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# Pulmonary Asbestosis

*Associated with Primary Carcinoma of the Lung, Bronchial Adenomas, and Adenocarcinoma of the Stomach*

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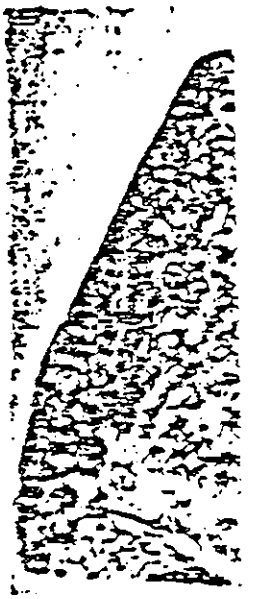
The simultaneous occurrence of asbestosis and carcinoma of the lung has been reported frequently in the literature and has assumed considerable importance in industrial medicine.[1] At the present time most observers believe that there is a statistically significant increase of pulmonary malignancy among asbestos workers. As far as we can determine, however, the coexistence of asbestosis with bronchial adenomas and bronchial carcinoma has not been established. The association of asbestosis with gastrointestinal malignant tumors has been briefly referred to in the literature.[2]

The purpose of this paper is to present a case of asbestosis not only associated with a squamous-cell carcinoma of the lung, but also with 2 bronchial adenomas and an adenocarcinoma of the stomach.

Asbestos belongs to the pyroxene or hornblende group of minerals and is classed with syenite and granite; it is a silicate occurring in minerals in combination with iron, copper, calcium, or magnesium.[3-12] Various types of asbestos differ in chemical constitution and physical characteristics. It is quarried or mined in various parts of the world—Italy and the Mediterranean, South Africa, Rhodesia, and Canada. In its natural state it appears as strands of long silky fibers which are highly resistant to heat, strong acid, and alkalis. These masses are usually broken up into short lengths which are in turn crushed into a fine dust. They are then either mixed with various substances for hardening or used as an inert diluent and filling of a heat-resistant character. Microscopic dark-ground illumination of the asbestos fiber gives the impression of a shiny, brittle, metallic wire broken off at various angles and lengths, which is highly refractile. The asbestos fiber composes the central nidus of an asbestos body upon which colloidal aggregates of blood proteins and iron salts have been adsorbed and molded by currents in the bronchi and alveoli.

## Report of Case

Only pertinent clinical, gross and microscopic changes will be mentioned.* A 65-year-old Negro with the occupation of "plaster mixer" entered Michael Reese Hospital on Dec. 12, 1959, with the chief complaints of a progressively enlarging abdominal mass associated with black stools, hematemesis, anorexia, loss of weight, and a gradual onset of exertional dyspnea, jaundice, and pruritus. Symptoms first appeared 3 months before admission at which time he stopped working. He had worked as a plaster mixer in a casting company for approximately 12 years prior to the hospital admission. In his work he mixed the dry powdered materials used in making the casts. The material was known to contain a certain amount of asbestos and it was known to form considerable dust in the air.



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Submitted for publication Sept. 6, 1960.

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From the Department of Pathology, Michael Reese Hospital and Medical Center.

* We are grateful to Dr. Lawrence Perlman for the use of the clinical history.

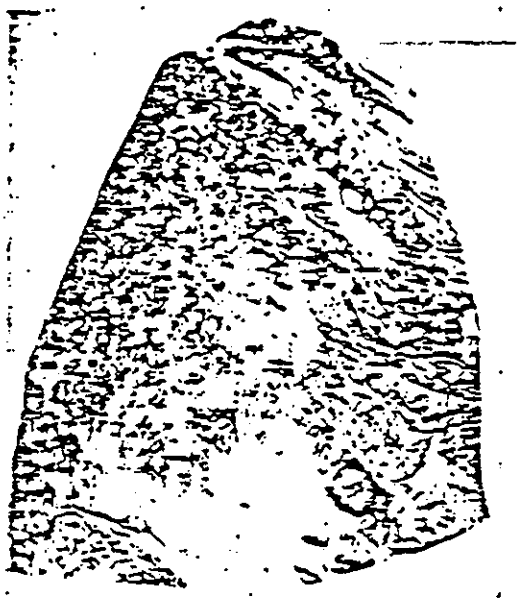

Fig. 1.—Pleural surface of lung, showing thickening and fibrosis.

Fig. 2.—Cut surface of lung showing severe fibrosis, bronchiectasis, and multiple tumors.

Physical examination revealed a chronically ill, emaciated, and jaundiced male, complaining of considerable weight loss and exertional dyspnea. The blood pressure was 90/70 mm. Hg, pulse rate 100/min, respiration 28/min, and temperature 98.6° F rectally. His chest and lungs were essentially normal to percussion and auscultation. A grade 2 systolic murmur was heard at the apex. The abdomen was scaphoid, and a hard, slightly tender mass was felt in the epigastric region. The mass did not pulsate and moved with respiration. X-ray examination of the gastrointestinal tract 2 months prior to admission disclosed an ulcerative prepyloric lesion. However, no x-ray of the chest, to our knowledge, had ever been taken. Hemoglobin was 11.4 gm. % and hematocrit 36%; the urine pH was 6.0 and the specific gravity 1015. There was a large amount of albuminuria but no glycosuria or acetonuria.

During his hospital course, the patient was maintained on intravenous and oral fluids, transfusions, and meperidine (Demerol) for pain. He died on the third day of hospitalization.

At autopsy the patient was severely emaciated and deeply jaundiced. There was extreme clubbing of the fingers and toes. On opening the thorax the lungs did not collapse but remained inflated, completely filling the pleural cavities. The right lung weighed 1,150 gm. and the left 1,000 gm. Both the visceral and parietal leaves of the pleura were markedly thickened and gray (Fig. 1). The visceral pleura in certain areas was covered with a fibrinous exudate. The lungs on palpation disclosed a number of nodular areas which were firm and measured from 3 to 5 cm. in greatest dimension. Between the nodules the lung was air-containing or seemed edematous or diffusely fibrotic. The lungs cut with increased resistance, in general appeared darker than normal, and were the seat of severe anthracosis. On section the nodules were obviously tumor and were gray, soft, and more pronounced in the left lung. The largest measured 5 cm. in greatest dimension and was located subpleurally in the left upper lobe. They varied in color and consistency. Some were slate gray and very firm with minute foci of seeming anthracosis. The larger ones were more gray or pink, presenting a finely granular or somewhat velvety cut surface. In the region of the upper lobes some of the nodules were in close approximation to dilated bronchi. Large foci of emphysema were noted in isolated regions. Tubular bronchiectasis was found in both upper and both lower lobes (Fig. 2). There was an abundant amount of glary, rather thick liquid covering the surfaces made by cutting. A similar material was also noted in the lumen of the tracheobronchial tree. The hilar lymph nodes were markedly enlarged but rather soft and grayish-red.

Random microscopic sections of the lung disclosed architectural obliteration by extensive, diffuse, acute and chronic inflammatory processes. The acute lesions consisted of edema and foci of nonspecific bronchopneumonia with minute multiple abscesses. The chronic lesions were characterized by vast areas of interstitial fibrosis and foci of organizing and organized bronchopneumonia.

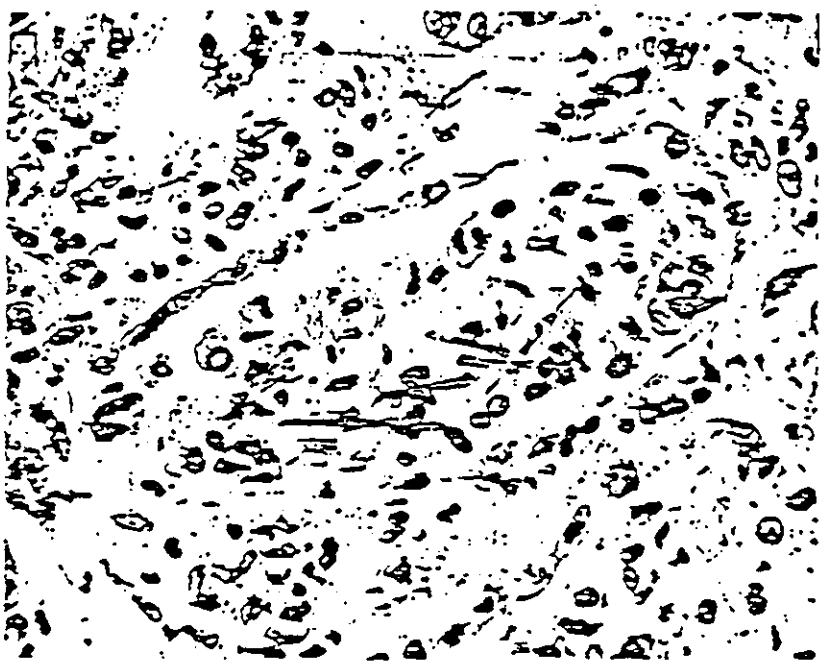

Fig. 3. — Alveolus of lung with macrophage histiocytes and asbestos bodies. Hematoxylin and eosin preparation; reduced 11% from mag. × 450.

There was also marked perivascular and peribronchial fibrosis. Between such areas, foci of emphysema were noted which were more pronounced in the subpleural areas. Within areas of interstitial fibrosis but sometimes also in regions of organized bronchopneumonia, typical asbestos bodies, to be described below, were noted. Adjacent to these bodies, foreign-body giant cells were present, as well as many lymphocytes and histiocytic cells. Asbestos bodies were also noted within alveoli (Fig. 3) either as individual bodies or arranged in small groups. They were often found imbedded in a dense connective-tissue stroma which was present between the alveoli and often also replaced alveoli (Fig. 4).

In a number of fields macrophages predominated. Often the lumens of alveoli and bronchioles were crowded with these cells

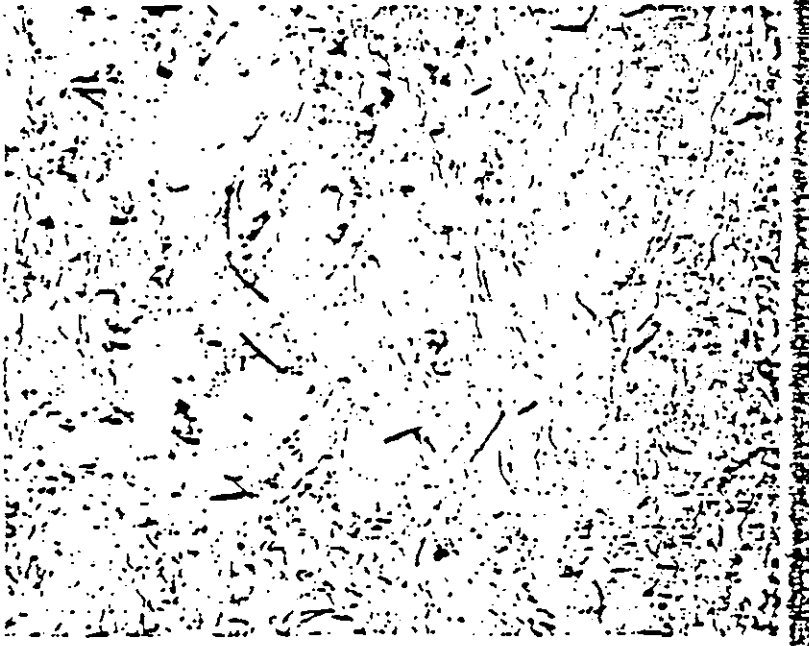

Fig. 4.—Interstitial fibrous tissue and asbestos bodies. Hematoxylin and eosin preparation; reduced 11% from mag. × 170.

Fig. 5.—Asbestos body. Note typical architecture. Hematoxylin and eosin preparation; reduced 11% from mag. × 1,200.

lost of these contained brown pigment granules, some of which gave a positive Prussian blue reaction. Many also contained anthracotic pigment. Aside from granulomas, multinucleated giant cells of the foreign-body type, lymphocytes, and plasma cells were found in abundance in many fields.

In a number of sections outspoken granulomas were encountered. These consisted of central areas of fibrinoid necrosis with a few giant cells and many lymphocytes and histiocytes at the periphery. Asbestos bodies—either intact or appearing as broken-up rods which gave a positive Prussian blue reaction were found either loose within the fibrinoid necrosis or within giant cells.

The asbestos bodies were segmented bodies, straight or club-like in shape, and

Fig. 6.—Asbestos bodies, positive Prussian blue reaction. Reduced 11% from mag. × 900.

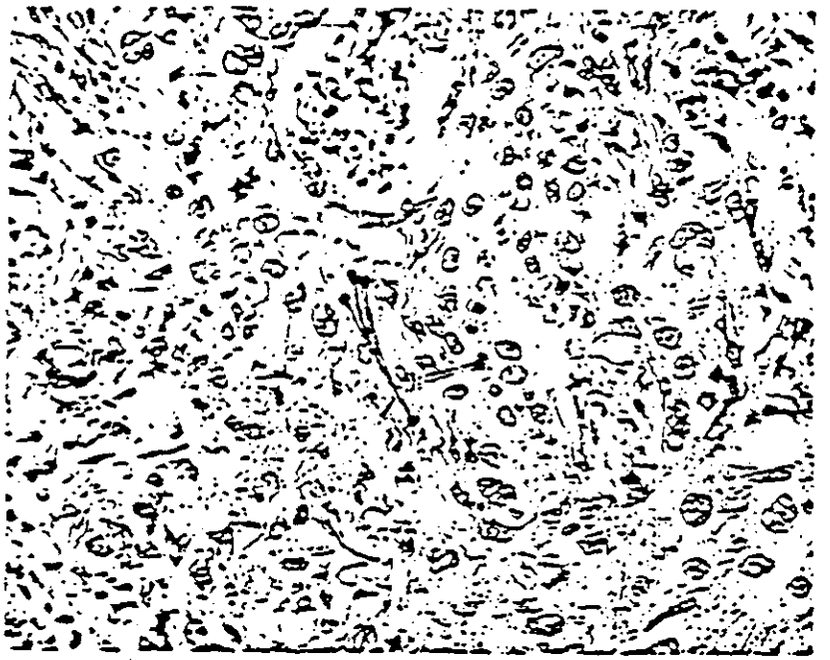

Fig. 7.—Lung: [illegible]mous-cell carcinoma [illegible] asbestos bodies. Hematoxylin and eosin [illegible]ration; reduced 11% [illegible] mag. × 295.

averaged 30μ in length. They were characteristically segmented with bulbous ends and yellow or orange in sections stained with hematoxylin and eosin (Fig. 5). They stained dark blue in sections stained for the presence of iron with potassium ferric cyanide and hydrochloric acid (Prussian blue reaction, Fig. 6). As stated, these bodies were found either imbedded in fibrous connective tissue or in the midst of small granulomas, sometimes engulfed in foreign-body giant cells, and occasionally also [illegible] alveoli.

The small bronchi were dilated, and peribronchial fibrosis was outstanding. A number of smaller bronchi showed focal areas of fibrosis of their muscular coat, combined with an infiltration of lymphocytes and plasma cells. Many blood vessels disclosed a considerable degree of perivascular fibrosis with

Fig. 8.—Lung: bronchial adenoma. Hematoxylin and eosin preparation; reduced 11% from mag. × 170.

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varying degrees of intimal fibrosis. Focal squamous-cell metaplasia of bronchial epithelium extending into alveolar ducts was common.

Sections which were taken from one of the softer nodules of the lung adjacent to the wall of the bronchus and replacing the bronchial mucosa disclosed large foci of rather well-differentiated squamous cells with many atypical mitotic figures and small and larger hyperchromatic nuclei infiltrating the surrounding tissues. Small foci of keratinization were also noted. These fields had the characteristics of a primary squamous-cell carcinoma. Numerous asbestos bodies were present within the tumor mass both lying free and in giant cells (Fig. 7).

Other nodules on microscopic studies showed tumor of an entirely different type. The tumor presented a more or less characteristic alveolar pattern, strands of connective tissue fibers enclosing smaller or larger groups of tumor cells. The tumor cells were relatively large with an indistinct cytoplasm. The nuclei were relatively small, round or slightly oval, and hyperchromatic. Mitotic figures were not encountered. Nowhere were any squamous cells encountered in the tumor nor was there any tendency towards the formation of glandular structures. While the cells somewhat resembled those composing a carcinoid tumor, argentaffine granules could not be identified (Fig. 8). Occasional asbestos bodies were noted.

There was also present a third tumor in the lung. This tumor consisted of small or larger glandular structures composed of low cuboidal cells which varied considerably in size, shape, and staining qualities and showed a number of mitotic figures. These tumor structures were identical with those found in the stomach and obviously represented metastases from the primary adenocarcinoma of the stomach described below.

The liver weighed 2,860 gm. and contained a number of irregular tumor nodules, the largest one measuring 15×15 cm. Grossly these nodules had the characteristic appearance of carcinoma metastases. Microscopically they consisted of adenocarcinomatous structures similar to those found in the stomach.

The stomach was distended and contained a large amount of dark-brown, thick liquid fluid. Just proximally to the pylorus there was a large fungating tumor occupying almost the entire circumference of the stomach. The tumor was ulcerated. On section it extended throughout the mucosa, muscular coats, and into the serosal surfaces.

Fig. 9.—Stomach: primary adeno-carcinoma. Hematoxylin and eosin preparation; reduced 11% from mag. ×70.

Fig. 10. — Highly refractile granules within stomach carcinoma as seen under polarizing microscope. Hematoxylin and eosin preparation; reduced 11% from mag. × 900.

Along the lesser curvature a number of lymph nodes were replaced by tumor. Microscopically the tumor consisted of atypical glandular structures. The absence of basement membranes, marked variety in size, shape, and staining quality of the tumor cells, and large numbers of atypical mitotic figures, were characteristic of adenocarcinoma (Fig. 9). In hematoxylin-and-eosin-stained sections, minute brown pigment granules were seen throughout the tumor as well as small groups of asbestos bodies in the mucosa and on the serosal surface of the stomach. Some of these granules gave a positive Prussian blue reaction and under the polarizing microscope were highly refractile (Fig. 10). In addition, a few bodies closely resembling broken-up asbestos bodies were found lying loosely not only in the mucosa of the stomach but also in the serosal areas.

## Comment

Asbestosis is regarded as an occupational disease caused by inhalation of asbestos fibers which leads to a progressive fibrosis and scarring within the lungs.[10] It has been demonstrated by Gardner[1] and again by Vorwald[12] that the disease will not occur with fibers less than 20μ in length or in a concentration of less than 5,000,000 particles per cubic foot of air. The pathologic processes resulting from the inhalation of asbestos particles are not believed to be due to their chemical nature but rather to the mechanical irritation of fibers lodged in the respiratory tree. The inhaled particles are in general, too large to pass beyond the respiratory bronchioles. They may remain in the respiratory tree and initiate a foreign body reaction which eventually leads to fibrosis.[5] The pathologic sequence of events can be considered as occurring in 3 stages: (1) desquamation and exudation; (2) formation of asbestos bodies, and (3) fibrosis and scarring. In the first stage, the asbestos fibers traumatize the epithelial cells lining the smaller bronchioles, and the constant irritation and friction causes the cells to desquamate. Macrophages aggregate in an effort to phagocytize the fibers. There is a gradual change from the asbestos fiber to the asbestos body formation.[3,12] This is due to the deposition of a protein matrix, containing iron, over the fibers along its core which probably serves to reduce the irritating mechanism of the fibers. Foreign-body granulomas and masses of phagocytic cells are also encountered. The third and most significant tissue response is the production



...ULMONARY ASBESTOSIS

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anced form is asbestosis a conspicuous
nd the sole factor in the fatality.

s not known whether the patient
ted in this paper demonstrated any
ant progressive pulmonary symptoms
ive of the natural course of the
, since no chest x-ray had ever been
However, it is obvious that he had
d approximately 12 years in an atmos-
known to contain asbestos particles,
though the concentration is not known.
presume it was sufficient to produce
asbestosis. It is important to note
ver, the factory at which the patient
nployed may not have been aware of
ncentration of asbestos in the material
which the patient worked, and thus
e chest x-rays were not insisted upon.
Only after the autopsy findings were the employers made aware of the situation, and x-rays of all employees were suggested. The patient had clubbing of the fingers and toes and exertional dyspnea, the duration of which is not clear. The histological features of the lungs were typical of the disease. There was a rapid downhill course due to dissemination of carcinoma of the stomach with severe involvement of the liver and obstructive jaundice. The terminal event was extensive confluent bronchopneumonia. Since the patient was in the hospital only 3 days and had had no previous hospitalization, clinical and laboratory data were meager. An important point to be stressed was that the occupational history of the patient was not contained in the clinical history. Yet the actual facts revealed that the diagnosis, though admittedly difficult because of the complicating carcinoma of the stomach with pulmonary metastases, could only have been thought of with the occupation of the patient carefully noted and investigated.

A 1% saline suspension of a sample of the material used by the patient in his work was injected into the trachea of rats. These rats were killed after one week. Typical foreign-body granulomas were seen in the lungs with thin, long, refractile fibers which had the appearance of asbestos fibers. Because of the short time interval asbestos bodies had as yet not formed.

The interest in this case lies, of course, in the associated findings of the bronchogenic squamous-cell carcinoma, the bronchial adenomas, and the adenocarcinoma of the stomach. In the literature there is a difference of opinion as to asbestos being the cause of lung cancer. Some authors believe that pertinent cases[7] are too few in number to be of significance: others, especially Vorwald and Karr,[14] stated that inhaled dusts—except those containing recognized carcinogenic substances such as tar and radium—cannot in general be considered as etiologic factors in the development of primary pulmonary carcinoma. However, considering the incidence of carcinoma among the cases with asbestosis (an average of 13.8% in 5 analyses recorded

in the literature) and comparing this incidence with that of bronchogenic carcinoma of the general population, the former is much higher. Gloyne [6] reported an incidence of 6.9% of primary carcinoma of the lung in silicosis and 6.7% in other forms of pneumoconiosis.

It is usually agreed that among the general population bronchogenic carcinoma is much rarer in the female than in the male (4.4 males to 1 female [6]). Ochsner [11] stated that from statistical studies the highest incidence of pulmonary carcinoma in the female was 10.3%. Among asbestos workers, however, the incidence of pulmonary carcinoma in the female was 2% as quoted by Merewether [10] and 41.2% as quoted by Gloyne.[6] These figures may be even more significant if one realizes, as Gloyne [6] remarked in his series, there are in general more female workers in the asbestos industry than male workers.

The average time interval between the initial exposure to the asbestos dust and the development of bronchogenic carcinoma is 16-18 years. Also, a short but intensive exposure to asbestos dust may cause pulmonary carcinoma long after the exposure has ceased. One of Gloyne's patients, a female, who was exposed only 19 months died 15 years later with a squamous-cell carcinoma of the lung. As to the site of carcinoma, it has been noted that in four-fifths of the patients in whom primary site is indicated, the origin of the neoplasm was in the lower lobes. Rohlig and Jacob [3] found carcinoma in the upper lobe in only one-third of their cases. This is in contrast to the location of a bronchogenic carcinoma in the general population where carcinoma seems to be more frequent in the upper lobe.[5] As to the type of carcinoma of the lung associated with asbestosis, squamous-cell carcinoma outnumbers other types. In our case the carcinoma was small, recognized only microscopically so that the site of origin could not be detected. However, the adenomas in our case were subpleurally located and were in both the upper and lower lobes.

Besides the bronchogenic squamous-cell carcinoma, multiple pulmonary adenomas were also found. As for as could be determined there are no data indicating any relationship between pulmonary adenomas and asbestosis in man. However, Lynch et al.[3] conducted experiments on $ACF_1$ mice by exposing them for various lengths of time to dust containing asbestos float. They demonstrated that in the 127 animals which were "dusted," 46% had developed primary lung adenomas; in 222 control animals only 36% had developed pulmonary adenomas. There were no histological or cytological differences in the tumor in the controls and "dusted" animals. Also, there was no evidence of malignancy found in any of the lungs. These authors have been unable to demonstrate carcinogenicity of the asbestos under the conditions of experiment, but the increased incidence of lung tumor in "dusted" animals was regarded as a possible accentuation of an existing tendency to develop lung tumor.

It is, of course, possible that these pulmonary adenomas in our case were incidental findings. However, because experiments just quoted are suggestive of a relationship between pulmonary adenomas and pulmonary asbestosis and because such pulmonary adenomas per se are rather rare, we are more inclined to believe that they also are related to asbestosis. It would thus seem important in future cases of asbestosis, even after a primary lung carcinoma has been demonstrated, to search the lungs by means of multiple sections to see whether or not multiple other tumors may not be encountered. This seems particularly important since examination of an organ is usually considered completed after once a major lesion such as a primary carcinoma is encountered.

The main disease which the patient had and for which he was admitted to the hospital was a primary adenocarcinoma of the stomach which had caused pyloric obstruction. A check of the available literature disclosed one report of 8 cases where pulmonary asbestosis was associated with carcinoma of the lung and neoplasms at other sites.[4] Multiple sections of the carcinoma disclosed numerous highly refractile dots and short

rods, but no typical asbestos fibers were encountered and certainly no asbestos bodies. However, sections of the adjacent mucosa and also of the serosal surface of the stomach showed the occasional presence of not only asbestos fibers but also asbestos bodies which gave a positive Prussian blue reaction. The pertinent question is, of course, whether or not the gastric carcinoma was related to the pulmonary asbestosis or not. Since asbestos bodies can be demonstrated in the sputum, it seems reasonable to assume that they are also swallowed and may lodge in the stomach as was demonstrated in this case. Thus its role as a carcinogen in its contact with the gastric mucosa much be borne in mind. However, since true asbestos bodies could not be demonstrated in the tumor of the stomach, it would seem that the stomach carcinoma in this case was an accidental finding.

## Summary

An elderly plaster mixer in a casting company where he worked with dry powdered materials used in making casts and which contained asbestos was admitted because of considerable weight loss and exertional dyspnea. At the hospital, x-ray examination disclosed an obstructive prepyloric lesion.

At autopsy, chronic pulmonary asbestosis was present in addition to a primary bronchogenic squamous-cell carcinoma and multiple pulmonary adenomas. There was also a primary adenocarcinoma of the stomach which had produced metastases to the lungs. The relationship of chronic asbestosis to pulmonary carcinomas and to pulmonary adenomas is discussed. While asbestos bodies were also found in the stomach and broken-down asbestos fibers within the gastric carcinoma itself, it was not considered likely that there was any relationship between the gastric carcinoma and pulmonary asbestosis.

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