

August 23, 1967

Mr. J. M. Barnhart
National Insulation Manufacturers Association
441 Lexington Avenue
New York, New York 10017

Dear Jack:

SUBJECT: J.A.M.A. Article, "Mesothelioma and Its Association With
Asbestosis"

A copy of the attached article should be sent to Members of
the Health and Safety Committee. It is a good review on mesothelioma.

Sincerely,

Lee B. Grant, M.D.

lmg
Enc.

cc: Mr. Russell Brittingham



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Mesothelioma and Its Association With Asbestosis

Maxwell Borow, MD, Alfred Conston, MD,
Lawrence L. Livornese, MD, and Norbert Schalet, MD

Within a three-year period in a community hospital, 17 cases of mesothelioma, nine of the pleura and eight of the peritoneum, were found at surgery. Two of our patients contracted this malignancy with only environmental exposure consisting of living in a community adjacent to the asbestos mill. In the same hospital, there has been a high incidence of bronchogenic carcinoma with asbestosis. A review of the autopsy material of the past decade brought to light only one additional case. It is our belief that the incidence of mesothelioma is increasing as is the incidence of asbestosis, with the increasing application of this product in many different industries.

Primary tumors of the serosal surfaces are so rare that for years they were considered to be pathologic curiosities. The first reference to such tumors can be found in a report by Von Rokitsansky,¹ who in 1854 described primary tumors of the peritoneum which he called "colloid cancer." During the next 100 years, there were sporadic reports of similar types of tumors. However, this entity remained so ill defined that there was much doubt as to its precise nature. Brown and Johnson² in 1951 considered these mesothelial tumors (mesothelioma) to be the end result of an inflammatory process, with organization of the exudate. Willis³ in his pathologic text made the following statement: "To the present day accounts of supposedly primary serosal tumors continue to be descriptively inadequate and insufficiently critical, displaying a lack of awareness of the possible behavior of small undetected carcinomas," and he also cautioned the reader to preserve an open mind regarding the exact histogenesis of these tumors. In 1954, Ackerman⁴ stated that it was the majority opinion that although primary mesotheliomas are rare they do

exist. Since Godwin⁵ in 1957 laid down strict criteria for the diagnosis of pleural tumors and Winslow and Taylor⁶ in 1960 for peritoneal tumors, the diagnosis of these neoplasms has become more common. The incidence of primary mesothelioma has varied statistically from .02% to .2% of all autopsies, with a ratio of one to two in favor of the male.

The first large series of cases of diffuse mesothelioma was diagnosed histologically in 1957 at the Pneumoconiosis Research Unit at Johannesburg, South Africa. In trying to explain this mysterious epidemic, Wagner et al,⁷ noting that asbestos bodies could be found in the lungs of some of their patients, obtained detailed life histories of these patients. By 1960, they were able to establish an association with the Cape of Good Hope asbestos fields, or the industrial use of asbestos, in 32 of 33 patients with histologically proven pleural mesotheliomas. The majority of these patients had not actually worked with asbestos but had lived in the vicinity of the mines and mills and some had left these areas of exposure as young children. The average period between exposure and development of the tumor was 20 to 40 years. By 1962, Wagner et al⁸ had diagnosed a total of 87 pleural and two peritoneal mesotheliomas. In only two cases was it not possible to establish a history of exposure to the asbestos dust. Of these 87 cases, 12 had had industrial exposure and the remainder had had environmental exposure from living in the vicinity of the mills and dumps. This association between mesothelioma and asbestosis was made even more intriguing when, in 1955, Bonser et al⁹ described a series of 72 autopsies on patients with asbestosis, in which four cases of peritoneal mesothelioma were found. Subsequently, Mancuso and Coulter¹⁰ found five peritoneal mesotheliomas in autopsies on 1,495 asbestos workers, and Hourihane,¹¹ upon reviewing the necropsy files of the London Hospital from 1917 to 1962, found 34 cases of mesothelioma, 17 of the pleura and an equal number of the peri-

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toneum. All of these patients had pulmonary asbestosis, even though in a few there was no history of exposure to the asbestos dust. In the same year, Enticknap and Smither¹² reported 11 cases of peritoneal mesothelioma in patients exposed to asbestosis.

In an attempt to determine whether mesothelioma of the serosal surfaces had any relationship with asbestos exposure in the United States, Selikoff et al¹³ studied 307 consecutive deaths among asbestos insulation workers in Northeastern United States. They found ten deaths caused by mesothelioma, four pleural and six peritoneal mesotheliomas. In addition, these workers had an extremely high death rate attributed to cancer of the stomach, colon, and rectum. Of the 307 deaths, 40.4% were attributed to cancer, 5.5% to asbestosis, and 54.1% to other causes. In a second study where they reviewed 26 consecutive autopsies of patients with asbestosis, they found four mesotheliomas of the pleura and three of the peritoneum.

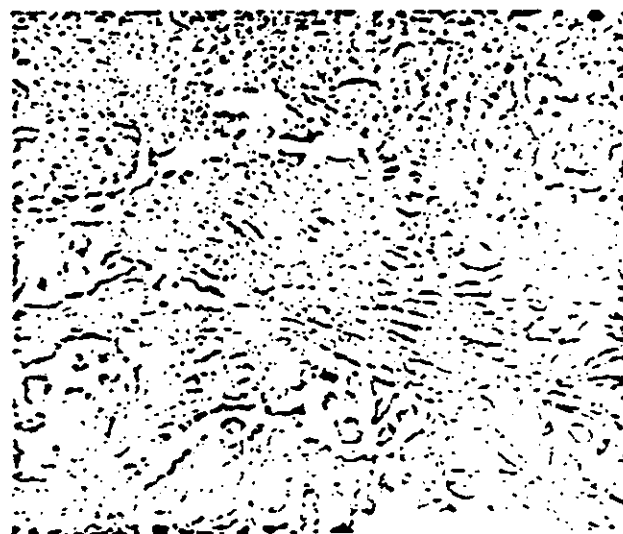
One of us (M.B.) has had the unique experience of operating, within the past two years, on 11 patients who proved to have mesothelioma. Six of these were of the peritoneum and five of the pleura. These cases added to those diagnosed previously made a total of 17 cases of mesothelioma, of which eight were peritoneal and nine were pleural mesotheliomas. All 17 cases were diagnosed within the past three years. A review of the autopsy material at Somerset Hospital, Somerville, NJ, from 1948 through 1965 did not disclose any additional cases of mesothelioma. This high concentration of what is considered to be a rare tumor can be explained by the close proximity of a major asbestos mill. Approximately 75% of all the asbestos fiber which is mined in North America is converted to commercial use in an industrial facility which is located only two miles from Somerset Hospital.

The association between pulmonary cancer and asbestosis has been recognized at this institution for many years. The number of patients admitted with these conditions is difficult to determine, as in earlier years many of them were diagnosed as pulmonary fibrosis or silicosis. The only accurate statistics could be obtained from the autopsy material of the past decade, 1955 to 1965, when 1,330 autopsies were performed. In this group, there were 22 cases of bronchogenic cancer with pulmonary asbestosis, as well as the 17 cases of mesothelioma. An interesting observation is that, despite the fact there were large numbers of women also employed at this industrial facility and many contracted asbestosis, there is only one female with mesothelioma in our series, and she never worked in the asbestos plant but lived nearby. This experience is in contrast to other reported series, particularly those from South Africa where there was a significant number of females afflicted with mesothelioma. Newhouse and Thompson,¹⁴ in studying the occupational histories of 83 patients with mesothelioma, noted that 42 of these patients were female.

We might attribute our absence of females involved with this disease due to a difference in occupational exposure between the male and female workers. However, other studies would not substantiate this, as there appears to be a high incidence of mesotheliomas in people just living in the vicinity of the asbestos mines or industries. In Wagner's series from South Africa, more than half of the people had not been employed by the asbestos industry. These people had had environmental exposure due to living in the vicinity of the mills and dumps. The statistics from the London Hospital, as reported by Newhouse and Thompson¹⁴ are very much the same, with one half of the patients having only an environmental exposure to asbestos. With this information, one wonders why we have not seen similar circumstances in our community, especially since there is a large asbestos dump adjacent to a residential area.

Another interesting observation in our series is the fact that 16 of the 17 patients with mesothelioma were diagnosed within the past three years. A review of the autopsy material for the previous decade brought to light only one additional case which initially had been misdiagnosed. Since the refinement of the asbestos fiber has been one of the major industries in this geographic area for over 60 years, it is difficult to explain why we are only now aware of this disease. One possible explanation is that in our group of patients, once the diagnosis was suspected, an intensified effort was made to obtain an autopsy when the patient died. However, prior to our recognition of this entity, patients with mesothelioma were most likely diagnosed as having a generalized carcinomatosis and little effort was made to obtain an autopsy when they did. Regardless whether this reasoning is correct or not, it is our distinct impression that there has been a definite increase in incidence of this malignancy within the last few years.

1. Tubulopapillary type mesothelioma (case 1, slightly reduced from $\times 120$).





2. Asbestosis of the lung (case 1, X120).

Report of Cases

CASE 1.—A 52-year-old white man was admitted to the hospital with increasing constipation, an enlarged abdomen of one month's duration, and an ill-defined abdominal pain. He had been retired with a medical disability from pulmonary asbestosis after working 23 years at an asbestos mill. He suffered a myocardial infarction two years before admission. He smoked only occasionally.

Physical examination revealed a slightly emphysematous chest with harsh breath sounds and abdominal distention. No intra-abdominal masses could be palpated at that time. Chest x-ray of the lungs demonstrated basilar fibrosis, bilaterally, interpreted as most likely due to asbestosis. An anteroposterior x-ray film, without contrast material, of the abdomen demonstrated a ground glass appearance suggestive of ascites. Some attenuation of the rectosigmoid on the x-ray film taken after evacuation of the barium enema raised the possibility of a pelvic mass. A paracentesis yielded approximately 1,500 cc of straw-colored fluid. Surgical exploration revealed the visceral and parietal serosal surfaces to be studded with fine papillary, almost granular-like, projections. A diagnosis of papilloma mesothelioma was made from a biopsy specimen (Fig 1).

Following an intraperitoneal injection of gold AU-198, he remained symptom free and afebrile for nine months. Fourteen months after surgery he died from a myocardial infarction.

Autopsy examination revealed pleural cavities to be free of tumor. Pleural plaques were present at the bases and there were multiple adhesions. The lungs demonstrated bullae emphysema with an irregular delicate fibrosis throughout. The heart was enlarged with old scarring and a fresh infarct. The peritoneal cavity yielded 1,000 cc of slightly mucoid yellowish fluid, and all the coelomic cavity organs as well as the parietal peritoneum were covered with white hard nodules, varying from 5 mm to 5 cm in diameter and having a mucoid appearance on the cut surface. In many areas there was a tendency for these nodules to coalesce to form larger tumor masses. The tumors did not penetrate for any appreciable distance be-

neath the surface, and all other organs were unremarkable.

Microscopic examination demonstrated an extensive interstitial fibrosis of the lungs with many asbestos bodies (Fig 2). The hypertrophied heart showed areas of fibrosis and acute necrosis. The tumor was characteristic of mesothelioma with cuboidal cells showing some pleomorphism and superficial papillation.

CASE 2.—A 51-year-old white man was admitted to Somerset Hospital because of abdominal pain. For 23 years he was an employee at an asbestos refining plant. He smoked less than one pack of cigarettes per day.

Results of physical examination were normal, and all laboratory studies were unrevealing. Chest x-ray showed a fibrotic infiltration of both lower lobes. An upper gastrointestinal roentgenographic series demonstrated duodenitis and gastritis. He was discharged on a regimen for ulcer convalescence only to be readmitted seven months later with postprandial abdominal pain and a 10-lb weight loss. On palpation the abdomen appeared board-like, though there was no tenderness, and an extraluminal mass could be palpated through the anterior portion of the rectal wall. A barium enema demonstrated rigidity and narrowing of the sigmoid colon. At surgery, the abdominal cavity was found to be almost completely obliterated by large masses of neoplastic tissue which had enveloped the intra-abdominal organs and was infiltrating the parietal peritoneum. A diagnosis of mesothelioma was made from a biopsy specimen. The patient died four months later.

Pertinent findings at autopsy included numerous large plaques on the parietal pleura and congestion at the bases of both lungs. The peritoneal cavity was virtually obliterated by a large, yellowish-white hard tumor which was completely encasing the abdominal organs (Fig 3). Except for this surface involvement, the organs were unremarkable.

Microscopic examination demonstrated bronchial pneumonia with a mild pulmonary fibrosis and many asbestos bodies. The tumor consisted of fusiform cells in a hyalinized stroma with papillary formation characteristic of mesothelioma (Fig 4).

CASE 3.—A 47-year-old white man was admitted to the hospital with a nonproductive cough and ill-defined discomfort in the right lower lobe of the lung. The initial chest x-ray film was normal, but a second one taken two days before admission demonstrated a small pleural effusion in the right costophrenic angle. Though he had been an insurance agent and more recently a liquor salesman, he had worked as a stock boy in an asbestos refining plant for 18 months, 24 years ago.

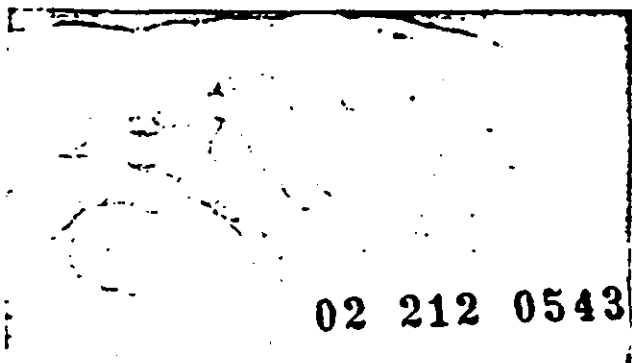
Physical examination and complete work-up were unrevealing, including scalene node and two needle pleural biopsies. Thoracocentesis yielded 100 cc of straw-colored fluid with some mesothelial cells. At exploratory thoracotomy the patient was found to have a greatly thickened parietal and visceral pleura with encasement of a partially atelectatic lung. In certain areas the parietal and visceral pleura were intimately adherent to one another and could not be separated. There was no nodularity of the serosal surfaces.

A diagnosis of pulmonary asbestosis and mesothelioma was made from a biopsy specimen. Postoperatively he received steroids and cobalt radiation with a poor response, and he died ten months later with bilateral pleural involvement.

Clinical Features

Our patients with peritoneal mesothelioma presented themselves in one of two ways. Four had ascites of unknown origin and the other three complained of vague abdominal pain and weight loss. In this latter group an ill-defined mass was usually palpated either through the abdominal wall or on rectal examination. Laboratory work-up and roentgenographic examination of the gastrointestinal

3. Serosal tumor encasing loops of bowel (case 2).



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tract were unrevealing. The diagnosis was made either by surgery or peritoneoscopy and biopsy. Those patients with ascites were found to have small papillary projections studding the visceral and parietal peritoneum. The ascitic fluid varied from a clear syrupy to a thin straw-colored consistency. Those patients with the palpable masses were found on exploration to have complete obliteration of the peritoneal cavity by large tumor masses which were occupying most of the coelomic cavity and invading the parietal peritoneum. We believe that this picture is but the end stage of the disease, while those patients with ascites represent an earlier stage. This is substantiated by the finding of papillary projections at surgery in several of our patients who having presented with ascites and in whom obliteration of the peritoneal cavity with large tumor masses developed later, as seen at autopsy.

Patients with pleural mesotheliomas all presented with varying degrees of chest pain and pleural effusion. A work-up was likewise unrewarding with the exception of positive findings from a pleural biopsy in one patient. The fluid in the pleural cavity varied from a gross bloody effusion to straw-colored fluid, and the tumor involvement varied from papillary projections on the parietal and visceral pleura to a generalized thickened pleura. In areas the visceral and parietal pleura were intimately adherent and could be separated only with difficulty.

Treatment with cobalt radiation therapy, radioactive gold and chromium, and chemotherapy, used alone or in combination, had little effect on the course of this disease. Fifty percent of the patients suffering either from pleural or peritoneal mesothelioma died within one year and the remainder by the second year.

Criteria for Diagnosis

Although it is now accepted that mesothelial tumors of the serosal surfaces do exist and possess a number of characteristics which justify their segregation as an entity, the criteria for the identification of these tumors are still largely imprecise. The currently accepted criteria for the diagnosis of these tumors are that: (1) The diagnosis should be applied to those groups which show an unequivocal predilection to spread along the serosal membranes, with either none or only a shallow invasion of the underlying organs. (2) All other sources for the tumor have been excluded. (3) If metastases are present, they should be limited to the regional lymph nodes, rarely occurring in liver, bone, and lung.

Special staining or histologic techniques may aid in a diagnosis of this disease. Wagner et al¹⁸ have suggested that metachromatic staining (removable by exposure to hyaluronidase) within a tumor is strong evidence for the diagnosis of mesothelioma in a patient.

Pathologic Characteristics.—In the earlier stages, the tumor is made up of many small, rounded, firm nodules on the visceral and parietal surfaces. Later,

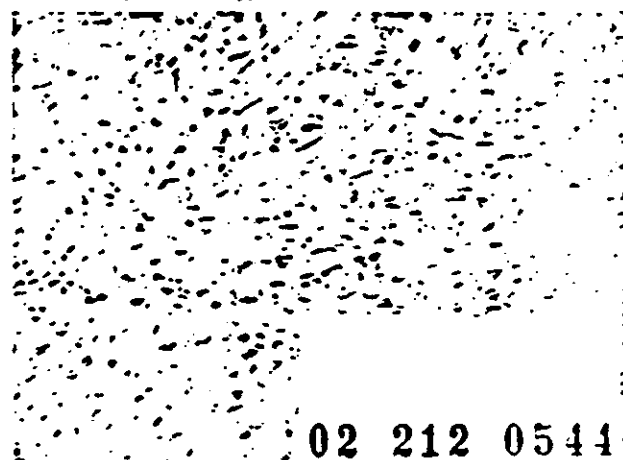
there is a coalescence of these nodules, so that the terminal state usually consists of solid, broad, thick bands which encompass the viscera and fix them within a dense mass. Often the delineation between parietal and visceral peritoneum is lost, so that the usual autopsy dissection is impossible due to this encasement. The tumor is generally white and firm and may have a mucinous appearance on the cut surface.

Histologic Characteristics.—We have seen two major histologic types of mesothelioma. The most common variety is the epithelial form where there are cuboidal or polyhedral cells producing a tubulopapillary appearance or a solid group of cells without a clear tubular formation. Usually there is a fairly uniform cellular structure, but occasionally bizarre nucleated cells can be seen. Pathologic mitotic cells are rarely found, but doubly nucleated and multinucleated tumor cells are often seen. The other variety is the mesenchymal or fibrous type of mesothelioma in which spindle cells are arranged in an almost fascicular pattern within a stroma of abundant hyaline collagen. Occasionally the cells may be arranged loosely in indistinct fasciculi or may occur in solid nests. The most striking histologic characteristic of mesothelioma is the structural variation which may occur from area to area within the same tumor, so that in one area the growth may have epithelial structure, while in another a purely mesenchymal appearance or in between combinations.

Pathogenesis

The mode of action of asbestos in producing neoplasia is at present poorly understood. Furthermore, a puzzling feature has been the presence of mesothelioma in one mining area, while in another mining area a few miles distant, the disease has as yet to be identified. There are two major mining districts in the Republic of South Africa. In the north-west Cape of Good Hope province, crocidolite is the fiber mined, whereas in the Transvaal asbestos field, both crocidolite and more importantly amosite are mined. Up to the present time there has been a

4. Spindle cell type mesothelioma (case 2, X60).



high prevalence of mesothelioma of the pleura and peritoneum in northwest Cape of Good Hope. On the other hand no case as yet has been reported from the Transvaal asbestos area or its surroundings. Sluis-Cremer¹⁶ has studied the geographical and environmental differences in these two areas and has come to the conclusion that none of the factors examined explained satisfactorily the absence of mesothelioma in the Transvaal region. Other than for the mineralogic difference between the two areas, he found no variation in the intensity or length of production of these fields or in the extent of the environmental pollution and incidence of pulmonary asbestosis. In North America, chrysotile is the main fiber mined although crocidolite and amosite are present in lesser amounts. Both pleura and peritoneal mesothelioma have been found in workers exposed to these fibers.

Wagner¹⁷ in 1962 induced mesothelioma by inoculating various dusts into the pleural cavity of rats. Pleural tumors developed in those inoculated with crocidolite, chrysotile, and a finely divided silicon powder (99.9% silicon dioxide). Recently Skidmore and Wagner¹⁸ showed that crocidolite, chrysotile, silica powder, and to a lesser extent, amosite, all induced pleural mesotheliomata in guinea pigs after interpleural injection. Peacock and Peacock¹⁹ induced malignant tumors in fowls with crocidolite and amosite. A number of hypotheses to explain the pathogenesis of this disease have been proposed, but none of them have been widely accepted. The first theory was that of physical irritation due to the presence of asbestos fibers deposited in the terminal lymphatics of the serosal surfaces or due to the migration of the asbestos fiber from the lung following inhalation or from the gut as a result of ingestion. Fibers have been demonstrated in a number of tissues, including parietal pleura, gastric mucosa, and spleen, but there have been no reports of fibers in the peritoneal surfaces.

Another concept is the auto-immune theory in which the presence of asbestos bodies in the lung is said to elicit the production of an abnormal globulin. Up to the present time, there is little positive evidence for this concept. The serum of patients with either asbestosis or neoplasia shows only a slightly raised titer for the rheumatoid factor, and immunofluorescent staining has not shown evidence of an antigen-antibody aggregate. Recently, Harrington and Roe²⁰ suggested that the carcinogenicity of asbestos may be related to the presence of natural and contaminated oils associated with the asbestos fiber or to certain carcinogenic metals or metal complexes in the fibers. They found that crocidolite and amosite contained appreciable amounts of natural oils. Furthermore, all the asbestos fibers, including chrysotile, may contain secondary oils as a result of an addition of oil to the asbestos during the processing or as a result of contamination. Furthermore, almost universally, the asbestos is transported and stored in jute bags and the oil from the jute fiber is absorbed to a great extent by all three types of asbestos fiber.

Both chrysotile and amosite have a significant ferrous content, particularly of certain macromolecular complexes of iron, such as iron-dextran which is known to be highly carcinogenic in animals. The iron content of chrysotile is much lower than the other two fibers. It is proposed by Harrington and Roe²⁰ that the carcinogenic agent or agents may not be the fiber themselves but either the natural oil or secondary oils which are present on the fiber and or possibly the iron complex. The authors are currently performing biologic tests for the carcinogenicity of these materials. However, these studies were in a preliminary form at the time of the report.

Generic and Trade Names of Drug

Gold Au 198—Aurocloid-198, Aureotape-Au 198, Aureoscan-198, Radiogold Colloidal Au 198, Aureotape.

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