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RELATION BETWEEN EXPOSURE TO ASBESTOS AND MESOTHELIOMA*

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In 1960 Wagner, Sleggs and Marchand[1] reported 33 cases of diffuse pleural mesothelioma from the North Western Cape Province of South Africa. The collection of such a large number of cases of a rare tumor within a short time (1956-1960) in one area was considered unusual enough. Even more striking was the fact that close questioning and investigation revealed that 32 patients had evidence, admittedly circumstantial in most cases, of some potential or actual contact with asbestos by virtue either of residence in mining areas or in industry twenty to forty years before.

This remarkable concentration of cases in one area of South Africa was explained by the hypothesis that mesothelioma was the result of exposure to one special type of asbestos (crocidolite), mined almost entirely in that region. The report of a mesothelioma associated with asbestosis in Western Australia,[2] one of the few other regions of the world in which crocidolite is mined, was consistent with this hypothesis. Similarly, the occurrence of other cases of mesothelioma, including several of the peritoneum, in Great Britain[3,4] was not disturbing since British asbestos companies have long been intimately related in ownership and management with the South African asbestos industry and the largest portion of crocidolite mined in South Africa had in previous years been imported into Great Britain.[5,6]

Present Investigation

We undertook to study the question whether mesothelioma of the pleura and peritoneum had an important relation with asbestos exposure in the United States. We had previously found that lung cancer and possibly gastrointestinal cancer were markedly increased in incidence among asbestos-insulation workers.[7] The investigation was planned to demonstrate whether another potential neoplastic hazard of asbestos exposure existed in the United States. Secondly, data developed in the investigation would have epidemiologic and pathogenetic bearing on the problem since the condition of American asbestos utilization differed to some extent from British and South African experience in at least one important respect. Crocidolite is a relative newcomer to the American asbestos-industry scheme. Thus, American imports of crocidolite (none is mined here) were less than 500 tons in 1935 and had reached a level of only 20,000 tons even in 1962. In contrast, chrysotile, the type of asbestos fiber widely used in the American asbestos industry, was imported at a level of 165,000 tons in 1935 and 650,000 tons in 1962.[5]

Our investigations sought to determine whether mesothelioma is more common among people dying with asbestosis than those without this disease in the United States, conversely, whether proof of asbestos inhalation can be found among cases of mesothelioma and whether an estimate of the incidence of this neoplasm can be made among workers with known exposure to asbestos.

The answers to these questions are potentially of considerable practical importance. If the hypothesis that mesothelioma associated with asbestos contact is a special case of asbestos cancer, caused by exposure to one kind of asbestos fiber (crocidolite), is correct the problem is a rather limited one. Although it would be important in the areas in which crocidolite is mined, and to those working with it, the United States asbestos industry could be advised to avoid this type of fiber in favor of other forms of asbestos.

Our investigations could serve to test this hypothesis. Crocidolite has had a small role in the United States asbestos industry and that but recently. Neoplasms associated with asbestos exposure generally occur only twenty to forty years after exposure. If mesothelioma could be found with increased frequency in association with asbestos *in this country*

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would demonstrate that this tumor was another neoplastic hazard of asbestos exposure in general and *not* limited to one area or to one type of fiber.

Materials and Methods

First of all, since diffuse pleural and peritoneal mesotheliomas are fatal conditions we decided to study their relation to asbestosis in autopsy series. For this purpose, we analyzed 2500 consecutive autopsies, which comprise the personal autopsy experience from 1953 to 1964 of two pathologist members of our investigative group.* All patients showing characteristic asbestos bodies and pulmonary fibrosis were accepted as having had pulmonary asbestosis, and the cause of death was reviewed. All cases of diffuse mesothelioma were also selected, and the tumors carefully restudied to verify pathological classification and histologic characteristics of the tumor.[3]

Secondly, even if mesotheliomas were frequently found in patients dying with asbestosis, this would still not prove whether or not the tumors were commonly caused by asbestos inhalation since few patients are known to die with asbestosis. To study this second question, we reviewed all cases of pleural and peritoneal mesotheliomas in the files of the Armed Forces Institute of Pathology, in co-operation with Dr. S. Rosen of the Institute. Forty-five cases (19 pleural and 26 peritoneal) of diffuse pleural or peritoneal cancer were found in which the diagnosis of mesothelioma had been strongly considered although in some cases alternate diagnoses such as peripheral bronchogenic carcinoma, fibrosarcoma and metastatic carcinoma of undetermined origin were entertained. In addition, each of these cases had available at least a small portion of lung for histologic study (sometimes very small, such as a tag of lung at the border of tumor tissue). Other cases of diffuse mesothelioma are present in the files of the Institute, but since lung tissue was not available, they were not studied.

Each case was carefully restudied, both to verify the pathological diagnosis and histologic characteristics of the neoplasm[3] and to search for asbestos bodies in the lung tissue available. We appreciate that any attempt to evaluate the presence or absence of asbestos *fibers* in tissues, limited to identification of asbestos *bodies*, may grossly underestimate the true frequency of the presence of asbestos. In other studies, we have demonstrated that in workers exposed to asbestos, asbestos fibers may be present in large numbers in the absence of asbestos bodies, which are altered and coated fibers. Unfortunately, since in most cases tissue was not available for the additional studies necessary, it was not possible to investigate the problem in this material further.

Thirdly, to study the incidence of mesothelioma among persons exposed to asbestos, we undertook a survey of 1522 members of the Asbestos Workers Union in the New York metropolitan area, members of New York Local 12 and Newark, New Jersey, Local 32 of the International Association of Heat and Frost Insulators and Asbestos Workers. These men are insulation workers, primarily engaged in building, powerhouse and shipyard construction work in which they have relatively light, intermittent exposure to asbestos-containing insulation materials.

Some of the insulation materials used by these men, such as fibrous glass, cork and hair felts, contain no asbestos, whereas others, such as magnesia or calcium silicate insulation block and insulation cements, may contain 10 to 15 per cent asbestos.[9,10] Exposures are therefore to a number of dusts, but asbestos appears to be the only biologically active fibrogenic material present in significant amounts. Little free silica is found, and histologic study in our laboratory of lung tissue of 45 of these insulation workers showed diffuse interstitial fibrosis characteristic of asbestosis and no evidence of the whorled nodular fibrosis of silicosis.[11]

Our survey covered every man who was a member of either of these locals at any time from December 31, 1942, to December 31, 1962. Six hundred and thirty-two men were enrolled in these locals in 1942, and 890 men subsequently joined in the years between 1942 and 1962.[7] On January 1, 1963, 264 of these men were dead, 1258 were alive, and, of these, 1117 have been examined by us. From January 1, 1963, to August 31, 1964, 43 men died. Thus, from January 1, 1943, to August 31, 1964, there have been 307 deaths among this group of asbestos workers. Each death has been investigated, and the cause ascertained. Copies of death certificates were obtained in all but 1, autopsy protocols were reviewed (69 cases), histologic specimens were examined (71 cases), and hospital records were obtained and reviewed in the deaths (165 in number) in which the terminal illness had occurred in a hospital.

The types and intensity of exposure to asbestos were studied in several ways, including analysis of the occupational histories detailed during the interviews with the examined men, review of trade practices with union and industry sources, analyses of materials retrieved during repair work and review of pertinent published data in this field. Finally, work histories of the men were obtained from the examined men when available and from union records for the others. These data gave the baseline for calculation of the onset and duration of exposure.

In the group of 307 consecutive deaths among these asbestos-insulation workers no diagnosis of mesothelioma was accepted without a review of histologic material and verification of pathological classification.[3] It is possible that mesotheliomas were present in persons who died and in whom we had no opportunity to examine histologic material, and

that our data represent an underestimate of the true incidence of mesothelioma among asbestos workers. Nevertheless, only histologically verified cases are so classified in this report.

Results

Mesothelioma in Autopsies with Asbestosis

In the autopsy series studied 2500 cases were examined in 1953-1964, including 1020 adult males. Among these asbestosis was recorded in 26 cases. The causes of death in these cases are summarized in Table 1. Mesothelioma of the pleura was present in 4, mesothelioma of the peritoneum in 3, and bronchogenic carcinoma in 7.

This frequency of 4 pleural mesotheliomas among 26 autopsies (15 per cent) with asbestosis may be contrasted with the frequency of pleural mesothelioma in a general autopsy series. Hochberg[12] collected 43,732 reports of autopsied cases from the literature, with 36 mesotheliomas recorded, for an autopsy incidence of 0.07 per cent. He added 7 mesotheliomas among 16,310 autopsies studied by him, an incidence of 0.04 per cent. König[13] found 102 pleural mesotheliomas among 13,307 consecutive autopsies without asbestosis at the St. Georg Hospital in Hamburg (0.77 per cent), but 4 of 26 autopsies with asbestosis (15.4 per cent).[12] In the same study he reported 22 "peritoneal carcinomas" among the 13,307 autopsies without asbestosis (0.16 per cent) and 3 among 26 autopsies with asbestosis (11.5 per cent).

In this autopsy series we found no case of mesothelioma in the absence of asbestosis.

Asbestosis among Cases of Mesothelioma*

A search for asbestos bodies demonstrated them to be present in 12 of 45 cases of pleural and peritoneal mesothelioma in which lung tissue was available for study: in 5 of 19 pleural mesotheliomas and in 7 of 26 peritoneal mesotheliomas (Table 2). In 2 cases asbestos bodies were already known to be present. In the other 10 the present review first brought them to notice.

The discovery of previously undetected asbestos bodies on re-examination of lung tissue in these cases of mesothelioma parallels the experiences of McCaughey, Wade and Elmes[14] and of Hourihane.[4] It reflects the rarity of these bodies in lung sections, easily missed on random scanning and often found only with difficulty on prolonged examination even when deliberately sought.

How often such diligent search of histologic lung sections would uncover asbestos bodies in routine autopsy material has not yet been completely studied. The negative results of ordinary autopsy experience should not be accepted as an answer to this question since detailed, prolonged review of lung sections is usually not undertaken in the absence of special indications. However, in one study, in an institution in which mesotheliomas were found to be frequently associated with asbestos bodies in lung sections, 50 consecutive autopsy cases (excluding chest tumors) were studied specifically to demonstrate asbestos bodies in lung sections. In none were they present.[4]

The results of our review of this group of mesotheliomas may well represent an underestimate of the true incidence of asbestosis among cases of mesothelioma in the United States. In the first place, as noted, very little lung tissue was available for scanning in many cases since the submission of the material to the Institute had been for review of the neoplasm, with the status of the lung not of immediate concern. This was particularly true of biopsy specimens. Secondly, no information was available concerning the portion of the lung from which the specimen was taken. In the search for asbestosis the lung bases are preferred, since these areas are more heavily involved. Thirdly, we had to be satisfied with a review of sections for asbestos bodies as a diagnostic criterion. Yet in some cases of asbestosis, these may be virtually absent despite the presence of many unaltered asbestos fibers, which usually require special technics for demonstration. These were not available in this study.

Incidence of Mesothelioma among Asbestos Workers

We have analyzed 307 consecutive deaths among asbestos-insulation workers. These comprise all deaths of members of the New York City and Newark, New Jersey, locals of the insulation workers' union from January 1, 1943, to August 31, 1964.

Table 1. *Mesothelioma in 2500 Consecutive Autopsies, 1953 to 1964.**

Classification	No. of Cases
Total autopsies	2500
Cases with asbestosis	26
Pleural mesothelioma	4
Peritoneal mesothelioma	3
Bronchogenic carcinoma	7
All other	12

*Personal autopsy series of Churg & Moolten: 25 of 26 cases of asbestosis among 1020 adult males, with 1 case (associated with lung cancer) in a woman; no mesotheliomas other than those associated with asbestosis observed.

Table 2. *Presence of Asbestos Bodies in Lung Sections among 45 Cases of Pleural and Peritoneal Mesothelioma.**

Location of Mesothelioma	No. of Cases	Asbestos Bodies	
		found	not found
		no. of cases	*no. of cases*
Pleura	19	5	14
Peritoneum	26	7	19
Totals	45	12	33

*Armed Forces Institute of Pathology material.

*Armed Forces Institute of Pathology material.

TABLE 3. *Underlying Cause of Death in 307 Consecutive Deaths among Asbestos Insulation Workers, January 1, 1943, to August 31, 1964.*

CAUSE OF DEATH	NO. OF DEATHS	PERCENTAGE
Bronchogenic carcinoma	53	17.3
Gastrointestinal cancer	34	11.1
Pleural mesothelioma	4	1.3
Peritoneal mesothelioma	6	1.9
All other neoplasms	27	8.8
Asbestosis	17	5.5
All other causes	166	54.1
Totals	307	100.0

Table 3 summarizes the causes of death among these men.

Ten mesotheliomas, 4 of the pleura and 6 of the peritoneum, were found. This incidence of more than 3 per cent of deaths is remarkably high for a tumor ordinarily so rare that neither mesothelioma of the pleura nor mesothelioma of the peritoneum is separately classified in the *International Classification of Diseases* used by health departments for reporting causes of death.

In the absence of data segregated by such coding of recorded deaths it is difficult to ascertain the comparative incidence of mesothelioma among deaths in general. We have been able to obtain some information, however, that emphasizes the infrequency of this neoplasm in the general population of the United States at the present time.

Between October 1, 1959, and February 15, 1960, 68,116 volunteer workers of the American Cancer Society enrolled 1,078,894 men and women in a prospective study. The subjects are traced annually and once every two years are requested to fill out a brief questionnaire. Whenever a death is reported a copy of the death certificate is obtained, and when cancer is mentioned on the certificate, inquiry is made of the certifying physician concerning diagnosis and histologic type of the neoplasm; 1,048,183 men and women between the ages of thirty and eighty-nine years were traced through September 30, 1962,[15] of whom 31,652 were dead. Only 3 had died of mesothelioma of the pleura, and none of mesothelioma of the peritoneum.

In addition to the neoplasia among the recorded deaths of the asbestos workers, 3 men are alive with known neoplasms (1 lung cancer and 1 pleural and 1 peritoneal mesothelioma), 1 is apparently cured of cancer of the colon and 1 of tongue cancer, and 3 are alive after successful resection of localized lung cancer discovered in the examinations.

DISCUSSION

Scattered reports of neoplasia of the pleural and peritoneal surfaces in association with asbestosis variously labeled "undifferentiated carcinoma." "endothelioma" and "mesothelioma" have been available for thirty years. Although a special relation had been proposed[16] such considerations faced the difficulty of the infrequency of reported cases and the absence of population and epidemiologic studies. Similar difficulties plagued the question of the relation between lung cancer and asbestos exposure until their resolution by adequate epidemiologic investigations, which confirmed the accurate but unverified pathological and clinical studies. It appears that a similar process is being completed regarding the complication of mesothelioma.

Lung cancer has previously been demonstrated to be a frequent complication of asbestos exposure among insulation workers in the United States.[7] The data in Table 3 may be considered an extension of previously reported observations, which were based upon age-specific death rates among 632 men with at least twenty years' elapsed time from onset of first exposure to asbestos and which were concerned with 255 consecutive deaths. There were 42 deaths due to lung cancer at that time (16.5 per cent). In the 52 additional deaths 11 have been due to lung cancer (21.2 per cent). Originally, there were 4 mesotheliomas among the 255 deaths; there are now 10. Ten deaths from mesothelioma among 307 consecutive deaths is an extraordinarily high rate and permits the conclusion that this disease is an important complication of asbestos exposure. This conclusion, moreover, refers to such exposure in the United States, under working conditions of the recent past, with relatively light and intermittent asbestos ex-

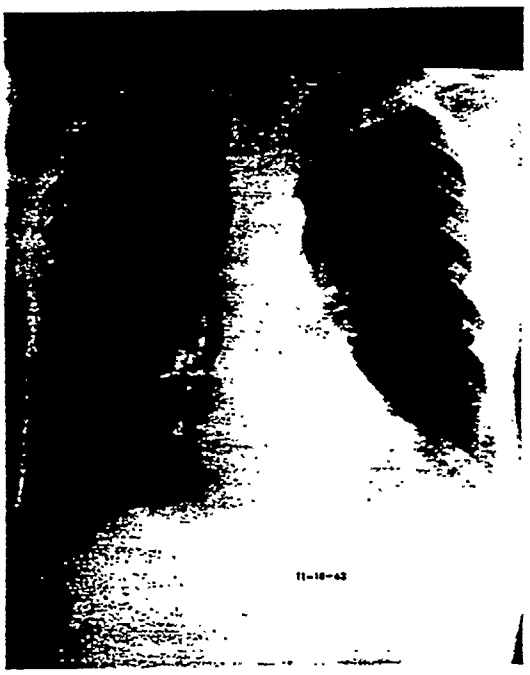

FIGURE 1. *Film of the Chest of an Asbestos-Insulation Worker. At thoracotomy, there was very thick parietal pleura, with normal visceral pleura. The decorticated specimen showed mesothelioma (Fig. 2).*

FIGURE 2. *Microscopical Appearance of the Tumor (X75). There are compressed tubules of epithelial-like cells in dense connective-tissue stroma.*

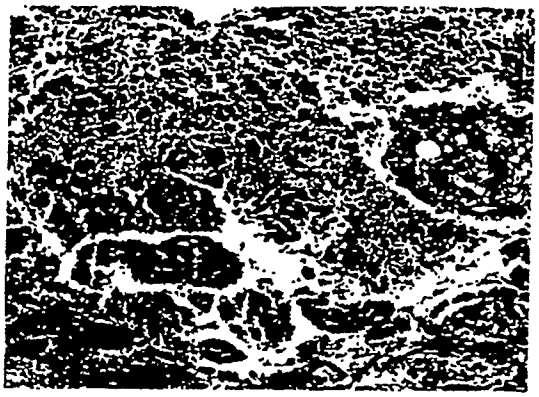

FIGURE 3. *Peritoneal Mesothelioma in an Asbestos-Insulation Worker with Minimal Pulmonary Fibrosis (X75). This is a biopsy of one of many nodules that studded the peritoneum, showing papillary and solid areas of epithelial-like cells.*

posure. It indicates, too, that mesothelioma may not necessarily be entirely a problem of only one kind of asbestos (crocidolite) and that it is surely not limited to South Africa.

We undertook three different types of investigations because each is subject to the difficulty of small numbers of cases of mesothelioma available for study, and with small numbers, there is a danger that findings may be due to chance. Autopsy series are selected; they exclude the patients with a disease who do not die, and carry the risk of including an undue proportion of the more unusual and complicated cases. Thus, the finding of 7 cases of mesothelioma in the autopsy series of 26 cases of asbestosis cannot be interpreted as necessarily indicating the true incidence of this neoplastic complication although it does point to its significant frequency. Secondly, the search for asbestos in cases of mesothelioma, as in the Armed Forces Institute of Pathology material, carries the hazard of underreading because only small specimens of lung parenchyma are available and it is simultaneously difficult to demonstrate scant asbestos bodies. On the other hand, there is the risk of overemphasis of the importance of such bodies since they are occasionally found in "normal" lungs without asbestosis, owing to chance environmental contact.[17] Analysis of the results of our clinical study, with review of 307 consecutive deaths among 1522 asbestos insulation workers, has the advantage of suggesting an estimate of the incidence of mesothelioma. However, even this estimate may underevaluate the incidence since, whereas each of the 10 mesotheliomas was confirmed by histologic examination of operative or autopsy material, only 110 of the remaining 297 deaths had such confirmation.

We have analyzed the work experience of the 10 men in the union group who died of mesothelioma. Age at death varied from fifty to seventy-five years (average, fifty-nine). Exposure to asbestos varied from fifteen to forty-three years (average, thirty-one and four tenths), but there was no man in whom this neoplasm developed in less than thirty-two years from the onset of exposure (average, thirty-eight and five tenths). Seven of the men were working as insulation workers at the time of onset of the fatal illness, and 2 at other occupations. One was retired. The 3 no longer exposed to asbestos had left insulation work three, fifteen and fifteen years before. There was no evident correlation between the occurrence of mesothelioma and the severity of asbestosis (Fig. 1-3).

Six of the 7 men with mesothelioma in the autopsy series also had histories of prolonged employment in the asbestos industry although in asbestos-factory work rather than insulation work. Two of the 6 had left such work five and fifteen years before their fatal illness.

The seventh man in the autopsy series raises a potentially important problem. He was seen by one of us in 1961, and the diagnosis of mesothelioma of

FIGURE 4. *Thoracotomy Specimen, Demonstrating an Extensive Unilateral Pleural Tumor in a Fifty-four-Year-Old Carpenter. Autopsy confirmed the diagnosis of pleural mesothelioma.*

FIGURE 5. *Asbestos Body (Arrow) in an Area of Pulmonary Fibrosis (X440).*

the pleura was made clinically and by biopsy (Fig. 4). Because of the suspected association with asbestos exposure, he was closely questioned with regard to such exposure. This questioning was particularly thorough because he was employed as a carpenter (employment in the construction industry is suspect). This man denied ever having seen, used or handled any asbestos product. He later died, and on post-mortem examination, both asbestos bodies and fibers were found in the underlying lung (Fig. 5). In another case we found asbestos fibers in the lung of a man who died of pleural mesothelioma and who had worked in a dry-cleaning plant as a "spotter." This observation calls to mind the finding of asbestos bodies and fibers in the sputum of people employed in a dry-cleaning works in South Africa in an area 100 miles away from the nearest mine,[18] as well as cases of berylliosis caused by handling contaminated work clothes.[19] These examples of indirect occupational exposure and community exposure raise the important question whether mesothelioma will be found to be a community problem in addition to that existing with industrial exposure to asbestos.

SUMMARY AND CONCLUSIONS

Our study of 307 consecutive deaths (1943-1964) among asbestos-insulation workers in New York and New Jersey disclosed 10 deaths caused by mesothelioma of the pleura (4 cases) or peritoneum (6 cases). This is an extraordinarily high incidence for a tumor generally so rare that it is not separately coded among causes of death. In contrast, in a prospective study of the general population, among 31,652 deaths (in patients thirty to eighty-nine years of age), only 3 were due to mesothelioma.

In 2 additional studies, the association of mesothelioma with asbestos was further indicated by the finding of 4 mesotheliomas of the pleura and 3 mesotheliomas of the peritoneum among 26 consecutive autopsies of cases of asbestosis and, also, by the finding of asbestos bodies in lung sections in more than 25 per cent of cases of mesothelioma.

It appears that mesothelioma must be added to the neoplastic risks of asbestos inhalation, and joins lung cancer (53 of 307 deaths) and probably cancer of the stomach and colon (34 of 307 deaths) as a significant complication of such industrial exposure in the United States.

We are indebted to the AFIP for making available collected cases of mesothelioma for our review and. in particular. to Dr. S. H. Rosen, of the Institute, for co-operation.

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