Malignant Mesothelioma With Occupational and Environmental Asbestos Exposure in an Illinois Community Hospital

PLAINTIFF'S EXHIBIT

MBL-128

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• **Clinical, radiologic, pathologic, and epidemiologic data on 32 patients with diffuse malignant mesothelioma (DMM) diagnosed between 1968 and 1984 at a 427-bed community hospital in Berwyn, Ill, were reviewed. Independent pathologists' review of light microscopy, supported by electron microscopy, immunoperoxidase staining, or autopsy, confirmed 29 pleural and three peritoneal DMMs. Clinical and radiologic characteristics were similar to those in published case series. Median age at diagnosis was 67 years, and median survival after diagnosis, seven months. Fourteen patients were women. Exposure histories were obtained through 22 interviews supplemented by hospital charts and death certificates. Thirty patients (94%) had a history of asbestos exposure through work (15 [47%]) and/or residence near an asbestos facility (27 [84%]). Medical records and death certificates underreported asbestos exposure and DMM.**

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Since the establishment of the asbestos–malignant mesothelioma relationship by Wagner et al in 1960,[1] the majority of reported mesothelioma cases and associated medical data have come from geographic areas of known asbestos exposure. These regions, within Europe, South Africa, Great Britain, Canada, and the United States, include shipbuilding, asbestos mining, and manufacturing sites. The midwestern United States is one locale assumed to have had minor involvement in the asbestos-using industries[2] and, therefore, to be at low risk for asbestos-related diseases. In support of this assumption, only 255 patients with diffuse malignant mesothelioma (DMM) have been reported from the Midwest.[3-13] Of these, only 16% were documented to have asbestos exposure (Table 1). Although the majority of the reports were not intended to be epidemiologic studies, these relatively unimpressive data significantly contribute to the perception that the Midwest is a minimally asbestos-affected area. More importantly, these studies provided little basis to conduct etiologic investigations.

From 1968 through 1984, 32 patients with DMM were diagnosed at MacNeal Hospital in Berwyn, Ill, a 427-bed community hospital serving approximately 289 000 residents of western Cook County. This number of cases of DMM was unexpected not only because of the hospital's location in a low-risk area, but also because MacNeal Hospital is a primary care, not a referral, center. A retrospective study was undertaken, therefore, to (1) confirm the diagnoses with independent pathologists' review and updated pathologic technology, ie, electron microscopy and immunoperoxidase methods, (2) clinically characterize the patients, and (3) investigate asbestos exposure history. Substantively, this study differed from prior midwestern reports by its use of multiple epidemiologic data sources to assess asbestos exposure. Detailed occupational and complete residential histories were compiled through next-of-kin or patient interviews for the majority of cases. History of asbestos exposure from hobbies or household contact to an asbestos-exposed worker, or from residential proximity to an asbestos product manufacturing plant, was obtained. In addition, a historical review of the nearby communities was conducted to identify asbestos product manufacturing facilities.

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PATIENTS AND METHODS

Case Ascertainment With Pathology Review

The presentation of two patients with DMM within a nine-month period at the MacNeal Hospital weekly medical mortality conference formed the basis to begin a case ascertainment phase. To do so, hospital medical records, tumor registry files, and radiologic and pathologic files were reviewed for all suspected primary pleural or peritoneal neoplasms or pneumoconioses diagnosed at MacNeal Hospital from 1968 through 1984. Fifty-seven potential cases were found in this preliminary search. Nineteen cases were excluded for one of the following reasons: (1) pneumoconiosis was present but there were no signs of malignant disease, (2) the initial clinical suspicion of DMM was not supported by the subsequent medical evaluation, or (3) sufficient pathologic material was lacking.

Of the 38 cases identified by the ascertainment phase, one was considered verified by its inclusion in the McDonald and McDonald study.[8] Histologic materials from the remaining 37 were retrieved and the majority processed for electron microscopy and/or immunoperoxidase staining for carcinoembryonic antigen (CEA) and cytokeratin (KER). These specimens and the original pathology slides were analyzed by one of us (L.G.B.). Two of the patients were accepted without further review because of light microscopic and necropsy characteristics consistent with DMM.[11] The light microscopic specimens from the remaining 35 patients were then presented in a blinded fashion to two independent pathologist reviewers. The reviewers were asked to decide if any of the histologic materials demonstrated DMM. They were given the patient's age and sex but no further medical or exposure data. Cases reviewed in this manner were considered pathologically "confirmed" if they met one of the following acceptance criteria: (1) a cumulative score of 4 or less from the three pathologists' quantification of light microscopy findings using a scale in which 1 indicates definite; 2, probable; 3, possible; and 4, unlikely (note that the two independent pathologist reviewers had access to only the light microscopic materials), or (2) a three-reviewer summation score of 8 or less in addition to positive KER and negative CEA staining or characteristic electron microscopic features.[14-17] Six of the 35 cases reviewed were rejected. These 29 reviewed cases, the patient previously described by McDonald and McDonald,[8] and the two accepted by light microscopy and autopsy criteria comprised the 32 confirmed patients in this case series. Table 2 presents the pathologic review results for each patient.

Clinical and Roentgenographic Review

For each confirmed case, presenting symptoms and physical findings were recorded from examinations performed during the first admission in which a pleural or peritoneal neoplasm was considered. Chest roentgenogram data were obtained for all confirmed cases from the first chest roentgenogram report from that same admission (anteroposterior, posteroanterior, with or without left lateral). A blinded reading was conducted by radiologists who were not "B-readers" (ie, radiologists not certified in pneumoconiosis radiography as established by the American College of Radiology).

Exposure Review

History of occupational asbestos exposure, from age 16 years and up to five years before death, was obtained from personal

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Table 1.—Summary Data From Previously Published Midwestern United States Malignant Mesothelioma Studies

Source, y	Source of Case Ascertainment	No. of Patients	No. With Definite or Probable Asbestos History	Source of Data to Examine Asbestos Exposure
Godwin,[3] 1957	Hospital medical charts	14	...*	Hospital medical charts
Godwin and Jagatic,[4] 1970	Hospital medical charts	7	6 (86%)†	Hospital medical charts
Oels et al,[5] 1971	Hospital autopsy files	27/37‡	10 (27%)†	Hospital medical charts
Grundy and Miller,[6] 1972	National death certificate files	3	...*	Hospital medical charts
Hinds,[7] 1978	Tumor registries in Iowa and Detroit	76	...*	Tumor registries
McDonald and McDonald,[8] 1980§	National survey of US and Canadian pathologists	36	...*	Hospital medical charts and next-of-kin interviews
Cunningham et al,[9] 1980	Tumor registries in Illinois	28	...*	Tumor registries
Vogelzang et al,[10] 1984	Hospital medical charts	28	15 (54%)	Hospital medical charts and physician interviews
Adams and Unni,[11] 1984	Hospital autopsy files	16	10 (62%)	Hospital medical charts
DeKraay,[12] 1985	Hospital medical charts	12	1/2‖	Hospital medical charts
Lilienfeld and Gunderson,[13] 1986	State death certificates	8	...*	Death certificates

*This information was not reported or was not available in the reported study.
†Godwin and Jagatic reported on six patients with "asbestos bodies" present. Oels et al reported on ten patients with "asbestos bodies."
‡Of 37 patients presented, 27 were from the Midwest. Asbestos exposure data were not grouped by geographic region.
§Frequencies were reported by region. Occupational exposure data were reported for United States and Canada combined.
‖Only two representative case histories were described, one of which had asbestos exposure.

interview when possible. In 21 cases (66%), interviews were conducted with a surviving next of kin and, in one instance, with the patient. Five interviews were refused, and relatives could not be located for five cases (31%).

The interviews were conducted using a standardized questionnaire adapted by the National Cancer Institute from the research by McDonald and McDonald[8] and Selikoff.[18] All job titles, work tasks, and known work-related exposures were ascertained. Additional queries were made regarding residential histories since birth, hobbies that included asbestos materials, and household members' asbestos-related employment. The location, period of operation, and description of asbestos product manufacturing facilities mentioned during the interviews were confirmed using multiple historical resources. These included Illinois manufacturers' directories from that period, local newspaper accounts, city directories, and locally published reports.[19]

For all patients, a premortem histologic diagnosis of DMM had been made. The presence or absence of documentation of mesothelioma as an underlying or contributing cause of death on the death certificate was noted. Any indication of asbestos exposure history in the medical record and the usual occupation entered on the death certificate were recorded. The date of death was confirmed from the death certificate.

RESULTS

Clinical Findings

Twenty-nine patients had primary pleural and three had primary peritoneal involvement. The age at diagnosis ranged from 19 to 86 years, with a median of 67 years. Of the 32 patients, 14 (44%) were women. In those with pleural primary tumors, the most common presenting symptoms were dyspnea, chest pain, and cough. The duration of symptoms until the time of presentation varied from one week to three years. Of the three peritoneal mesotheliomas, two were found at laparotomy as incidental findings. Presenting chest roentgenogram interpretations documented pleural effusions in 27 cases (84%), pleural masses in five, pleural plaques in three, interstitial pulmonary fibrosis in two, bone involvement in two, and pleural thickening in one. Thoracenteses (38 performed) and pleural biopsies (17 performed) were nondiagnostic for the majority (80%). Percutaneous lung biopsy was positive in one of the two performed. Excisional biopsies of chest-wall masses (three performed), thoracotomies (25 performed), and laparotomies (three performed) were 100% diagnostic. Data regarding radiation and chemotherapy treatments were insufficient for analysis because of outside referral for the former and infrequent utilization and nonstandardized protocols for the latter. Length of survival from time of diagnosis ranged from one week to 31 months, with a median of seven months.

Pathologic Findings

Of the 29 patients whose histologic materials underwent light microscopic review (Table 2), 22 (76%) were judged to have definite or probable DMM by all three reviewers using light microscopic criteria alone.

The results of electron microscopy and immunoperoxidase staining for CEA and KER were as follows. Of the 22 cases rated by the three reviewers as definite or probable by light microscopic analysis, electron microscopy was performed in 16. The electron microscopic findings were supportive of DMM in 12 of the 16 and inconclusive in four.

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Table 2.—Characteristics and Pathology Evidence of Verification of Cases

Patient/ Sex	Survival, mo After Diagnosis	Time of Diagnosis, Age, y/Year	Light Microscopy Reviewer*			Electron Microscopy	Immunoperoxidase†		Autopsy
			A	B	C		KER	CEA	
1/M	13	68/1971	1	1	1	...	...	...	...
2/M	12	62/1972	1	...	...	...	...	...	Yes
3/M	14	64/1975	1	1	1	...	Positive	Negative	...
4/M	19	58/1976	1	1	1	Supportive	Positive	Negative	...
5/M	21	69/1977	1	2	2	Supportive	...	...	...
6/M	10	44/1978	1	1	1	Supportive	Positive	Negative	...
7/M	11	67/1978	2	2	4	...	Positive	Negative	...
8/M	6	19/1980	1	1	2	Supportive	...	...	...
9/M	13	63/1981	1	1	1	Supportive	Positive	Negative	...
10/M	7	65/1981	1	1	1	Supportive	...	...	...
11/M	12	70/1982	1	2	1	Supportive	Positive	Negative	...
12/M	9	69/1983	1	1	1	Supportive	Positive	Negative	...
13/M	2	70/1983	2	3	1	Inconclusive	Positive	Negative	...
14/M	3	74/1983	1	2	1	Inconclusive	Negative	Negative	...
15/M	2	70/1983	1	1	1	Supportive	Positive	Negative	...
16/M	10	54/1983	1	2	2	Supportive	...	...	...
17/M‡	4	51/1984	1	1	1	...	Positive	Negative	Yes
18/M‡	3	67/1984	1	1	1	...	Positive	Negative	Yes§
1/F	5	55/1968	1	1	2	...	...	...	Yes
2/F	6	74/1969	1	...	...	...	...	...	Yes
3/F	18	62/1971	...‖	...‖	...‖	...	...	...	...
4/F	4	67/1975	1	3	3	Supportive	Positive	Negative	...
5/F	30	49/1975	1	2	1	Inconclusive	Negative	Negative	...
6/F	1	70/1977	1	1	1	Inconclusive	Positive	Negative	...
7/F	26	65/1978	2	2	3	...	Positive	Negative	...
8/F‡	26	78/1980	1	1	1	...	...	...	...
9/F	9	68/1981	1	3	2	Supportive	...	...	...
10/F	7	66/1981	1	1	1	Inconclusive	Positive	Negative	...
11/F	5	79/1982	1	2	1	Supportive	Positive	Negative	...
12/F	0.25	69/1982	1	3	2	...	Positive	Negative	...
13/F	5	69/1983	1	3	3	Supportive	Positive	Negative	...
14/F	12	86/1984	1	1	1	Supportive	Positive	Negative	...

*Pathologist quantification of the likelihood of malignant mesothelioma based on light microscopy: 1 indicates definite; 2, probable; 3, possible; and 4, unlikely. Only reviewer A (L.G.B.) had access to electron microscopy, immunoperoxidase, and autopsy materials.

†KER indicates cytokeratin; CEA, carcinoembryonic antigen.

‡Peritoneal primary.

§Autopsy completed after the pathology review.

‖Tissue obtained by pleural biopsy and thoracotomy was reviewed and accepted into the McDonald and McDonald study.[8]

Immunoperoxidase staining for KER and CEA was performed in 15 of these 22 cases. The staining was positive for KER in 13 and negative for CEA in all 15, findings consistent with DMM. Seven of the 29 reviewed cases were given a "less than certain" rating, that is, one or more of the three reviewers had judged the specimen to be possible or unlikely DMM (a three-reviewer summation score ≥6). For these the diagnosis of DMM was established by the demonstration of characteristic immunoperoxidase staining in four, both electron microscopy and immunoperoxidase criteria in two, and electron microscopy criteria in one.

Epidemiologic Findings

The yearly rate and trend of DMM at MacNeal Hospital was obtained by dividing the number of patients newly diagnosed with DMM by the total number of admissions for each year (approximately 15 000/y) from 1968 to 1984. This yielded an average yearly rate of 12 new patients with DMM per 100 000 MacNeal hospital admissions (an average of two cases per year). The differential rate was four per 100 000 admissions from 1968 to 1974, ten per 100 000 admissions from 1975 to 1979, and 25 per 100 000 admissions from 1980 through 1984.

From historical records, two large primary asbestos product manufacturing plants were identified within 4.8 km of MacNeal Hospital. The first company, which began operations in 1920 and employed approximately 1200 people during 1949, manufactured gaskets, a specialized appliance of metal covered with asbestos, and asbestos millboard. Chrysotile asbestos was used. This manufacturer was housed in multistory buildings occupying approximately 1½ square blocks. The second site, which began operation in the 1930s and closed in the early 1950s, employed about 200 workers at one time in a one-story plant with an area of 14 400 m² (160 000 sq ft). This company manufactured insulation from chrysotile asbestos. Three smaller asbestos product companies with a combined work force of up to 300 were identified. Whether or not the smaller sites were asbestos factories or asbestos product

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Table 3.—Type of Occupational and Environmental Asbestos Exposure

Exposure	No. (%)* Men	Women	Combined
Occupational			
Asbestos product manufacturing in neighborhood facility (interview data)	4/13 (30)	3/9 (33)	7/22 (32)
Probable or definite work-related asbestos exposure (interview and chart data)	8/18 (44)	0/14 (0)	8/32 (25)
Total	12/18 (67)	3/14 (21)	15/32 (47)
Environmental			
Household exposure through family member with occupational exposure (interview data)	3/13 (23)	3/9 (33)	6/22 (27)
Hobby with exposure to asbestos (interview data)	3/13 (23)	1/9 (11)	4/22 (18)
Residence <3.2 km from neighborhood asbestos product manufacturing facility (interview and chart data)	15/18 (83)	12/14 (86)	27/32 (84)
Total	16/18 (89)	13/14 (93)	29/32 (91)†

*Percentages are based on different numbers of patients: interviews, 13 men and nine women; and interviews plus chart data, 18 men and 14 women. In addition, some patients had more than one route of exposure, so entries in "Total" rows may not be sums.

†Of the three patients who had no history of environmental exposure, one had a history of work exposure to asbestos (patient 17/M). Thus, 30 (94%) of 32 patients had occupational or environmental asbestos exposure.

user factories could not be determined from available historical records. Women made up approximately 40% of the total work force of the five companies.[19]

A review of census of manufacturing data in the late 1940s and early 1950s[20] showed that Illinois was ranked first or second among the contiguous United States in the number of facilities or the number of production employees in asbestos product manufacturing. The asbestos-related industries in Illinois manufactured asbestos products such as textiles, building materials, floor tile, insulation, cement, and gaskets. Raw asbestos was shipped into the Chicago area from both Canada and South Africa, the former primarily producing chrysotile, and the latter, crocidolite asbestos.[18,21]

Based on interview and chart data, 30 (94%) of these 32 patients had some history of asbestos exposure through one or more of the following: occupation, household contact, or residential proximity (Table 3). (A detailed breakdown of asbestos exposure by patient is available from Z.H.P.). Twenty-seven (84%) resided within a 3.2-km radius of one of the two major neighborhood asbestos product manufacturing facilities at some time five or more years before diagnosis. Fifteen (47%) had definite or probable work exposure to asbestos (three women, 12 men). Seven of these 15 (four men, three women) had worked in one of the two large neighborhood asbestos facilities. Six had household exposure to asbestos through a relative in the home with definite or probable work exposure, and four had exposure through hobbies (eg, insulating their own homes with asbestos-impregnated siding). Only two of the 32 patients had no documented evidence of asbestos exposure of any type.

Review of the hospital charts documented probable or definite occupational asbestos exposure for only nine patients. No reference was made to residential proximity to an asbestos plant as a risk factor in the recorded medical histories. With personal interviews, six additional patients with definite or probable work asbestos exposure were identified. The death certificates provided information on possible asbestos exposure for ten men and one woman. Nine (28%) of the death certificates failed to cite mesothelioma as an underlying or contributing cause of death despite premortem tissue diagnosis.

COMMENT

The midwestern United States is one of many regions assumed to be at low risk for asbestos-related diseases. For the Midwest, this belief may be due in part to the presumption that few or insignificant asbestos-using industries existed in the area.[2] The infrequent reporting of DMM, as summarized in Table 1, may also have contributed to this perception. Hospital medical charts[3-6,11,12] and death certificates[6,13] data are not reliable for asbestos exposure histories or the detection of DMM. These points are well illustrated by our study's finding that although all but two of 32 patients with DMM were found to have had asbestos exposure, only nine of the medical records mentioned such exposure. Death certificates provided evidence for asbestos exposure in only 11 instances and underreported the diagnosis of DMM by 28%.

Of more importance was the historical review of the community that ensued once the high asbestos exposure rate was determined. A common asbestos exposure source hitherto not suspected was found. Two major asbestos product manufacturing sites in close proximity to MacNeal Hospital were identified. Eighty-four percent of the patients had lived within a 3.2-km radius of these plants. We were able to document that 22% had worked in them. An additional eight patients had other definite or probable work-related asbestos exposure, bringing the total with direct occupational exposure to 47% of the entire group. We found that 31% of the patients had household exposure to asbestos through a relative in the household with definite or probable work exposure or through a hobby. Overall, 94% of the patients had documented asbestos exposure. Only two patients had no evidence of asbestos exposure of any type.

Exposure to crocidolite asbestos is most frequently associated with the development of DMM.[22] That chrysotile was the predominant asbestos fiber used in the neighborhood asbestos plants[18] does not contradict the theory that these facilities were a common source for the risk of developing DMM. Churg et al[23] demonstrated only chrysotile ore components within the lungs of five miners and millers with pleural mesotheliomas.[23] Furthermore, raw asbestos was shipped into this region from both Canada and South Africa, the latter a major source of crocidolite asbestos. The residential and working populations might have actually been exposed to a mixture of these fibers.

Additionally, most published series of DMM have demonstrated a male-female ratio of 3:1 or 4:1.[21,24,25] In contrast, this study found an almost equal number of men and women with DMM (1.3:1). Only three of the 14 women had documented definite work exposure to asbestos. Four had household exposure to family members who worked with and/or had hobbies that involved the use of asbestos. Five women had no known asbestos exposure other than residential proximity to the asbestos plants. The observed lower rate of occupational asbestos exposure among women may be due to next-of-kin recall bias. The role of occupational and nonoccupational exposure among women warrants further epidemiologic study.

Churg[26] recently compared the lung asbestos burdens of chrysotile mining town residents with those of non–mining

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town residents. The chrysotile concentration of the mining town residents (median, 1.2 million/g of dry lung) was about six times that of the non–mining town residents. A scanning electron microscopy study of asbestos fiber concentrations by Mowe et al[27] demonstrated that a critical level as low as 1 million fibers per gram of dry lung tissue was associated with an increased risk of DMM. Since this concentration may be found in the general population,[28] it does strengthen the argument for a "no-threshold" risk for the development of mesothelioma from minor asbestos exposures. Furthermore, it increases the likelihood that the "indirect" exposures experienced by these women, ie, to household asbestos users or residential proximity to asbestos industries, may be causally related to their development of DMM.

It is likely that additional cases of DMM have gone unreported from western Cook County. The stringent pathologic criteria used for this study may have led to the exclusion of several patients with DMM. Furthermore, other hospitals within the area serve the same population. A pathologic review should be extended to those hospitals.

That an even larger group of patients with asbestos-related disease exists in metropolitan Chicago is probable for several reasons. Other asbestos product manufacturers have been identified within the metropolitan Chicago area.[19] Data that support significant asbestos exposure from these manufacturers include the demonstration by Suta and Levine[29] that the Chicago area has an average atmospheric asbestos concentration of 24 ng/m^3, a level comparable with that of American coastal cities such as Los Angeles and New York. Churg and Warnock,[30] in a case-control study of Chicago patients with nonmesothelioma pulmonary and gastrointestinal tract cancers, found lung asbestos body counts as high as 9200 asbestos bodies per gram of wet weight of lung. Chest roentgenography performed in 120 spouses of asbestos workers in a screening program in a local pipefitters' union in Chicago showed that 17% had classic pleural plaques consistent with asbestos exposure.[31] Malignant mesothelioma is a "sentinel health event," the occurrence of which indicates excess disability and untimely death from diseases such as asbestosis, pleural effusions, and lung, laryngeal, and gastrointestinal tract carcinomas.[32] McDonald and McDonald[33] reviewed three epidemiologic studies and concluded that about 7% of lung cancer deaths in American men in 1985 resulted from occupational asbestos exposure.

The national incidence of pleural mesothelioma among men is estimated to be from seven to 13 per million during the last ten years. This rate is increasing at a yearly average of about 13%. The incidence may be substantially higher in select geographic areas where asbestos industries existed.[25,34] Manufacturing census data have shown that Illinois along with other midwestern states had many asbestos product manufacturing factories between 1940 and 1960.[20] The MacNeal Hospital patients may represent a "sentinel community" for malignant and nonmalignant asbestos-related diseases in the Midwest. Other such unrecognized communities may exist worldwide.

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