of mesothelioma (135). On the other hand, the association of asbestos exposure, occupational or nonoccupational, with malignant mesothelioma has been confirmed by investigators throughout the world (136–143).

The United Kingdom instituted a mesothelioma register where comparisons are made with carcinoma of the bronchus and lung in cases of asbestosis. Mesotheliomas occur earlier than the other pulmonary cancers. Table VI gives a comparison of mesotheliomas by site and sex for the years 1967–1968 and covers the United Kingdom. It has been suggested that even these data may be an understatement of the prevalence of the disease (144).

Asbestos Bodies in Pulmonary System—Having considered the consequences of asbestos exposure, it is necessary to discuss the actual means used for identification of the fibers themselves in asbestos bodies. The finding of asbestos bodies in the lungs does not indicate that asbestosis or pleural mesothelioma will occur or has occurred, because such bodies have been detected in 50% of the general population in certain areas. Moreover, other fibrous materials produce similar bodies, so asbestos must be positively identified (145). These other bodies may be formed from nonfibrous particulates and carbonaceous fibrous particles. Those with black fibrous core probably are derived from burning leaves, wood, or coal (146). These observations were confirmed (147). Electron micrographs have identified a large variety of dusts and fibers, which become iron coated in the lungs but do not give rise to pulmonary complications like asbestosis (148).

Classification of asbestos *versus* nonasbestos fibers

Table VI—246 "Definite" Mesotheliomas Analyzed by Sex and Site of Tumor[a]

Pathologists	Site of Tumor	Percent of All Mesothelial Tumors		Total
		Males	Females	
UICC[b] panel	Pleural	96	22	118
	Peritoneal	14 (12.8%)	2 (8.3%)	16 (11.9%)
Other pathologists	Pleural	81	17	98
	Peritoneal	10 (10.9%)	4 (19.0%)	14 (12.5%)
All	Pleural	177	39	216
	Peritoneal	24 (12.0%)	6 (13.3%)	30 (12.2%)

[a] Reference 144. [b] Unio Internationale Contra Cancerum.

is difficult, but ultramicroscopic criteria have been developed. At magnifications of 20,000 or 25,000×, asbestos fibers have profiles characterized by steplike interruptions up or down from each other and a surface characterized by parallel longitudinal lines delineating the fibrils. Nonasbestos fibers have uninterrupted linear profiles, and their surface is devoid of longitudinal parallel lines (149). Inhaled fibers become coated with an iron–protein envelope, and the central fiber can be identified as asbestos by electron microscopy.

As the asbestos body matures it changes from a thin yellow headed shape to a shorter, thicker, dark-brown segmentated form with a granulated coating which fragments and is phagocytized. This change in form can make identification difficult (150). Asbestos bodies have been demonstrated in lung smears in 30% of males and 20% of females in 500 autopsies in an urban area, but no pulmonary changes were reported (151). Another study found no correlation between nonoccupationally exposed individuals with asbestos bodies and inflammatory or neoplastic pulmonary disease (152).

An Israeli study could not evaluate the biological and clinical significance of asbestos bodies in the absence of pulmonary carcinoma (153). A New York study, in which 28 cases showed asbestos bodies, suggested that urban dwellers were being subjected to nonoccupational asbestos exposure (154). A Swedish study also reported asbestos bodies in lungs of nonoccupationally exposed individuals (155).

Methods suggested for positive identification of asbestos bodies in lung smears and sections include X-ray diffraction, phase contrast optical microscopy, optical microscopy, and electron microscopy (156–159). The last procedure is the best, particularly when combined with the scanning electron microscope. Isolation of fibers from asbestos bodies requires a digestion procedure that will not dissolve the fibers and still will allow quantitation of the total fiber population in a tissue specimen. Formamide dissolves the fibers while perchloric acid does not, and further solvent removes the excess carbonaceous material, resulting in a more exact determination (160).

Epidemiology—Occupational and environmental exposure to asbestos has been correlated with both pulmonary carcinoma and mesothelioma; but in an area where diagnostic procedures are in a state of flux, an epidemiological study is extremely difficult and unknown factors can make the results of limited value. Cohort studies of individuals in the same geographic areas and in a similar type of industry are required to obtain meaningful information (161). Epidemiological studies of asbestosis point out the long latent period before cancer development and the difficulty in determining the degree of exposure. However, when total deaths for a given locale and age group are compared by the life table technique, it is evident that asbestos does increase both pulmonary and bronchiolar neoplasia (162).

To standardize asbestos epidemiological surveys, the International Union Against Cancer suggested

Table VII—Cause of Death in Insulation Workers, Belfast, Northern Ireland, 1940–1965 (Total: 107; Mean Age: 55.3 ± 11.25 Years)[a]

Cause	Observed	Expected
Malignant:		
Intrathoracic neoplasms	28	5.3
Abdominal neoplasms	15	9.0
Other neoplasms	4	6.7
Nonmalignant:		
Pulmonary disease	31	25.6
Cardiac and circulatory	21	37.1
Other causes	5	21.3
Unknown	3	—

[a] Reference 164.

that detailed information covering social (smoking habits), occupational, environmental, and medical history from early childhood be collected for the individual and family units. As much information as can be obtained should be compiled on cardiopulmonary diseases and various fibroses and carcinoma of the lung, pleura, peritoneum, GI tract, and ovaries. Retrospective, cross-sectional, and prospective epidemiological surveys should be conducted, and one or more control groups should be included. Consultation with statisticians should occur prior to data collection and good experimental design should be employed (163).

The usefulness of a retrospective study is illustrated in Table VII, where the intrathoracic and abdominal neoplasms in insulation workers is excessive compared to the general population. The nonmalignant pulmonary deaths are related to the tuberculosis incidence (164). A cohort study of 1265 white males and 228 white females employed in an asbestos plant in 1938–1939 was analyzed in mid-1964, using Social Security records. Methodology was refined by including both age and duration of employment as well as all causes of death, asbestosis, cardiovascular disease, and malignant neoplasms. Upon this basis, it was possible to relate exposure to asbestos directly to a general increase in mortality rate from all of these causes (165). A further substantiation of the relationship between asbestos exposure and mesothelioma in this same plant was reported in which three more cases of mesothelioma not in the previous cohort were found (166). Further confirmation of the relationship between mesothelioma and slight asbestos exposure 20–30 years previously was shown (167).

Validation of death certificates using the British Registrar General and correlating necropsy reports with histological observations showed that bronchial carcinoma was not underestimated but that mesothelioma was (168). A German epidemiological study associated pleural mesothelioma with asbestos exposure many years previously (169). Material for future epidemiological studies will be obtained from the many industries involved in mining and processing asbestos.

Mining and Milling—The difficulties in associating asbestosis with mining are illustrated by a Bulgarian study of 3325 people living near an asbestos mine. Out of 155 cases of pleural asbestosis, only 23 were involved in mining; the remaining 132 cases

were tobacco workers. Air pollution was not involved, but the farms were composed of rocky soil containing asbestos minerals (170).

An Italian study of 288 cases of asbestosis gave the following distribution: mining, 32; friction products, 161; cement, 60; and insulation, 35; the indication was that finer asbestos dust was more dangerous (171). Exposure to Finnish anthophyllite asbestos in two mines resulted in an excess number of deaths from asbestosis and lung cancer (172, 173). Asbestosis has been reported in Australian miners but no mesotheliomas because the latent period for their development has not been passed (174).

Exposure to South African crocidolite asbestos produced 33 cases of diffuse pleural mesothelioma in the asbestos mining area of the country (175). Thirty-one other cases of asbestosis were examined but no pulmonary carcinomas were observed. This result is probably related to the short-time interval of exposure and the known latency for mesothelioma development (176).

There appears to be a difference between the development of mesotheliomas after exposure to crocidolite and amosite fibers, which suggests that the latter may be the least carcinogenic of the two forms of asbestos or require a longer time interval for tumor induction (177). This difference between the two varieties of asbestos is not evident when fibrosis is considered because they are then equally potent (178).

In a study of mortality in Quebec chrysotile mines covering 9981 individuals, only 97 lung cancers and three mesotheliomas were found. It was suggested that this form of asbestos may be less carcinogenic than the other varieties. Accumulated dust exposure and duration of employment apparently influenced the figures (179). Present dust exposures in these mines and mills are now 10 million particles/ft^3 down from the 75 million particles/ft^3 in 1948; thus estimation of total dust exposure must be adjusted not only for time but for work area and must take into account both fibrous and nonfibrous dust (180). Respiratory symptoms and function tests were related to dust exposure of 1015 individuals in these industries, but the other parameters had little or no influence (181, 182). Mining and milling in other countries do not differ from those reported here, but the types of asbestos do.

Asbestos Friction Materials—One occupation in which exposure to asbestos dust occurs in unsuspecting individuals is routine brake and clutch maintenance of automobiles and trucks. The amount of dust evolved in blowing out the brake drums varies from 1.42 to 3.62 fibers/cm^3; personnel samplers give an average of 0.68 fiber/cm^3 in the breathing area for automobiles, 7.09 fibers/cm^3 for brakes, and 2.25 fibers/cm^3 for trucks. Thus, over a time period, daily exposure could result in the development of asbestosis (183). Most of these figures are above the recommended level of 2 fibers/cm^3 (46).

On the other hand, the temperature generated on braking, 600°, causes the asbestos fibers to be converted into a series of olivine minerals which are unlike asbestos chemically, physically, and physiologically. It was suggested that dust clouds from brake drums are filthy but much less harmful than asbestos (184). Vacuum cleaning reduces the number of escaping particles to a minimum and should be used (185), but a vacuum brush is even better (186).

Asbestos Textiles—All areas of textile production (fiberizing, carding, spinning, plaiting, and weaving) have contributed to the induction of asbestosis, with subsequent development of peritoneal mesothelioma. In one factory, with asbestos exposures ranging from 10 months to 32 years, there were 11 cases of the disease; survival time varied from 20 to 46 years following the initial exposure (187). In the London area, textile industry asbestos exposure produced 83 cases of mesothelioma: 27 peritoneal and 56 pleural tumors. Terminal illness ranged between 16 and 55 years. In nine of these cases, domestic exposure occurred from asbestos dust on work clothes, pointing out one of the many ways the disease may be brought about (188). A factory in Pennsylvania had 68 cases of asbestosis with 21 malignancies; again the time to induction was long, 10–36 years (189). In 42 cases of mesothelioma, 10 persons worked in the factory, eight lived nearby, three were family members, 10 had some degree of asbestos exposure, and 11 had no history of exposure. Thus, environmental exposure was involved to a great extent (190).

Overall mortality from cancer of the respiratory and digestive tracts and cor pulmonale in asbestos textile workers was 21% above the U.S. national average in 1948–1951 (191). German experience indicates a similar type of response to asbestos, complicated with tuberculosis (192). An example of English textile workers dying of pleural mesothelioma is given in Table VIII. Again, long latency is evident (193). In Hamburg, 119 cases of pleural mesothelioma, 79 men and 40 women, were reported for 1958–1968 and 51 cases were definitely linked to asbestos exposure. The average latency for tumor development was 35.2 years (194).

A survey of 1160 asbestos textile workers revealed excess deaths from lung and pleura cancer and cancer at other sites in workers receiving heavy asbestos exposures. Excessive mortality from respiratory disease was also found in this group (195). Examination of smoking records in asbestos workers indicated possible synergism between these lung irritants and the induction of pulmonary fibrosis (196). Study of over 900 female asbestos workers showed that low to moderate exposure produced excess death from cancer; high exposure produced excess death from lung and pleural cancer as well as respiratory disease. Synergism between asbestos and smoking was observed (197).

Asbestos Insulation—The use of asbestos fibers in the insulation of homes and high-rise structures has been a source of asbestosis not only to the appliers but also to those occupying the building and those passing by in the area. Even with a history of prolonged exposure to asbestos, it may be difficult to reach a diagnosis of pleural mesothelioma because so-called benign mesotheliomas do occur and tuberculosis can stimulate the mesothelial cells to give the ap-

Table VIII—Occupational and Pathological Data Relating to Asbestos Workers Dying with Pleural Mesothelioma: All Employees[a]

Year of Death	Sex	Age, Years	Occupation	Period of Exposure	Duration of Exposure, Years			Necropsy		Death Certificate	
					Total	Before Jan. 1, 1933	From Beginning to Death	From End to Death	Performed	Asbestosis Present	Asbestosis Mentioned	Attributed Cause of Death
1936	Male	65	Fiberizer	1913–1936	23	19	23	<1	+	+	+	Endothelioma of pleura
1964	Male	57	Carder, spinner	1922–1923[b]	1 5/12	1 5/12	42	41	+	0	+	Malignant pleural tumor
1966	Female	55	Carder, spinner	1926–1935	9	6	40	31	+	0	0	Carcinoma of lung
1966	Male	59	Weaver	1937–1938[c] 1960–1965	6	0	29	1	+	+	+	Carcinoma of lung
1967	Male	72	Weaver	1914 1919–1920	0 7/12	0 7/12	53	47	+	0	0	Myeloid leukemia (carcinoma of lung associated)

[a] Reference 193. [b] Also employed for 15 years in the rubber department (1929–1944) and 20 years in the warehouse (1944–1964). [c] Also employed in the warehouse (1929–1930).

pearance of neoplasia (198). Examination of 632 building insulation workers revealed 45 deaths from lung or pleural cancer and 39 deaths from cancer of the stomach, colon, or rectum. The relationship of the latter to asbestos exposure could not be definitely proven (199).

The risk for asbestos insulation workers of developing mesothelioma of the pleura or peritoneum is much greater than for the general population, 10 per 307 *versus* 3 per 31,652 (200). Long exposure to asbestos fibers may not be required for the induction of mesothelioma of the lung, because an accountant exposed to asbestos insulation for 1 month developed the disease 6 years later (201).

Asbestosis has also been observed in hardboard and transformer winding workers but the minor exposure, while producing fibrotic changes in the lungs, gave no evidence of pulmonary cancer (202). Studies on 152 asbestos insulation workers revealed 46 deaths with 23 due to malignancy. All workers had 15 years of exposure to asbestos dust, and the range of ages was 33–81 (203). An increase in pleural mesothelioma was projected for Australian insulation workers since increased amounts of asbestos are being used in that country (204). A survey of 370 asbestos insulation workers indicated that those who smoked cigarettes have a 92 time greater risk of developing pulmonary cancer than those who did not smoke (205).

The most hazardous area in the insulation trade is the removal of old asbestos and its replacement, during which pounding of asbestos blocks and mixing finishing muds lead to high environmental fiber levels (206). The high risk of death from asbestos exposure, 300 out of 632 union members, resulted in a modern industrial hygiene program sponsored by the union, industry, government, and medical science. This preventative program should decrease the exposure of insulation workers (207).

Asbestosis has been shown to be a major cause of pulmonary disease in Northern Ireland, Sweden, and Finland (208–211). It had been suggested that insulation workers exposed to amosite might not get cancer, but 25 cases of lung cancer occurred in 230 workers exposed to this form of asbestos (212). A recent report indicates that there is a relationship between asbestosis and cancer of the larynx (213).

Pipe Insulation—The installation and removal of insulation on pipes in ships, power stations, factories, and buildings are very dusty operations. Pipe sections, slabs, powder, and mattresses are composed of 85% magnesia and 15% amosite asbestos. Exposure occurs during sawing and fitting pipe sections, mixing asbestos plaster, and stripping off old lagging (214). A comparison of fiber glass, polyurethane, and asbestos pipe insulation showed that only the latter could be considered hazardous. An evaluation of 33 death certificates gave a 24.2% incidence of malignant neoplasms in the asbestos workers (215). A revision of the threshold limit value for asbestos was suggested when it was discovered that pipe coverers working for 20 or more years had a 38% incidence of asbestosis when exposed to apparently "safe" dust concentrations (216).

Table IX—Ranges of Dust Concentrations in Various Dockyard Areas[a]

Process	Range, Fibers/cm³
Storerooms	0.1–36
Application of amosite sections	9–40
Application and stitching of asbestos cloth	0.05–0.26
Removal of amosite sections (boiler room)	29–1040
Removal of blue sprayed asbestos	112–1906
Removal of asbestos acoustic board	48–683
Bagging asbestos debris	106–3815

[a] Reference 219.

Ship Repairs—Shipboard pipe covering and insulation during overhaul and repairs are extremely hazardous, and it is difficult to prevent massive exposures (217). Diffuse mesothelioma was related to asbestos exposure in 14 shipyard workers in Liverpool (218). The range of fiber counts in various occupations in a dockyard is given in Table IX; removal of asbestos gives the highest counts and the greatest worker exposure (219). Asbestos exposure in English shipyards has been shown to produce pleural fibrosis (28%) but only a few cases of mesothelioma (220, 221).

Dutch investigators found an unusually high incidence of pleural and peritoneal mesotheliomas in shipyard asbestos workers (222). A Scottish retrospective study, covering 1950–1967, discovered 80 cases of malignant mesothelioma in shipyard workers handling asbestos (223). In 1965–1970, 25 cases of pleural mesothelioma were reported in Plymouth shipyard workers (224). A similar observation was made for Italian (225) and Dutch (226) shipyard workers.

In a cohort study, it was found that asbestosis in shipyard workers was 11 times more prevalent than in the controls and prolonged exposure to asbestos, even at low dust concentrations, was hazardous (227, 228). Continuous surveys of British dockyard workers turned up 37 cases of mesothelioma since 1965 and many cases may go undetected (229).

Other Sources of Exposure—The widespread use of asbestos, including asbestos-cement water pipes, beverage filter media, household iron-holders, and asbestos in cigars, is a nonoccupational route of exposure which contributes to the worldwide distribution of cancer (230). The incidence of English males dying from asbestosis and having lung cancer during 1924–1963 is given in Table X. The percent of those with lung cancer has been increasing because the victims have been living longer (231).

Table X—Incidence of Lung Cancer in Males Dying with Asbestosis[a]

Period	Deaths from Asbestosis	Percent with Contaminant Cancer of Lung	Average Age at Death from Uncomplicated Asbestosis, Years
1924–1940	79	16.4	49.3
1941–1950	92	22.8	55.9
1951–1960	144	31.3	58.1
1961–1963	77	54.5	60.4

[a] Reference 231.

Protective asbestos clothing (aprons, gloves, and aluminized asbestos garments) give rise to high fiber counts in the respiratory area (232).

Asphalt–asbestos or vinyl–asbestos tile contains 15–25% asbestos, which becomes airborne during the sanding operation associated with their installation. Mesotheliomas have resulted from inhalation of this dust (233).

Fire-eater's asbestosis has occurred from extinguishing the torch by placing it in the mouth (234).

Coke oven or silo construction requires effective insulation containing asbestos, and workers have developed asbestosis with lung carcinoma and/or mesothelioma (235, 236).

Asbestos cement and wall board present hazards to both the producer and the user. In the latter case, sawing such boards without using a respirator has resulted in the development of asbestosis years later (237, 238).

Asbestosis has also been associated with severe rheumatoid disease with necrobiotic foci similar to those encountered in subcutaneous rheumatoid nodules (239, 240). In 80 cases of asbestosis, antinuclear and rheumatoid factors were found in 28 and 27%, respectively. There was a relationship between these autoantibodies and the degree of radiographic abnormality but not between the duration of asbestos exposure (241).

COMMENT AND CONCLUSIONS

In the controversy concerning amosite fibers in water supplies, it is necessary to identify and establish exact amounts of asbestos per unit volume. It has been established that the Duluth water supply contains 1–30 × 10^6 fibers/liter, equivalent to 1–30 μg/liter (242). This amount would appear to present a hazard to the individuals exposed daily (243). An analysis of cancer mortality in the region indicated no increase in cancer mortality patterns of persons of any age group. However, only 14 years have passed and asbestos-induced cancer requires at least 20 years (244). It was suggested that this lack of carcinogenic effect is related to the inability of particle transmigration through the intestinal mucosa (245). The size of the fibers, less than 5 μm in length, may be incapable of causing fibrosis or cancer (246).

Thus, after reviewing the asbestosis problem, covering chemistry, industrial hygiene, animal and human toxicology, and carcinogenic aspects, it becomes evident that more attention must be paid to analytical chemistry, particle size, and epidemiology. The difficulties encountered in the analysis of asbestos reside in the fact that its chemical composition differs only slightly from one variety to another and, depending upon the method of preparation, it may become contaminated with other metallic ions. Since particle size appears to be the controlling factor in the induction of asbestosis and cancer, accurate sizing must be done to prevent a negative result. Epidemiology should include a continuing follow-up of known cases of asbestosis and the addition of new cases as they become apparent. Cohort studies should

be initiated where possible, and assessment of the degree of exposure should be undertaken to correlate the amount of asbestos inhaled with individual response as related in time.

Experimental studies covering ingestion of various forms of asbestos should be initiated to ascertain the effect of such ingestion on GI penetration and the development of fibrosis and carcinoma. A good statistical design should be employed, utilizing both physical (fiber glass of the same particle-size distribution) and chemical control groups. In the latter case, the chemical should have its major carcinogenic effect on the GI tract. The animal species selected for this experiment should have a low spontaneous incidence of carcinoma of the target tissue and, hopefully, an overall low incidence of tumors in other tissues. The observation of time to tumor should also be included. Diet variations (*e.g.*, ulcerogenic) should be considered as a possible additional aspect of the problem.

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