Johns-Manville

Internal Correspondence

To: Dennis H. Markusson - 2-20

Date: August 20, 1982

From: Helen L. Marsh - 2-20 (x4949)

Copies: File/Chrono

Subject: GAENSLER ARTICLE, NEW ENGLAND JOURNAL OF MEDICINE, 7-8-82

Pat Beaudette advised me of your interest in having the attached medical report reviewed by me. The report is a case study in which the principal discussant is Edward Gaensler. The subject of the case is a 64 year old man with right pleural effusions and pleural placques. The patient had been employed in a shipyard for six months during World War II and later was employed in the upholstery business with possible additional exposure to asbestos at that time. The patient had stopped smoking 28 years before becoming the subject of this report. His medical history included persistant problems with rheumatoid arthritis. The probable diagnosis before biopsy was malignant pleural mesothelioma. After biopsy, the suggested diagnosis was either 1) pleural effusion relating to rheumatoid disease; or 2) benign asbestos effusion. Malignant mesothelioma was ruled out by biopsy.

The discussion contains several significant clinical statements by Dr. Gaensler. First of all, he identifies a disease process which he calls benign asbestos effusion. This disease was identified by four criteria: 1) direct or indirect exposure to asbestos; 2) the presence of an effusion; 3) lack of evidence of any other disease related to a pleural effusion; and 4) failure to detect a malignant tumour within three years after the effusion. Gaensler concluded the prevalance of benign pleural effusions among person directly exposed to asbestos was 7%, and that this prevalence declined as the severity of the exposure declined. Moreover, Gaensler concluded that benign effusions were the only asbestos related disorders commonly observed during the first ten years after commencement of exposure, and that it was the most common manifestation of asbestos disease during the first twenty years after commencement of exposure. Gaensler states further

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that exposure to asbestos was the most common cause of all effusions existing during the past thirty years in the Massachusetts General Hospital Ambulatory Chest Referral Clinic.

With respect to smoking, Gaensler concludes that, because the patient had stopped smoking 28 years previously, he should be treated as a non-smoker. Because of this, he indicated that bronchogenic carcinoma could be excluded as a possible diagnosis.

Gaensler made some helpful remarks regarding the importance of a finding of asbestos bodies in the lung on biopsy. Gaensler indicated that city dwellers all have asbestos bodies in their lungs and that it is not indicative of any disease. He further stated that "if a patient has normal results of pulmonary function studies, normal lung fields on roentgenograms of the chest, and no rales, clubbing or dyspnea the diagnosis is not asbestosis from a clinical viewpoint despite the presence of a minimal fibrotic reaction in the lungs." (at page 111)

Gaensler also discussed the relationship between pleural placques and asbestos exposure. He indicated that pleural placques are present radiographically 30 to 40 years after initial exposure in 50 to 60% of the cases, and are found post mortem in almost all cases. Gaensler did state, however, that placques do not result in any illness or impairment, and further noted that there is no evidence that placques degenerate into malignancies. Gaensler did note, however, the relationship between placques, as hallmarks of exposure to asbestos, and pulmonary and pleural tumours. Thus, although a placque does not cause a tumour, individuals who have placques are at greater risk of malignancy because of their proven exposure to asbestos.

Gaensler further noted that 95% of patients with mesothelioma present with a pleural effusion. Gaensler indicated a belief that exposure to asbestos can be established in 80% of the cases of pleural mesothelioma, and that 1 to 3% of asbestos workers will succumb to it.

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Gaensler's discussion also contains some references which relate to our state of the art case. Discussing World War II, Gaensler states "during that period the work force at the shipyards increased rapidly, and there was little time or interest in the control of asbestos dust. Furthermore, many yards in this area were largely engaged in the refitting of old ships, a procedure that was dangerous not only to pipe coverers and laggers but also to members of the related trades who worked below deck in poorly ventilated holes, walking on the asbestos material that had been removed from the pipes before refitting could take place. At the Thorndike Memorial Laboratory at the Boston City Hospital in the 1950s virtually all our cases of severe asbestosis were seen in members of a variety of trades engaged in ship refitting. At that time the dangers of asbestos exposure in the asbestos industry itself were recognized, but the dangers to secondary users were not appreciated. Indeed, shortly after World War II investigators from the Harvard School of Public Health issued a very reassuring report indicating that there was no danger to shipyard workers, and it was not until 25 years later that the generally accepted threshold limit value of 5,000,000 particles per cubic foot was found to be excessive." (at page 106)

HLM:alt

Attachment

08-20-82

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NEW ENGLAND J. OF MED.CINE 7/8/82 V 307 #2

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

104-112

PLEURAL THICKENING IN A MAN WITH RHEUMATOID ARTHRITIS AND EXPOSURE TO ASBESTOS

EDWARD A. GAENSLER AND EUGENE J. MARK

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JMEA — 7977

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

ROBERT E. SCULLY, M.D., *Editor*
EUGENE J. MARK, M.D., *Associate Editor*
BETTY U. MCNEELY, *Assistant Editor*

Case 27-1982

PRESENTATION OF CASE

A 64-year-old man was admitted to the hospital because of a right pleural abnormality.

He was in his usual state of health until one month before admission, when microscopic hematuria was found in a routine urinalysis. A culture of urine was negative, and cytologic examination of urine was negative on three occasions. An intravenous urographic examination with nephrotomograms showed a normal appearance of the kidneys; there was slight trabeculation of the bladder, with a small post-voiding residuum. Five days before admission cytoscopic examination revealed that the prostatic urethra appeared erythematous and friable. Routine x-ray films of the chest (Fig. 1) disclosed considerable loss of volume and pleural thickening at the right-lung base, which had appeared since films obtained one year earlier; no calcification or associated rib abnormality was seen; the pleural spaces and lungs were otherwise normal, and the heart was at the upper limit of normal in size; there was slight ectasia of the thoracic aorta. Three days before admission another x-ray film of the chest, with bilateral decubitus views, disclosed no evidence of free pleural fluid. The patient recalled nonpleuritic right subscapular pain for one day shortly before the cytoscopic examination but denied all other chest pain. A dry cough and mild fever were noted on physical examination, and a course of erythromycin was prescribed, without improvement. On the day of admission the cough and fever persisted, with occasional sweats.

There was a history of dyspepsia since the age of 18 years. Thirty-seven years before entry a duodenal ulcer was found on an upper gastrointestinal series, and a Billroth II gastrectomy was performed. He had worked in a shipyard for six months during World War II; thereafter he was employed in the upholstery business. He had smoked two packs of cigarettes daily in the past but stopped smoking 28 years before entry. There was a 20-year history of seropositive rheumatoid arthritis and a 10-year history of hypertension, which was controlled with hydrochlorothiazide and triamterene. For several years before entry he experienced repeated bouts of upper gastrointestinal bleeding from a marginal ulcer. There was no history of sputum production, hemoptysis, or dyspnea.

The temperature was 37.3°C, the pulse 80, and the respirations 24. The blood pressure was 140/80 mm Hg.

On examination the patient appeared well. No rash or lymphadenopathy was found. The lungs were clear except for diminished breath sounds at the right base and reduced excursion of the right hemidiaphragm. The heart was normal. Abdominal examination was negative. There was synovial thickening in the proximal interphalangeal joints bilaterally; no digital clubbing was observed.

The urine gave a + test for protein; the sediment contained rare granular casts. The hematocrit was 41.2 per cent; the white-cell count was 10,300, with 69 per cent neutrophils, 1 per cent band forms, 15 per cent lymphocytes, 13 per cent monocytes, and 2 per cent eosinophils. The platelet count was 189,000, and the erythrocyte sedimentation rate 63 mm per hour. The urea nitrogen was 23 mg per 100 ml (8.2 mmol per liter), the glucose 119 mg per 100 ml (6.61 mmol per liter), the bilirubin 0.4 mg per 100 ml (7 μmol per liter), the uric acid 10.4 mg per 100 ml (0.619 mmol per liter), the calcium 9 mg per 100 ml (2 mmol per liter), the phosphorus 3.5 mg per 100 ml (1.1 mmol per liter), and the protein 7.2 g (the albumin 3.5 g, and the globulin 3.7 g) per 100 ml. The sodium was 140 mmol, the potassium 4.4 mmol, the chloride 98 mmol, and the carbon dioxide 30 mmol per liter. An electrocardiogram demonstrated a normal rhythm at a rate of 67, with nonspecific ST-segment and T-wave abnormali-



Figure 1. Roentgenogram of the Chest Taken Five Days before Admission, Showing a Right Pleural Abnormality with Blunting of the Right Costophrenic Angle.

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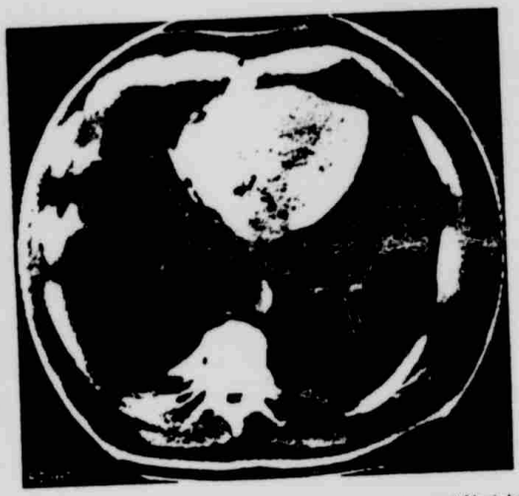


Figure 2. CT Scan of the Chest, Showing Irregular and Nodular Pleural Thickening and Possibly a Loculated Effusion. The underlying lung is normal.

ties. X-ray films of the chest were unchanged. A computed tomographic (CT) scan of the chest (Fig. 2) disclosed diffuse nodular thickening and possibly a loculated effusion of the pleura on the right side, with loss of volume in the underlying lung; no pulmonary mass was observed; there was a suggestion of a pleural plaque on the left side. A test for antinuclear antibodies was positive in a titer of 1:32, with a homogeneous pattern. A culture of sputum yielded a normal throat flora; cytologic examination was negative for tumor cells.

A diagnostic procedure was performed.

Differential Diagnosis

Dr. Edward A. Gaensler*: In summary, this 64-year-old man was found to have a right pleural abnormality during a routine radiologic examination. The past history is of interest with respect to duodenal-ulcer problems for over 37 years, a 20-year history of seropositive rheumatoid arthritis, and treated hypertension. The occupational history, although scanty, is noteworthy with respect to shipyard work during World War II and upholstery work since that time. In regard to the latter, it may be of historical interest that some of the earliest descriptions of asbestosis in Great Britain concerned mattress workers. The patient stopped smoking 28 years ago and in terms of cancer statistics must be regarded as a nonsmoker. The initial admission to the hospital was prompted by microscopic hematuria, but culture and cytologic examination of urine and an intravenous urographic study of the kidneys were negative. Radiologic examination of the bladder and cystoscopic examination suggested changes probably due to benign prostatic hypertrophy, although we are not told about examination of the prostate gland. Abnormalities were found in the chest and the interphalangeal joints. The further work-up was prompted by the findings on roentgenograms of the chest. May we see the films at this time?

Dr. Theresa C. McLoud: The intravenous urograms show normal renal contours, with no evidence of a mass. Slight, irregular trabeculation of the bladder and slight elevation of the bladder floor are demonstrated, with a small post-voiding residuum, consistent with benign prostatic hypertrophy. Tomograms of the kidneys are also normal.

A roentgenogram of the chest obtained one year before admission reveals slight unfolding of the thoracic aorta. The pleural spaces, including the costophrenic angles, are normal, with no evidence of pleural thickening or plaques. A film obtained five days before admission (Fig. 1) shows blunting of the right costophrenic angle and a pleural abnormality laterally extending about a fourth of the way up the chest. A lateral view reveals minimal blunting of the right posterior costophrenic angle. A decubitus film taken two days later discloses no evidence of a free pleural effusion. The appearance is consistent with either pleural thickening or possibly loculated pleural fluid.

A section from the CT scan (Fig. 2) at the level of the great vessels demonstrates irregular, nodular pleural thickening on the right side, which extends caudad to the level of the diaphragm. There is no evidence of a mass in the lung, hilus, or mediastinum. A small pleural plaque is visible on the left side.

In summary, the radiologic studies show evidence of diffuse nodular pleural thickening on the right side, with loss of volume of the underlying lung. In addition, a loculated effusion is suggested.

Dr. Gaensler: The radiologic findings may be explained in two ways. The patient had a right pleural effusion. It is possible that the fluid became loculated and after its resorption a somewhat uneven fibrotic pleura remained. An alternative explanation is a tumor.

The last time that I was invited to discuss a case at one of these conferences the diagnosis seemed obvious, and I had difficulty in manufacturing a differential discussion. This time the opposite is true; the differential diagnosis is large, and no diagnosis fits very well. In the end we shall have to rely on a biopsy, and even after a biopsy the diagnosis may remain in doubt. I shall discuss the various possibilities by excluding the unlikely ones first.

If the effusion was benign we can rule out a transudate because the patient appeared entirely well when the effusion was discovered; he was not in left ventricular failure and did not have nephrosis or ascites. Furthermore, transudates rarely leave a fibrotic residuum. Therefore, the fluid was an exudate. There is nothing in the history to suggest pulmonary infarction or a subphrenic lesion. A pulmonary infection, the most common cause of a pleural exudate, cannot be excluded entirely. The serial roentgenograms of the chest

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and the clinical course during the weeks before admission are not suggestive of a bacterial or viral pneumonia. However, we must always consider the possibility of tuberculosis. Certain impressions from medical school are never forgotten. When Dr. Henry Jackson, Jr., lectured on pleural effusion in 1943 he wrote on the blackboard the most common cause, which was tuberculosis, and then for 55 minutes he listed 11 additional causes, all of them tuberculosis. Only during the last five minutes did he suggest that there were also other, more unusual causes. In this case we are not even told the results of a tuberculin test. How times have changed! Nevertheless, we must consider tuberculosis, especially in view of the low-grade fever, the elevated sedimentation rate, the occasional sweats, and the history of a gastrectomy. One might add the finding of red cells in the urine. Tuberculosis is a distant possibility, even though tuberculous effusions rarely become loculated and rarely leave a fibrotic residuum.

A more important clue is the 20-year history of seropositive rheumatoid arthritis. Involvement of the pleura by granulomatous lesions of rheumatoid origin, first documented by Baggenstoss and Rosenberg,[1] is the most common manifestation of rheumatoid lung disease. Some investigators have found pleurisy to be slightly more frequent in patients with rheumatoid arthritis than in persons without this disease,[2] and others have demonstrated an unexpectedly high frequency of otherwise unexplained effusions both in patients with rheumatoid arthritis[3] and in series of cases of that disease with post-mortem examination.[4] In this connection it has been pointed out that conclusions about the relation of any two conditions must be made with caution and that the more common the conditions are the greater is the likelihood of error.[5] Although there is still some controversy, the results of controlled studies by Walker and Wright[6] appear convincing; pleural effusions were 10 times more prevalent in a group of patients with rheumatoid arthritis than in a control group of patients with degenerative arthritis. This patient had synovial thickening in the proximal interphalangeal joints bilaterally, and a test for antinuclear antibodies was weakly positive, with a relatively low titer of 1:32 and a homogeneous pattern. Furthermore, rheumatoid effusions occur predominantly in middle-aged men,[7] and residual pleural thickening is occasionally extensive and may require decortication.[7,8] However, the patient under discussion apparently had no complaints suggestive of severe rheumatoid arthritis, there were no subcutaneous nodules, and the disease seems to have been fairly inactive, whereas rheumatoid effusions are generally seen during exacerbations and in patients with active and progressive disease.[7,9,10] Therefore, a rheumatoid cause for the effusion is possible but not very likely.

The last and probable explanation for this patient's pleural abnormality is what we have called "benign asbestos effusion."[11] There is a convincing history of asbestos exposure, with work in a shipyard for six months during World War II. During that period the work force at the shipyards increased rapidly, and there was little time or interest in the control of asbestos dust. Furthermore, many yards in this area were largely engaged in the refitting of old ships, a procedure that was dangerous not only to pipe coverers and laggers but also to members of the related trades who worked below deck in poorly ventilated holds, walking on the asbestos material that had been removed from the pipes before refitting could take place. At the Thorndike Memorial Laboratory at the Boston City Hospital in the 1950s virtually all our cases of severe asbestosis were seen in members of a variety of trades engaged in ship refitting. At that time the dangers of asbestos exposure in the asbestos industry itself were recognized, but the dangers to secondary users were not appreciated. Indeed, shortly after World War II investigators from the Harvard School of Public Health issued a very reassuring report indicating that there was no danger to shipyard workers,[12] and it was not until 25 years later that the generally accepted threshold limit value of 5,000,000 particles per cubic foot was found to be excessive.[13]

Bilateral recurrent effusions were first described in an insulation worker in 1962,[14] and nine years later we reported the findings in a series of 12 patients with historical and histologic evidence of exposure to asbestos who had pleural effusions, which were often bloody, sometimes bilateral, and sometimes recurrent.[11] Subsequently, we became interested in the prevalence of benign asbestos effusion. We defined this disorder by four criteria: direct or indirect exposure to asbestos; the presence of an effusion confirmed by thoracentesis or by the finding of a transient pleural change on serial x-ray films; lack of evidence of any other disease related to a pleural effusion; and failure to detect a malignant tumor within three years after the effusion. We followed prospectively 1135 employees of the asbestos industry and shipyards for 10 to 15 years, and retrospectively we reviewed roentgenograms of the chest and records for up to 35 years. The results were compared with those in 717 unexposed control patients who had serial roentgenograms for three to 35 years (Table 1).[15] In the entire survey group there was a prevalence of 3.1 per cent of asbestos effusions, with a frequency of 5.2 per thousand person-years. Among the 717 controls there were no otherwise unexplained effusions during the observation period. The prevalence of asbestos effusions was related to the severity of the exposure: among persons directly exposed to asbestos, such as pipe coverers, laggers, and asbestos paper-pulp mixers, the prevalence was 7 per cent; among indirectly exposed persons who worked nearby in the plant the prevalence was 3.7 per cent; and among 511 distantly exposed persons, mostly executives, draftsmen, and secretaries, the prevalence was 0.2 per cent.

We are all familiar with the concept of the latent period between the initial exposure and the manifestations of asbestos-related disease. In our series the latent period for all asbestos-related diseases, including

asbestosis, pleural plaques, lung cancer, and mesothelioma, was usually 20 years or more, whereas a benign effusion was the only asbestos-related disorder observed during the first 10 years after exposure and was the most common manifestation during the first 20 years (Fig. 3). The possibility of a mesothelioma was the principal differential diagnostic problem, but that tumor was always seen more than 20 and usually 30 to 40 years after the initial exposure. Radiographic signs of other asbestos-related disease, such as plaques or pulmonary fibrosis, were not helpful in differentiating between a benign effusion and a mesothelioma. It has been estimated that between 2,000,000 and 6,000,000 persons have received appreciable exposure to asbestos in the United States.[16] A prevalence of 3.7 to 7.0 per cent of benign effusions should alert us to the importance of this disorder in the differential diagnosis of idiopathic effusions. Indeed, in our ambulatory chest referral clinic exposure to asbestos was the most common cause of all effusions seen during the past 30 years. Therefore, we must consider the possibility of a benign asbestos effusion in this case, but it is not very likely for two reasons. Virtually all our patients with this disorder were seen during the first 20 years after exposure, with only a few at 30 to 39 years and none thereafter (Fig. 3). This patient's effusion, in contrast, probably occurred about 38 years after the initial exposure. Also, most asbestos effusions leave in their wake nothing but a blunted costophrenic angle or, at most, a smooth pleural residue, whereas this man had a rather thick, nodular residual shadow.

The pleural lesion in this case was described as nodular, suggesting the likelihood of a tumor with a secondary effusion. Primary benign and malignant tumors may arise from any of the tissue components between the ribs and the lungs, but most such tumors are so rare that, except for a mesothelioma, they are not even mentioned in standard textbooks.[17] Carcinoma metastatic to the pleura, on the other hand, is the most common form of localized pleura-based tumor with an effusion. The most frequent primary sites are the lung and the breast, which together account for more than half the cases.[18] In this case we can virtually exclude a bronchogenic carcinoma on two grounds. Neither the conventional roentgenograms of the chest nor the CT scan showed a pulmonary lesion. Furthermore, for practical purposes the patient was a nonsmoker. Other relatively common primary sites include the stomach, pancreas, colon, and prostate gland. There is no indication of disease in any of these organs in this patient except for the prostate gland, and nothing suggests metastatic tumor arising from it. Renal-cell carcinoma brings to mind "cannon-ball" metastases to the lungs. It is not usually considered in connection with pleura-based tumors, although there are occasional cases with pleural metastases. We have seen an enlarging pleural tumor with an effusion in a shipyard pipe coverer who was followed with a clinical diagnosis of mesothelioma for about three years; at autopsy the tumor encased the lung like a mesothelioma, but microscopical examination revealed that it was a metastatic renal-cell carcinoma. In the case under discussion the early finding of microscopic hematuria suggested initially a renal-cell carcinoma metastatic to the pleura, but I had to abandon that diagnosis when Dr. McLoud assured me that the normal intravenous pyelograms and nephrotomograms excluded the presence of a renal tumor.

We are thus left with the problem of an elderly, nonsmoking former shipyard worker in whom a nodular pleura-based mass with an effusion developed 35 to 40 years after the initial exposure to asbestos. I suppose that most second-year medical students and vir-

Table 1. Pleural Effusions in Asbestos-Exposed Employees and Controls — Radiographic and Clinical Observations from Three to 35 Years.

Subjects	Observation		
	Total no. of employees	Pleural effusions	
		no.	%
Asbestos-exposed employees	1135		
All effusions		54	4.8
Due to known disease		19	1.7
Benign asbestos effusions *	1135	35	3.1
Directly exposed	329	23	7.0
Indirectly exposed	295	11	3.7
Peripherally exposed	511	1	0.2
Unexposed controls	717		
All effusions		7	1.0
Due to known disease		7	1.0
Effusions of unknown cause		0	0

*Defined by a history of asbestos exposure, effusion confirmed by transient pleural changes on serial radiographs or by thoracentesis, lack of evidence of any other disease related to effusion, and lack of detection of a malignant tumor within three years after effusion.

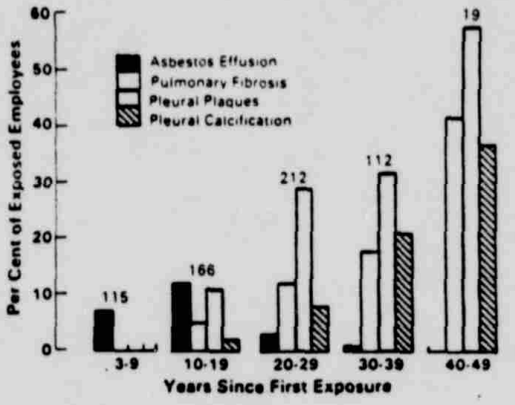


Figure 3. Asbestos-Related Manifestations in Employees Directly and Indirectly Exposed.[15]
The prevalences are grouped according to years since the first exposure. The numbers above the columns indicate the numbers of employees. Benign asbestos effusion was seen earlier than other disorders. It was the only manifestation during the first 10 years and was the most common disorder during the first 20 years.

tually every lawyer would make a diagnosis of a malignant mesothelioma. This tumor, exceedingly rare and relatively unknown until about 15 years ago, has recently received an enormous amount of publicity, not only in the medical literature but also in the lay press and on television. An informative discussion of mesothelioma and especially the problem of distinguishing it from adenocarcinoma was given at a recent clinicopathological exercise at this institution by Dr. Raymond L. H. Murphy.[19] Briefly, the relation of this tumor to exposure to asbestos was first established by Wagner et al.[20] only 20 years ago. Extensive publications since that time indicate that an exposure to asbestos can be established in about 80 per cent of the cases of pleural mesothelioma. It is now estimated that 1 to 3 per cent of asbestos workers will eventually succumb to this invariably fatal tumor. There are numerous reports of the development of a mesothelioma in presumably indirectly or peripherally exposed persons, such as remote workers in the plant or relatives of asbestos workers. Except for anthophyllite, all types of asbestos can cause a mesothelioma, but there is probably a gradient of the risk, with crocidolite the most dangerous, chrysotile the least dangerous, and amosite somewhere in between.

There is much to support the diagnosis of a mesothelioma in this case. The patient had a history of adequate exposure. The latent period of 35 to 40 years is much more suggestive of a mesothelioma than a benign pleural effusion. Furthermore, approximately 95 per cent of all patients with a mesothelioma present with a pleural effusion. The fact that the patient was a nonsmoker does not mitigate against the diagnosis because no relation has been described between the prevalence of a mesothelioma and a history of smoking. The CT scan showed a pleural plaque on the contralateral side, a finding that confirms that the patient had had exposure to asbestos, however slight. I am not suggesting that asbestos-related plaques undergo malignant degeneration. The presence of plaques themselves is unimportant except in the epidemiologic sense that they are markers of exposure or what have been called "leading fossils."[21] Indeed, plaques have been referred to in the German literature as "Schonheitsfehler," which literally translated means a beauty defect of the x-ray.[22] Plaques are demonstrable radiographically 30 to 40 years after the initial exposure in 50 to 60 per cent of the cases[23] and are found at post-mortem examination in almost all the cases.[24]

Plaques do not cause symptoms or loss of pulmonary function, and there is unanimous agreement that they never undergo malignant degeneration.[25] The frequency of pulmonary and pleural tumors in persons with plaques is another matter. Obviously, inasmuch as plaques are markers of exposure to asbestos and inasmuch as pulmonary and pleural tumors are more common in exposed persons the prevalence of such tumors must be higher in persons with plaques. For example, plaques were found in 27 of 47 cases of mesothelioma studied at autopsy, a prevalence far greater than that in the general population.[26] The prognostic value of plaques in a uniformly exposed population is much more difficult to determine. It has been suggested that there is no evidence that their presence has any meaning with respect to the development of a mesothelioma.[27] In Great Britain a 10-year follow-up study of 408 dock workers with plaques and 444 without them showed that mesotheliomas occurred slightly more often in those with plaques, but the difference was not statistically significant.[28]

A mesothelioma, then, would be the obvious diagnosis if it were not for the absence of certain clinical findings. I cannot recall a patient with this type of tumor who did not complain of chest pain and weight loss. We have stored on tape the histories, clinical findings, physiologic data, coded roentgenograms, and pathological findings concerning all 8000 patients seen at our laboratory since 1950. Yesterday I scanned this tape to refresh my memory. We had no mesotheliomas from 1950 to 1960 but since then have seen 41, two abdominal and 39 pleural. At the initial visit 97 per cent of the patients complained of chest pain, which was usually pleuritic in nature, and 97 per cent had a weight loss of more than 5 kg. A pleural effusion was present in 97 per cent, and 36 of 38 patients from whom we obtained an adequate occupational history gave a history of exposure to asbestos.

In this case there is no record of weight loss, and the patient recalled only one day of nonpleuritic right subscapular pain. A mesothelioma grows readily along tissue planes, and for that reason most patients have advanced lesions and extensive spread when first seen. The absence of chest pain and weight loss is therefore unusual, although not unprecedented. As I stated in the beginning, no single diagnosis fits this case perfectly, but if pushed to commit myself I would favor the diagnosis of a malignant mesothelioma.

DR. EUGENE J. MARK: This patient was seen on the Pulmonary Service. Dr. Kradin, do you have any comments?

DR. RICHARD L. KRADIN: We favored the diagnosis of a malignant tumor, either metastatic carcinoma or a mesothelioma, on the basis of both the radiographic appearance and the absence of identifiable pleural fluid.

DR. MARK: Dr. Calderwood, may we have the medical students' diagnosis?

DR. STEPHEN B. CALDERWOOD: They discussed infectious processes involving the pleura, collagen vascular diseases, and neoplasms, either arising in or metastatic to the pleura. They carefully considered rheumatoid involvement of the pleural surface but noted the absence of demonstrable pleural fluid or of subcutaneous nodules. They favored the diagnosis of a pleural mesothelioma with asbestosis, based on the history of remote exposure to asbestos, the presence of bilateral pleural plaques, and the appearance

of the right pleural abnormality on x-ray films of the chest and computed tomographic examination.

Clinical Diagnoses

? Malignant mesothelioma or metastatic carcinoma.
Rheumatoid arthritis, ? with rheumatoid lung disease.

Dr. Edward A. Gaensler's Diagnoses

? Mesothelioma.
? Benign asbestos effusion.
? Rheumatoid effusion.
Asbestos-related pleural plaques.

Pathological Discussion

Dr. Mark: Dr. Goodson took care of this patient initially. Will you comment?

Dr. John D. Goodson: He was asymptomatic except for mild prostatism and came to the hospital for cystoscopic examination. He had moderately active rheumatoid disease, which had been refractory to all previous types of therapy, including gold and various nonsteroidal antiinflammatory drugs. I started penicillamine treatment approximately two months before admission. Since this drug is nephrotoxic a urinalysis was done and showed hematuria. The cystoscopic examination revealed that the prostate gland was somewhat enlarged and was the source of the hematuria. The urine subsequently cleared. The pulmonary symptoms were limited to a very mild cough, and the right subscapular pain was fleeting. On the initial x-ray film of the chest it was not clear how much of the abnormality was an effusion and how much was an infiltrate. I suspected at first that it might be a postinfectious process of viral origin or possibly due to a mycoplasma or a legionella infection. When it became clear that the patient had primarily a pleural abnormality my concern shifted to whether it was rheumatoid lung disease or a mesothelioma related to the exposure to asbestos. He had been deferred from military service because of the duodenal ulcer and as part of his obligation had been assigned to refit ships. He had substantial exposure to asbestos as a result.

Dr. Mark: A PPD skin test was planned, but I cannot find the result.

Dr. Goodson: It was negative, but the result was not entered in the hospital record. Subsequent cultures of the sputum showed no growth of fungi or tubercle bacilli.

Dr. Mark: Dr. Hilgenberg, will you describe the operative findings?

Dr. Alan D. Hilgenberg: I thought that a needle biopsy would not provide enough tissue to make a definitive diagnosis and therefore performed a very small right thoracotomy. The parietal pleura was slightly thickened. In the pleural cavity we encountered a yellow, fibrinous exudate and about 200 ml of clear, yellow, loculated fluid. After the fluid and exudate were removed no tumor was visible. A pleural plaque was seen posteriorly just above the diaphragm. The lower lobe of the lung was restricted by thickened visceral pleura. We biopsied the lung, the pleural plaque, and the parietal pleura.

Dr. Mark: The open-lung-biopsy specimen was 2 cm in greatest dimension. The pleural surface was diffusely thickened by organizing fibrin and fibrous tissue. An elastic-tissue stain demonstrated that the thickening was superficial to the external and internal elastic lamina of the pleura, although the subjacent lung was fibrotic and atelectatic as well (Fig. 4). The pleural fibrous tissue contained many evenly distributed fibroblastic nuclei. The histologic pattern was not that of a hyaline plaque, in which the pleura is replaced by sparsely cellular, avascular hyalinized fibrous tissue. Portions of the surface of the visceral pleura and of a piece of separately biopsied parietal pleura exhibited a vigorous mesothelial-cell hyperplasia with organization of fibrin (Fig. 5). In some areas histiocytes were palisaded perpendicular to the pleural surface. The mesothelial cells had abundant cytoplasm and large nuclei, without clumped chromatin or other features of a malignant tumor. Cytologic exami-



Figure 4. Lung-Biopsy Specimen (Verhoeff–van Gieson Stain, ×100).
Internal and external elastic laminas of the pleura (arrows) separate compressed, fibrotic lung (bottom) from thickened, fibrotic visceral pleura (top).



Figure 5. Pleural Surface (×256).
The hyperplastic mesothelial cells (arrows) are cytologically benign. A clump of fibrin (right) is undergoing organization.

nation of the pleural fluid also showed only benign cells. Culture of the fluid was negative for tubercle bacilli and fungi.

The probable explanation for the pleural change is rheumatoid pleuritis. No rheumatoid nodule was found in the pleura, and thus a definitive diagnosis is not possible.[29] However, the pathological findings in the pleuritis of rheumatoid lung disease may consist of only mesothelial hyperplasia, with or without palisading of histiocytes and a lymphocytic infiltrate.[30] The mesothelial cells in this case contained metachromatic, PAS-positive granules within their cytoplasm, which have been described in rheumatoid pleural effusion.[31]

The lung had a moderate increase of interstitial fibrous tissue around bronchovascular bundles (Fig. 6) and beneath the pleura but not in the interalveolar septa. These areas of fibrosis contained abundant anthracotic pigment, which is a marker of possible deposition of injurious materials.[32] In these regions we found numerous asbestos bodies, which were long, thin, symmetric, beaded, and brown on hematoxylin and eosin staining (Fig. 7). The brown beads contained iron, as demonstrated by the Prussian blue reaction. Each asbestos body had a central, clear, translucent crystalline fiber, which distinguishes a true asbestos body from a pseudoasbestos body.[33] The concentration of the asbestos bodies and the subpleural and peribronchiolar location of the fibrosis are consistent with a diagnosis of parenchymal asbestosis. Direct immunofluorescence of the lung-biopsy specimen would have been useful in excluding rheumatoid lung disease as the cause of the interstitial fibrosis. Marked deposition of IgM has been demonstrated in arterioles, interalveolar septa, and nodules in cases of rheumatoid lung disease.[34]

In the presence of the interstitial fibrosis and numerous asbestos bodies one must consider whether the pleural reaction was that seen in recurrent pleural effusions related to exposure to asbestos.[35] I cannot exclude that possibility. In my experience the mesothelial cells in patients with asbestosis associated with pleuritis and recurrent effusions but without a mesothelioma have tended to have dysplastic nuclei, a feature not present in this case.

Dr. McLoud, you have written about the normal findings on x-ray films of the chest in patients with clinical or physiologic evidence of chronic diffuse infiltrative lung disease. Will you comment on the normal appearance of the lungs in this case in view of the mild interstitial fibrosis found on pathological examination?

Dr. McLoud: The lung parenchyma appeared normal for the patient's age. Some increase in linear densities throughout the interstitium is seen radiographically in normal persons with aging, and the densities may be more marked if the person has had previous infections or is a heavy smoker. We have found that approximately 9 per cent of patients with biopsy-proved interstitial lung disease have normal x-ray films of the chest.[36] In the patients with normal x-ray films, however, the most common diagnoses were sarcoidosis, desquamative interstitial pneumonia, and allergic alveolitis.

Dr. Mark: Dr. Gaensler, in view of the additional information about this man's rheumatoid arthritis that Dr. Goodson has presented and the pathological find-



Figure 6. Bronchovascular Bundle with Increased Adventitial Fibrous Tissue Containing Anthracotic Pigment (×64).
The fibrosis extends for only a short distance into interalveolar sept.

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Figure 7. Asbestos Bodies (×1600).
The bodies have typical symmetric beading and clear central fibers.

ings, what do you think caused the pleural and pulmonary abnormalities?

DR. GAENSLER: An asbestos-induced effusion would be very unusual so late after exposure. If I had known that the patient had problems related to the rheumatoid arthritis I would have suggested rheumatoid disease of the pleura as more probable than an asbestos effusion.

The presence of asbestos bodies in the lung is not diagnostic of asbestosis. Indeed, all city-dwellers have some asbestos bodies in their lungs. The pulmonary fibrosis in this case is difficult to evaluate because the piece of tissue was immediately subpleural, and the patient had had pleural disease in that area. It is difficult to make a diagnosis of asbestosis from a biopsy specimen because of sampling problems and particularly in the presence of other pulmonary or pleural disease. If a patient has normal results of pulmonary-function studies, normal lung fields on roentgenograms of the chest, and no rales, clubbing or dyspnea the diagnosis is not asbestosis from a clinical viewpoint despite the presence of a minimal fibrotic reaction in the lungs. The discrepancy in this case between the clinical and the pathological findings suggests that the subpleural fibrosis may well have been the result of pleural disease.

DR. MARK: Dr. Goodson, will you describe what has happened to the patient?

DR. GOODSON: Since the process proved to be benign we continued the penicillamine therapy. In addition to the information in the case record we did request acute and convalescent titers for influenza A and B, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and adenovirus, and the results, reported several weeks after the operation, were negative. The patient has continued to respond to the penicillamine as far as the rheumatoid arthritis is concerned, and the x-ray films of the chest obtained three months after the operation show improvement as well. Improvement of rheumatoid pleural reactions as a result of penicillamine therapy has been reported.[37]

DR. HOMAYOUN KAZEMI: We cannot ignore the possibility of a pulmonary reaction to penicillamine, which may result in pulmonary fibrosis. Were there any measurements of pulmonary gas exchange?

DR. GOODSON: Full pulmonary-function testing was not done.

DR. MARK: Penicillamine has been reported to cause diffuse interstitial inflammation and fibrosis with dysplasia of alveolar lining cells,[38] features common to many types of drug pneumonitis but absent in the biopsy specimen in this case. Peribronchiolar and subpleural fibrosis with normal interalveolar septa, which was seen in this case, is not characteristic of drug reactions in the lung. Bronchiolitis obliterans[39] and peripheral-blood eosinophilia[40] have also been described with penicillamine therapy. These findings were also absent in this case.

DR. GAENSLER: We have seen patients with a pulmonary reaction to penicillamine, but it has been principally bronchiolitis or bronchiolitis obliterans rather than diffuse fibrosis.[39] The bronchiolar changes have also been described in Great Britain.[41]

DR. ROBERT FIENBERG: Is this patient still at risk for the development of a mesothelioma?

DR. MARK: Occasional patients with recurrent hemorrhagic pleural effusions due to asbestosis[15] or of indeterminate cause[42] later have a diffuse malignant mesothelioma. In this case we have not proved that the pleural disease was due to the exposure to asbestos.

DR. GAENSLER: We tend to think of the biopsy as the definitive solution to many diagnostic problems. The lungs can react to injury or disease in a relatively limited number of ways, and yet an open biopsy of the lung for diffuse disease is diagnostic in 91 per cent of the cases.[43] The spectrum of pleural reactions is much more limited. A pleural effusion reflects an imbalance between fluid production and resorption. It may not be due to disease in the pleura itself. It is not surprising, therefore, that a thoracotomy to determine the cause of an effusion is nondiagnostic in nearly half the cases.[42] The biopsy in this case probably excluded the diagnosis of a mesothelioma, although the problems of sampling and of differentiation of this tumor from active non-neoplastic mesothelial proliferation have been described.[42] The possibilities of an effusion related to the exposure to asbestos or rheumatoid disease were raised by the history and were not resolved by the biopsy. The findings of asbestos bodies and pleural thickening reinforced the former possibility, but the subsequently revealed history of moderate rheumatoid arthritis treated unsuccessfully with a number of drugs supported the latter diagnosis.

ANATOMICAL DIAGNOSES

Pleuritis, fibrinous, and pleural fibrosis, probably rheumatoid.
Peribronchial and subpleural fibrosis with numerous asbestos bodies, consistent with pulmonary asbestosis.
(Rheumatoid arthritis).

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Continued preparation of these Case Records has been made possible by a generous grant to the Massachusetts General Hospital from Pfizer Pharmaceuticals

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