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Case Reports

Asbestosis and Bronchogenic Carcinoma*

Report of One Autopsied Case and Review of the Available Literature

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THERE are several reasons for presenting in detail a case report and a review of the available literature dealing with the relationship between occupational exposure to asbestos and respiratory tract malignancy. The apparent increase in bronchogenic carcinoma, especially in males, reported in the past decade has led to scrutiny of respirable dusts as possible etiology. Most English observers[1-3] are satisfied that there is a statistically significant increase in pulmonary malignancy among asbestos workers. Some American writers consider that the experience to date does not support this contention.[4,5] The work of Graham,[6,7] Doll and Hill[8] and Ochsner[9,10] has created much interest in the correlation of cigarette smoking with bronchogenic carcinoma. E. R., whose case is herein presented, was exposed to harmful amounts of asbestos dust and was a chain smoker. This provides speculation as to the possible role of two etiologic agents.

Few reported cases of lung cancer related to industrial asbestos exposures provide data on the character and quantity of dust exposure. This is a serious deficit in exact study of etiologic correlation. In the clinical report presented herein State authorities have determined by measurement that the asbestos dust exposure of this man during his twelve years of work was considerably above the safe level, which is considered to be five million particles per cubic foot of air for an eight-hour working day.

It is pertinent to this presentation that there are probably about 10,000 workers engaged in potentially hazardous asbestos manufacturing operations in the United States.[11] Middleton reports the number in Great Britain as between 3,000 to 5,000.[12] Most of the industry is engaged in asbestos textile manufacturing producing insulating mattresses, brake linings, fire proof curtains and clothing. The chief operations are disintegration of the crude mineral, carding the fiber, separating the more useful long from the short fiber, spinning, plaiting and weaving the asbestos, often with cotton. Insulating material is produced by mixing magnesia, diatomaceous earth and other materials with asbestos to make cements or fillings for insulating boilers, engines and pipes. Other non-textile asbestos products so made include asbestos cement, sheets, brake and clutch linings, electrodes and switchboard panels.

Asbestos is a hydrated magnesium silicate. The chief supplies are in Canada, Cape Province, Italy, Rhodesia and Russia. Asbestos dust given off in manufacturing processes consists of fragments of fibers and small rounded or angular particles. Actual studies in industry show the size and shape of the particles of asbestos to be such as may gain entrance into the bronchioles.[14] Experience has led to the acceptance of five million particles of asbestos per cubic foot of air, of small enough size to be respirable, to be the safe working concentration.

Some operations because of their dustiness are more hazardous than others in asbestos manufacturing. Bagging the asbestos, separating the long from the short fibers, carding, spinning and weaving show a greater statistical evidence of asbestosis than do other operations. As might be expected, the longer the duration of exposure the greater the number of cases. In the Merewether and Price series there was one case under four years' exposure, and up to 53.6 per cent with fifteen to nineteen years' exposure.[15]

CASE REPORT

E. R. (MGH #735586),[16] a forty-one year old asbestos mill worker, entered the Massachusetts General Hospital in April, 1951. The chief

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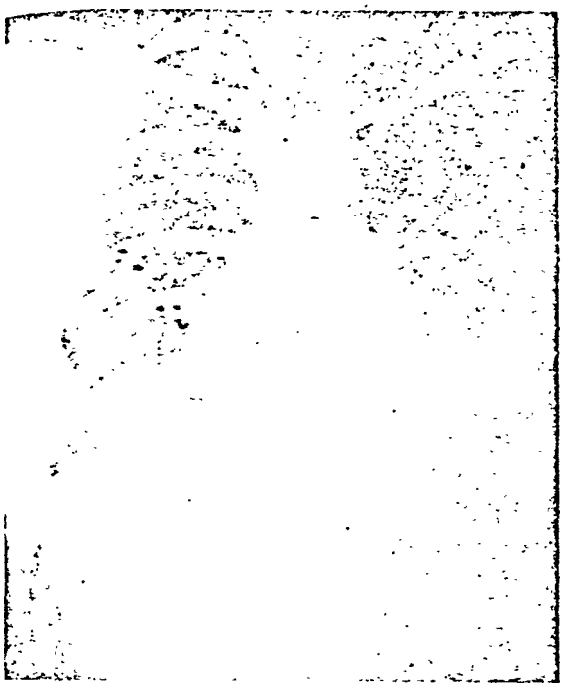

FIG. 1. X-ray of chest. The lower lobes are reduced in size and show a "honeycomb" pattern. There is an increase in linear and nodular markings. A density is seen in the region of the lingula with enlargement of lymph nodes in the left lung root, suggesting a tumor in that area.

complaint was progressive low back pain which had been present for four months and was only partially relieved by aspirin. In addition, one month before admission the patient noticed increasing dyspnea on exertion, a worsening of his chronic productive cough, night sweats, anorexia, feverishness and a 10-pound weight loss. He had worked in an asbestos mill for about twelve years but had stopped working there for two years prior to this hospital admission. In the mill he had spent one year in the "picker room" where crushing, grinding and sorting of long asbestos fibers was carried out. He also worked five years in the carding room where the concentration of fibers had been determined by authorities to be considerably above the safe level. He used one can of snuff and smoked on an average of one to two packs of cigarettes daily for many years. For seven or eight years he had been aware of clubbing of his fingers; one flight dyspnea was present for about two years. There had been no hemoptysis.

Physical examination revealed a chronically ill and dyspneic man with evidence of weight loss and cyanosis of the lips and nail beds. The blood pressure was 110/75, pulse 96, respirations 30, and temperature 99°F. orally. His chest was thin and showed poor expansion. There were dullness and reduced breath sounds at both lung bases with sticky inspiratory crackling rales over the region of the left lower lobe. The left border of cardiac dullness was 10 cm. to the left of the midsternal line in the fifth interspace; there were occasional extra systoles; P_2 was greater than A_2; there was some pulsus paradoxus. Liver and spleen were not felt. There was tenderness of the spine over L-4 with spasm of the lumbar musculature. He had extreme clubbing of fingers and toes.

TABLE 1

PULMONARY FUNCTION STUDIES* BEFORE AND AFTER ACTH†

	Before ACTH	After ACTH	Approximate Normal Values‡[10]
Vital capacity (L.)	2 4	2.18	3 9
Maximum breathing capacity (L./min.)	52 5	79 5	105
Residual volume (L.)	1 575	1 49	1 30
Effective alveolar ventilation (L./min.)	7 63	5 48	5 02
Alveolar pO_2 (mm Hg)	115 0	105 0	105 107
Arterial pO_2 (mm Hg)	88 0	76.0	95–97
Arterial pCO_2 (mm Hg)	36 0	42.0	40–43
Arterial O_2 saturation (%)	97 3	94 4	95–97
Serum pH	7 45	7 42	7 39
Alveolar-arterial O_2 difference (mm Hg)	27.	29.	10.

* These studies were performed by Dr. John Affeldt, Department of Physiology, Harvard School of Public Health

† ACTH 100 mg. intramuscularly for ten days

‡ Body surface area was 1.62 sq. m.

Laboratory data revealed a normal urinalysis. Hemoglobin was 14.0 gm. per cent and the white count was 5,700, with a normal differential. Chest x-ray revealed the lower lobes reduced in size and showing a honeycomb pattern. (Fig. 1.) There appeared to be a homogenous density in the lingula with enlargement of lymph nodes in the left lung root suggesting a tumor in the region of the left lower lobe. Films of the spine indicated areas of increased and decreased density in the fourth lumbar vertebra giving the appearance of metastatic malignancy. Electrocardiogram showed non-specific T wave changes. Non-protein nitrogen was 27 mg. per cent, CO_2 29.4 mEq./L., alkaline phosphatase 4.9 Bodansky units. Repeated examinations of the sputum were negative for acid-fast organisms, asbestosis bodies and malignant cells. Two bronchoscopies revealed obstruction of the left lower lobe bronchus. The patient was given a trial of ACTH 100 mg. daily intramuscularly

for ten days. Clinically there was no change except for euphoria. Pulmonary function and cardiac catheterization studies were performed before and after ACTH and likewise showed no significant changes. (Tables I and II.) Cardiac catheterization did reveal chronic cor pulmonale with slight pulmonary hypertension; after exercise the pulmonary hypertension increased and significant arterial oxygen unsaturation appeared.

Before discharge from the hospital he received radiation (1,200 r) to the lumbar spine with no relief of the back pain.

For several weeks after discharge the patient seemed somewhat better and returned to light work. However, the cough increased markedly and he had severe dyspnea at rest so that after two months he had to be readmitted. Physical examination on re-entry revealed a temperature of 100.4°F. rectally, pulse of 120-144, respirations 30 per minute. He had marked tachypnea, moderate cyanosis and such dyspnea that it was very difficult for him to speak. There were many inspiratory and expiratory wheezes throughout the lung fields. At the right base there were moist bubbling rales together with dullness, reduced tactile fremitus and increased vocal fremitus. The left border of cardiac dullness now extended out 12 cm. from the midsternal line. P_2 was much louder than A_2. The liver was percussed down two and a half fingerbreadths and there was 2 plus ankle edema. At this time the white blood count was 6,500, hemoglobin 11.5 gm. per cent.

It was believed that the patient had pneumonitis in the right lower lobe and early cor pulmonale with congestive failure. He was digitalized, given mercurial diuretics, antibiotics (penicillin and streptomycin), and was in an oxygen tent most of the time. Chest x-rays now were suggestive of lymphatic spread of tumor. In spite of all therapeutic measures fever, dyspnea and cyanosis grew worse. He became confused and died on the thirty-fourth hospital day.

TABLE II

CARDIAC CATHETERIZATION STUDIES* BEFORE AND AFTER ACTH†

	O_2 Consumption (cc./min./sq. m.)	O_2 Capacity Radial Artery (cc./100 cc.)	O_2 Content Radial Artery (cc./100 cc.)	O_2 Saturation Radial Artery (%)	Pulmonary Artery Pressure (mm. Hg)	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Index (L./min./sq. m.)
Approximate normal values[36]	145	20.0	19.0	96	30/10	15	3.2
Before ACTH — Rest	180	19.3	18.1	94	36/14	21	4.47
Before ACTH — Mild exercise (2 min.)	370				43/14	28	5.55
After ACTH — Rest	156	17.4	16.6	95	38/15	23	4 02
After ACTH — Mild exercise (2 min.)	349				52/22	36	6 97

* These studies were performed by the Cardiac Catheterization Unit of the Massachusetts General Hospital including Drs. G. S. Myers, A. L. Friedlich, J. R. O'Neill, G. Cohen and J. G. Scannell.

† ACTH 100 mg. intramuscularly for ten days.

At necropsy the patient was emaciated; the thorax was lengthened in the anteroposterior diameter. There was clubbing of the fingers and toes.

On opening the thorax the lungs did not collapse but remained inflated, completely filling both pleural cavities. The majority of the pleural space was obliterated bilaterally by dense fibrous adhesions between the visceral and parietal layers. Both the visceral and parietal pleurae were markedly thickened, gray fibrous membranes measuring up to 0.3 cm. thick. There were 100 cc. of clear straw-colored fluid loculated in the left base. The interlobar fissures were obliterated by fibrous tissue. Scattered throughout the adherent layers of the diaphragmatic pleura, especially on the right, were a number of whitish gray, shiny plaques 0.5 cm. long; these resembled similar plaques

FIG. 2. Cut surface of left lung after formalin fixation. Note diffuse pulmonary fibrosis and marked pleural thickening which obliterates the interlobar fissure.

FIG. 3. Asbestosis bodies in the lung. The club-shaped, beaded asbestosis bodies are seen in the alveolar ducts, surrounded by macrophages and "dust cells"; × 900.

seen on the upper surface of the liver, to be described. The lungs weighed 2,710 gm., were voluminous and very firm throughout; no discrete nodules could be felt. (Fig. 2.) Multiple sections showed a uniform brownish gray surface throughout except in the left lower lobe where there appeared to be a diffuse marked fibrosis throughout the parenchyma. The left lower lobe bronchus was completely occluded 1 cm. from its origin by pinkish gray, firm tissue for a distance of 1.4 cm.; here the bronchus measured 0.7 cm. in diameter; the firm pinkish gray tissue extended into the parenchyma for a distance of 1.7 cm. Similar tissue extended from this point in the bronchus to the pleura and into the wall of the left atrium which was adherent to the pleura at this point; the gross atrial involvement measured 2.3 by 0.7 cm. in extent. The upper lobe bronchi were rigid and narrowed by a thick, white fibrous tissue. The right lower and to some extent the right middle and left lower lobe bronchi were dilated, and there was collapse of the intervening parenchyma. The veins and arteries appeared normal.

There were adhesions between the visceral and parietal pericardium both at the apex and the base. The apical adhesions were thin fibrous strands but those at the base were extensions of the firm tissue described in the left lower lobe bronchus. The heart weighed 360 gm. There was involvement of the left atrium and auricle by thick, firm, grayish pink tissue for an area measuring 2.3 by 0.7 cm. The remaining myocardium appeared uninvolved and measured 0.6 cm. thick in the right ventricle, 1.3 cm. in the left. The endocardium and valves were negative.

The diaphragms contained firm grayish pink areas of plaque-like thickening which measured up to 0.5 cm. in diameter. These were seen on both the pleural and peritoneal surfaces, were apposed and loosely adherent to similar confluent areas in Glisson's capsule. The remaining organs, with the exception of the fourth lumbar vertebra, were negative. This vertebra appeared opalescent and resembled marble, but its consistency was softer than the adjacent vertebrae. The body appeared to have increased porosity.

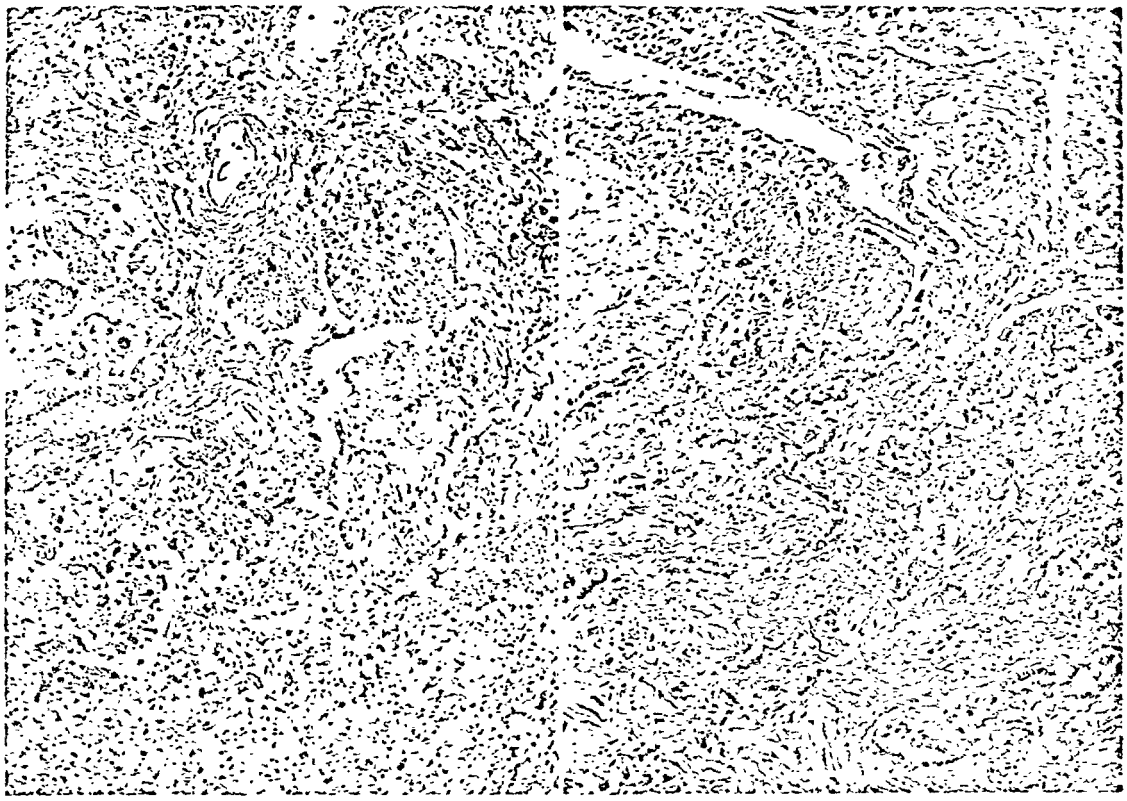

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FIG. 4. Squamous metaplasia in the alveolar ducts; note also asbestosis bodies and interstitial fibrosis; × 100.

FIG. 5. Adenocarcinoma invading the myocardium; × 100.

The lungs were sectioned topographically; sections from all segmental bronchi were taken near the hilum, the mid-lobar and the peripheral areas. These basic histologic patterns could be seen:

Fibrosis: Throughout the lungs there was proliferation of fibrous tissue around the bronchi, the arteries, alveolar ducts; the interlobar septa and pleurae were also thickened. There was peribronchial and alveolar duct fibrosis in both apices, and slight alveolar wall thickening as demonstrated by connective tissue stains. The fibrosis increased in the remaining portions of the lungs, was heaviest in the hilar and mid-lobar areas but extended to the periphery. This confirmed the gross impression of diffuse fibrosis.

Asbestosis bodies: Asbestosis bodies were present in all sections. (Fig. 3.) These were segmented fibers averaging 50μ long, some straight and some club-shaped, others resembled dumb bells which stained dark brown on hematoxylin-eosin preparations, and blue on Prussian blue (iron) preparations. Particles of iron-staining dust and larger, easily identifiable asbestosis body particles, were present in the macrophages. The distribution was equal bilaterally, being slight to moderate in the apical segments, quite marked in the remainder of the lung and occurring with equal intensity in the hilar, mid-lobar and peripheral zones.

While most of the asbestosis bodies were seen in the bronchioles and alveolar ducts, a few could be seen in the alveoli, and fragments were found both in the macrophages and in the lymphatics. Several aggregations of asbestosis bodies were found in the bronchi. Fragmented asbestos fibers were found mostly in the macrophages but occasional iron-staining particles were found free on the alveolar walls. Much, but by no means all, of this material in the macrophages took the iron stain.

Inflammatory response: The chief inflammatory cells responding to the irritant were the macrophages. These cells were seen in abundance in every section; they lined up along the walls of the alveolar ducts, filled the lumina of bronchioles and alveoli, and were found throughout the septa and fibrous tissue. Most of these con-

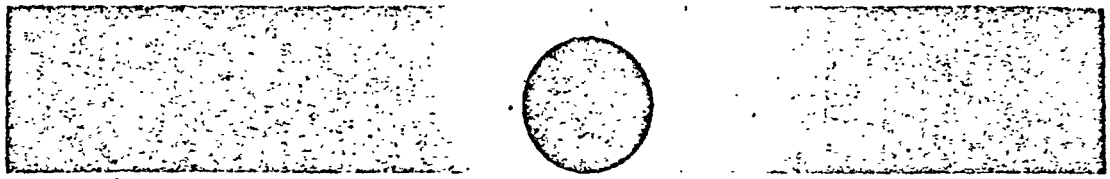

FIG. 6. X-ray diffraction film of lung residue of E. R.* The lines listed when compared to the known pattern for asbestos give positive proof that the lung residue is essentially asbestos.

Table of "D" lines:

4.52	2.42	1.61
4.20	2.38	1.531
3.35	2.115	1.49
2.98	1.84	1.44
2.67	1.70	1.38

* A 68.5 gm. sample of formalized lung tissue was digested in 20 volumes hydrogen peroxide, the digestion being accelerated with gentle heating. The residue from the digestion was treated with dilute hydrochloric acid, filtered, washed and ignited at 500°F. The ignited residue was analyzed by x-ray diffraction by the method described in the article by Hanawalt, J. D., Rinn, H. W., Frevel, L. K., "Chemical analysis by x-ray diffraction," *Indust. & Eng. Chem., Anal. Ed.*, vol. 10, no. 9, 1938. This work was done by R. I. Chamberlin and A. Woewucki, Jr. of the Massachusetts Bonding and Insurance Company, Boston, Mass.

tained brown pigment granules many of which took an iron stain, and portions of asbestosis bodies were also found in the macrophages. (These cells have been called dust cells and are thought to lay down the iron on the asbestos fiber, constituting the asbestosis body.) Anthracotic pigment was also present in the macrophages. Multinucleated giant cells of the foreign body type were found in abundance in all areas; many of these contained birefringent asteroidal bodies. Few lymphocytes were seen; those present were scattered around the bronchi near the hila. A few focal areas of bronchopneumonia with polymorphonuclear infiltration were present; these had no particular relation or location to any grouping of the asbestosis bodies and were undoubtedly a terminal phenomenon.

Throughout the lungs many air sacs were dilated and contained a granular eosinophilic material, probably fibrin. Some of these plugs were undergoing organization, mainly in alveolar ducts; this type of fibrosis probably accounts for a small percentage of the total fibrosis seen.

Bronchi: The bronchi of the lower lobes showed marked bronchiectasis; there was dilatation, fibrosis of the muscular coat and peribronchial fibrosis. While the latter was most marked in the lower lobes it was seen in the hilar and midzonal regions of almost all segments. Another striking feature was widespread squamous metaplasia of the bronchial epithelium. (Fig. 4.) This was most marked in the alveolar ducts; it was found in all areas and was not particularly related topographically to the adenocarcinoma described later.

Blood vessels: The arteries and arterioles of the right middle and both lower lobes showed moderate intimal thickening with hyalinization and narrowed lumina. This was most marked near the hila but was found occasionally farther into the periphery.

Tumor: Adenocarcinoma was found originating in the inferior lingual segment of the left upper lobe bronchus. The tumor was present in the mid-zonal area of the apical posterior segment of the left upper lobe, the entire lingula and left lower lobe, as well as the right middle and lower lobes. It had spread by submucosal and lymphatic routes. Sections of the left atrium showed direct extension through the left hilum into the pericardium and myocardium. (Fig. 5.) Metastatic tumor was seen in the fourth lumbar vertebra.

Asbestos "granulomas": The white plaques described in the diaphragm and Glisson's capsule were made up chiefly of hyalinized connective tissue. No asbestosis bodies or giant cells were seen. These distinctive areas grossly suggested granulomas.

X-ray diffraction studies were carried out on a sample of formalized lung tissue. The resulting pattern indicated that the lung residue was mostly asbestos. (Fig. 6.)

COMMENTS

Asbestosis may be defined as a specific occupational disease caused by the inhalation of asbestos fibers and leading to a progressive fibrosis and scarring within the lungs.[17] It has been demonstrated by Gardner[20] and again by

Vorwald[18] that usually the disease will not occur with fibers less than 20μ in length or a concentration below five million particles per cubic foot of air.

The pathologic processes resulting from the inhalation of asbestos particles are believed to be due not to their chemical nature but, rather, the consequence of mechanical irritation from fibers lodged in the respiratory tree.[18–20] The inhaled particles are, in general, too large to pass beyond the respiratory bronchioles and so they remain there to initiate a foreign body reaction which eventually leads to fibrosis.[21] The pathologic sequence of events can be considered as occurring in three stages: (1) desquamation and exudation, (2) formation of asbestosis bodies and (3) fibrosis and scarring.

The long fibers traumatize the epithelial cells lining the smaller bronchioles and the constant irritation and friction cause the cells to desquamate. Macrophages pour forth in an effort to phagocytize the fibers. In our case fragmented asbestosis bodies were also seen within macrophages and lymphatics. A second reaction to the asbestos fiber in the lung is the production of the so-called "asbestosis body."[22–24] This results from a reaction occurring between the asbestos particle and surrounding tissues. It is a thickening of the fiber due to the deposition along its course of a protein matrix containing iron which probably serves to reduce the chronic irritation.[25] These bodies may be found in the sputum, lung, pleura, lymph nodes and spleen.[25] Their presence is held to be evidence of exposure to asbestos but by themselves are not necessarily an indication of asbestosis.[17,27,28]

The third and most significant tissue response is the production of fibroblasts and the deposition of collagen about the distal bronchioles and alveoli. There ensues a diffuse fibrosis which compresses the alveoli and capillaries, resulting in complete obliteration of the involved pulmonary tissue. This process is more pronounced in the lower lobes of the lung for it is there that the particles are most abundant. By x-ray one sees a fine, ground glass or granular pattern in the lower lobes and frequently emphysema in the upper lobes.

The sequence of pathologic events described previously occurs slowly. In man the fibrosis tends to progress even after the exposure has ceased; however in animals this does not seem to be the case. It may be that intercurrent infection contributes to the progression in man.[18]

In general there is a delay of five to seven years between the initial exposure to high concentrations of asbestos dusts and the onset of clinical asbestosis. The average interval reported by Merewether is eleven years.[17] While most patients with asbestosis have had an exposure of ten to sixteen years, it is important to realize that the disease has occurred with as short an industrial exposure as 0.5 years.[1,2]

Usually no symptoms appear until a large part of the respiratory reserve has been reduced by the fibrosis. Merewether has frequently commented how markedly the lungs can be affected and yet the patient be fairly comfortable.[17] However, when symptoms once begin and significant dyspnea becomes apparent, there is usually a definite and rapid progression. Then productive cough, anorexia, weight loss and fatigue are the common complaints. Death eventually results from intercurrent infection, cor pulmonale or carcinoma of the lung.

The case herein presented demonstrates many of the significant features in the pathogenesis, symptomatology and natural course of asbestosis. The patient had worked for twelve years in an atmosphere having a concentration of asbestos particles known to be sufficient to produce pulmonary pathology. However, it was only during the last year of life that dyspnea, cough, anorexia and weight loss manifested themselves. Clubbing had been present for at least five years. He had a very rapid downhill course, due undoubtedly to the two associated factors—the asbestosis and carcinoma of the lung. The physical findings of clubbing, cyanosis and dullness at the lung bases were all consistent with asbestosis as were the x-ray findings in the lungs, apart from the evidence suggesting neoplasm. The outstanding symptom, the severe and progressive dyspnea, was attributed to a combination of pulmonary fibrosis, superimposed and spreading lung neoplasm, pulmonary infection and finally congestive failure on the basis of cor pulmonale.

As indicated in the case history, the ten-day period of ACTH therapy was accompanied only by euphoria but objective measurements revealed no significant changes. This was not surprising for two reasons: (1) the fibrosis had obviously been of long duration and therefore one would not expect it to change much at this time; and (2) he had superimposed bronchogenic carcinoma. It is of interest to compare these results to patients with chronic beryllium

poisoning who usually show a favorable response to steroid therapy.[2,3]

Two further aspects of this case merit more detailed consideration and analysis: (1) the pulmonary function and cardiac catheterization studies; and (2) the significance of the superimposed bronchogenic carcinoma.

PULMONARY FUNCTION AND CARDIAC CATHETERIZATION STUDIES

Table 1 indicates, as one might expect, that the patient had a reduction in vital and maximum breathing capacities. However, the finding of an alveolar-arterial oxygen gradient of 27 mm. Hg demonstrates that one of the disturbances in pulmonary function was a defect in the diffusion of oxygen from the alveoli of the lungs to the capillaries. This corresponds to the syndrome of "alveolar-capillary block" described by Baldwin, Cournand and Richards[31,32] and again by Austrian et al.[33] This diffusion defect is not surprising when one recalls the fibrosis about the alveoli, alveolar ducts, capillaries and bronchioles that occurs in asbestosis. In order for the patient to maintain a near normal arterial oxygen saturation, a high alveolar oxygen was necessary; and this apparently was accomplished in part by hyperventilation. The patient had an average respiratory rate of 40 per minute at rest. This compensatory mechanism apparently was not adequate during stress or exercise for under those conditions the arterial oxygen saturation fell. There was a considerable degree of pulmonary hypertension and, as in the cases of pulmonary fibrosis studied by Cournand and his associates, a rise in the pulmonary artery pressure occurred with exercise. (Table II.) The partial pressure of carbon dioxide in the blood (36 mm. Hg) was low normal rather than elevated. Had there been a defect in alveolar ventilation, the pCO_2 would probably have been higher. As Arnot emphasized in discussing this case[16] carbon dioxide is not impaired in its transfer from the blood to the alveoli because of its great diffusion capacity. This speed of diffusion plus the increased alveolar ventilation no doubt accounted for the lowered pCO_2 value.

ASBESTOSIS AND CARCINOMA OF THE LUNG

The association of asbestosis and carcinoma of the lung has been mentioned frequently in the literature.[1–3,34–53] Heretofore some authors have believed that the cases were too few in number to be of significance; others, especially Vorwald and Karr, have stated that "inhaled dusts, except those containing recognized carcinogenic substances (as radium and tar) cannot in general be considered as etiologic factors in the development of primary pulmonary carcinoma."[54] Our conclusion at present is in favor of the concept that the association of bronchogenic carcinoma with asbestosis is more than coincidence. That there is a significant incidence of bronchogenic carcinoma in asbestosis is apparent from Table III.

TABLE III
INCIDENCE OF ASBESTOSIS AND CARCINOMA OF LUNG

Author	No. of Deaths with Asbestosis	No. Due to Cancer of Lung	Incidence (%)
Merewether[1]	235	31	13 2
Wedler[45]	92	15	16.3
Wyers[3]	115	17	14 8
Lynch, Cannon[47]	40	3	7.5
Gloyne[3]	121	17	14 1
Total	603	83	13 8

Merewether has cited the largest series—of 235 cases of asbestosis there were thirty-one with bronchogenic carcinoma, or 13.2 per cent.[1] An average of the five analyses recorded in the literature is 13.8 per cent. This is considerably higher than the incidence of lung carcinoma in routine necropsies, which in a comparable period (1935–1948) ranged from 0.8 to 2.4 per cent.[9,47,54]

In contrast to asbestosis the incidence of bronchogenic carcinoma in silicosis as recorded in the two largest series has been similar to what might be expected in the general population. The data compiled by Merewether[1] and the Miner's Phthisis Medical Bureau of South Africa[55] are based on a total of 6,884 and 1,438 autopsied cases of silicosis respectively, and disclose an incidence of lung carcinoma of 1.32 and 0.70 per cent. Vorwald and Karr found two lung carcinomas in 136 silicotics (1.47 per cent). Klotz[56] noted an incidence of 8 per cent, but his series of fifty cases does not seem large enough to be statistically significant. However Gloyne[3] in reviewing necropsy material from 1929 to 1949 (796 cases) also described the surprisingly high incidence of lung carcinoma in silicosis of 6.9 per cent, and 7.7 per cent in

the pneumoconioses as a whole. In this same series 8.3 per cent of cases without any pneumoconiosis had cancer of the lung. Merewether and Gloyne's cases were analyzed over a comparable period of time so that it seems unreasonable to interpret the figure of 6.9 per cent as reflecting the increase of lung carcinoma in the general population. The discrepancy in the data probably is explained by the fact that Gloyne's material was selected from the pneumoconioses in which the histories and x-rays were "unusual."

Gloyne noted that 14.1 per cent of patients with asbestosis had lung carcinoma. This figure parallels the observations of previous workers and is significantly above that recorded for silicosis. As has been mentioned the asbestos particle probably acts as a mechanical irritant while the pulmonary changes in silicosis are considered due to the chemical properties of silica.[18,20]

Carcinoma of the lung appears to be prominent in females with asbestosis. Of Merewether's thirty-one cases nine were females, or 29 per cent, and in Gloyne's series of seventeen cases the incidence was 41 per cent. In the published autopsy reports data as to the sex of the patient are available in twenty-three, of which five (21 per cent) were females. In contrast, the incidence of bronchogenic carcinoma in females in the general population is considerably lower. Lindskog noted an incidence of 4.0 per cent,[57] Graham[7] 5.4 per cent, Doll and Hill[6] 8.4 per cent and Ochsner[10] 10.3 per cent. The higher figure in asbestosis supports the theory that asbestos particles act as carcinogens.

Experimental production of neoplasms has demonstrated that chronic irritation of body tissues by mechanical means may predispose to the development of malignancy. Asbestos particles when lodged in the finer bronchioles serve as mechanical irritants to the bronchial epithelium. The squamous metaplasia of the lungs found frequently in asbestosis is presumably a consequence of prolonged irritation in the lower respiratory tract. Some pathologists consider squamous metaplasia as an alteration in the cellular structure that may precede or be the initial step towards the development of squamous cell carcinoma.[58]

A "lag period" between the exposure to a possible carcinogen and the onset of malignancy is characteristic. Nordmann[58] noted in his cases that the average duration between the initial exposure to asbestos and the development of bronchogenic carcinoma was about eighteen years. Similarly Merewether[1] found that patients dying of carcinoma of the lung had a longer mean exposure to asbestos (16.5 years) than those dying with no evidence of malignancy (13.4 years). Finally, a short but "adequate" exposure may be followed by pulmonary malignancy many years later. In Merewether's series is the case of a woman who was an asbestos worker for only six months yet later developed lung carcinoma. Gloyne[35] reported the case of a woman with an exposure of nineteen months who died fifteen years later at the age of seventy-one with a squamous cell carcinoma of the right lower lobe.

Table IV summarizes the pertinent information of the twenty cases of asbestosis with lung carcinoma that have been autopsied and recorded in the available literature. Four cases have been added to the list compiled by Homburger[46] in 1943. It is noted that in about four-fifths of the cases in which the primary site is indicated the origin of the neoplasms was in the lower lobes. This is in contrast to the general population where bronchogenic carcinoma seems to be more frequent in the upper lobes. In Lindskog's[59] series there was an incidence of 57 per cent in the upper lobes, 26 per cent in the lower lobes. Ochsner[10] found 56 per cent in the upper lobes and 35 per cent in the lower lobes. No conclusions should be drawn from the small number of cases listed in Table IV. Nevertheless, since asbestos particles lodge to a greater extent in the lower respiratory tree where the changes of asbestosis are also more pronounced, a higher incidence of carcinoma in this location should be expected if an etiologic relationship exists. In our case the asbestosis was widespread and severe, and the tumor, which originated in the inferior (lingual) segment of the left upper lobe, was in an area significantly involved by the fibrosis and inflammation of asbestosis.

It is also noted in Table IV that twelve of the nineteen previously recorded cases had lesions of the squamous cell type. The incidence of squamous cell carcinoma is said to be high in male cigarette smokers with pulmonary malignancy.[6] At autopsy our patient showed both squamous metaplasia and adenocarcinoma of the lingula. It may be of significance that he was a chain smoker for over twenty years in view of the observation by Wynder and Graham[7] that males with adenocarcinoma of the lung are

frequently chain smokers. However, it is our belief that the presence of an adenocarcinoma rather than one of the squamous cell type may be explained by the fact that it is not unusual to find several cellular types in various sections of the same tumor.[58] Therefore morphologic differences in cell arrangements may not really represent different etiologic varieties of cancer.

TABLE IV

SUMMARY OF PUBLISHED CASE REPORTS IN WHICH AUTOPSY DATA ARE CITED

Authors	Year	Sex and Age	Occupation	Duration of Exposure (yr.)	Freedom from Exposure before Death	Nature of Tumor	Primary Site	Metastases
Lynch, Smith[34]	1935	M, 57	Weaver	21	4 mo.	Squamous cell	R.L.L.	Many nodules in R.L.L.
Gloyne[35]	1935	F, 35	Spinner	8	9 yr.	Squamous cell	R.U.L.	Pleura
Gloyne	1935	F, 71	Mattress and opening departments	1½	15 yr.	Squamous cell	R.L.L.	None
Egbert, Geiger[37]	1936	M, 41	Weaver	17	2 yr.	Glandular	L.L.L.	Widespread
Gloyne[38]	1936	M, 59	Packer, stores department	10½	? mo.	Oat cell	L.U.L.	L.U.L. and pleura
Nordmann[38]	1938	F, 35	Carder, spinner, weaver	7	9 yr.	Squamous cell	L.L.L.	Liver, kidneys
Nordmann	1938	M, 55	Prespinning assembly room	7	12 yr.	Squamous cell	L.L.L.	Widespread
Lynch,[39] Smith	1939	M, 50	Weaver	13	3 yr.	Squamous with glandular features	R.L.L.	Pleura, mediastinal nodes
Holleb,[41] Angrist	1941	M, 52	Pipe insulator	25	9 yr.	Non-keratinizing squamous celled	R.U.L.	Mediastinal nodes, adrenal, kidney
Holleb, Angrist	1941	M, 50	Pipe insulator	25	10 yr.	Oat cell	R.L.L.	Widespread, including brain
Linzbach, Wedler[41]	1941	M, 61		> 3	Not known	Squamous cell	R.L.L.	None
Desmeules et al.[42]	1941	M, 57	Machine adjustor	25	1 mo.	Alveolar cell	L. lung	Pleura
Desmeules et al.	1941	M, 56	Bagger	22	4 mo.	Squamous cell	R. lung	Pleura
Homburger[45]	1942	M, 45	Not known	5	1 yr.	Squamous cell	R. lung	Diaphragm
Homburger	1942	M, 43	No. known	20	17 mo.	Anaplastic	L.L.L.	Pleura
Homburger	1942	F, 49	No known contact with asbestos	Not known		Squamous cell	R. lung	Liver, adrenal, stomach, hilar lymph nodes
Cureton[49]	1948	F, 3?	Pipe coverer	7	15 yr.	Squamous cell	L.L.L.	Pericardium, liver, kidney, ovaries, femur
Owen[51]	1951	M, 39	Asbestos worker	1	20 yr.	Adenocarcinoma	R. lung	None
Stoll, Bass, Angrist[52]	1951	M, 40	Pipe coverer	6	About 4 to 5 yr.	Anaplastic	No definite site	Kidneys, brain, liver
Present authors	1952	M, 41	Asbestos mill worker; sorter	12	2 yr.	Adenocarcinoma	Lingula	Myocardium, pericardium, spine, regional nodes

SUMMARY AND CONCLUSIONS

1. A case of asbestosis with superimposed adenocarcinoma of the lung with metastases, following documented harmful industrial exposure, is presented.

2. ACTH (adrenocorticotrophic hormone) was given with no objective changes in the patient's clinical course.

3. Pulmonary function and cardiac catheterization studies were performed before and after ACTH. They revealed an alveolar diffusion defect and pulmonary hypertension.

4. Asbestos is associated with bronchogenic carcinoma in 13.8 per cent of the cases cited in the literature. In silicosis the incidence is considerably less than this. The asbestos particle may serve as a carcinogen because of the chronic mechanical irritation it produces.

5. Since there are approximately 10,000 workers engaged in potentially hazardous asbestos operations in this country, it is reasonable to assume that there are many unrecognized cases of asbestosis. From the evidence presented a higher incidence of bronchogenic carcinoma should be expected in this group.

Addendum: Since the submission of this manuscript a similar case has been observed by us (MGH #778205). The patient was a forty-six year old contractor's helper whose work since age seventeen consisted of cutting and sawing asbestos board to insulate pipes, boilers and refrigerators. For years he had smoked one package of cigarettes daily. He died after a year of illness during the last four months of which he received 5,000 r of deep x-ray to the left chest.

At autopsy the lungs were firm and weighed 3,350 gm. There was a poorly differentiated adenocarcinoma arising from the left lower lobe bronchus, almost completely replacing the left lower lobe. The tumor had spread to the left upper lobe, hilum, pericardium, pleura and diaphragm; and had metastasized to the right lung and adrenal. The remaining lung tissue showed peribronchial fibrosis, focal alveolar wall thickening and numerous asbestosis bodies, surrounded by macrophages filled with asbestosis body particles and foreign body giant cells. The asbestosis bodies were seen in equal distribution in all parts of the lungs not completely involved by tumor.

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