

MESOTHELIAL TUMORS AND EXPOSURE TO ASBESTOS DUST

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The carcinogenic properties of asbestos have been recognized for several years,^{1,2} but only recently has particular attention been given to the occurrence of mesothelial tumors in workers exposed to asbestos dust.³⁻⁵

In the present investigation evidence of asbestos exposure was sought in recorded examples of diffuse mesothelioma occurring in Liverpool and in neighbouring towns of the Merseyside area of North West England. This is an industrial area with a population of over two million people. Ship building and ship repairing are prominent among the industries which use asbestos, and there are a number of factories in the area where processing of raw asbestos is carried out.

METHODS

Thirty cases were considered. All had malignant growths of the pleura or peritoneum and in all of them the diagnosis of diffuse mesothelioma had been suggested at one time, though sometimes inaccurately or on inadequate grounds. A review of clinical histories and post-mortem records was followed by reassessment of all available histological material. In only one instance was the diagnosis accepted without histological confirmation. In this case post-mortem findings typical of diffuse mesothelioma of the pleura had been recorded, but the sections and blocks of tumor tissue had been lost. With this exception the diagnosis of diffuse mesothelioma was only accepted if, in addition to all other evidence, the histological appearances of the tumor were thought to be characteristic. Tumor tissue had been preserved in 26 cases, the specimens being obtained at thoracotomy alone in 13 patients, at autopsy alone in eight patients, and from both these sources in another five patients.

Evidence of exposure to asbestos was sought by microscopic examination of lung tissue for the presence of asbestos bodies and by obtaining detailed occupational histories from the patients or from their nearest relatives.

Histological Diagnosis

Of the 30 cases considered 17 were finally selected as true examples of diffuse mesothelioma (including one on post-mortem evidence alone). Sixteen were primary growths of the pleura and one was a primary peritoneal mesothelioma. Of the remaining 13 tumors five were identified as secondary adenocarcinomas infiltrating the pleura, two as fibrosarcomas, and one as a bronchial oat cell carcinoma involving the pleura. Conclusive diag-

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is recognized for several years and has been given to the occurrence of asbestos dust.²⁻⁵

Exposure was sought in the shipbuilding industry in Liverpool and in the engineering industry in the West of England. This is a problem for 10 million people. Shipbuilding and engineering industries which use asbestos in a large area where processing

of the pleura. Diffuse mesothelioma had been diagnosed accurately or on inadequate post-mortem records was rare material. In only one case was histological confirmation. In the case of mesothelioma of the lungs, tumor tissue had been obtained at thoracotomy patients, and from both

microscopic examination and by obtaining detailed histological material from their nearest relatives.

These were taken as true examples of primary evidence alone. Six cases were identified as secondary mesotheliomas, and one as a primary peritoneal fibrosarcoma, and one as a primary pleura. Conclusive diag-

nosis of the remaining five tumors could not be achieved. On histological grounds two of these may have been mesotheliomas but the appearances were not entirely characteristic and the available material was small in amount. In the other three cases the diagnosis of mesothelioma had been put forward on clinical grounds alone. No tumor tissue had ever been submitted for histological examination, and neither exploratory thoracotomy nor post-mortem examination had been carried out. Cytological examination of pleural fluid in two of these cases had shown the presence of malignant cells of unspecified type.

Difficulties in the histological diagnosis of diffuse mesothelioma arise mainly from similarity to secondary adenocarcinoma or to fibrosarcoma. Detailed descriptions of the microscopic appearances have been given by a number of authors.⁶⁻⁸ All agree that the main diagnostic feature is the presence of a mixed structural pattern which they attribute to the dual potentiality of the mesothelium. Characteristically, an endothelial component of papillary or tubulo-papillary structure is mixed with areas of fibroblastic activity often of sarcomatous appearance. A mixed pattern of this type was clearly visible in 11 of the 16 mesotheliomas examined microscopically in this series. Two others were predominantly sarcomatous in appearance, one was mainly papillary in structure, and two were poorly differentiated growths composed of sheets of malignant cells including spindle cells and several tumor giant cells. But even in these tumors of predominantly one-cell-pattern there were some areas in which other features of mesothelioma could be distinguished.

The demonstration of hyaluronic acid production assists the diagnosis of diffuse mesothelioma.⁹ A substance giving positive reactions with alcian blue and with Hale's colloidal iron stain was demonstrated in all the mesotheliomas in this series, but in the majority it was present in very small quantities, being confined in some instances to a few isolated tumor cells. These color reactions were abolished or markedly reduced by previous treatment of the tissues with testicular hyaluronidase, in contrast to the behavior of mucin in secreting adenocarcinomas. On the other hand there was failure of the tissues to stain with Southgate's mucicarmine in all but one of the examples. This tumor gave a faint reaction which was abolished by digestion with hyaluronidase. Only material present within tumor cells or within spaces lined by cells of endothelial type was considered significant. Similar reactions in stromal elements were regarded as nonspecific as hyaluronic acid may be produced by any actively growing connective tissue.¹⁰

Post-mortem Appearances

Post-mortem examinations had been performed on 12 of the patients suffering from mesothelioma including the one where no histological material

had been preserved. In all cases tumor was present which was confined to the lining layers of serous cavities. There was one primary peritoneal mesothelioma. In this subject the growth had spread widely over the surface of the bowel and over both surfaces of the liver but no primary tumor could be detected in these or in any other organ. The remaining examples were considered to be primary growths of the pleura though extensive peritoneal involvement had occurred in two of them. In nearly all instances the lung on the affected side was shrunk and encased in thick tumor tissue which obliterated the pleural space and which extended deeply into the interlobar fissures.

Only one blood-borne metastasis was encountered. This was an isolated nodule of tumor situated deeply within the substance of the liver. Lymphatic spread was recorded more frequently, axillary or mediastinal lymph node deposits being present in half the cases.

No bronchial or other intrapulmonary neoplasm was detected at any of the post-mortem examinations and no primary tumors were found in any other organs.

Evidence of Asbestos Exposure

Evidence of exposure to asbestos was obtained in 14, or 82 per cent, of the group of 17 cases selected as examples of diffuse mesothelioma. Each of the other three patients in this group had worked in places where they may have handled asbestos but no detailed information could be obtained about the nature of their duties. None of the patients in the second group was known to have worked with asbestos and in none were asbestos bodies found in the lungs. Two men in this group had spent several years at sea, one as a ship's stoker, and both could possibly have been exposed to asbestos though there was no direct evidence to suggest this. The tumor in the first case was one of the two which were difficult to classify histologically and which may have been mesotheliomas. The tumor in the second case had never been submitted for histological examination. In neither case had lung tissue been preserved.

Very little lung tissue had been preserved for examination, most of the thoracotomy specimens and much of the post-mortem material consisting only of blocks of tumor tissue. Asbestos bodies were never seen within tumor tissue. Sections containing lung were available in 10 of the confirmed mesothelioma cases, and asbestos bodies were identified in seven of these. They were scanty in most specimens so that prolonged search was necessary to find them. In the three negative cases only small fragments of lung attached to tumor tissue were available for examination. In contrast, asbestos bodies were found in only 18, or 9 per cent, of 200 consecutive pneumonectomy and post-mortem specimens of lung seen during the same period. In this group routine histological methods were supplemented

by the examination of from lung tissue, a number of asbestos bodies.

Because of the limit to assess the degree of from mesothelioma but a slight to moderate deg with the clinical history had complained of respiratory tumor within the pleura.

Twelve of the mesothelioma cases had worked in asbestos dust during their lives. Ten of the coverers, who had been engaged in ship repair had been engaged mainly in ship repair. Two patients were boiler makers, mainly sheet metal work for fireproofing and heating. One patient had been engaged in preparing asbestos and both had frequently worked with other men who were handling asbestos factories. A male patient had started working in a factory years before the introduction of asbestos workers. The other patient had worked at an asbestos factory in 1919, and had then married a woman who had been in health for forty years, a woman who died two years after marriage. The patients had been employed in department stores, handling of old sacks. Sacks of various contents and were generally asbestos sacks were noted in handling. Close environment working in the offices of a factory, where bags of cement were made, the entire area became extremely dusty, and with a layer of fine white dust every day.

Five patients gave negative results.

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or examination, most of the mortem material consisting of fragments were never seen within the material available in 10 of the cases. In seven of these cases the fragments were identified in seven of the cases that prolonged search was made. In only a few cases only small fragments were available for examination. In contrast, 9 per cent, of 200 consecutive autopsies of lung seen during the study. The methods were supplemented

by the examination of smears made from spun deposits of fluid expressed from lung tissue, a much more sensitive method for the detection of asbestos bodies.

Because of the limited amount of lung tissue available it was difficult to assess the degree of pulmonary fibrosis present in the patients suffering from mesothelioma but none of the specimens examined showed more than a slight to moderate degree of fibrous reaction. This finding correlates well with the clinical histories. All patients had enjoyed good health and none had complained of respiratory symptoms until the development of malignant tumor within the pleural cavity.

Occupational Histories

Twelve of the mesothelioma patients are known to have been exposed to asbestos dust during the course of their work. Five were ladders, or pipe coverers, who had been employed by firms of insulation engineers and who had been engaged mainly in the insulation of steam pipes. Three of these had worked in ship repairers' yards and all had handled asbestos regularly. Two patients were boiler makers in the ship building industry. Though mainly sheet metal workers, both gave clear accounts of the use of asbestos for fireproofing and heat insulation in ship construction. Both had been engaged in preparing and fitting asbestos sheets in ships' compartments and both had frequently worked in confined spaces in close proximity to other men who were handling asbestos. Only two patients had worked in asbestos factories. A man employed for forty-three years at one asbestos factory had started work at fifteen years of age in 1915, nearly twenty years before the introduction in Great Britain of legislation to protect the asbestos worker. The other patient was a female card room operative. She had worked at an asbestos factory for a period of five years from 1914 to 1919, and had then married and left the industry. She remained in good health for forty years and then developed a pleural mesothelioma from which she died two years after the onset of the first symptoms. Two female patients had been employed by firms of sackware manufacturers. Both had worked in departments dealing with the sorting, cleaning, and repairing of old sacks. Sacks submitted for repair contained traces of their previous contents and were generally extremely dusty. At each of the factories asbestos sacks were notorious for the fine dust which they produced on handling. Close environmental exposure had occurred in the case of a typist working in the offices of a firm of concrete manufacturers. Regular deliveries of cement were made from a nearby asbestos cement works and the entire area became extremely dusty when the loads of cement were tipped into the factory yard. On these occasions the office furniture became coated with a layer of fine white powder which had to be removed at least once every day.

Five patients gave negative or inconclusive occupational histories but in

two of these asbestos bodies were detected in the lungs. One was a lorry driver for a firm of ship repairers and fitters. Though he denied asbestos exposure it was later learned that he did carry loads of asbestos on several occasions. The second patient was a woman who had done several different types of work, none of which involved the use of asbestos. The time and place of exposure in this case remain unknown. Of the remaining three patients one had been a boiler maker in the ship building industry, one was apprenticed to a firm of ship repairers and fitters for a period of seven years, and the other was a general laborer on the dock railway system. All may have handled asbestos but there was no direct evidence that they had done so.

General Information

No attempt was made in this investigation to ascertain the type of asbestos fibers to which patients had been exposed, and no information was sought from factories or other industrial concerns where patients had been employed.

The series covers a period of ten years from 1953 onwards. In the mesothelioma group there were 12 male and five female patients. All but one have died. Their average age was 58 years, the youngest being 42 and the oldest 82 years of age at death.

Duration of exposure to asbestos ranged from five to 45 years. The shortest interval recorded between the first known exposure to asbestos and the development of tumor was 13 years, and in all but two cases this interval exceeded 20 years. There were latent intervals of up to 40 years between the end of exposure and the development of tumor.

CONCLUSION

A close association between exposure to asbestos dust and the development of diffuse mesothelioma is confirmed, and it is concluded that asbestos exposure is a major factor in the causation of this tumor.

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