# Atlas of Occupational and Environmental Diseases

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# Asbestosis and Pulmonary Carcinoma

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Although asbestosis, a disabling industrial disease, has been recognized for only some 50 years, the mechanism by which the dust particles produce tissue alterations in this condition is better understood than for any of the other pneumoconioses. Asbestos, a hydrated magnesium silicate, evokes characteristic abnormalities of the bronchi and bronchioles, alveoli, and pleura as a result of mechanical irritation, and in some 10% to 15% of persons with asbestosis the changes progress to malignant neoplasms.[1]

Asbestosis usually affects persons from whom a history of industrial exposure to asbestos dusts is readily obtained, but instances of the disease occur with increasing frequency in which the circumstances of exposure are not known to the physicians or even to the patient.

Submitted for publication Oct 5, 1964.
Accepted for publication Oct 28, 1964.

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## Report of Case

*A10484, San Francisco Veterans Administration Hospital.*—The patient was a 70-year-old white man who complained of the insidious progressive clumsiness of the left upper extremity, first noted three weeks before admission. The patient had been diabetic for at least five years and was being treated with insulin zinc suspension (Lente Iletin) (45 units per day). The only recorded occupational history is that he had been a pipe fitter; no details were given.

He was an alert, chronically ill man in no acute distress. Blood pressure was 155 systolic and 80 diastolic, pulse, 82 per minute and irregular. Posteroanterior diameter of the chest was increased, there was diffuse hyperresonance, and scattered inspiratory rales were heard over the bases. A grade II systolic apical murmur was noted and auricular fibrillation was present. The liver edge was palpable 2 cm below the costal margin. Strength was diminished in the left upper extremity and flattening of the left nasolabial fold was noted. Chest films (Fig 1 and 2) showed moderate pulmonary emphysema with some increase in bronchovascular markings. Hematologic findings: Hgb, 17.8 gm/100 ml, WBC 11,000/cu mm, and normal differential. Blood chemistry analytical results: BUN, 16 mg and FBS 229 mg/100 ml. Urinalysis: 1+ albumin, 1 to 6 white blood cells per high-power field.

He seemed to be improving in the hospital until the 11th hospital day when he suddenly became weak and semicomatose. He did not respond to intravenous glucose and died approximately 20 minutes later.

Autopsy: Death had been caused by thrombosis of intracranial and coronary arteries with acute cerebral and myocardial infarction. The lungs

weighed 1,000 gm together and their pleural surfaces were smooth, gray, and emphysematous. Hilus were not present. In the lateral superior region of the upper lobe of the left lung was a subpleural spherical mass measuring 1.5 cm in diameter. This was covered by unbilicated pleural surface.

Microscopically, the pulmonary alveolar spaces as well as the bronchial lumina contained scattered clusters of pigment-laden macrophages and a few asbestosis bodies. Emphysema was manifest by stretched, thinned, and broken alveolar septa creating small cystic spaces. There was perivascular, peribronchial, and nodular interstitial fibrosis. The fibrotic areas contained a moderate amount of anthracotic pigment and numerous typical asbestosis bodies.

Microscopically, the mass in the upper lobe of the left lung was a tumor which originated in an ectane bronchus. It extended in a haphazard and stellate fashion into the adjacent pulmonary parenchyma. The architecture was comprised of immature and atypical squamous cells among which keratin and intracellular bridges were not demonstrable. The nuclei were large and vesicular; some were of relatively gigantic proportions with irregularly clumped chromatin and distinct, wrinkled nuclear membranes. The cytoplasm ranged from colorless to finely granular and amphophilic. Typical asbestosis bodies were numerous both in and about the tumor mass (Fig 3).

## Pathology of Asbestosis

The crystalline asbestos fibers become wedged in the lumens of the respiratory bronchioles, and with the inspiratory narrowing-elongation and expiratory widening-shortening of these tubes through each respiratory cycle the fibers are worked into the walls of the bronchioles. This mechanical irritation accounts for the fibrosis, which at first is peribronchiolar. As the disease progresses, irregular diffuse fibrosis occurs throughout the pulmonary tissues with effacement of alveoli in the areas of fully developed disease. Ultimately, the reactive tissue interferes with lymphatic drainage of the lung and stasis becomes an additional factor predisposing fibroplasia. Increasing flow of lymph toward the subpleural lymphatic network tends to produce irritation of the pleura with attendant pleural thickening and adhesions to the parietal pleura.

The "ground glass" appearance of the lung shadows in films of patients with asbestosis may in part be due to diffuse parenchymal fibrosis and in part to the pleural thickening; in advanced cases pleural-pericardial adhesions and fibrosis may become so pronounced that a characteristic "porcupine-heart shadow" results.[2]

Concomitant with the development of fibrosis, distortion and emphysematous enlargement of many alveoli become prominent. Bronchitis and bronchiolitis become chronic and often lead to bronchiectasis. The dependent portions of the lungs are usually more profoundly affected than the upper halves. This serves as a gross diagnostic point in differentiating asbestosis from the more widespread and nodular alterations of silicosis.

Asbestosis bodies are essential to the microscopic diagnosis of the condition. Some of these structures may lie free in alveoli, but most of them are embedded in fibrous tissues of the walls of alveoli or bronchioles. A few may be surrounded by giant cells of foreign body type. These bodies are comprised of asbestos fibers surrounded by albuminous material, calcium salts, and iron salts. The ends are usually knobbed, while the central regions may be notched. The color is yellow to pinkish red in the usual histologic preparations. A few are as small as 1$\mu$ in length but the majority are 10$\mu$ to 60$\mu$ long.

## Clinical Findings

Dyspnea is usually the first sign of disease, and it seldom occurs with an industrial exposure to asbestos dusts of less than five years. Loss of weight is often marked. Dry cough is common, and more than half of the patients expectorate small amounts of blood-streaked sputum sometime during their illness. Asbestosis bodies may be found in the sputum of most patients by microscopic examination.

The chest becomes emphysematous, and fine crackling rales are present over the lower lobes. Cyanosis and clubbing of the nails are frequently present in patients with moderately advanced disease, and cor pulmonale is often a late complication. Asbestosis does not predispose to tuberculosis, differing in this respect from silicosis.[4]

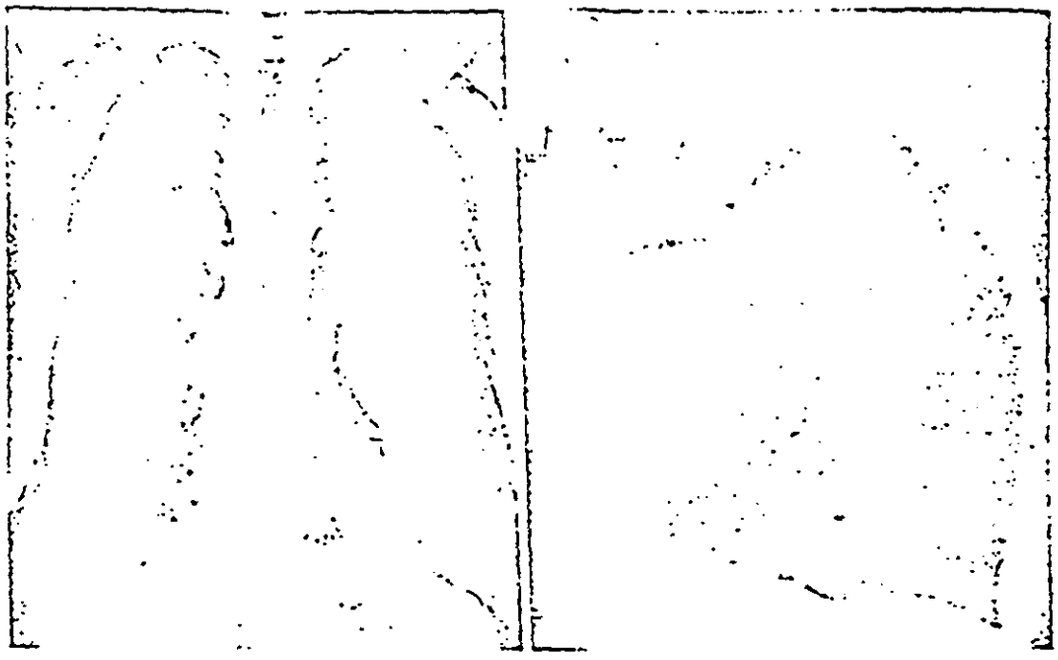

Fig 1 (left) and 2 (right).—Posteroanterior and lateral films of chest at time of admission. Evidences of emphysema with regions of increasing density of bronchovascular markings. There were no recognizable signs of fibrosis, and nodularity is absent.

## Roentgenologic Findings

Attempts to correlate the roentgenographic changes with the physical findings and degree of disability is hazardous in any given case of any of the dust diseases. This axiom is especially true in asbestosis.[4] Pulmonary disability may occur in patients who have the most minimal alterations of the chest films, while others with films reflecting significant pulmonary changes may have little or no rec-

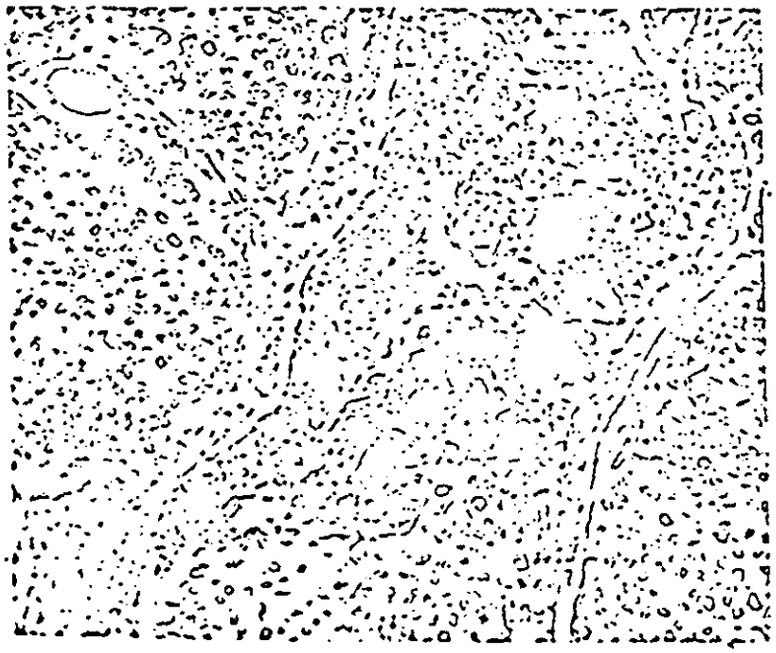

Fig 3A.—Squamous cell carcinoma invading tissues of lung. Distorted alveoli containing phagocytes are in the upper right corner, and several asbestosis bodies are near the center of the field. Hematoxylin and eosin; ×192.

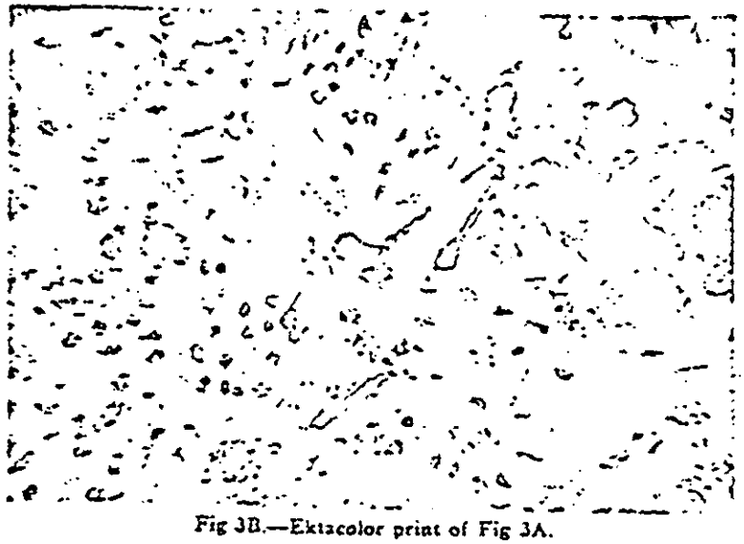

Fig 3B.—Ektacolor print of Fig 3A.

Fig. 3C.—Ektacolor print showing asbestos bodies beneath pleura.

ognizable alteration of lung function. Generally, the first roentgenographic sign of asbestosis is diffuse haziness over the lower third of the lung fields. In more advanced cases this has progressed to a "ground glass" appearance which obscures the bronchovascular markings. Later, the upper portions of the lungs also become fibrotic, but the upper areas always remain more radiolucent than the lower.

### Asbestosis and Carcinoma of the Lung

In recent years it has become clear that there is a more than fortuitous relationship between asbestosis and bronchogenic carcinoma. This belief is based on the following observations: (1) Approximately 13.8% of patients with asbestosis develop squamous cell carcinoma of the lung,[1] an incidence considerably greater than in persons the same age without other lung diseases or who have other pneumoconioses.[6] (2) The cancer is usually in one of the lower lobes where the number of asbestos fibers is greatest. This contrasts with the data from cases of bronchogenic carcinoma not associated with asbestosis, in which the greater proportion are in the upper lobes.[6] Squamous metaplasia of the membranes lining the bronchi and bronchioles is often observed in asbestosis, and the metaplastic cells frequently are atypical with appearances suggesting transition toward carcinoma.

It has also been suggested that asbestosis may predispose to mesothelioma of the pleura. Thirty-three cases of this tumor were observed over a period of four years among South African workers in asbestos mining operations, and one case of asbestosis complicated by pleural mesothelioma has been described in this country.[7]

At the present time, the mechanism by which asbestosis predisposes to neoplasm of the lung or pleura is unknown. Squamous metaplasia of bronchial columnar epithelial cells, predisposing to carcinoma, is known to occur as a result of chronic inflammation from the smoking of cigarettes as chronic endocervicitis can lead to squamous carcinoma of the uterine cervix through the same series of anatomical progression. Mechanical irritation of the asbestos fibers probably leads to squamous cell metaplasia of the bronchi and to bronchogenic carcinoma in the same way.


### Summary

Asbestosis is a chronic progressive pulmonary disease which results from irritation of the lungs by crystalline asbestos fibers.

The disease is often unsuspected clinically because the occupational exposure to dust containing asbestos fibers has not been elicited, and because the chest films may not be diagnostic even in the presence of disabling abnormality.

In asbestosis, pulmonary and subpleural fibrosis distort the lungs and lead to respiratory insufficiency.

Squamous metaplasia of the bronchial epithelium is induced by the irritating fibers, and in some cases there is progression to squamous cell carcinoma of the lung. Pleural mesothelioma is also reported, particularly in cases of asbestosis in South Africa.


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## Editorial Comment

This case presentation excellently illustrates many aspects of the relationship of asbestosis to pulmonary carcinoma. An especially pertinent statement is made in reference to clinical history of previous exposure to asbestos, and well worth repeating "but instances of the disease occur with increasing frequency in which the circumstances of exposure are not known to the physicians or even the patients." Perhaps a positive history of exposure would be obtained more often if the questioner, who is trying to obtain a previous history of exposure to asbestos, was more fully aware of the various industrial processes or products in which a worker might be exposed to asbestos fibers. Asbestos fibers consist of silicate minerals often referred to as amphiboles. Ten percent of the mined rock consists of these mineral fibers which contain complex silicates. The best known sources are located in Canada (about three fourths of the world supply), Rhodesia, South Africa, and the USSR. The complex mineral fibers are removed from the powder and then the long fibers are separated from the short ones. It is during these processes that the most dangerous exposure occurs. The long fibers are used for the manufacture of asbestos cloth and gaskets, while the short ones are used for paper, heat resistant boards, filter pads, and brake blocks and linings, and are increasingly found in plastics. Each year new uses for these fibers are constantly being developed. In the currently reported case, the only occupational history is that the individual had been a pipe fitter. It is conceivable that part of his work was concerned with the use of asbestos-containing coverings for these pipes. This might have been the possible source of exposure in that it may have been necessary for him to saw through this asbestos material and thus produce a certain amount of asbestosis-containing dust.

In this case, the carcinoma was of the squamous type. There seems to be a difference of opinion as to the most prevalent histologic type of carcinoma that is found in association with asbestosis. In this report, it is stated that squamous cell carcinoma is the usual form, whereas Spencer [1] states that adenocarcinoma is the most frequent form. It has become increasingly apparent that pulmonary cancers arising in scars are more frequent than was formerly believed. These are generally adenocarcinomas. Whether or not some substance or substances, as for instance the iron in the asbestosis body, is specifically carcinogenic or whether carcinoma arises because of the nonspecific alterations produced by the asbestos remains to be determined. With the squamous cell carcinoma, it is conceivable that the squamous metaplasia, the bronchiectasis, and the fibrosis caused by the asbestos fibers might impair the lung's ability to effectively rid itself of other carcinogens, and by this process enhance the development of carcinoma. In particular, it would be important to note what proportion of individuals with asbestosis and pulmonary carcinoma were cigarette smokers. At any rate, the incidence of pulmonary carcinoma in individuals with asbestosis in various reports has ranged from 13%-20%. Statistically, this is a highly significant relationship.

Of more immediate interest are the cases of mesothelioma of the pleura that occur in individuals with asbestosis. In a most recent report [2] from Liverpool, England, evidence of exposure to asbestos was noted in 14 of 16 consecutive cases of pleural mesothelioma. Asbestosis bodies were present in lung tissue in ten of these cases. In another study on two patients with mesothelioma, one individual had not been in contact with asbestos for 20 years and in the other case the exposure had been only intermittent and slight. In all individuals with mesothelioma careful search should now be made for asbestosis bodies and fibers in the lung and tumor tissue. It

is suggested that thick frozen sections be used because asbestosis bodies may easily be missed in thin sections.[3] Fibrosis of the pleura with adhesions to surrounding structures is commonplace in asbestosis. The asbestosis bodies produce alterations in the periphery of the lung whereby these bodies gain entrance to the pleural tissues via the peripheral lymphatics in the lung. Because of the occurrence of mesothelioma in association with asbestosis, it is likely that substances in asbestos fibers are specifically carcinogenic. It is unlikely that other inhaled carcinogens would gain access to the pleura and produce carcinoma in tissue previously rendered less resistant by the asbestos. A case of asbestosis in which the individual had both bronchogenic and gastric carcinomas and in which the latter tumor contained refractile granules lends support to this concept of the specific carcinogenicity of the asbestos fibers.

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