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MESOTHELIOMA

Ruth Lilis

DEFINITION

The primary malignant neoplasm of the pleura —diffuse pleural mesothelioma—has been recognized and accepted as a nosologic entity only during the last 20 years (77), although as early as 1767 Joseph Lieutand (cited by Robertson) reported two cases of probable mesothelioma among 3,000 autopsies, and E. Wagner described the pathology in 1870 (53)(72).

It is not known with certainty when the term "mesothelioma" was first used; one of the early reports indicating a primary and malignant tumor of the pleura and using the term mesothelioma was that by DuBray and Rosson (14).

In 1931, Klemperer and Rabin published a comprehensive description of the distinctive features of diffuse pleural neoplasms and recommended these tumors "should be designated mesothelioma;" since they arise from the surface lining cells of the pleura, the mesothelium (27). The malignant, diffuse pleural mesothelioma arises from the multipotential coelomic mesothelial cell of the pleura. Similarly, malignant tumors originating in the mesothelial cells of the peritoneum are peritoneal mesothelioma.

The definition of pleural mesothelioma thus includes:

- the origin of the tumor in the mesothelial cells of pleura
- the diffuse character of the tumoral growth, often involving a large surface or even the entire pleura of one lung, at the time of diagnosis
- the characteristic rapid growth and extension over the surface of the pleural serosa (closely related to the diffuse character)
- the high degree of malignancy, expressed in rapid growth, local invasiveness (soft tissue and bone structures of chest wall, underlying lung, adjacent pericardium, regional lymph nodes), and frequent metastases to a variety of organs, including brain, liver, kidney, adrenals, etc. These characteristics of pleural mesothelioma have an integrative expression in the mean survival time after diagnosis, which does not exceed 12 months in most reported series, with or without therapeutic attempts.

The association between malignant "endothelioma of the pleura" (mesothelioma) and asbestos exposure was first reported by Wyers (80). Wagner et al., published a report on 33 cases of diffuse pleural mesothelioma from the North West Cape Province of South Africa; most of these cases had occurred over a four year period, and in all but one, exposure to asbestos (crocidolite) could be established (77). Mesothelioma was not necessarily preceded by asbestosis (interstitial pulmonary fibrosis); the exposure was occupational in some cases, but in others, only environmental (residential) exposure had occurred. The long latency period—a mean of 40 years—between initial asbestos exposure and the development of malignant pleural mesothelioma was another striking characteristic of these cases. The carcinogenic hazard of relatively low levels of asbestos exposure; the possibility that pleural mesothelioma associated with asbestos exposure may develop in the absence of preceding pulmonary interstitial fibrosis; and the long latency period between onset of exposure and development of the malignant mesothelioma, were thus outlined.

LIST OF CAUSATIVE AGENTS

Asbestos fiber is widely accepted as the causative agent in the vast majority of mesothelioma cases. So far, asbestos is the only fibrous mineral

where epidemiologic data have shown an association between exposure and pleural and peritoneal mesothelioma in man.

Asbestiform minerals are grouped in two major categories: chrysotile, which is a serpentine, and the amphiboles, which include crocidolite, amosite, anthophyllite, and tremolite.

The first large group of malignant pleural mesothelioma cases due to asbestos exposure was related to crocidolite in South Africa (77). This fact, and subsequent reports on mesothelioma cases from Great Britain where crocidolite had been extensively used, contributed to the empirical and one-sided view that crocidolite was the main or even the only type of asbestos with a specific carcinogenic potential resulting in the eventual development of mesothelioma.

The major increase in mesothelioma incidence in the United States—where chrysotile has been and still is the main type of asbestos used—supports a causal association between chrysotile exposure and development of mesothelioma (4)(31)(59)(63)(64). Epidemiologic evidence for worker cohorts has shown chrysotile to be equally as potent as other fiber types insofar as lung cancer is concerned (13)(49)(80). While the number of mesothelioma cases from populations exposed only to chrysotile has been small, an association with chrysotile exposure has been definitively established. Amosite has also been shown to have a similar carcinogenic effect; a significant number of mesothelioma cases have occurred in a cohort of 933 amosite factory workers(62). Experimental studies on rats using inhalation of five types of asbestos fiber resulted in the development of mesothelioma with chrysotile (Canadian), crocidolite, amosite, and anthophyllite (74). Previous experiments using intrapleural administration of amosite, chrysotile, and crocidolite had given similar results, with chrysotile giving the largest number of mesotheliomas, followed by crocidolite and amosite (73). Shabad et al. also reported on the experimental production of pleural mesothelioma in rats, with intrapleural administration of chrysotile (65). Thus, both epidemiologic evidence and experimental confirmation indicate that chrysotile, amosite, and crocidolite asbestos are causative agents for mesothelioma.

Recently another type of fibrous mineral—naturally occurring zeolites (aluminum silicates) of the fibrous variety (erionite, mordenite)—has come under close scrutiny as a potential causative agent for malignant mesothelioma. The evidence for this association is based on the findings in a rural area of endemic mesothelioma in Turkey, where mineralogic investigations have not found any asbestos minerals, but have identified fibrous zeolites. Although this is still being actively researched and conclusive evidence is not yet resolved, fibrous zeolites are considered highly suspicious at the present time.

Reports on endemic mesothelioma in other parts of the world—such as in a rural area in India—have not yet identified the etiologic agent; the possibility that zeolites may be the causative agent cannot be excluded, since zeolites are known to be present in that area.

Experimental studies using intrapleural application suggest that other fibrous materials, such as fibrous glass, may also induce malignant mesothelioma (68). Epidemiologic evidence for fibrous glass as a causative agent for mesothelioma has not been reported, but fibrous glass has to be included as a suspected causative agent.

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

Occupations and industries at risk to mesothelioma include all of those listed for asbestosis.

All available information indicates that mesothelioma may be the result of low levels and/or relatively short (of the order of several weeks to several months) asbestos exposure. The dose-response relationship for mesothelioma is therefore different than that for asbestosis (which develops with higher exposure levels over longer time periods) or bronchial carcinoma associated with asbestos exposure (which increases in incidence even after short periods of high asbestos exposure levels, but shows a marked increase in incidence with duration of exposure)(58). Since low asbestos exposure levels carry a significant risk of mesothelioma, occupations and industries characterized by relatively low asbestos levels (auto mechanics and brake repair, tapers in dry wall construction, handling of finished asbestos products including asbestos cement), while at relatively low risk for the development of parenchymal interstitial fibrosis (asbestosis), are nevertheless at high risk for mesothelioma.

Equally important is the fact that numerous workers in the various trades which do not simply direct asbestos exposure, such as electricians, painters, welders, carpenters, etc., in shipbuilding or ship repair, in construction, in maintenance

work at chemical plants, and even automobile salesmen supervising repair work, are frequently exposed to asbestos due to their mere presence in work areas where asbestos is being handled. This "bystander" exposure has been repeatedly documented to be responsible for numerous cases of mesothelioma (20)(51). It is therefore important to establish the principle that such indirect exposure carries a significant risk of mesothelioma.

Whitwell et al. found that 83% of mesothelioma cases reviewed contained over 100,000 asbestos fibers per gram of dried lung tissue; in cases of asbestosis the number of asbestos fibers was much higher, exceeding 3,000,000 per gram of dried lung tissue (79).

In shipyard workers, more and more mesothelioma cases have been reported; most of these have occurred in trades other than insulation workers, indicating that the risk is widespread (20)(61). The distribution of trades in private shipyards in the United States in 1943 is presented in Table VIII-24. A list of occupational titles in an Eastern U.S. shipyard in 1975 is given in Table VIII-25.

It is difficult to construct a complete list of all occupations in which asbestos exposure may occur at one time or another. Since short-term asbestos exposure (several weeks to several months) is often responsible for mesothelioma occurring 25, 30, 40, or 50 years later, the occupation/industry involved at the time of the diagnosis of a malignant tumor may differ from the occupation/industry where the exposure actually occurred. Therefore, at any point in time, much higher numbers of individuals are at risk for the development of mesothelioma than those working in industries and occupations known to be associated with asbestos exposure. Recollection of remote past exposures and of specific jobs in which they occurred is a formidable task, but crucial when assessing whether one particular case of mesothelioma is related to past asbestos exposure.

Table VIII-24

PERCENTAGE DISTRIBUTION OF TRADES IN PRIVATE SHIPYARDS IN THE UNITED STATES, JUNE 1943

Trade	*Percentage*
Welders	15.3
Shipfitters	11.0
Machinists	8.1
Pipefitters	7.2
Electricians	6.6
Carpenters	6.1
Laborers	5.5
Burners	3.8
Painters	3.1
Sheetmetal workers	3.0
Riggers	2.8
Chippers and caulkers	2.8
Boilermakers	2.3
Crane operators	1.3
Pipe coverers	0.2
All other	21.1

Source: Bureau of Labor Statistics, Bulletin 824, "Wartime Employment, Production, and Conditions of Work in Shipyards," 1945.

EPIDEMIOLOGY

The relationships between asbestos exposure and pleural mesothelioma regarding latency period, dose-response characteristics, populations at risk, and incidence of disease have been presented in the section—List of Occupations and Industries Involved, page 672.

Pleural mesothelioma is a rapidly progressing malignant tumor, the resulting disability is total, and the condition is usually fatal in one to two years. There are no confounding conditions or risk factors which limit the ability to establish cause-effect relationships.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF DISEASE

The population at risk for developing mesothelioma includes:

- all occupations with direct contact and handling of asbestos.
- employees with other occupations (electricians, welders, painters, carpenters, etc.) who work or have worked—even for short periods—in areas where asbestos has been handled by others.
- family members (household contacts) of asbestos workers who have been exposed to asbestos fibers brought into the household by the worker. Household contamination has been found to result in asbestos exposure of family members of asbestos workers, sufficient in magnitude to induce mesothelioma (1)(2)(5)(32)(41)(46)(55)(56).
- individuals who have resided in the vi-

Table VIII-25

OCCUPATIONAL TITLES IN AN EASTERN U.S. SHIPYARD, 1975

Guard & Watchman	Heat Treater	Power House Engineer	Shipfitter
Construction Mechanic	Tool Grinder	Molder	Lead Bonder
Laborer	Tool Room Attendant	Foundryman	Welder
Firefighter	Lathe Operator	Foundry Chipper	Burner
Scrap Material Sorter	Miller	Melter	Rigger
Painter	Drill Operator	Coremaker	Sheetmetal Mechanic
Painter Cleaner	Grinder	Pipefitter	Joiner
Maintenance Painter	Machinist	Silver Brazer	Carpenter
Truck Driver	Engraver	Pipecoverer	Industrial Radiography Technician
Fork Lift Operator	Layout	Electrician	Radiological Control Monitor
Warehouseman	Machine Rigger	Electronics Technician	Clerk
Transportation Locomotive Operator	Make Ready Man	Maintenance Electrician	Data Processor
Toolmaker	Crane Operator	Loftsman	Secretary
	Maintenance Machinist	Blacksmith	Timekeeper
	Dock Crew	Furnaceman	
	Inspector		

cinity (one mile) of an asbestos plant, shipyard, or other source of asbestos contamination.

The population at risk at any point in time has to include all persons who have been exposed *in the past*. Given the long latency period between asbestos exposure and development of mesothelioma (on the average 35-40 years), individuals who have been exposed (even for short periods of time) during the last 50 years have to be considered potentially at risk.

Contributing to the population size at risk is (1) the fact that short duration of asbestos exposure (several weeks to several months) is sufficient to induce mesothelioma; (2) the high job mobility, especially during World War II; (3) the marked increase in the total amount of asbestos used per year; and (4) the diversification of its uses. The estimate of the population at risk is, for the same reasons, a complex and difficult task.

Attempts to assess the incidence of mesothelioma in populations at risk are also fraught with difficulties; these have multiple sources.

1. The complexity of the diagnostic criteria, which require pathologic confirmation; the most rigorous criteria make the diagnosis dependent on a complete autopsy (for the exclusion of another primary site of the tumor, which might have metastasized to the pleural cavity). Only a proportion of all deaths are followed by a postmortem examination. This proportion varies with geographic area, with the time period considered, and with other factors.
2. Even when tissue specimens are examined by experienced pathologists, the diagnosis is not always simple; differences of opinion may persist and result in conclusions on the pathologic characteristics such as "possible mesothelioma" or probable mesothelioma."
3. Evaluation of the incidence of mesothelioma from death certificates has been reported, by all those who have investigated this problem, as incomplete, leading to a marked but quantitatively variable underestimate of the number of cases. This problem is compounded by the fact that the coding of causes of death does not provide a separate code for mesothelioma, but includes it with cancer of the lung or pleura.
4. The most reliable data are those based on the cohort approach: asbestos-exposed employees followed for many years, with a comprehensive assessment of causes of death. The long latency period between

onset of asbestos exposure and mesothelioma has resulted in a limited number of studies with a long enough follow-up period to realistically reflect its incidence. In all these cohort studies, most with several reports published over time, it is a rule without exception that the longer the observation period, the higher the incidence of mesothelioma.

Although the most relevant data on mesothelioma risk in asbestos-exposed populations are derived from long-term cohort studies, other studies following different approaches have also revealed the paramount importance of long-term follow-up and completeness of diagnostic means. The most significant information follows.

By 1965, 160 cases of mesothelioma had been recorded in the United Kingdom, 123 from England and Wales, 36 from Northern Ireland, and only one from Scotland (39). When a systematic review of all necropsy and surgical biopsy reports in all hospitals was undertaken, 80 cases of mesothelioma were found to have occurred in Scotland for the years 1950-1967. Many cases were in employees who had had no direct exposure to asbestos but had been employed in the shipbuilding industry, in a wide variety of trades.

The Mesothelioma Register in Great Britain (Employment Medical Inspector's Advisory Service)—with data sources in death certificates, Cancer Bureau registrations, Pneumoconiosis Medical Panels (claims for benefits under the National Insurance Acts), chest physicians, surgeons, pathologists and coroners—had 413 cases reported for 1967-1968; 75% of the confirmed cases with definite asbestos exposure came from shipbuilding, asbestos factories, and insulation work; the other 25% from a variety of occupations (welders, electricians, gas workers, mechanics, chemical workers, etc.). The highest rate/million per year of mesothelioma (confirmed cases) figures were 8.93 and 8.24, both in shipbuilding areas. The incidence of definite mesothelioma in the United Kingdom for the period 1967-1968 was 120 per year. It was concluded that this figure may considerably understate the true incidence.

McDonald and McDonald reviewed evidence published between 1959 and 1976, including cohort studies of asbestos workers; "population studies" (mesothelioma surveys in Canada and the United States describing "case-series referable to some kind of denominator"); case reports unrelated to any denominator; and mortality statistics, mainly in Canada, the United States, and the United Kingdom (37). Data from the Third U.S. National Cancer Survey (42) was also reviewed. A total of 4,539 cases had been published after 1958. (This figure did not include cases from official mortality statisitics and Third U.S. National Cancer Survey.) The incidence of mesothelioma for the period preceding 1958 had been very low: in 1957 Hachberg mentioned 43 cases in 60,042 autopsies over the 40-year period, 1910-1949, i.e., less than 1 case per year and only 0.07% of the autopsies performed (Philadelphia, Baltimore, Minneapolis, New York, and Toronto in North America and Munich, Prague, and Copenhagen in Europe).

The marked increase in the incidence of mesothelioma over the last 20 years is evident when comparing the total number of reported cases (436) for the period 1955-1959, with that of 1,697 cases of mesothelioma for the period 1965-1969 (an almost fourfold increase). Interestingly, 9% of cases were due to neighborhood or household-family exposure.

In the Third National Cancer Survey (1975), a thorough ascertainment was done using hospital records and pathology material, besides death certificates, in selected areas comprising approximately 10% of the population of the United States (deaths in 1971). The annual rate per million for males 45 and over was 11.20 and for females in the same age range, 3.53.

Reports from other countries, such as Germany, Sweden, the Netherlands and Great Britain, indicate much higher rates than those published for Canada by McDonald (10 per million for males and 4 per million for females, over 45-years-old) for some cities and regions, most with large shipyards: Walcheren had a death rate 23.3 times higher than that expected according to the Canadian rates; Wilhelmshaven (21.5 times higher); Plymouth (14.3 times higher); and Rotterdam, Harlem, Hamburg, Malmo, Nantes, and Trieste (with rates 7-8 times higher) (38)(51)(69). These data indicate that annual incidence rates for mesothelioma in geographical areas with shipyards and/or other important asbestos industries or uses are of the order of 200/1 million or higher, for men aged 45 or over.

The most relevant data on the incidence of mesothelioma in exposed populations are derived from cohort studies of occupational groups. But

only studies with long follow-up (30-40 years) can provide comprehensive information, although even these might not include all the cases. It has been estimated, from the relatively limited number of such studies, that between 5% and 11% of all deaths in asbestos-exposed workers are due to mesothelioma (16)(26)(43)(45)(61)(62)(63). In a cohort of 632 asbestos insulation workers observed prospectively from January 1, 1943 to December 31, 1976, 38 out of a total of 478 deaths were due to mesothelioma (see Table VIII-26) (60). The mortality experience of a large cohort of 17,800 asbestos workers in the United States and Canada (Table VIII-27) observed from 1967 to 1977 indicates that 175 out of 2,270 deaths were due to mesothelioma. In a cohort of amosite asbestos factory workers employed from 1941-1945, and observed until 1977, 16 out of 594 deaths were due to mesothelioma (Table VIII-28) (62). In another cohort of 689 asbestos factory workers employed before January 1939, and observed from 1959 through 1975, 26 out of 274 deaths were due to mesothelioma (48)(60). Newhouse reported the mortality experience of workers in an East London asbestos factory, 1931-1970; out of a total of 461 deaths, 35 were due to mesothelioma (43).

The importance of long-term observation is shown in Tables VIII-29, VIII-30, and VIII-31.

Two further problems are: 1) the correct assessment of all those at risk for developing mesothelioma in various occupations, or who have had such exposure even for short periods of time sometime during the last 40-50 years; and 2) quantification of the risk for "bystander" exposure, neighborhood or other types of environmental exposure (buildings, schools, etc.), and household-family exposure.

Although no firm data are as yet available for these types of asbestos exposure, according to the information available on cases occurring after short (several weeks) and relatively low levels of exposure, it has to be assumed that the risk is of the same order of magnitude as that for occupationally-exposed groups.

PATHOLOGY, PATHOGENESIS, AND PATHOPHYSIOLOGY

The pathology of mesothelioma is largely determined by the potential of the mesothelial cells to produce tumors of epithelial, mesenchymal, or most commonly a mixed type. This potential is related to the embryologic origin of the mesothelium, which is derived from coelomic epithelium developed from the mesoderm and underlined by mesenchymal tissue (27).

The macroscopic features of pleural mesothelioma are those of a gray-white or yellow-gray mass, varying in extent from a part of the lung's surface to a complete, or almost complete, encasement of the lung. The tumor has a rapid growth rate, extending along the serosa, with a tendency to grow along the interlobar fissures. Both the parietal and visceral pleura are involved; often the tumor seems to have originated in the visceral pleura (for example, in the minor fissure).

Two types of mesothelioma can be observed: 1) the scirrhous type, presenting as a hard sheet, with variable thickness often exceeding one inch, rapid encasement and compression of the lung, partial or total obliteration of the pleural cavity, and contraction of the hemithorax; and 2) the encephaloid type, presenting as large tumor masses, often multiple, sometimes with extremely rapid growth (seen on chest x-rays as "scalloping").

Continuous spread—with local invasion of the pericardium, mediastinum, chest wall, diaphragm, and, through it, the liver and peritoneum, or into the controlateral pleura—is frequent. The underlying lung can be invaded directly, into the pulmonary parenchyma immediately underlying the pleura, or by spread into septal and perivascular lymphatics, with lymph node involvement in about 50% of cases. Distant metastases, thought in the past to be rare, are, on the contrary, quite frequent, affecting the brain, liver, kidney, adrenals, thyroid, lung, or other organs in more than 50% of cases. Tumor growth along the needle biopsy track or surgical scar after thoracotomy is common.

Microscopic features are characterized by diversity of appearance, not only from case to case, but also in the same tumor, where both epithelial (or tubulo-papillary) and mesenchymal (or fibrosarcomatous) areas can be observed. According to the microscopic pattern, mesothelioma can be classified into four types: 1) epithelial or tubulo-papillary, with the epithelial cells usually cuboidal or flattened, tending to form tubular and papillary structures, separated by a more or less abundant matrix; 2) mesenchymal or fibrosarcomatous, appearing as a spindle cell sarcoma, but sometimes with extensive areas of acellular collagen; 3) mixed, the most frequent form, containing both epithelial and fibrosarcomatous areas; 4) the undifferentiated type, with polygonal, less often spheroidal cells, with large nuclei and scanty mitotic figures. These cells resemble those of the tubulo-papillary

Table VIII-26

EXPECTED AND OBSERVED DEATHS AMONG 632 NY-NJ ASBESTOS INSULATION WORKERS OBSERVED PROSPECTIVELY JANUARY 1, 1943 - DECEMBER 31, 1976

Number of Men	**632**
Man-years of observation	**13,925**

	Deaths 1.1.43-12.31.76	
Cause of death	*Expected**	*Observed*
Total deaths, all causes	328.9	478
Total cancer, all sites	51.0	210
Lung cancer	13.3	93
Pleural mesothelioma	**	11
Peritoneal mesothelioma	**	27
Cancer of esophagus	1.4	1
Cancer of stomach	5.4	19
Cancer of colon - rectum	8.3	23
All other cancer	28.06	36
Asbestosis	**	41
All other causes	262.6	227

*Expected deaths are based upon age and sex-specific U.S. death rates of the National Center for Health Statistics, 1949-1975 actual rates, 1943-1948 extrapolated from 1949-1955 rates, and 1976 extrapolated from 1967-1975 data.
**These are rare causes of death in the general population.

Table VIII-27

DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA JANUARY 1, 1967 — JANUARY 1, 1977

Number of Men	**17,800**
Man-years of observation	**166,855**

	*Expected**	*Observed*	*Ratio*
Total deaths, all causes	1,660.96	2,270	1.37
Total cancer, all sites	319.90	994	3.11
Lung cancer	105.97	485	4.58
Pleural mesothelioma	**	66	—
Peritoneal mesothelioma	**	109	—
Cancer of esophagus	7.01	18	2.57
Cancer of stomach	14.23	22	1.55
Cancer of colon - rectum	37.86	59	1.56
All other cancer	154.83	235	1.52
Asbestosis	**	162	—
All other causes	1,351.06	1,114	0.82

*Expected deaths are based upon white male age-specific mortality data of the U.S. National Center for Health Statistics for 1967-1975 and extrapolation to 1976.
**These are rare causes of death in the general population.

Table VIII-28

EXPECTED AND OBSERVED DEATHS
AMONG 933 AMOSITE FACTORY WORKERS EMPLOYED
1941-1945, OBSERVED TO DECEMBER 31, 1977

	Deaths 1941-1977		
	Expected[a]	*Observed*	*Ratio*
Total deaths	368.62	594	1.61
Cancer, all sites	73.35	195	2.66
Lung cancer	19.16	100	5.22
Pleural mesothelioma	[b]	8	—
Peritoneal mesothelioma	[b]	8	—
G.I. cancer	21.55	32	1.48
All other cancer	32.64	47	1.44
Asbestosis	[b]	30	—
Other noninfectious respiratory disease	8.47	19	2.24
All other causes	286.80	350	1.22

[a] Expected deaths based upon age-specific death rate data for New Jersey white males in corresponding years. In 4 cases, ages were not known; omitted from calculations. 39 men partially traced and 890 traced to death on December 31, 1977.

[b] Death rates not available, but these have been rare causes of death in the general population.

type.

A property of mesothelial cells is the production of acid mucopolysaccharides, especially hyaluronic acid, which stains strongly with colloidal iron, but not with periodic acid Schiff (PAS). This last characteristic is useful in differentiating mesothelioma from adenocarcinoma; the latter usually gives a positive stain with PAS. The hyaluronidase test (digestion of hyaluronic acid by the enzyme) is useful in a limited number of cases, since the tubulopapillary type of the tumor is the only form which consistently produces hyaluronic acid. Therefore a negative hyaluronidase test does not exclude the diagnosis of mesothelioma.

The pathogenesis of mesothelioma is not yet completely understood. Nevertheless, the following facts of major theoretical and practical consequence have been established:

- mesothelioma may result from exposure to crocidolite, chrysotile and/or amosite; the evidence is derived from epidemiologic and experimental animal studies.
- relatively low levels and short duration of exposure can produce mesothelioma.
- while a dose-response relationship may exist, it has not been quantitatively clarified, and therefore available information can only be interpreted to indicated that any asbestos exposure, given a long enough period of follow-up, may induce mesothelioma.
- the hypothesis according to which polycyclic aromatic hydrocarbons adsorbed on asbestos fibers are important in the induction of mesothelioma has not been confirmed, nor has that attributing a similar effect to adsorbed trace metals (19).
- cigarette smoking has no etiologic relationship with mesothelioma.
- in experimental studies, intrapleural administration of asbestos, but also of similarly sized fibers of fibrous glass and fibrous aluminum oxide, resulted in pleural mesothelioma (66)(67)(68). This seems to indicate that fibrous characteristics, rather than the chemical composition, are crucial for this specific carcinogenic effect.
- a special selectivity in the distribution of asbestos fibers, relevant to the problem

Table VIII-29

EXPECTED AND OBSERVED DEATHS AMONG 689 ASBESTOS FACTORY WORKERS, EMPLOYED BEFORE JANUARY 1, 1939 DURING THE SEVENTEEN YEARS FROM JANUARY 1, 1959 THROUGH DECEMBER 31, 1975

	1959-1964		1965-1970		1971-1975		1959-1975		
	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.	Exp.	Obs./Exp.
All causes	59	52.41	123	69.85	92	65.93	274	188.19	1.46
Cancer, all sites	21	10.47	45	14.70	33	14.73	99	39.92	2.47
Lung cancer	6	2.96	18	4.65	11	4.92	35	12.53	3.91[a]
Pleural mesothelioma	1	n.a.	5	n.a.	7	n.a.	14	n.a.	—
Peritoneal mesothelioma	1	n.a.	6	n.a.	4	n.a.	12	n.a.	—
Cancer of esophagus, stomach, colon and rectum	4	2.23	5	2.92	3	2.83	15	7.99	1.88
Cancer, all other sites	9	5.28	11	7.13	8	6.98	23	19.40	1.19
All respiratory disease	14	3.01	10	4.56	18	4.60	42	12.16	3.45
Asbestosis	12	n.a.	8	n.a.	15	n.a.	35	n.a.	—
Other respiratory	2	(b)	2	(b)	3	(b)	7	(b)	—
All other causes	24	38.93	68	50.59	41	46.60	133	136.11	0.98
Person-years of observation	3,962		3,411		2,273		9,646		

(a) Pleural mesothelioma included with cancer of bronchus in calculating ratio since expected rates are based upon "cancer of lung, pleura, bronchus, trachea."
(b) This rate is virtually identical with that of "all respiratory disease."
n.a.—not available.

Table VIII-30

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA 1967-1977: OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS

	Number of men	**17,800**							
	Man-years	**166,855**							
		Duration from onset of work exposure (years)							
Cause of death	*Total*	*<10*	*10-14*	*15-19*	*20-24*	*25-29*	*30-34*	*35-39*	*40-44*	*45+*
All causes	2,270	51	85	188	320	388	340	253	203	442
Cancer, all sites	994	7	17	59	125	193	186	128	95	184
Lung	485	0	7	29	59	104	112	66	39	69
Pleural mesothelioma	66	0	0	2	6	15	10	16	4	3
Peritoneal mesothelioma	109	0	0	3	3	18	22	18	16	29

Table VIII-31

EXPECTED AND OBSERVED DEATHS AMONG 933 AMOSITE ASBESTOS FACTORY WORKERS EMPLOYED 1941-45 OBSERVED TO DECEMBER 31, 1977

		Deaths of lung cancer and mesothelioma				
Time from onset (years)	*Man-years*	*Lung cancer*			*Mesothelioma*	
		Exp.	*Obs.*	*Ratio*	*Pleural*	*Peritoneal*
<5	4,331	0.95	0	—	0	0
5-9	4,095	1.78	3	—	0	0
10-14	3,784	2.57	13	5.06	0	0
15-19	3,362	3.19	20	6.27	0	0
20-24	2,837	3.49	18	5.16	1	0
25-29	2,250	3.59	25	6.96	2	4
30-34	1,553	3.16	17	5.38	5	3
35+	192	0.41	4	—	0	1
	22,404	19.14	100	5.22	8	8

of mesothelioma induction, has been demonstrated by Roe et al. (54). After subcutaneous injection in mice (experiments with three types of asbestos), wide dissemination from the site of injection and a highly selective distribution were observed; the main sites of asbestos accumulation were the visceral and parietal pleura and the serosal surface in the abdominal cavity.

- the fiber size (cross-sectional diameter and length) seems to be important, since smaller fibers penetrate deeply into the periphery of the lung and subpleural areas (21)(22)(67)(68)(70)(75).

The evidence for marked effects, including the carcinogenic mesothelioma inducing effect of small fibers (length less than 5 um) has emerged relatively recently (122)(24)(75). This is important in view of the fact that handling or treating asbestos as well as use of asbestos products gen erates fragmentation (both longitudinally and transversely) of fibers resulting in a larger number of shorter and thinner fibers or even fibrils. Chrysotile is especially prone to undergo such

fragmentation.

CLINICAL DESCRIPTION

Symptoms

Chest pain (unilateral) and shortness of breath are the most common presenting symptoms. The chest pain may be diffuse and dull or it may be of the pleuritic type; it often progresses to be severe. Shortness of breath may rapidly progress, especially with the development of a pleural effusion.

Other relatively frequent symptoms are loss of appetite, weight loss, fatigue, and in some cases fever; cough is infrequent.

Physical Signs

Pleural effusion occurs in the majority of cases, with dullness on percussion and decreased breath sounds. Rapid recurrence after aspiration of pleural fluid is the rule. The pleural fluid may be serous and clear but sometimes is hemorrhagic.

Retraction of the affected hemithorax, and shifting of the mediastinum to the side of the lesion may occur.

Natural History

Rapid tumor growth—often after pleural biopsy, i.e., needle biopsy or thoracotomy—with subcutaneous tumor nodules may involve the chest wall, the ribs and vertebrae, the mediastinum (sometimes with superior vena cava syndrome), and/or the pericardium with pericardial effusion. Distant metastases to the liver or other intra-abdominal organs, sometimes with ascites, can be clinically detected.

The metastatic spread of mesothelioma is much more frequent than previously thought and has been shown to occur in the majority of cases in which an autopsy was performed; both lymph node metastases and distant hematogenous metastases can be found. Spread of the mesothelioma to the opposite pleural cavity, and also to the peritoneum, is frequent; most often this is the result of a local invasive process, through the mediastinum or through the diaphragm.

The natural history of the disease is that of a rapid downhill course; death occurs in the majority of cases after an interval of months to one or two years. The mean survival from first diagnosis does not exceed 12 months. Although all therapeutic methods have been used, often in combination (surgery, radiotherapy, chemotherapy), no significant difference in survival of patients with pleural mesothelioma has been consistently achieved.

Laboratory Investigations

Radiographic changes are characteristically unilateral and progressive. The two main modalities of radiologic changes in pleural mesothelioma are: 1) unilateral pleural effusion; 2) large, nodular, protuberant opacities projecting from the pleura into the pulmonary parenchyma. Most often a combination of these changes is found.

Aspiration of the pleural fluid may be helpful in revealing underlying solid tumoral opacities. Extension of the tumoral growth over the apical pleura and into the mediastinal pleura is frequent. PA chest radiographs should be complemented by oblique views of the chest whenever a suspicion of pleural mesothelioma arises. Other radiographic evidence of asbestos-related parenchymal and/or pleural changes may or may not be present. Pleural plaques or calcifications are a useful marker of past asbestos exposure.

Pulmonary function studies are irrelevant for the diagnosis of mesothelioma.

Pleural fluid aspiration, while often necessary to alleviate respiratory distress, is of limited diagnostic use. Cytology of the pleural effusion is often fraught with the difficulty of distinguishing between mesothelial malignant cells and "atypical" mesothelial cells. The detection of hyaluronic acid in the pleural fluid is useful, although it can be found with other malignant tumors of the pleura; a negative result does not discard the diagnosis (6)(25)(76).

Needle biopsy specimens are insufficient for tissue diagnosis, since tissue specimens so obtained might not include malignant changes (although such changes may well be present in adjacent areas of the pleura) and since there is marked variability of pathologic changes.

Thoracotomy with surgical pleural biopsy, although providing adequate tissue specimens for diagnostic purposes, is often followed by local extension of tumor growth into the chest wall.

Treatment

There is no effective therapeutic approach, although surgery to reduce the tumor mass (9), radiotherapy (17)(57)(71), chemotherapy, single drugs (7)(18)(29)(30)(40), or combinations of two, three, or four drugs, and all possible combinations of these methods have been attempted (35).

Wanebo et al. reported on 66 cases with

malignant mesothelioma (78). For the epithelial type, pleurectomy combined with irradiation and chemotherapy seemed to be more effective; in the fibrosacromatous type, surgery resulted in longer survival.

Prognosis

The disease is fatal, and progression is usually rapid, with marked deterioration over short periods of time. In exceptional cases, longer survival (several years) can occur even in the absence of any therapeutic procedure.

DIAGNOSTIC CRITERIA

The diagnostic criteria for pleural mesothelioma are:

- a history of asbestos exposure in the past. Occupational exposure (even for short periods) or household or neighborhood exposure has to be actively searched for and can be established in the vast majority of cases if histories are taken by a physician with experience in occupational medicine (11).
- long latency period, usually more than 20 years from onset of exposure, most often between 30 and 40 years.
- clinical symptoms: unilateral chest pain and/or significant increase in dyspnea over a short period of time (weeks or months).
- physical findings: consistent with pleural effusion.
- radiographic abnormalities presenting as pleural effusion or pleural thickening often with large nodular opacities projecting from the pleura. Rapid increase in pleural thickening or the the appearance of irregularities of the pleura are highly suspicious. Rapid progression of radiologic changes.
- tissue diagnosis on an adequate specimen (thoracotomy with pleural biopsy). Microscopic findings consistent with the epithelial (tubulopapillary), mesenchymal (fibrosarcomatous), or mixed or undifferentiated type.

The complexities and difficulties of the pathologic diagnosis have been discussed. The finding of hyaluronic acid in the pleural fluid of tissue specimen is useful, but the diagnosis cannot be discarded when the test is negative.

In the differential diagnosis of pleural mesothelioma, the following problems are of practical importance: (a) Benign pleural effusions may occur in a patient with present or past asbestos exposure. The clinical course is usually indicative, since benign pleural effusions tend to resolve spontaneously over several weeks. Nevertheless, such a "benign pleural effusion" has been observed, in some cases, to be a precursor of pleural mesothelioma. (b) Pleural fibrosis is a common finding in persons with present or past asbestos exposure; the prevalence increases with time since onset of exposure. In cases with extensive pleural fibrosis, especially when the width on chest x-ray exceeds 10 mm, the differential diagnosis between pleural fibrosis and pleural mesothelioma may be difficult. The presence of similar pleural changes on previous x-ray films makes the diagnosis of mesothelioma less likely; repeat chest x-ray films after several weeks are necessary when no previous chest x-ray are available. (c) The differential diagnosis between pleural mesothelioma (*primary* malignant tumor originating in the pleura) and secondary involvement of the pleura by a malignant tumor, either lung cancer or another primary malignant tumor with metastatic spread to the pleura, has been given much attention. In the case of lung cancer, sputum cytology and fiber optic bronchoscopy with bronchial biopsy, in addition to the radiologic appearance, contribute to the differential diagnosis. The proportion of cases which remain undecided is small. The possibility of a malignant primary tumor originating in another site, with metastatic spread to the pleura is investigated by the routine clinical work-up. Patients with no other detectable primary tumor but with clinical and radiologic features of mesothelioma have, with a high degree of probability, pleural mesothelioma. The absolute certainty of this differential diagnosis is reached only after postmortem examination.

In reviewing the experience accumulated over the last 20 years, it becomes obvious that pleural mesothelioma has been largely underdiagnosed in the past. This has been established in prospective cohort studies of asbestos-exposed workers (28)(33)(34)(38)(44)(47)(60); in many studies investigating diagnostic accuracy in series of reported mesothelioma cases (15); and in systematic reviews of all pathology material—as in Scotland where 80 undiagnosed cases were discovered (39).

In the 1967-1977 cohort study of 17,800 asbestos insulation workers in the United States and Canada, out of a total of 2,270 consecutive deaths, 60 were recorded on the death certificate as mesothelioma (31 pleural, 29 peritoneal). Review of medical records, including pathology reports, chest x-ray films, postmortem examinations (when available) and independent review of tissue specimens by experienced pathologists resulted in a diagnosis of mesothelioma in 175 cases (66 pleural, 109 peritoneal). The death certificate accuracy was 47% for pleural mesothelioma and 27% for peritoneal mesothelioma (Table VIII-32). In another cohort of 689 asbestos workers, 11 cases of mesothelioma (4 pleural, 7 peritoneal) were recorded on death certificates for the period 1959-1975. Review of medical records and pathology material resulted in a diagnosis of mesothelioma in 26 cases (14 pleural, 12 peritoneal), with the death certificate accuracy only 28% for pleural mesothelioma, and 58% for peritoneal mesothelioma (Table VIII-33).

In the majority of pleural mesothelioma cases it is possible to establish the diagnosis intravitam. The greater awareness of population groups with present or past exposure, of the Department of Health, Education and Welfare, of other governmental agencies, and of the medical community are expected to result in earlier diagnosis. This is a prerequisite for future meaningful attempts of therapy.

The requirement of postmortem examination for the definitive diagnosis is necessary for the complete assessment of mesothelioma incidence from an epidemiologic point of view, although it is expected that a higher index of suspicion will substantially reduce the difference between the number of cases diagnosed while alive and those in which the diagnosis is reached only after postmortem examination.

METHODS OF PREVENTION

The prevention of pleural mesothelioma is dependent on the reduction of exposure to asbestos fiber to the minimum possible level, since this adverse health effect has been specifically associated with low level and short-term exposure. In December 1976, NIOSH, based on a "Reexamination and Update of Information on the Health Effects of Occupational Exposure to Asbestos," recommended to the DHEW and OSHA that the standard be reduced to 0.1 fibers /cm^3. This was based on the lowest concentration at which asbestos fibers can be reliably identified by phase contract microscopy.

RESEARCH NEEDS

Critical problems where research is needed:

1. Determine mechanisms of carcinogenicity (mineral fibers; potential effect of other mineral fibers, such as zeolites, titanite fibers, etc.).
2. Define, to the extent that it is at all possible, the lowest level of asbestos exposure which may result in mesothelioma. This is of paramount importance for the acceptable standard.
3. Establish the role(s) of immune mechanisms in individual susceptibility for mesothelioma.
4. Determine mechanisms of carcinogenicity in peritoneal mesothelioma, including the significance of ingestion of fibers. This is important since water may be polluted with mineral fibers from various sources, and the risk of mesothelioma from such a situation has not yet been assessed.
5. Establish mesothelioma therapy.

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Table VIII-32

MORTALITY EXPERIENCE AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA 1967-1977: OBSERVATIONS IN 2,270 CONSECUTIVE DEATHS

Accuracy of death certificate categories

Cause of death	*Expected*	*Death Certificate*		*Ascertained*	
		Number	*o/e*	*Number*	*o/e*
Cancer, all sites	319.90	888	2.77	994	3.10
Cancer, lung	105.97	403	3.80	485	4.57
Pleural mesothelioma	—	31	—	66	—
Peritoneal mesothelioma	—	29	—	109	—
Cancer, esophagus	7.01	16	2.28	18	2.56
Cancer, stomach	14.23	19	1.34	22	1.55
Cancer, colon	37.86	58	1.50	59	1.56
Cancer, pancreas	17.46	48	2.75	22	1.26
Cancer, liver	7.50	18	2.40	5	0.66
Cancer, brain	10.34	19	1.84	14	1.35
Asbestosis	—	108	—	162	—
Chronic obstructive lung disease	58.58	127	2.17	66	1.13

Death certificate accuracy: Cancer, 89%; lung cancer, 83%; G.I. cancer, 94%; pleural mesothelioma, 47%; peritoneal mesothelioma, 27%.

Table VIII-33

RELATION BETWEEN DIAGNOSIS OF CAUSE OF DEATH AS RECORDED ON THE DEATH CERTIFICATE AND AS ASCERTAINED BY REVIEW OF ALL AVAILABLE INFORMATION, IN 274 DEATHS AMONG 689 ASBESTOS WORKERS OBSERVED JANUARY 1, 1959 - DECEMBER 31, 1975

	Death certificate	*Ascertained*
Cancer, all sites	94	99
Cancer of lung	36	35
Pleural mesothelioma	4	14
Peritoneal mesothelioma	7	12
Mesothelioma — unspecified site	7	0
Cancer of esophagus, stomach, colon, and rectum	12	15
All other cancer	28	23
All respiratory disease	43	42
Asbestosis	26	35
Pneumoconiosis	8	0
All respiratory disease	9	7
All other causes	137	133

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