Mesothelioma and Asbestos Exposure

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WITHIN the past five years several articles have called attention to the association between mesotheliomas of the pleura and peritoneum with asbestos exposure.[1-3]

Wagner et al[4] studied 33 cases of mesothelioma. All but one had probable exposure to crocidolite, the blue asbestos.

Asbestos has become a ubiquitous material in our civilization. Cauna et al[5] reported that asbestos bodies were found in the lung smears of 41% of 100 consecutive autopsies at the Presbyterian University Hospital in Pittsburgh. Similar findings were reported by Thompson[6,7] in 500 consecutive lung smears from Capetown, South Africa, and Miami, Fla. Asbestos bodies were found in 30% of the men and 20% of the women. Asbestos has been conclusively associated with increased incidence of lung cancer and other malignancies[8,9] and an increasing number of studies associate its presence with malignant mesothelioma of the pleura and peritoneum.

Pathology

Mesotheliomas of the pleura and peritoneum are rare neoplasms. Controversy involves histological types, nomenclature, origin, and their very existence. Recently, mesotheliomas as an entity have become generally accepted. Their morphologic variability makes classification difficult and differentiation from other malignancies is often a problem.

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Sacconi and Coblenz[10] give the incidence of pleural mesotheliomas as 1.1 cases per 1,000 autopsies. Campbell reported four cases of pleural mesotheliomas in 3,533 consecutive autopsies.[11]

Mesothelioma occurs primarily in adults and is twice as common in males as in females.[10,12]

Pleural mesotheliomas occur equally on the right and left though Weissman feels that pleural mesothelioma occurs on the right more frequently than on the left side.[12]

The criteria for diagnosis of pleural mesothelioma are presence of a firm pleural mass encasing the lung, histological structure compatible with mesothelioma, and absence of a demonstrable primary malignant neoplasm elsewhere. The histologic architecture may be mesenchymal, "epithelial," or mixed.

A complete autopsy is necessary for unequivocal diagnosis, but for the purpose of this study, criteria were made less rigid in that unautopsied cases were accepted if a definite diagnosis of pleural mesothelioma had been made by biopsy, and malignancy elsewhere had been excluded clinically; chest x-ray examination, bronchoscopy, and cytologic studies of sputum or bronchial washing assisted in excluding the presence of bronchial carcinoma.

Primary tumors of the peritoneum are among the rarest of tumors. Generally called mesotheliomas, they form large spreading masses over the peritoneum and histologically appear the same as pleural mesotheliomas. As with pleural mesotheliomas, exclusion of a primary tumor is necessary.

This study is an attempt to learn the extent of the relationship of asbestos exposure with mesothelioma diagnosed in southeastern Pennsylvania.

Method

One hundred and sixty-two hospitals serving a population of 6½ million people were requested to report all mesotheliomas diagnosed between 1958 and 1963. Replies were received from 152 hospitals. Hospital records of 62 reported cases were reviewed and only mesotheliomas confirmed by operation, biopsy, or autopsy were included in the study. Forty-two cases satisfied our critera. There were 34 mesotheliomas of the pleura and eight of the peritoneum. Among the pleural mesotheliomas there was a definite preponderance for occurrence on the right side of the chest. Of 34 pleural mesotheliomas only seven occurred on the left side, 25 on the right side, and two were not stated.

Sections of as many of the tumors and lungs as possible were borrowed and reviewed by a single consultant pathologist familiar with mesotheliomas. In the 15 instances in which lung sections were available, they were examined for the presence of asbestos bodies. All slides were reviewed without the benefit of the complete history and autopsy protocol available to the pathologists who made the original diagnosis.

Results of the 33 cases reviewed (Table) by our pathologist agreed with those of the outside pathologists in 17 cases; he rejected seven cases as unacceptable histologically, had serious doubts in nine cases (of these one slide was read as metastasis and one slide as anaplastic malignancy). Of the 15 cases in which lung tissue was available, asbestos bodies were identified in seven.

The discrepancies between the original pathological diagnosis and that of our pathologist are reported to illustrate the difficulties and disagreements which are so frequent in the diagnosis of this tumor. For inclusion in this study the diagnoses of the originally reporting pathologists have been accepted and cases reported by them were investigated.

Efforts were made to obtain a complete employment and residence history for each patient. Inquiry was also made into the employment history of family contacts. Data were obtained from the individual if alive, from family members, or employers.

Of the 42 patients, ten had definite occupational exposure to asbestos during lifetime, three were family contacts of asbestos workers, eight either lived in the immediate neighborhood of asbestos plants or had been employed next to an asbestos plant. Ten patients had a questionable asbestos exposure and, in the other 11 patients, either no asbestos exposure could be elicited on direct questioning or no survivor could be located.

Table 1.—*Readings of Consultant Pathologist*

Case No.	Mesothelioma	Asbestos Bodies
1-O	Yes	No lung tissue
3-O	Not acceptable	Yes
4-O	Probably not	No lung tissue
5-O	Yes	Yes
6-O	Probably not	Yes
9-O	Probably not	No lung tissue
10-O	Yes	Yes
2-N	Yes	No lung tissue
3-N	Probably not	No lung tissue
4-N	Not acceptable	No lung tissue
6-N	Yes	No lung tissue
1-F	Yes	No lung tissue
2-F	Yes	No lung tissue
3-F	Yes	No lung tissue
1-Q	Probably not	No lung tissue
2-Q	Yes	Yes
4-Q	Yes	No
5-Q	Probably yes	No
6-Q	Not acceptable	No
7-Q	Yes	No lung tissue
8-Q	Yes	No
9-Q	Probably not	No
10-Q	May be Metast	No
1-X	Yes	Yes
2-X	Yes	No lung tissue
3-X	Not acceptable	No lung tissue
4-X	Not acceptable	No lung tissue
5-X	Anaplastic malignancy	No
6-X	Probably not	No
7-X	No epithelial cells Mesothelioma must be proven	No lung tissue
8-X	Probably not	No lung tissue
9-X	Yes	No lung tissue
10-X	Yes	Yes

Exposure of Ten Mesothelioma Patients Who Worked With Asbestos.—Patient 1-0 worked 35 years in the textile department of a large asbestos plant.

Patients 2-0, 3-0, and 4-0 worked more than 20 years in asbestos insulation plants and patient 5-0 worked in an insulation plant for only one year.

Patient 6-0 worked 15 years in a plant manufacturing acoustic tile and linoleum.

Patient 7-0 was a boiler maker in a railroad yard where, for 25 years, he worked on insulation of steam engines.

Patient 8-0 built bakery ovens in which large amounts of asbestos insulation were used.

Patient 9-0 was a certified accountant who worked more than 30 years in the office of an asbestos textile plant.

Patient 10-0 was a plasterer who came in contact with a large amount of asbestos in his work.

Of these ten men, patients 1-0, 8-0, and 10-0 had mesotheliomas of the peritoneum; the other seven men had pleural mesotheliomas.

Neighborhood Cases.—Patient 1-N was a 55-year-old woman who never had any occupa-

tional asbestos exposure. Her work was always secretarial; she was born and lived until the age of 8, in the immediate neighborhood of an asbestos textile and friction material plant where patient 1-0 had worked for 35 years. From the age of 18 she lived for 30 years across the street from the plant where patient 6-0 had worked for 15 years.

Patient 2-N, a clergyman from 1935 until his death in 1961, never had any occupational asbestos exposure. Prior to becoming a minister he lived for 19 years within one half of a mile of the insulation plant where patients 3-0, 4-0, and 5-0 had worked as insulation manufacturing workers.

Patient 3-N never had any occupational asbestos exposure except that, 20 years prior to his death, he had worked for one year across the street from the insulation plant mentioned in the history of patient 2-N.

Patient 4-N worked for 26 years across the street from the insulation plant mentioned in connection with patients 2-N and 3-N.

Patients 5-N, a nurse, and 6-N, a meat distributor, had no occupational exposure nor family contact with asbestos. They both lived within three fourths of a mile of two asbestos plants in a town with the greatest incidence of mesotheliomas in this study.

Patients 7-N and 8-N were both foremen in a storage battery plant. A careful check of the plant and their employment records revealed no asbestos exposure, past nor present. The plant is located less than 1½ miles from an asbestos textile plant. The exposure of these two cases is questionable.

Patients 1-N and 4-N had peritoneal and patients 2-N, 3-N, 5-N, 6-N, 7-N, and 8-N had pleural mesotheliomas.

Mesothelioma Patients With Family Contacts Exposed to Asbestos.—Patient 1-F, a 3-year-old child, was the daughter of a ceramic engineer who worked in an insulation plant that utilizes 400 tons of Canadian chrysotile and 1,500 tons of South African amesite annually.

Patient 2-F, a 40-year-old nurse, never had any occupational asbestos exposure, but her father had worked for 35 years in the insulation plant where patients 3-0, 4-0, and 5-0 had worked and which was also credited with three neighborhood cases. The nurse's brother also had worked in this plant for one year.

Patient 3-F, a 67-year-old woman, never had any asbestos exposure nor had she lived near an asbestos plant. She had two sons who worked as insulators in a shipyard for six years. These sons lived at home until 15 years prior to their mother's death.

Patients 1-F and 3-F had peritoneal and patient 2-F pleural mesotheliomas.

Mesothelioma Patients With Questionable Asbestos Exposure.—A study of these ten men elicited either a relatively minor or questionable exposure to asbestos.

Patient 1-Q was a welder for 35 years. According to a common reference,[13] eight out of 12 welding electrodes contain asbestos, which is used as a filler.

Patient 2-Q was a self-employed Swiss-born Swiss cheesemaker. A thorough study of the processes of Swiss cheese manufacture revealed no use of asbestos. During the study of the manufacturing process a 500-gal boiler was noticed. This boiler was covered with a friable asbestos insulation which flaked off on contact.

Patient 3-Q, a 14-year-old boy with mesothelioma, had no occupational contact with asbestos nor did any of his family. On questioning, the boy's father told the authors that his boy had lived with him and had helped him while he had replaced most of the plaster board during extensive remodeling of his house. Plaster board contains a high percentage of asbestos.

Patient 4-Q is employed in industrial sales and never had any occupational asbestos exposure. Extensive questioning revealed that, on two occasions several years before, he applied asbestos insulation to boilers in his home, mixing asbestos cement himself. His total exposure during these applications was only a matter of hours.

Patient 5-Q was a brewery worker for 20 years. The brewery was no longer in business when the case was investigated. Reviewing the literature of beer production the following paragraph was discovered:

"When ready for packaging the beer is filtered through pulp filters consisting essentially of cotton fibers and asbestos. After each filtration this 'FILTERMASS' is removed, mangled, and washed in clear, warm water, then bleached and sterilized at 160 to 180 F with chlorine. The washed pulp then goes directly to a pad-forming machine where it is compressed at 89 to 90 pounds per square inch to form new filter pads.[14]"

Asbestos-containing pipe insulation is used in breweries.

Patients 6-Q, 7-Q, and 8-Q were all steel workers. Patient 6-Q was a crane operator; 7-Q a forger; and 8-Q a foreman and supervisor. In all cases the companies did not recall any asbestos exposure for these men. Pipe insulation containing asbestos is extensively utilized by steel companies.

Patient 9-Q was a spinner in a silk company

from 1925 to 1938, and later in a plastic fabrication plant which utilized fiber glass; he also had been a welder for 25 years. He thinks he has used asbestos but could not recall when and where.

Patient 10-Q, a 63-year-old man, was a core-maker all his life. He worked in two foundries in one of which asbestos cement is used in small quantities but, according to the plant manager, the core-maker did not have any contact with this material. The son stated that his father had used asbestos pipe insulation for pipes in the basement of their home several years prior to the onset of his illness and that he had done some sawing of this pipe insulation material.

All cases in this group had pleural mesotheliomas.

Mesothelioma Patients Without Asbestos Exposure.—In the other 11 patients (1-X to 11-X) no occupational, familial or neighborhood asbestos exposure evidence could be elicited. Ten of these patients had mesothelioma of the pleura and one peritoneal mesothelioma.

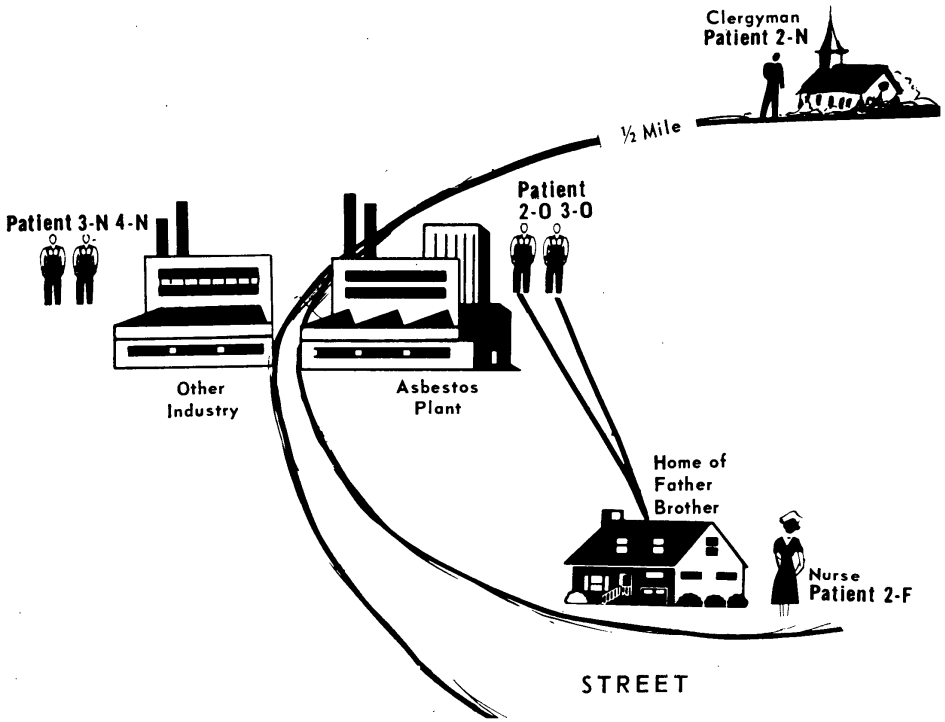
Comment

This study presents a good deal of circumstantial evidence and many unanswered questions.

Asbestos is a ubiquitous material used much more frequently than is generally realized. Some uses, such as in the brewery, were not previously known to the writers. There are undoubtedly many others.

If we assume that asbestos may be the causative or trigger agent for malignant mesothelioma in some of the cases described above, we must admit that the minimal dose-effect relationship and duration of a latent period are unknown. The occupational exposure of the insulation workers or asbestos textile workers were certainly many thousand times higher than those of the neighborhood cases or family contacts. Similar findings have recently been reported from England.[1]

The attack rate for mesotheliomas is ex-



Occupational, neighborhood, and family contact patients with mesothelioma associated with one insulation plant.

tremely low. Not all mesotheliomas were reported to us by the hospitals, but, even if we double the incidence, only a minute fraction of the exposed population was affected. There are precedents for this with beryllium disease which acts in a somewhat similar pattern; occupational diseases, familial contacts, neighborhood cases plus a very low attack rate, and a long latent period between exposure and onset of disease.

Another question which arises is why pleural mesotheliomas are so much more frequent than peritoneal mesotheliomas.

The most striking finding of this study was that of the 42 mesotheliomas which came from a geographical area of approximately 30,000 sq mi, six were clustered in and around an insulation plant (Figure). These included two insulation manufacturing workers (Cases 2-0 and 3-0), three neighborhood cases (Cases 2-N, 3-N, and 4-N) and one family contact (Case 2-F)—the daughter of an insulation worker.

Summary

Forty-two cases of mesotheliomas reported from 152 hospitals over a five-year period, were studied with regard to exposure to asbestos. Survivors or employers, or both, were questioned regarding the possibility of asbestos exposure. Ten patients actually worked in asbestos plants; eight lived or worked close to an asbestos industry; three patients were family members of asbestos workers. In ten patients a history of assumed exposure to asbestos was obtained after prolonged questioning. In 11 other patients no history of asbestos exposure could be obtained.

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DISCOVERY OF QUININE

Many of the drug sources known in ancient times were apparently discovered by accident. For example, according to an old South American Indian legend, the curative power of cinchona bark (containing quinine) for malaria was discovered by a sick, feverish Indian lost in the jungle. He quenched his thirst by drinking from a pool of water. From the bitter taste of the water, he recognized that it was tainted with the poison from the quina-quina tree. Although he shared this fictitious belief, he drank deeply so as to bring about a quick death. To his great surprise, he recovered completely. When he returned to his village, he told the store of his cure and thereafter cinchona bark was used as a medicine for the fever prevalent in that region. The Incas later taught the Spanish conquistadors that malaria could be cured with cinchona extract.—Rossman, R.E.: The History and Significance of Serendipity in Medical Discovery, *Trans Coll Physicians Phila* **33**:104-120 (Oct) 1965.