

Asbestos Pleural Effusion

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The differential diagnosis of pleural effusion is large but has not included asbestos exposure. For 1 to 9 years we followed 12 patients with "idiopathic" effusions that were frequently recurrent, usually bilateral, and often followed by continued chest pain. The fluid was a sterile, serous, or blood-tinged exudate. Physical findings were limited to clubbing, dry rales, and signs of effusion. Asbestos exposure was from 3 to 38 years, but often this history was elicited only with difficulty. Usually, mechanics of breathing were normal, lung diffusing capacity reduced, and alveolar-arterial PO_2 differences elevated. Decortication and lung biopsy specimens in seven patients and postmortem examination in one showed nonspecific pleuritis with rare asbestos bodies and fibers; all had various degrees of chronic interstitial pneumonitis with asbestos bodies. One case of mesothelioma was recognized 9 years after the first documented effusion. With better understanding of the dangers of asbestos and better surveillance of workers, asbestos pleural effusion will be recognized oftener. It occurred in 21% of all patients with asbestosis seen at our laboratory.

PLEURAL DISEASE, including thickening, plaque formation, calcification (1-8), and mesothelioma (9-13), are well-recognized manifestations of asbestos exposure. Benign pleural effusion related to such exposure has not been reported. During the past 8 years we have seen an increasing number of patients who had both an exposure to asbestos and pleural effusion of undetermined cause which was frequently recurrent, usually bilateral, and often followed by continued chest pain. The purposes of this report are to show that "asbestos pleural effusion" is not uncommon, to call attention to an additional etiologic agent to be considered in patients with "idiopathic" pleural effusion, to suggest a possible precursor to the development of mesothelioma or the possibility

of slowly growing mesothelioma, and, incidentally, to emphasize that biopsy-proved chronic interstitial pneumonitis caused by asbestosis may be present without radiologic or even physiologic abnormalities.

Selection of Patients and Methods

Our attention was first drawn to a possible relationship between asbestos exposure and pleural effusion by experiences with two patients (Cases 1 and 4) who were seen 8 years ago after recurrent pleural effusions and who eventually required decortication; a diagnosis of asbestosis was made from pleural and lung biopsy material. For this report our computer program searched for simultaneous diagnosis of pleural effusion and asbestosis or asbestos exposure among 4,077 entries of patients seen in our laboratories between 1951 and 1969. The results confirmed the frequency of this relationship. Excluded from consideration were patients from our Sanatorium Division, individuals seen in survey situations, and those with pleural thickening only, with empyema, and with an unconfirmed history of effusion. Methods for evaluation of lung function and normal values used in our laboratories have been summarized (14).

Results

Among the 4,077 patients, 91 had confirmed pleural effusion (Table 1) and 57 had asbestosis or asbestos exposure (Table 2); 24 of these appeared in both groups. For this study we excluded 12 of the latter in whom the effusion occurred in relation to mesothelioma, bronchogenic carcinoma, or congestive heart failure. The remaining 12 patients, that is, 21.1% of all those with asbestosis or asbestos exposure (Table 2), were thought to have "asbestos pleural effusion." This diagnosis was based on occupational history, absence of any known disease that has been associated with pleural effusion, and pathologic material in 8 of the 12 cases.

CLINICAL OBSERVATIONS

Most patients were referred because of recurring pleural effusion of unknown cause and pleuritic chest pain (Table 3). None had had respiratory problems before their present illness, and all but one were cigarette smokers. Abnormal physical findings were

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Table 1. Etiology of Pleural Effusions in 91 Patients

	no.	%
Congestive failure*	20	22.0
Malignant tumor	22	24.2
Bronchogenic (no asbestos exposure)	9	
Bronchogenic (with asbestos exposure)	5	
Mesothelioma (with asbestos exposure)	5	
Metastatic	3	
Infections†	13	14.3
Tuberculosis	8	
Viral	4	
Fungal	1	
"Asbestos pleural effusion"	12	13.2
Asbestos only	10	
Asbestos with talc	2	
Connective tissue disorders	8	8.8
Rheumatoid arthritis	3	
Lupus erythematosus	3	
Progressive systemic sclerosis	2	
Pulmonary infarction	3	3.3
Chronic interstitial pneumonitis	3	3.3
Usual	2	
Desquamative interstitial pneumonia	1	
Laennec's cirrhosis	2	2.2
Undetermined cause	8	8.8

* Including two with asbestos exposure.

† Not including pyogenic and empyema.

limited to variable evidence of pleural effusion, finger clubbing, and dry crackling rales with a "close-to-the-ear" sound in a few cases (Table 3).

The amount of pleural fluid was generally moderate (Table 3). Mere blunting of the costophrenic angle (1 +) was seen only once (Case 12), and massive effusion (4 +) was not observed. Documented effusions occurred unilaterally in three patients, and bilaterally, either simultaneously or in sequence, in the other nine. Six patients had but a single episode; five had from two to four episodes; and in Case 10 bilateral effusions never disappeared. No calcifications were seen on tomography. The fluid ranged from clear yellow to bloody but was usually serosanguinous; in the latter the RBC counts ranged from 5,000 to 50,000/mm³. Aerobic and anaerobic cultures for pyogens, fungi, and tubercle bacilli always failed to show growth. In most cases the fluid was an exudate. Sediment and cell blocks showed no tumor cells. No thoracentesis was performed in Cases 6 and 11.

The severity of parenchymal infiltration is indicated in Table 3. Two patients had sufficient residual pleural thickening to rule out the presence of parenchymal infiltration (Figure 1). Five patients showed mottling and linear or reticular shadows in all or the lower two thirds of the lung fields (Figures 2 to 4). Eventually, honeycombing became evident in some of these. In three patients (Cases 4, 7, and 12) the lung fields appeared normal after the effusion had disappeared. Patient 3 had massive hilar and superior mediastinal adenopathy and coarse pulmonary nodulation (15).

Most laboratory examinations were unrevealing. The tuberculin skin test was positive in Patients 2 and 12, as was the histoplasmin test in Case 7. Lupus erythematosus (LE) preparations were always negative, and the latex fixation test was positive only in Case 10. Evidence of respiratory tract infection preceding or with effusions, including fever, elevated WBC counts, and growth of a predominant organism from sputum, was lacking. Only Patient 8 had heart disease with a myocardial infarction 1 year earlier. Malignancy did not become evident during a follow-up period that averaged 4 years, except for Patient 2 who developed a mesothelioma 11 years after his first effusion (Table 3).

OCCUPATIONAL HISTORIES (TABLE 4)

Nine patients were engaged in occupations where significant asbestos exposure was easily documented; in the others the exposure was more subtle. Patient 7, a bricklayer who had never used asbestos himself, is reported below; Patient 8 was a body shop man for 30 years and revealed only after lengthy questioning that he had done undercoating 1 day a week for many years.

Talc was used regularly by Patients 1 and 3 (15) and was an important nuisance in the section of the plant where Patient 12 was a pipefitter.

The duration of exposure was predictably long, from 20 to 38 years, in five patients and only 3 to 4 years in two patients. Most had worked with asbestos until the time of their illness, but in three patients there was a 6- to 18-year interval between last exposure and first effusion.

RESPIRATORY PHYSIOLOGIC STUDIES

Eleven patients had respiratory physiologic studies, usually on several occasions. In an attempt to evaluate the severity of interstitial disease, we selected those studies for inclusion in Table 5 that were

Table 2. Pleural Diseases in 57 Patients with "Asbestosis"

	no.	%
Pleural effusion	24	42.1
"Asbestos pleural effusion"	12	
With mesothelioma	5	
With carcinoma	5	
With congestive failure	2	
Pleural thickening	21	36.8
Slight	3	
Moderate	8	
Severe	6	
With calcifications	2	
With tuberculosis	2	
Condition of pleura undetermined because of dense parenchymal infiltration	3	5.3
No pleural reaction	9	15.8

* Does not include individuals seen in survey situations only.

Table 3. Clinical Data of 12 Men with Asbestos Pleural Effusion

Case	Age	Initial Complaint	Clubbing/ Rales/ Dyspnea *	Pleural Effusion				Type
				Extent		Number		
				Right	Left	Right	Left	
	yr							
1	47	Recurrent pleuritic chest pain, effusion	1+/0 /1+	3+	2+	2	2	Straw-colored
2	55	Severe progressive dyspnea, diffuse infiltration	2+/0 /3+	2+	0	4	0	Sanguinous
3	42	Mediastinal mass, dyspnea, pulmonary nodulation	2+/0 /1+	1+	2+	1	1	Clear, yellow
4	58	Recurrent pleuritic pain, effusion	0 /3+/1+	3+	3+	1	1	Serosanguinous
5	50	Progressive dyspnea	2+/0 /1+	2+	3+	1	1	Sanguinous
6	59	Abnormal survey film, progressive dyspnea	0 /2+/2+	2+	2+	1	1	No tap
7	33	Pleuritic chest pain and dyspnea	0 /2+/0	1+	2+	2	1	Clear, sanguinous
8	58	Pleuritic chest pain and dyspnea	0 /0 /1+	3+	1+	4	1	Serosanguinous
9	38	Progressive dyspnea	0 /0 /1+	2+	1+	1	1	Sanguinous
10	48	Joint pains, lumps on elbows	0 /2+/3+	3+	3+	1	1	Clear, yellow
11	53	Progressive dyspnea, fatigue and "heavy chest"	0 /2+/3+	3+	0	1	0	No tap
12	60	Severe progressive dyspnea	0 /0 /3+	1+	0	2	0	Clear, yellow

* Dyspnea during periods of little or no pleural effusion.

† Chronic, never dry since initial effusion.

obtained when there was no effusion or the least possible residual.

Mechanics of breathing were not greatly disturbed: only three patients had significant "restriction" indicated by reduced vital capacity. Obstructive disease, with reduced forced expiratory volume in 1 sec (FEV₁) and maximal voluntary ventilation (MVV) and increased residual volume, was shown only in Patient 6, who had bullous emphysema. One half of the patients, however, had severely disturbed respiratory gas exchange: a severe degree of "alveolar-capillary block" was shown in Patients 2, 3, 5, 6, 11,

and 12 by severely reduced single breath and steady state diffusing capacities. Arterial PO₂ ranged from 63 to 84 mm Hg and alveolar-arterial PO₂ differences from 23 to 44 mm Hg. Most patients hyperventilated during standard exercise, and their physiologic dead space was variably enlarged. Only Patient 7 had respiratory studies that were entirely within the normal range.

OPERATIVE FINDINGS

Patients 1, 2, 4, and 7 had parietal and visceral decortication, bilaterally. In Patient 4, to establish a

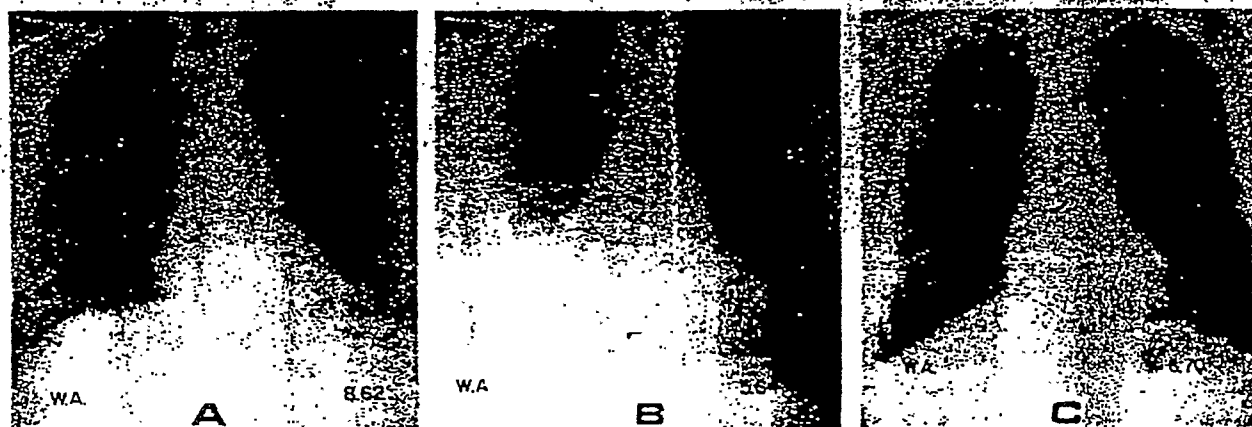


Figure 1. Serial chest films of Patient 1.

1A. Initially there was marked blunting and thickening of the pleura laterally, and the left lung field appeared hazy. Thereafter, 1,200 ml of straw-colored fluid was removed, and eventually a decortication was performed.

1B. He was readmitted in November 1963, February 1964, again in May 1964 because of recurring pleural effusion on the right.

1C. On follow-up examination in June 1970 he had been free of effusions for 5 years. There was bilateral slight pleural thickening and continued chest pain.

Table 3. (Continued)

Parenchymal Infiltration†		Other Disease	Follow-up Since First Effusion (See also Table 6)
Right	Left		
X	Min.	None	8 years; effusions 2 years; since then severe chest pain only
Adv.	Adv.	None	9 years recurrent effusions; mesothelioma 12 years
Nod.	Nod.	Talcosis	4 years; no recurrences; well and working
0	0	None	8 years; severe bilateral chest pain
X	0	None	7 years; no further effusions; well and working
Adv.	Adv.	Bullous emphysema	4 years; no further effusion; progressive dyspnea, working
0	0	None	1 year; no further difficulties
Min.	0	Arteriosclerotic heart disease	1 year; no further difficulties; retired
Mod.	Mod.	None	1 year; no further difficulties
Adv.	Adv.	Rheumatoid arthritis	5 years; progressive dyspnea; died of bilateral empyema after intubation
Mod.	Mod.	None	3 months; progressive dyspnea
0	0	None	4 years; one recurrent effusion; severe dyspnea

† Refers to reticulation and linear shadows associated with asbestosis: Min. = minimal; Mod. = moderate; Adv. = severe with honeycombing. Nod. = nodulation; X = no diagnosis because of overlying pleural disease.

diagnosis, to restore pulmonary function, and to prevent further recurrences of effusions (Table 6). Several lung biopsies were obtained at each operation. Patient 3 was explored primarily because of superior mediastinal enlargement (15). Patient 9 had only a needle pleural biopsy, and Patient 12 had lung biopsy because of progressive dyspnea.

At operation irregular pleural symphysis was seen in all patients, and serosanguinous fluid was found in all except in Patient 12. The cortex was quite vascular and varied in thickness from a few millimeters to 2 cm. Pleural calcifications or asbestotic "plaques" were not observed. The lung was often partially atelectatic but reinflated readily after decortication. The lung tissue was described as normal to excessively firm but without distinct nodulation except in Patient 3; no differences in texture were noted between upper and lower regions.

LUNG PATHOLOGY

Large biopsies from both upper and lower lobes were available for six patients, from both sides in one patient, and from autopsy in a seventh patient (Table 6). Biopsy specimens were fixed in inflated condition (16), and, in addition to routine treatment, 12 serial sections were stained with Perls' ferrocyanide; atypical lung regions immediately beneath the pleura and from the tip of the lingular segment were ignored. Chronic interstitial pneumonitis of various degrees was seen in all cases. The mildest reaction consisted of a diffuse, chronic, low-grade inflammation with in-

terstitial edema, histiocytic reaction, increased reticulin, and occasional hyaline membranes (Figures 5A and 6). Thickening and edema of the interlobular septa were often striking (Figure 6). Sometimes pleural fibrosis extended into the lung septa. At a more advanced stage the reaction was more diffuse, with the interstitium moderately thickened by increased collagen formation (Figure 7A). In the most severe form fibrosis predominated and was at first focal (Figure 8A). Finally, there was diffuse organization, obliteration of alveolar structures and bronchioles, and, in some areas, marked honeycombing (Figure 9). Macrophages filled with irregular granules were seen in all sections. These cytoplasmic granules were often brightly orange-brown and refractile and gave a strongly positive reaction for iron (Figure 7C). In some instances such cells, together with desquamated granular pneumocytes, were densely packed and filled many alveoli (Figure 7A); whereas elsewhere they were more scattered (Figure 5A). In the more severe cases foreign-body giant cells often contained both fibers and asbestos bodies. The lungs of Patient 3 also showed a moderate interstitial pneumonitis, but alveolar septa were filled with talc crystals, and there were many whorled silicotic nodules (15).

Asbestos or ferruginous bodies were seen in all lungs. However, their number varied greatly (Table 6). In 3 patients only a few were seen in 12 serial sections (1+); in 4 patients several were seen in each section (2+), and in Patient 10 innumerable asbestos bodies were seen in every field (4+) (Figure 9).

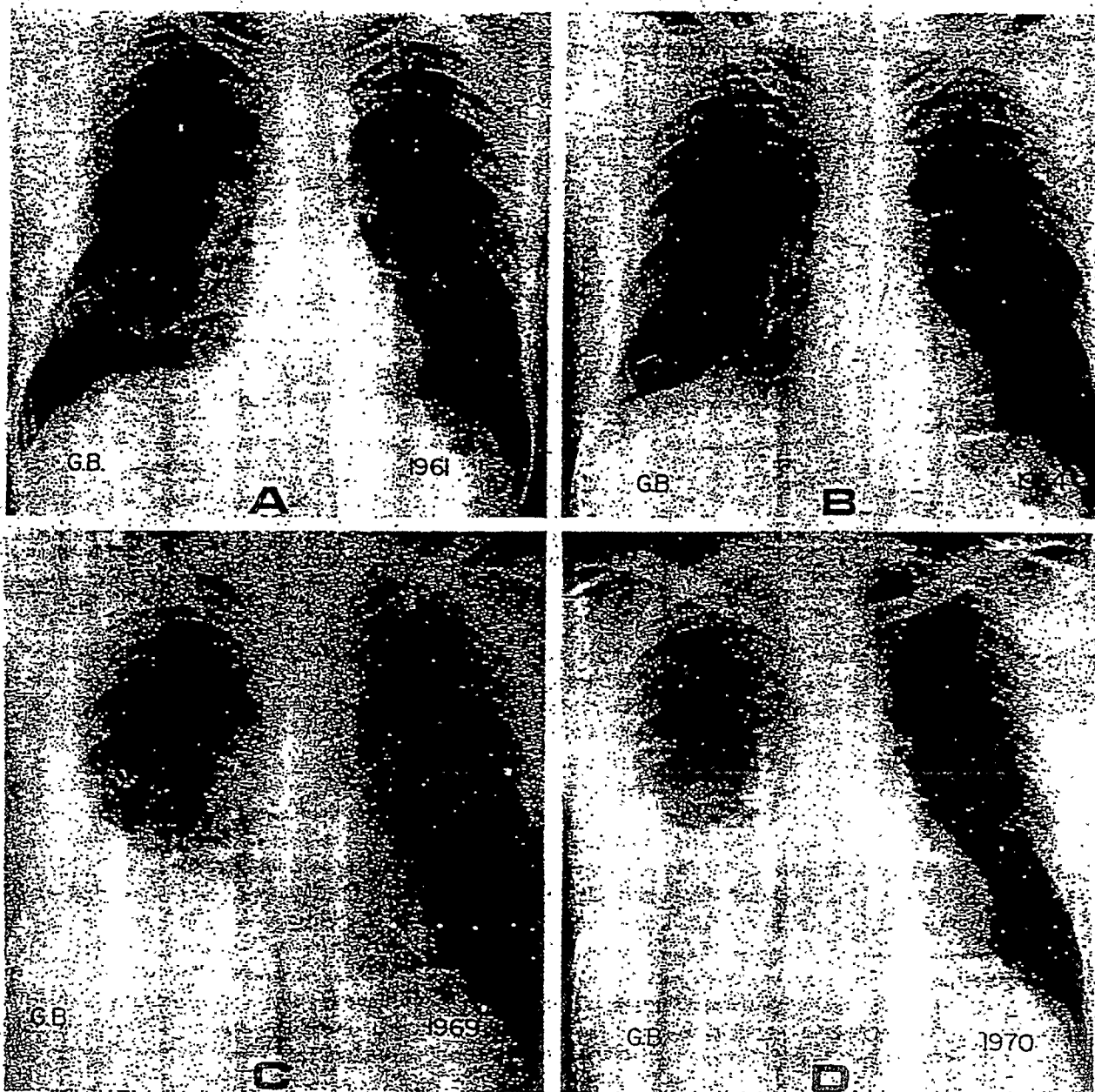


Figure 2. Serial chest films of Patient 2.

2A. In 1961 there was diffuse, fine nodulation and reticulation. When we first saw him, in 1962, there was, in addition, blunting of the right costophrenic angle.

2B. Effusions recurred, and by 1964 both the pleural residual and the parenchymal reticulation had progressed. Decortication and lung biopsy were performed in 1965, and he was readmitted in 1967 and again in 1969 for recurrent effusions and increasing dyspnea.

2C. In 1969 there was a thick cortex and early honeycombing.

2D. During his last admission in 1970 pleural thickening had increased, and there was a 2-cm nodule protruding from the pleura into the lung field, better seen in Figure 3.

PLEURAL PATHOLOGY

The pleural cortex varied from barely 1 mm to 15 mm in thickness. When lung was attached, the wavy line of the original pleura could be readily identified (Figure 7B). In all cases there was a marked "pleural drift" of carbon, other dust, and iron-positive

granular material (Figures 7B and 8A). There was often regenerating proliferating mesothelium, extensive collateral circulation, and, sometimes, hemorrhage. Granulomas or other more specific lesions were not seen. Twelve serial sections failed to show asbestos bodies or fibers in two cases; there were fibers alone in Case 1 (Figure 7C) and fibers inter-

spaced among rare asbestos bodies in others (Figure 5B). There were only 2 or 3 asbestos bodies in all 12 sections in 3 cases (Table 4). Whenever bodies and fibers were found, they were less than 1 mm outside of the original pleura.

A mesothelioma developed eventually in Patient 2, whose case is described below.

Case Reports

CASE 1

This 47-year-old Banbury machine operator and tile-maker was first referred in August 1962 for evaluation of dyspnea, pleuritic chest pain, and recurring left pleural effusion of 1 month's duration. Past and family histories were unremarkable. He had earlier worked as a cook in the merchant marine and as an elevator operator. For the past 12 years he had been a tilemaker operating a Banbury machine, mixing asbestos, sand, and other materials into a blender and then pouring and moulding the mixture to produce vinyl-asbestos and fire-retarding tile.

Examination showed slight clubbing and decreased breath sounds at the left base. Vital signs were normal, and he was afebrile. The chest roentgenogram showed haziness over the entire left lung field with marked pleural thickening laterally (Figure 1A). Blood and urine were normal. Skin tests for tuberculosis and common fungi were negative. About 1,200 ml of straw-colored exudate were removed. Bacteriologic and cytologic examinations were negative.

Parietal pleurectomy was eventually performed because of recurring effusion and persistent pain and because tumor was suspected. The pleura was markedly thickened (Figure 7B), and the lung was excessively

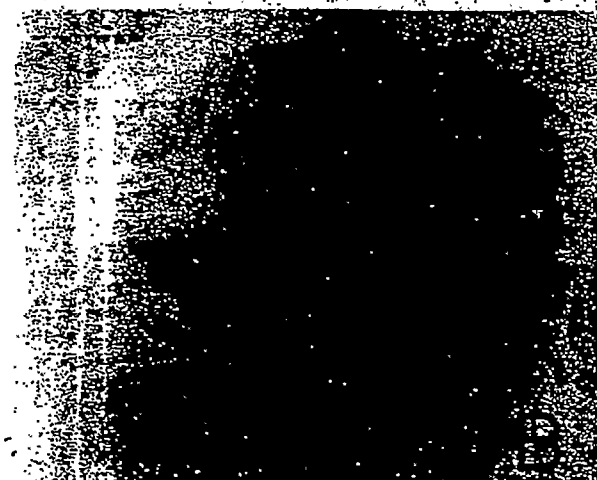


Figure 3. Patient 2. A spot film of the right upper lung emphasized the nodular lesion, the thick cortex, reticulation, and honeycombing not so well seen in Figure 2D.

firm and partially atelectatic. Biopsy specimens from upper and lower lobes showed diffuse interstitial pneumonitis with thickened alveolar septa; many alveoli were filled with granular pneumocytes and macrophages containing large orange-yellow granules that stained intensely blue for iron (Figure 7A). Occasional asbestos bodies were seen. The pleural cortex was quite vascular (Figure 7B), and the loose tissue just outside of the original pleura contained occasional granule-laden macrophages and asbestos fibers (Figure 7C).

After thoractomy "band-like" chest pain and dyspnea persisted. Subsequent admissions in November 1963 and February and May 1964 were prompted by increased

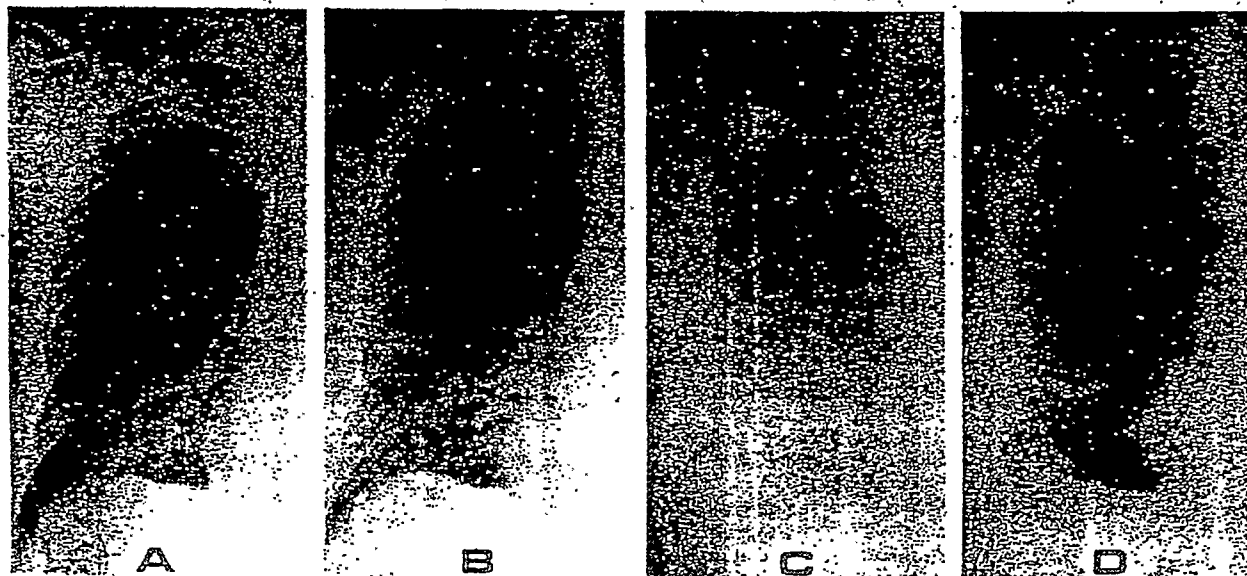


Figure 4. Chest films of Patient 11, a store controller in an asbestos products plant since 1950.

4A. Annual roentgenograms showed slight basal reticulation for the first time in 1962.

4B. By 1968 the infiltration had progressed somewhat.

4C. A film from January 1970, taken during an admission for evaluation of mild hypertension, was then obtained and showed a marked right pleural effusion.

4D. He was referred in June 1970 because of dyspnea of recent onset. The film at that time showed marked pleural thickening.

Table 4. Occupational History of 12 Men with Asbestos Pleural Effusion

Case	Occupation	Job Description	Asbestos Exposure	Interval*	Other Jobs
				yr	
1	Banbury machine operator; tile manufacture	Mixed sand, asbestos, vinyl, and so forth; moulded vinyl asbestos and fire-retarding brick; talc exposure	12	0	Cook, elevator operator
2	Steam fitter and gas fitter; (private and navy yard)	Covered new pipe 12 years; naval ship refitting (removed old covering) 10 years; gas fitter working near pipecoverers since then	38	8	0
3	Span grinder, rubber company	Shredded rubber tire, tile scrap; sprinkled with talc; mixed material for battery casings	22	0	Pullman attendant
4	Shipfitter, boiler insulator	Insulated boilers with magnesia block and asbestos cement; removed old insulation	13	6	Chemical worker
5	Asbestos Worker's Union	General insulation work, "mostly fiber glass"	4	0	Granite cutter
6	Pipecoverer, new naval ship construction	Fitted prefabricated insulation; made and shaped segments in shop	12	0	Lumber cutting
7	Bricklayer	Laid bricks in high-rise office buildings immediately below laggers who sprayed cement-asbestos-glass mixture on steel	8	0	0
8	Auto body shop man	Undercoating with asbestos mixture 1 day/week	30	0	0
9	Asbestos Worker's Union	General insulation work, mostly fiber glass; joints and boilers covered with asbestos	12	0	Stock boy, U. S. Army
10	Mill grinder in asbestos products plant	Mixed raw materials for fire-retarding brick and sheets	3	20	Draftsman
11	General laborer and store controller in asbestos products plant	Swept floors, piled fiber, racked sheets, worked on veneer press, unloaded freight cars	20	0	0
12	Pipe fitter in various companies using asbestos and talc	Pipe fitter in brake lining plant 7 years; pipe fitter in chemical plant making meteorological balloons 26 years, much talc exposure	33	0	0

* Interval between last asbestos exposure and first pleural effusion.

pain and repeated pleural effusions, now on the right side (Figure 1B). The fluid remained sterile and had a benign cytology.

Chest pain has persisted to the present and has been unresponsive to intercostal nerve blocks and resection of the costal arch. His last chest roentgenogram, in June 1970, showed minimal pleural thickening bilaterally (Figure 1C). Pulmonary function in 1966 (Table 5)

and 1970, when there was no effusion, was normal except for a slight increase of the alveolar-arterial P_{O_2} difference.

CASE 2

This 55-year-old plumber was first seen in 1962 because of progressive dyspnea and fatigue. These symptoms, together with intermittent right pleuritic chest

Table 5. Selected Respiratory Studies of 11 Men with Asbestos Pleural Effusion During Periods of Least Pleural Involvement

Case	Date (Month/Year)	Pleural Condition at Time of Study	Maximum Breathing Capacity*	Vital Capacity*	Vital Capacity 1 sec†	Residual Volume*
				%		
1	6/66	Slight fibrothorax, right	88	95	74	123
2	10/62	None	178	100	81	135
3	3/65	Blunted costophrenic angles	73	62	72	127
4	10/63	Slight fibrothorax, bilaterally	128	87	96	155
5	9/63	Bilateral effusion, 1+	84	52	68	55
6	7/66	Bullous emphysema only	—	89	41	—
7	11/69	Minimal blunted angles, bilaterally	123	104	83	97
8	6/69	Blunted costophrenic angle, right	89	93	58	121
9	11/69	Bilateral effusion, 1+	80	80	63	125
11	4/70	Fibrothorax, right 2+	92	69	86	49
12	4/66	None	116	94	71	75
100 normal subjects, our laboratory			118	108	82	115

* Percent predicted from Baldwin, quoted by Gaensler and Wright (14).

† Percent of total vital capacity delivered in one second.

pain, had led to his first admission 15 years earlier. A chest roentgenogram then showed "a form of silicosis," and bronchoscopy showed "coal dust." Cough increased with smoking between 2 and 4 packs a day. A right pleural effusion was first noted 1 month before. He began to work with his father as a steamfitter in 1923 and always covered all work with asbestos. From 1935 he worked at a navy yard at refitting. He did no covering but had to strip old insulation 1 day each week before installing new work. Since 1945 he had been a gas fitter, working side by side with pipecoverers in an usually dusty environment.

Examination showed marked clubbing and obvious hyperpnea but was otherwise unremarkable. The first available chest roentgenograms from 1961 showed fine mottling and reticulation throughout both lung fields (Figure 2A). In 1962 there was also blunting of the right costophrenic angle. Pulmonary function studies showed normal mechanics of breathing, severe hyperventilation, an elevated alveolar-arterial P_{O_2} difference, severely reduced diffusing capacities, and an elevated physiologic dead space (Table 5).

Two years later he was admitted twice because of dyspnea and right pleural effusion (Figure 2B). Thoracenteses yielded sterile, blood-tinged fluid with negative cytology. Dyspnea progressed, and in 1965 he stopped work and was readmitted once more. Physical findings were unchanged, and an intermediate tuberculin gave a "barely positive" reaction. Slightly pink pleural fluid contained 5,000 RBC and 250 WBC/mm³, with 64% polymorphonuclear leukocytes, 36% lymphocytes, 5.9 g/100 ml protein, and a lactic acid dehydrogenase of 113 units/100 ml. All cultures were negative. An exploratory thoracotomy for persistent pain and recurrent effusions showed a thickened cortex, which was removed together with two wedges from the right upper lobe. The parenchyma felt resilient, offered considerable resistance to sutures, and showed severe interstitial pneumonia with fibrosis, honeycombing, and many asbestos bodies (Figure 8A). The pleura showed nonspecific fibrosis with focal hemorrhage, mesothelial proliferation, and two asbestos bodies in serial sections.

Chest pain and effusions continued, requiring anal-

gesics for relief and hospitalizations in 1967 and again in 1969 (Figure 2C). His most recent admission, in 1970, was 23 years after onset of dyspnea and pleuritic chest pain and probably 12, and certainly 9 years after his first effusion. Cyanosis and dyspnea at rest were now present. The roentgenogram was largely unchanged but now showed a 1.5-cm nodule protruding laterally from the thickened pleura into the lung (Figures 2D, 3). At thoracotomy a firm pleural tumor was found to encase the lung and extend into the interlobar fissures. It was a malignant mesothelial tumor with large cuboidal cells with eosinophilic granular cytoplasm and vesicular nuclei, arranged in pseudotubules or papillary fashion. Few mitotic figures were seen (Figure 8B).

CASE 7

This 33-year-old bricklayer was referred for evaluation for pleuritic pain, recurrent bilateral pleural effusions, and dyspnea of 9 months' duration. During two previous hospitalizations he was afebrile, and physical examination was unremarkable except for signs of fluid bilaterally. Examination of blood and urine was normal, a histoplasmin skin test was positive, and intermediate tuberculin negative. Two thoracenteses yielded clear yellow fluid with a specific gravity of 1.030; glucose, 82 mg/100 ml; and 2,430 RBC and 840 WBC/mm³, with 23% polymorphonuclear leukocytes and 77% lymphocytes. Cultures and cytologic studies were negative. Bronchoscopy, right scalene triangle exploration, and pleural needle biopsies were unrewarding. The past history was unremarkable.

He had spent 2 years in Panama with the Navy. Since then, for 9 years, he had worked as a bricklayer on high-rise office buildings. Detailed questions and specific reference to asbestos eventually revealed that he had been continually exposed to a fine, white, wooly dust that came from the floors immediately above him where ladders sprayed steel beams with a fireproofing compound. The material consisted of short fibers of asbestos, fiberglass, and cement that often coated the floors and clothing of the bricklayers. The ladders wore masks but the bricklayers did not*.

* This type of lagging was prohibited in New York City by Mayor John Lindsay at this writing (*Boston Globe*, June 17, 1970).

Table 5. (Continued)

Exercise Ventilation	Lung Diffusing Capacity		Arterial P_{O_2}	Alveolar- Arterial P_{O_2} Difference	Arterial P_{CO_2}	Physiologic Dead Space
	S.B.†	S.S.‡				
liters/min per m ²	%	ml		mm Hg		ml
11.9	91	23	77	32	39	126
18.7	41	9.1	70	40	38	450
13.4	66	10	84	23	37	135
11.9	100	—	—	—	—	—
10.4	57	12.5	75	29	43	191
—	60	7.1	—	—	27	193
14.0	87	15.1	82	12	42	193
10.8	—	—	—	—	—	—
13.9	112	11.7	82	24	38	141
12	53	9.8	63	43	39	405
12.7	59	9.0	65	44	31	166
9 ± 1	100	14.8	91	14	39	150

† Single breath diffusing capacity, % predicted from Gaensler and Wright (14).

‡ Steady state diffusing capacity, ml/min per mm Hg, standard temperature and pressure, dry.

Table 6. Surgery and Pathology in 8 of 12 Men with Asbestos Pleural Effusion

Case	Date (Month/ Year)	Operation	Lung Pathology	Frequency of Asbestos Bodies*	Pleural Pathology	Frequency of Asbestos Bodies*
1	8/62	Left decortication and lung biopsy	Diffuse interstitial pneumonitis with moderately thickened septa; clumps of macrophages with iron-positive granules fill most alveoli (Figure 7A)	2+	1-3-mm cortex; pleural fibrosis; many asbestos fibers (Figure 7B and C)	F
2	5/65	Right decortication and lung biopsy	Severe chronic interstitial fibrosis and honeycombing	2+	1.5-mm pleura with marked hemorrhage and mesothelial proliferation (Figure 8A)	1+
	2/70	Right resection mesothelioma	Papillae and branching tubules of large cells without anaplasia (Figure 8B)			
3	1/62	Right biopsy of pleural nodule, lung, and mediastinal node	Silicotic nodules in lung and pleura, thickened interstitial tissue filled with talc crystals	1+	Pleura moderately thickened and studded with silicotic nodules	(3)
4	8/62	Left decortication and lung biopsy	Both sides: diffuse, chronic, low grade inflammation with interstitial edema, histiocytic reaction, and increased reticulin; many dust-laden macrophages; severe edema of interlobular septa (Figures 6A and B)	2+	Chronic pleuritis and fibrosis, 3-mm hyalinized cortex	0
	3/63	Right decortication and lung biopsy				
7	10/68	Left decortication and lung biopsy	Pleural fibrosis extends into lung along septae; slight diffuse interstitial pneumonitis (Figure 5A)	1+	2-mm cortex; regenerated proliferating mesothelioma, extensive collateral circu- lation (Figure 5B)	(3) F
9	2/69	Right needle pleural biopsy	—	—	Chronic pleuritis and fibrosis, increased collateral circu- lation	(2)
10	6/69	Bilateral closed thoracotomy; autopsy	Very severe, diffuse organi- zation; fibrosis and obliteration of alveolar structure and bronchioles; many nests of asbestos bodies with giant cells, some arteriolitis (Figure 9A)	4+ F	5-to-15-mm vascular cortex covered by fibrin, original pleura well demarcated, innumerable asbestos bodies and fibers on inner border	1+ F
12	2/66	Right lung biopsy	Focal interstitial pneumonitis with much increased collagen; lymphocytic infiltration and with germinal centers	2+	Slightly thickened and marked vascularity	0

* F = fibers; numbers in parentheses indicate total number of asbestos bodies found in 12 serial sections.

The chest roentgenogram showed blunting of both costophrenic angles with thickening of the left lateral pleura. This was the only patient who had entirely normal lung function (Table 5).

Persistent pain and recurring effusions led to left exploratory thoracotomy. A thin pleural cortex was removed, and two biopsy specimens were obtained from a normal-appearing lung. There was some focal interstitial pneumonitis with irregular thickening of alveolar septae (Figure 5A). The alveoli contained many macrophages filled with irregular, coarse, yellow granules and 16 asbestos bodies in 12 sections. The cortex was vascular, showed regenerating proliferating mesothelium, three asbestos bodies, and occasional fibers (Figure 5B). One year after thoracotomy pleural effusion had not recurred, intermittent pain continued, and pulmonary function remained normal.

Discussion

The breadth of diagnostic possibilities with pleural

effusion is well known. Few studies of large numbers of patients have been published in recent years; and the reported frequencies of various causes are not comparable because they depend on the reporting institution and the interests of the observer (17-22).

Tuberculosis, although decreasing, has remained important and, during the last 15 years, has accounted for from 6 to 81% of all cases of pleural effusion (17, 18, 21, 22). Pleural effusion without apparent cause but with a positive tuberculin reaction still must be considered of tuberculous origin, and the term "pleural effusion (presumably tuberculous)" should replace the term "idiopathic" (23). Indeed, among young adults with "idiopathic" effusion and a positive tuberculin test followed for 5 or more years, 66% developed active tuberculosis (19). Pleural effusion of undetermined cause in patients

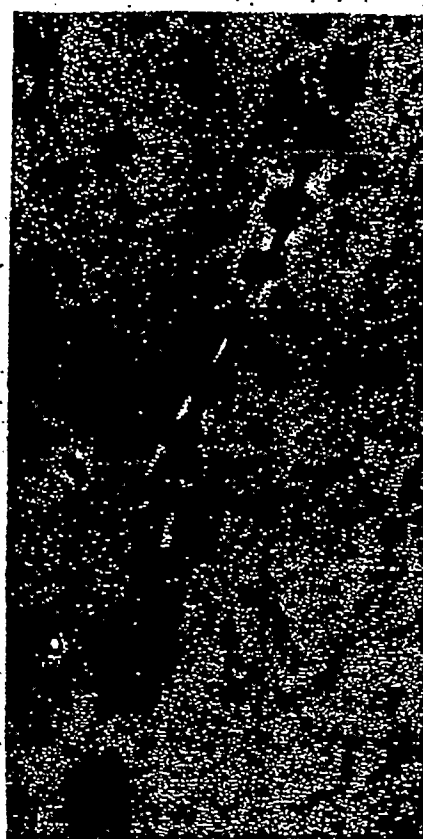


Figure 5. Biopsy specimen from Patient 7.

5A. The lung showed focal interstitial pneumonitis with thickening of alveolar septa; many alveolar spaces contained macrophages filled with coarse yellow granular material; asbestos bodies were rare. (Hematoxylin and eosin; microscopic magnification, $\times 60$, $\times 1.9$.)

5B. A 2-mm pleural cortex showed regenerating, proliferating mesothelium and extensive collateral circulation. It contained occasional asbestos fibers and only 3 asbestos bodies in 12 serial sections. High magnification shows two large asbestos fibers surrounded by broken segments of an asbestos body. (Perls' ferrocyanide; microscopic magnification, $\times 1,500$, $\times 1.9$, partially polarized.)

with a series of negative tuberculin skin tests remains a problem. Asbestos exposure has never been mentioned in the differential diagnosis (12, 13, 17-23).

Pleural thickening or calcifications have been noted in various pneumoconioses (24) and in recent years have been identified particularly with asbestosis (1-8). Indeed, pleural thickening and calcification are considered characteristic radiographic signs of asbestosis (1, 7). In surveys of asbestos workers with 20 or more years of exposure Frost, Georg, and Møller (2) found only 39% with a normal pleura, Selikoff (6) found only 44%, and in our patients who were referred because of their symptoms, only 16% had a normal pleura radiographically (Table 2). Benign pleural effusion was mentioned once by Eisenstadt (25), who described an insulation worker who presented with pleuritic pain and a left effusion that was brown, sterile, and had benign cytology. Despite antituberculous drugs, the effusion recurred twice on the opposite side, and decortication and lung biopsy were performed. The lung showed thickened alveolar walls with occasional asbestos bodies, and the pleura was fibrosed but without bodies.

DIFFERENTIAL DIAGNOSIS

A diagnosis of "asbestos pleural effusion" must be

made with caution. It may be an error to attach too much significance to the mere coexistence of two diseases, and the commoner the two diseases, the greater the likelihood of error (26). Careful study was made to exclude other known causes of pleural effusion. The negative cytologic examinations, lung and pleural biopsies, and follow-up have ruled out malignant tumor. There was no evidence of congestive heart failure, cirrhosis, thromboembolic disease, or trauma. The tuberculin test was negative in all but two patients, and in these tuberculosis was effectively excluded by open pleural biopsy. Only Patient 3 had an acute illness with his effusions, and neither clinical nor laboratory studies were indicative of bacterial, viral, or mycoplasma infection.

Only Patient 10 presented a somewhat nosologic problem that will be discussed in more detail elsewhere. Bilateral effusion and parenchymal infiltration were discovered when he presented with arthritis and nodules. The fluid persisted for 5 years despite multiple thoracenteses (Table 3). Numerous latex fixation tests were positive to 1:8,192 dilution, and LE preparations were always negative. His 3-year asbestos exposure, 20 years before his illness (Table 4), was discounted until he died of respiratory failure. Then the lungs were largely destroyed by massive fibrosis

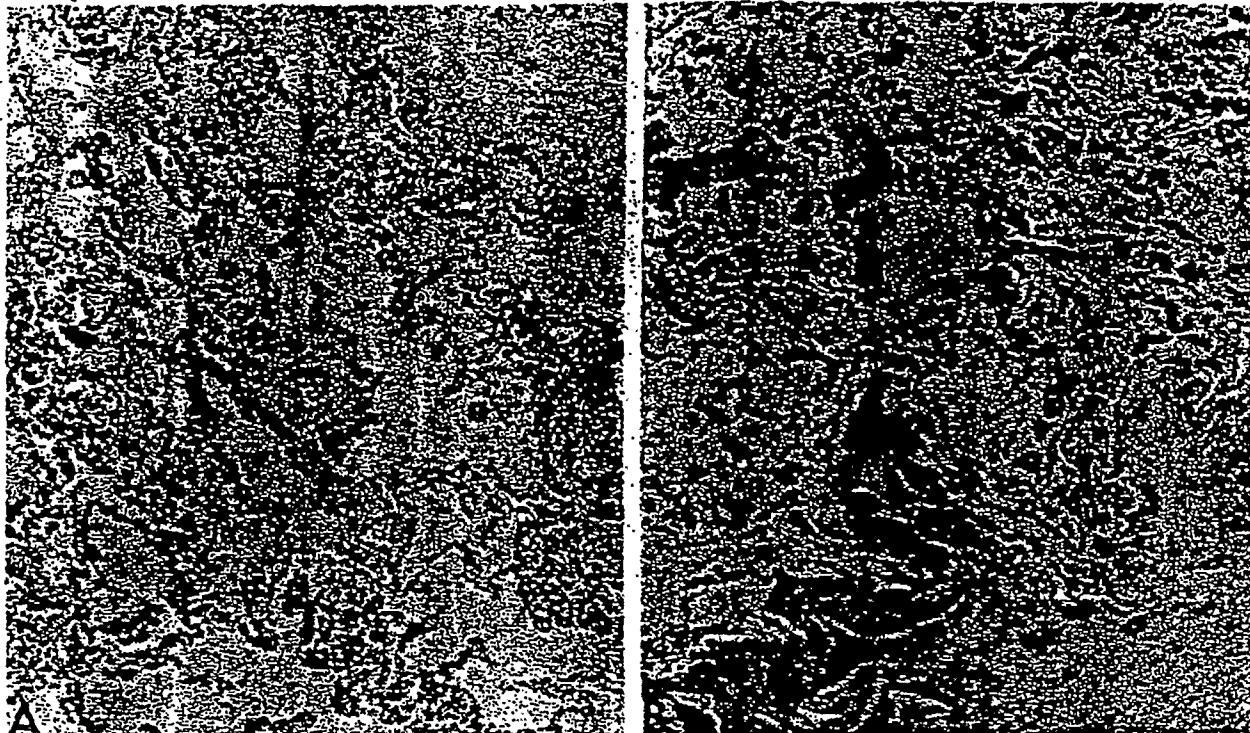


Figure 6. Lung biopsy specimen from Patient 4, obtained in August 1962 from the anterior segment of the left upper lobe (A) and in March 1963 from the right lower lobe (B). All sections showed diffuse, chronic, low-grade inflammation with interstitial edema, histiocytic reaction, increased reticulin, and occasional hyaline membranes; there were many dust-laden macrophages and an occasional lymphoid follicle. Marked thickening and edema of the interlobular septae are well seen in the right upper corner of A and the right lower corner of B; other sections from all five lobes were similar. (Hematoxylin and eosin; microscopic magnification, $\times 50$, $\times 1.9$.)

and honeycombing, spaces were filled with clumps of asbestos bodies (Table 6 and Figure 9), and a number of these bodies were in the thick cortex. Although the relationship between pleural effusion and rheumatoid arthritis has been questioned by some (26; 27), other studies appear to confirm the increased frequency of effusion in this disease (28). In this case the rheumatoid abnormality of tissue reaction may have had a modifying effect on asbestosis. Indeed, two patients with asbestosis and rheumatoid arthritis have been described, although their disease was nodular and not associated with effusion (29, 30).

RELATIONSHIP TO ASBESTOS EXPOSURE

The prevalence of asbestosis is related to both the concentration and duration of dust exposure. A dose-times-time relationship could not be established in our patients because their work was largely unsupervised and their exposure often unsuspected. Therefore, the duration of exposure indicated in Table 4 has little meaning. Until recently it was believed that, with a recommended threshold value for dust of 5 million particles/ft³, clinically recognizable asbestosis rarely developed in less than 20 years (31). In several of our patients the total exposure was probably

less than that (Cases 1, 4 to 6, and 8 to 10), intermittent (Cases 8 and 12), or to dusts containing much talc (Cases 3 and 12). The relationship of asbestos amphiboles to talc has been discussed recently (13, 15). It is thought that asbestos pleural effusion may develop with dust exposures that may be less than those that have been associated with the development of asbestosis. Perhaps "asbestos pleural effusion" resembles mesothelioma more than asbestosis in this regard.

RELATIONSHIP TO ASBESTOSIS

Pleural plaques and calcifications from asbestos exposure are said to occur without parenchymal asbestosis. We tried to determine whether this is true concerning asbestos pleural effusion. The commonest criteria for a clinical diagnosis of asbestosis are dyspnea, basilar dry rales, clubbing of the fingers, a reduced vital capacity, and a roentgenogram consistent with moderate or advanced asbestosis. Previously we defined the presence of at least three of these criteria as necessary for an epidemiologic diagnosis (31). Tables 3 and 5 show that by this definition of the present patients had "asbestosis" (Cases 2, 6, and 9 to 11). Only two had a vital capacity of less than 80%, which is surprising because the pleu-

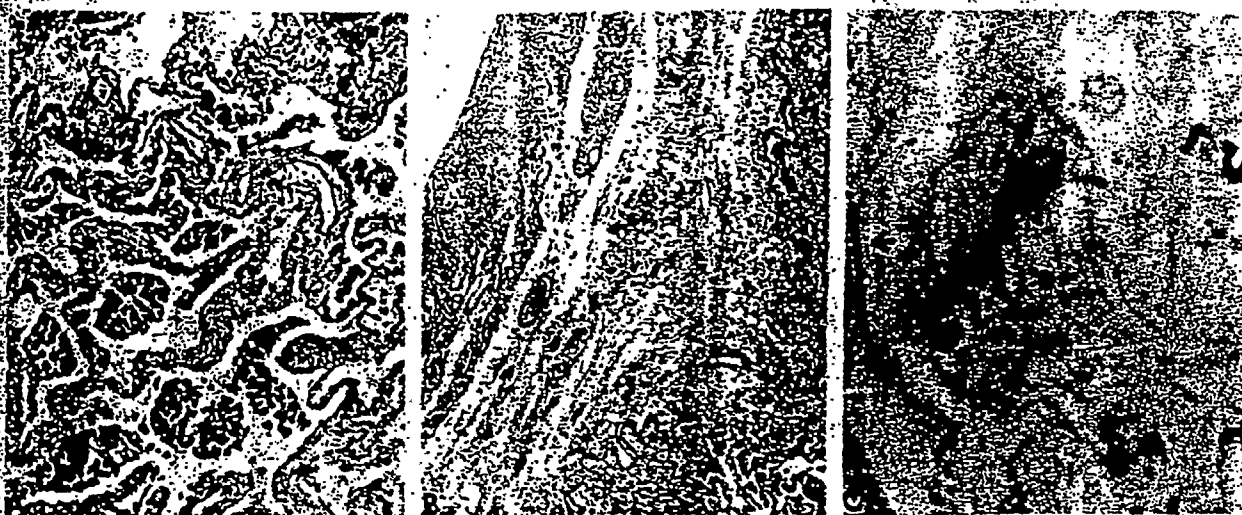


Figure 7: Biopsy sections from Patient 1.

7A. The lung biopsy shows diffuse interstitial pneumonitis with moderate thickening of alveolar septa; many alveoli were filled with macrophages containing large yellowish granules that stained intensely for iron. Occasional asbestos bodies were seen in all sections. (Periodic acid-Schiff and light green; microscopic magnification, $\times 125$, $\times 1.9$.)

7B. The pleural cortex was moderately thick and quite vascular; the wavy line of the original pleura was well seen. On the lung side there was a marked "pleural drift" of carbon and iron-containing granular material. (Perls' ferrocyanide; microscopic magnification, $\times 50$, $\times 1.6$.)

7C. Just outside the original pleura there were occasional macrophages containing irregular large brown granules. Within some of these cells, and sometimes around them, were asbestos fibers well seen in this partially polarized high magnification. One end of a fiber (arrow) has begun to stain for iron. (Perls' ferrocyanide; microscopic magnification, $\times 1,250$, $\times 1.9$ partially polarized.)

thickening has usually been thought to cause a reduced vital capacity and reduced compliance (4, 32-34). Among the six patients without these criteria for clinical asbestosis, two (Cases 1 and 12) had both impaired respiratory gas exchange (Table 5) and moderate interstitial pneumonitis (Figure 7A). Patients 4 and 7 had no signs or symptoms of "asbestosis" and essentially normal respiratory function (Table 5), but their biopsy specimens showed early inter-

stitial pneumonitis (Figures 5A and 6). These observations suggest that [1] among the clinical criteria for "asbestosis" the chest roentgenogram is the most sensitive—a conclusion that we have also reached from an epidemiologic survey (31); [2] studies of respiratory gas exchange, particularly of diffusing capacity and alveolar-arterial oxygen gradients, may show additional patients with asbestosis who have no clinical signs and symptoms—a finding that has been

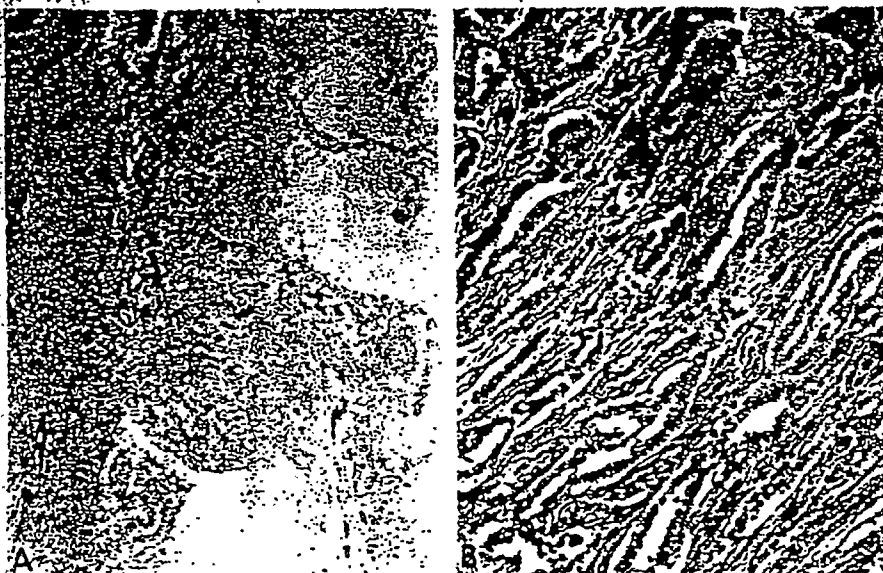


Figure 8: Tissue from Patient 2.

8A. Decortication and lung biopsy in 1965 showed a thick pleural cortex with marked hemorrhage and mesothelial proliferation. Asbestos bodies are seen within cortex and lung; there was severe chronic interstitial fibrosis and honeycombing. (Perls' ferrocyanide; microscopic magnification, $\times 50$, $\times 1.9$.)

8B. A second exploration in 1970 showed a firm pleural tumor encasing the lung. This epithelial type of malignant mesothelioma consisted of single layers of well-formed, large, regular cuboidal cells with eosinophilic granular cytoplasm and vesicular nuclei arranged in loosely formed tubules, epithelial folds, and papillae. Mitotic figures were very rare, and there was no epithelial mucin. (Hematoxylin and eosin; microscopic magnification, $\times 125$, $\times 1.6$.)

Figure 9. Lung sample from necropsy of Patient 10. There was severe diffuse organization, massive fibrosis, and obliteration of alveolar structures and bronchioles; all sections were filled with nests containing innumerable asbestos bodies (arrows). Many asbestos bodies were within macrophages and giant cells. In other areas there was marked arteriolitis. (Hematoxylin and eosin; microscopic magnification, $\times 31.2$; $\times 1.6$.)



suggested previously (4, 32); [3] early interstitial pneumonitis may be present without either clinical or physiologic abnormalities; and [4] asbestos pleural effusion occurs together with some degree of parenchymal asbestosis oftener than not, in this series in 10 of 12 cases.

PATHOGENESIS AND RELATIONSHIP TO MESOTHELIOMA

The mechanisms of pleural adhesions, basilar pleural thickening, and plaque formation have been studied extensively but remain unexplained. Kiviluoto (3) has suggested that asbestos fibers advance into the lung periphery to penetrate the visceral pleura; with lung movement, the sharp points are said to traumatize the parietal pleura, inducing minute hemorrhages that are later transformed into fibrous, calcagenous, and, finally, calcified plaques. Others have proposed an inflammatory reaction or possibly hypersensitivity (4). The implication of these theories, if any, for asbestos pleural effusion are not known.

The role of asbestos exposure in the development of mesothelioma has been explored extensively since the initial report by Wagner, Sleggs, and Marchand (9). Recent editorials have expressed different but not conflicting viewpoints (12, 13). Our Patient 2 developed clinical evidence of a mesothelioma probably 12 years after his first of many effusions (Figures 2, 3, and 8B). This may have been coincidence, or asbestos pleural effusion may be a precursor to the development of mesothelioma years later, or it may have been a very slowly growing tumor from the beginning, even though thoracotomy 5 years earlier

failed to show such a lesion. Unilateral pleuritic pain for 12 years before the development of a mesothelioma has been reported (25); and an unconfirmed history of self-limited pleural effusion years before clinical evidence of mesothelioma has been recorded among South African asbestos miners (9).

CONCLUSIONS

The diagnosis of asbestos pleural effusion must rest on an effusion that remains otherwise unexplained and a history of exposure to asbestos dust that may have been brief, intermittent, and in the immediate or distant past. An exhaustive occupational history may be required to elicit such exposure. The diagnosis can be confirmed by open biopsy material showing nonspecific pleuritis and thickening without or with rare asbestos bodies and fibers and, usually, an interstitial pneumonitis of various severities, with asbestos bodies. The pleural fluid is a sterile exudate and may be clear yellow to blood-tinged. Examination for sugar, hyaluronic acid, and asbestos bodies or fibers probably will not be helpful. Similarly, because of the nonspecific pleural changes and the rarity of asbestos bodies, pleural needle biopsy is likely to be of interest only to exclude other disorders.

The importance of asbestos pleurisy cannot be judged from our own data, which are not representative; our laboratories are oriented primarily to symptomatic ambulatory referrals. Nevertheless, the 12 cases presented here emphasize that asbestos pleural effusion may not be an uncommon manifestation of asbestos exposure. These cases represent more than 20% of all patients with recognized asbestos expo-

sure studied in our laboratories. The increased myriads of asbestos (12, 13, 35), together with increasing clinical and radiographic surveillance of asbestos workers, make it likely that benign pleural effusion associated with asbestos exposure will be recognized with increasing frequency.

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