46

(1943)

WAGONER
P. 66 L. 5
TO
P. 66 L. 20

THE CO-INCIDENCE OF PRIMARY CARCINOMA OF THE LUNGS AND PULMONARY ASBESTOSIS *

Analysis of Literature and Report of Three Cases

F. Homburger, M.D.
(From the Laboratory of Pathology, Yale University School of Medicine, New Haven, Conn.)

A review of the literature on pulmonary asbestosis by Egbert in 1935 resulted in the publication [1] of 25 cases supported by anatomic study, thus reflecting the increasing importance of the disease.

In 1935, Lynch and Smith [2] reported *primary carcinoma of the lungs associated with asbestosis.* Four years later the same authors [3] described 2 additional cases of their own and collected 5 more from the literature,[4-7] bringing the total to 8. A recent survey revealed 8 more cases, which are presented in Table I. Three more instances are contributed in the following report, thus bringing the total number to 19.

Pulmonary asbestosis has been diagnosed in this laboratory according to the following criteria:

1. Fibrosis of the lung.
2. Presence of asbestosis bodies.[8, 9] Kühn [10] presented photographs of asbestosis bodies obtained by the electronic microscope, enlargement × 20,500.

Reports of Cases

Case 1

The patient (autopsy no. 1705), a white male, 45 years old, was exposed to dust in an asbestos factory for 5 years. For at least 1 year before his death he had complained of gradually increasing weakness and dyspnea. This forced him to stay in bed for 6 weeks prior to his admission to the New Haven Hospital. The clinical impression at this time was diaphragmatic pleurisy and compression of the lung on the right side, possibly tuberculous in origin. Generalized arteriosclerosis and paroxysmal tachycardia were found as complicating factors. The patient expired after a short stay in the hospital.

Only those portions of the post-mortem findings important for this report are included.

Gross Description of the Lungs. Each lung weighed 700 gm. The surface of the right lung was covered by white, firm adhesions which bound it to the parietal pleura. Only a few small areas of the visceral pleura were free from adhesions. These areas were pink, mottled with the usual amount of black subpleural pigment. The diaphragmatic surface exhibited a large number of firm, white, opaque nodules, 2 to 5 cm.

* This study was aided in part by a grant from the Fluid Research Funds of the Yale University School of Medicine.
Received for publication, December 11, 1942.

Amer. J. Path. 19: 797-807, 1943

TABLE I

Collected Cases of Primary Carcinoma of the Lung Associated with Asbestosis

Number and author	Year	Sex and age	Occupation in asbestos industry	Duration of exposure	Freedom from exposure before death	Nature of tumor	Primary site	Metastases
* 1. Lynch and Smith[2]	1935	M., 57	Weaver	21 yrs.	4 mos.	Squamous cell	Right lower lobe	Many nodules in right lower lobe
* 2. Gloyne[5]	1935	F., 35	Spinner	8 yrs.	9 yrs.	Squamous cell	Right upper lobe	Pleura
* 3. Gloyne[5]	1935	F., 71	Mattress and opening department	19 mos.	15 yrs.	Squamous cell	Right lower lobe	None
* 4. Egbert and Geiger[4]	1936	M., 41	Weaver	17 yrs.	2 yrs.	Glandular	Left lower lobe	Widespread
* 5. Gloyne[6]	1936	M., 59	Packer	10½ yrs.	? mos.	Oat cell	Left lower lobe	Left upper lobe; pleura
* 6. Nordmann[7]	1938	F., 35	Spinner	7 yrs.	9 yrs.	Squamous cell	Left lower lobe	Liver, kidney
* 7. Nordmann[7]	1938	M., 55	Pre-spinning assembly	7 yrs.	12 yrs.	Squamous cell	Left lower lobe	Widespread
* 8. Lynch and Smith[3]	1939	M., 50	Weaver	13 yrs.	3 yrs.	Squamous cell	Right lower lobe	Pleura, mediastinal lymph nodes
9 and 10. Koelsch[11]	1940	No details known. Oral communication of Domenici, quoted by Koelsch.						
11. Linzbach and Wedler[13]	1941	No details known. Oral communication of Bohne, quoted by Linzbach and Wedler.						
12. Linzbach and Wedler[13]	1941	M., 61		At least 3 yrs.	Not exactly known	Squamous cell	Right lower lobe	None

TABLE I—(*Continued*)

Number and author	Year	Sex and age	Occupation in asbestos industry	Duration of exposure	Freedom from exposure before death	Nature of tumor	Primary site	Metastases
*13. Heller and [illegible]	1941	M., 52	Pipe insulator	25 yrs.	9 wks.	Squamous cell	Right upper lobe	Mediastinal nodes, kidney, adrenal

TABLE I—(*Continued*)

Number and author	Year	Sex and age	Occupation in asbestos industry	Duration of exposure*	Freedom from exposure before death	Nature of tumor	Primary site	Metastases
*13. Holleb and Angrist[13]	1941	M., 52	Pipe insulator	25 yrs.	9 wks.	Squamous cell	Right upper lobe	Mediastinal nodes, kidney, adrenal
*14. Holleb and Angrist[13]	1941	M., 58	Pipe insulator	25 yrs.	10 yrs.	Oat cell	Right lower lobe	Widespread
15. Desmeules and others[14]	1941	M., 57	Machine adjuster	25 yrs.	1 mo.(?)	Alveolar cell	Left lung	Pleura
16. Desmeules and others[14]	1941	M., 50	Bagger	22 yrs.	4 mos.	Squamous cell	Right lung	Pleura
17. Homburger	1942	M., 45	Not known	5 yrs.	1 yr.	Squamous cell	Right lung	Diaphragm
18. Homburger	1942	M., 43	Not known	20 yrs.	17 mos.	Anaplastic	Left lower lobe	Pleura
19. Homburger	1942	F., 49	No known contact with asbestos	Not known	Not known	Squamous cell	Right lung	Liver, adrenal, stomach, hilar lymph nodes

* Included in previous tabulations by Nordmann, Angrist and Holleb.

in diameter with scattered zones of necrosis. Similar masses were attached to the parietal wall of the pericardium. The lung was firm and only slight crepitation could be elicited. This was particularly true at the angle between the diaphragmatic and the mediastinal surface. On section this latter portion was white and opaque. Smaller nodules were seen in the lung parenchyma near the interlobar fissures. The color of the remaining lung parenchyma was mottled dark red and black. The cut surface was moist and exuded red frothy fluid upon slight pressure. Some of the black zones were firmer than the remaining parenchyma. In the left lung similar black, firm, fibrous nodules and a red, moist cut surface were encountered. There were no white nodules in this lung.

Microscopic Description. The white, firm nodules seen grossly in the right lung proved to be squamous cell carcinoma with mitoses and pearl formation. The tumor involved the walls of the bronchi. It extended into the pleura where it was associated with much fibrous tissue and marked thickening. The lung not involved by tumor was well preserved. Some interstitial fibrosis was noted in these areas. The alveoli were filled with mononuclear cells. *Asbestosis bodies* were present in the lumina of alveoli, in the alveolar walls, in the tumor proper and in the interstitial fibrotic tissue of the lung as well as in the pleura. There was a chronic bronchitis but the epithelium of the bronchi was essentially unaltered. The exact point of origin of the tumor was not determined (Figs. 2 and 3).

Anatomic Diagnosis. Pigmentation and fibrosis of lungs (histologically, asbestosis); bronchiectasis; fibrous pleural adhesions; squamous cell carcinoma (probably carcinoma of bronchus) involving right lung, pleura, pericardium and thoracic wall; cardiac hypertrophy and dilatation; passive congestion of viscera; emaciation. Subsidiary: Cyst of thyroid gland; adenoma of pancreas.

Case 2

The patient (autopsy no. 3841) was a white male, 43 years old, who had worked in an asbestos factory for 20 years. Asbestosis bodies had been found in his sputum 17 months prior to his death. For several years before his death he had complained of pain in the back, radiating to the lower limbs. This was shown to be associated with rotation of the first lumbar vertebra and sacralization of the fifth lumbar vertebra. There had been also an incomplete fracture of the left femur. Generalized mottling throughout both lungs was observed at this time. When the patient began to complain of shooting pain in the lower back, ascending to the midback and radiating to the left side of the chest, further roentgenograms were made of the chest and a circumscribed shadow in the left lower lobe was interpreted as a lung tumor. In retrospect it was possible to see this shadow on earlier films. The tumor displaced the left main bronchus and the esophagus to the right. Exploratory thoracotomy and biopsy established the diagnosis of anaplastic carcinoma. The

patient became cyanotic aft
lobe and expired.

Clinical Diagnosis. Pneum
with pressure on spinal root

Gross Description of
and shape. It was rema
its shape when removed
thickened, gray and tr
tively smooth, finely gr
mottled due to the pres
areas bounded by gray-
these areas were crepit
appearance and was stil
of the smaller bronchi a
reddening of the muc
posterior part of the le
5 by 6 by 7 cm., was e
and 9th intercostal ner
from the surface of t
pleurae were thickene
cm. in diameter, where
tissue. Medially it pro
mediastinum, being a
the aorta and esophag
bedded in the tumor n
below the cardiac ple

No other mediasti
were several large, s
presented a brownish

The cut surfaces of
those of the right lun
and marble-like with
and in one place app
main bronchus. Care
or metastasis to the r

Microscopic Descr
lungs, not only in the
in many of the alveo
were almost uniform
from the wall. Man
(Fig. 1). A few of
lymphatic tissue bu

patient became cyanotic after operation, developed pneumonia of the left upper lobe and expired.

Clinical Diagnosis. Pneumonoconiosis (asbestosis); lung tumor (left lower lobe) with pressure on spinal root or metastases to spine.

Gross Description of the Lungs. The right lung was normal in size and shape. It was remarkably heavy, only slightly crepitant and held its shape when removed from the body. It was covered by a uniformly thickened, gray and translucent pleura. The cut surface was relatively smooth, finely granular, pale, slate-gray tinged with pink and mottled due to the presence of innumerable small, slate-gray polygonal areas bounded by gray-white connective tissue septa. In the lower lobe these areas were crepitant; the surface had a gray, more homogeneous appearance and was still firmer than that of the upper lobe. The walls of the smaller bronchi and bronchioles were thickened; a rather marked reddening of the mucosa of the larger bronchi was evident. In the posterior part of the left lower lobe a firm, irregular mass, measuring 5 by 6 by 7 cm., was encountered. Immediately beneath it lay the 8th and 9th intercostal nerves. It projected posteriorly and also medially from the surface of the lung. Posteriorly, the visceral and parietal pleurae were thickened and fused over the tumor in an area about 4 cm. in diameter, where the mass was covered only by delicate areolar tissue. Medially it projected a distance of several centimeters into the mediastinum, being adherent to the descending aorta and displacing the aorta and esophagus to the right. The left vagus nerve was embedded in the tumor mass for a distance of about 3 cm. at a point well below the cardiac plexuses.

No other mediastinal structures appeared to be involved. There were several large, soft mediastinal lymph nodes which, on section, presented a brownish black surface.

The cut surfaces of upper and lower lobes of the left lung resembled those of the right lung. The cut surface of the tumor was gray-white and marble-like with scalloped edges. It was closely associated with, and in one place apparently involved, the wall of a branch of the left main bronchus. Careful examination revealed no evidence of extension or metastasis to the nearby vertebrae or ribs.

Microscopic Description. Diffuse fibrosis was present throughout the lungs, not only in the peribronchiolar and perivascular regions but also in many of the alveolar septa. The alveoli were lined with cells which were almost uniformly swollen, prominent and in many cases detached from the wall. Many of the alveoli contained typical *asbestosis bodies* (Fig. 1). A few of them lay within the peribronchial or perivascular lymphatic tissue but the majority were in the alveolar spaces. They

were rarely free, but usually surrounded and sometimes partially phagocytized by large mononuclear cells and multinucleated giant cells. Scattered anaplastic cells with atypical hyperchromatic nuclei and abundant cytoplasm were present in the tumor mass. Numerous mitotic figures were seen. In other sections the cells were in cords arranged on a scanty connective tissue stroma. There was a tendency to form alveoli. In one area the tumor cells had grown in sheet-like masses, suggesting an epidermoid carcinoma. Branches of the vagus nerve were found firmly embedded in neoplastic tissue and the perineurium was invaded by carcinoma cells. Rare small asbestosis bodies were seen in the sinuses of a tracheobronchial lymph node in addition to many phagocytes loaded with anthracotic pigment (Fig. 6).

Anatomic Diagnosis. Pulmonary asbestosis; carcinoma of lung (left lower lobe), compressing 8th and 9th intercostal nerves and surrounding and compressing left vagus nerve; scar of recent thoracotomy; serofibrinous pleurisy (left). Subsidiary: Fibrous apical scars (bilateral); fibrous pleural adhesions (bilateral).

Case 3

The rather incomplete history of this white female (autopsy no. 5443), 49 years old, failed to reveal contact with asbestos. Nineteen months prior to death she began to note shortness of breath and dry cough. There was scanty mucoid sputum. As her condition grew worse x-ray examinations led to the diagnosis of pneumonia and pleurisy on the right. Thoracic taps revealed right hemothorax. Some days prior to death, examination of the thorax showed displacement of the heart to the left and dullness over the right chest except for paravertebral tympany. There was also wheezing anteriorly and posteriorly. Straw-colored fluid was repeatedly aspirated from the right chest.

Clinical Diagnosis. Carcinoma of the right lung with metastasis to the liver.

Gross Description of the Lungs. The right lung weighed 1050 gm. The upper lobe was atelectatic and covered by thick, firm, fibrous adhesions. Crepitation was impaired in the peripheral portions of the middle and lower lobes.

The lungs were cut on a mechanical slicer into slabs 2.5 cm. thick. The medial third of the upper lobe was replaced by firm white nodules of neoplastic tissue in which compressed blood vessels and bronchi were still recognizable. In the upper portions of the middle lobe the tumor extended along the bronchi and blood vessels leading to the periphery, and the mediastinal lymph nodes were enlarged by tumor. The lung parenchyma, where free of tumor, was pale gray. Its interstitium was markedly thickened, gray and translucent. The consistency was rubbery and in the upper lobe there were some yellow areas of localized softening about 1 cm. in diameter. The bronchi,

carefully examined, were
The mucosa was red and
walls of several bronchi we
gous changes were found

The left lung weighed
translucent and free of cl
the color was gray in the
the usual pattern of anth
the parenchyma was dry
from the section of the
caliber; their mucosa wa
blood vessels of this side.

Microscopic Descripti
of dense nests of squam
sue. These tumor cells
were in mitotic division.

The neoplastic tissue
were also large areas of
the tumor. The pleura
There was also interstit
anthracotic pigment. A
In some areas, howeve
and large round cells
shaped brown deposits
in some of the alveoli.
(Fig. 4). They were
the tumor and also in

Most of the bronch
infiltration in the sub
and in some places wa
cells. Most of the lun
instance remnants of
tumor nodule. Here
dense fibrous tissue
cell carcinoma. Pea
purulent polymorph
some of the larger br

Anatomic Diagnos
bronchitis and bron
metastasis to hilar a
mucosa; infarct in s
endocarditis; nevus

carefully examined, were found to be free of intraluminal obstruction. The mucosa was red and swollen. No ulceration could be seen. The walls of several bronchi were thickened and the lumina reduced. Analogous changes were found in the intrapulmonic vessels on this side.

The left lung weighed 360 gm. Its pleural surface was thin and translucent and free of changes. The parenchyma was air-containing; the color was gray in the upper and red in the lower lobe. There was the usual pattern of anthracotic pigment in the pleura and, on section, the parenchyma was dry and only a few droplets of blood escaped from the section of the lower lobe. All the bronchi had the usual caliber; their mucosa was intact and pink. There was no change in the blood vessels of this side. The hilar lymph nodes were free from tumor.

Microscopic Description. The tumor in the right lung was composed of dense nests of squamous cells surrounded by fibrous connective tissue. These tumor cells varied in size and had pyknotic nuclei. Many were in mitotic division. The cytoplasm was clear and pale.

The neoplastic tissue had replaced the lung parenchyma. There were also large areas of round cell infiltration and foci of breakdown of the tumor. The pleura was locally thickened by dense fibrous tissue. There was also interstitial fibrosis. There was a moderate amount of anthracotic pigment. Adjacent to the tumor the lung was atelectatic. In some areas, however, the alveoli were dilated and filled with small and large round cells or amorphous pink-staining material. Rod-shaped brown deposits were present in the interstitial tissue and also in some of the alveoli. These had the appearance of *asbestosis bodies* (Fig. 4). They were scattered throughout the lung parenchyma near the tumor and also in more remote regions of the lung.

Most of the bronchi showed inflammatory changes with round cell infiltration in the submucosa. The epithelium was of the usual type and in some places was lifted from the limiting membrane by the round cells. Most of the lumina contained similar mononuclear cells. In one instance remnants of bronchial epithelium were seen in the center of a tumor nodule. Here the lung parenchyma was entirely replaced by dense fibrous tissue which constituted the stroma of the squamous cell carcinoma. Pearl formation was observed. There was also a purulent polymorphonuclear exudate in some of the bronchi and in some of the larger bronchioles.

Anatomic Diagnosis. Pulmonary asbestosis (microscopic); purulent bronchitis and bronchiolitis; bronchogenic carcinoma (right lung); metastasis to hilar and preaortic lymph nodes, liver, adrenal and gastric mucosa; infarct in spleen. Subsidiary: Uterine fibroids; healed mitral endocarditis; nevus on abdominal skin.

Discussion

In 4137 autopsies from 1918 to 1938 there were 45 cases of pulmonary carcinoma in this laboratory,[15] an incidence of 1.08%. Asbestosis was diagnosed 8 times, silicosis 17 times. Pulmonary carcinoma was found in 4* of the 8 instances of asbestosis and twice in the 17 silicotic cases.

A similar coincidence of silicosis and cancer was found by Klotz[16] (8%), but Vorwald and Karr[17] could not confirm this. Because of the small series of cases, the value of these data is limited. Lynch and Smith[2] suggested that asbestosis is a predisposing factor in carcinoma of the lung. They stated that advanced asbestosis "may lead to bronchial epithelial metaplasia of a type encountered in other locations where cylindrical epithelium may give rise to squamous cell carcinoma," a point of view also shared by Linzbach and Wedler.[12] They cited the case of a negro who was thought to be asthmatic and who apparently died of heart failure. At autopsy pulmonary asbestosis, chronic bronchitis and bronchiectasis, acute lobar pneumonia and pulmonary atheromatosis were found, together with hypertrophy and dilatation of the heart. In the bronchi "foci of transformation of undenuded epithelium into stratified squamous form were found." It seems questionable whether this statement is of significance as an indication that asbestosis predisposes to carcinoma. During a study on bronchial metaplasia in this laboratory, metaplasia of the bronchial epithelium was found in only one instance of pneumonoconiosis (case 5549, Fig. 10).

Metaplastic changes of bronchial mucosa were observed four times in a series of 44 consecutive autopsies, studied with special care from this point of view. Such metaplastic changes, illustrated in Figures 5, 7, 8 and 9, were seen in cases with various pulmonary lesions. None of these four cases presented any deposits of foreign material in the lungs.

These facts seem to indicate that neither from statistical calculations nor from purely morphologic studies is there any reliable answer to the question whether pulmonary asbestosis has to be considered as an etiologic factor in pulmonary carcinoma.

Summary

A review of the literature on the association of pulmonary asbestosis and carcinoma revealed that there are at least 19 known cases (including the 3 herein reported) of asbestosis associated with primary pul-

* One of these cases was published previously by Egbert and Geiger.[4]

monary carcinoma. In this laboratory the association of the two conditions is remarkably high. In 8 cases of asbestosis there were 4 instances of primary pulmonary carcinoma.

REFERENCES

1. Egbert, D. S. Pulmonary asbestosis; report of a case with necropsy findings. *Am. Rev. Tuberc.*, 1935, 31, 25–34.
2. Lynch, K. M., and Smith, W. A. Pulmonary asbestosis. III: Carcinoma of lung in asbesto-silicosis. *Am. J. Cancer*, 1935, 24, 56–64.
3. Lynch, K. M., and Smith, W. A. Pulmonary asbestosis. V: A report of bronchial carcinoma and epithelial metaplasia. *Am. J. Cancer*, 1939, 36, 567–573.
4. Egbert, D. S., and Geiger, A. J. Pulmonary asbestosis and carcinoma; report of a case with necropsy findings. *Am. Rev. Tuberc.*, 1936, 34, 143–150.
5. Gloyne, S. R. Two cases of squamous cell carcinoma of the lung occurring in asbestosis. *Tubercle*, 1935–36, 17, 5–10.
6. Gloyne, S. R. A case of oat cell carcinoma of the lung occurring in asbestosis. *Tubercle*, 1936–37, 18, 100–101.
7. Nordmann, M. Der Berufskrebs der Asbestarbeiter. *Ztschr. f. Krebsforsch.*, 1937–38, 47, 288–302.
8. Beger, P. J. Über die Asbestosiskörperchen. *Virchows Arch. f. path. Anat.*, 1933, 290, 280–353.
9. Dreessen, W. C., Dallavalle, J. M., Edwards, T. I., Miller, J. W., and Sayers, R. R. A study of asbestosis in the asbestos textile industry. *Pub. Health Bull.*, 1938, no. 241, 1–126.
10. Kühn, J. Übermikroskopische Untersuchungen an Asbeststaub und Asbestlungen. *Arch. f. Gewerbepath. u. Gewerbehyg.*, 1941, 10, 473–485.
11. Koelsch. Lungenkrebs und Beruf. *Acta, Union internat. contre cancer*, 1938, 3, 243–251. (Also: *Zentralbl. f. Gewerbehyg.*, 1940, 27, 32–33.)
12. Linzbach, A. J., and Wedler, H. W. Beitrag zum Berufskrebs der Asbestarbeiter. *Virchows Arch. f. path. Anat.*, 1941, 307, 387–409.
13. Holleb, H. B., and Angrist, A. Bronchiogenic carcinoma in association with pulmonary asbestosis. Report of two cases. *Am. J. Path.*, 1942, 18, 123–135.
14. Desmeules, R., Rousseau, L., Giroux, M., and Sirois, A. Amiantose et cancers pulmonaires. *Laval méd.*, 1941, 6, 97–108.
15. Kober, W. M. Primary Carcinoma of the Lung. Thesis (Department of Pathology), Yale, 1938.
16. Klotz, M. O. The association of silicosis and carcinoma of the lung. *Am. J. Cancer*, 1939, 35, 38–49.
17. Vorwald, A. J., and Karr, J. W. Pneumonoconiosis and pulmonary carcinoma. *Am. J. Path.*, 1938, 14, 49–57.

[*Illustrations follow*]

DESCRIPTION OF PLATE

PLATE 98

FIG. 1. Case 2 (A. 3841). Asbestosis bodies and phagocytes in pulmonary alveolar lumen. × 875.

FIG. 2. Case 1 (A. 1705). Nests of carcinoma cells, pulmonary fibrosis and numerous asbestosis bodies. × 220.

FIG. 3. Case 1 (A. 1705). Asbestosis bodies among carcinoma cells in lung. × 615.

FIG. 4. Case 3 (A. 5443). Asbestosis bodies and carcinoma cells in lung. × 395.

FIG. 5. White male, 36 years old (A. 5631). Death by violence. Pulmonary fibrosis. Bronchial metaplasia. × 220.

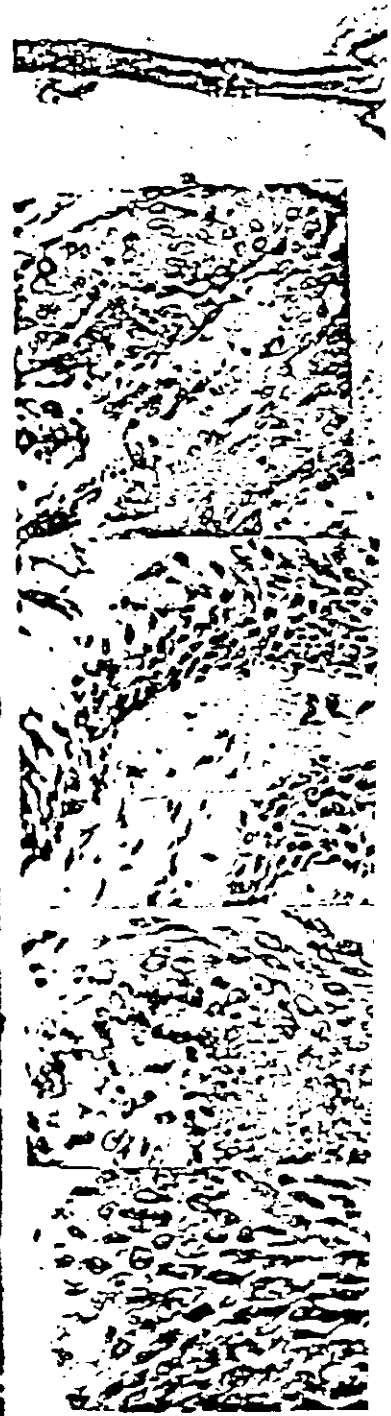
FIG. 6. Case 2 (A. 3841). Asbestosis body in sinus of peribronchial lymph node. × 655.

FIG. 7. White male, 57 years old (A. 5685). Healed endocarditis. Generalized arteriosclerosis. Pulmonary congestion. Bronchial metaplasia. × 370.

FIG. 8. White male, 40 years old (A. 5475). Caseous and ulcerative pulmonary tuberculosis. Bronchial metaplasia. × 370.

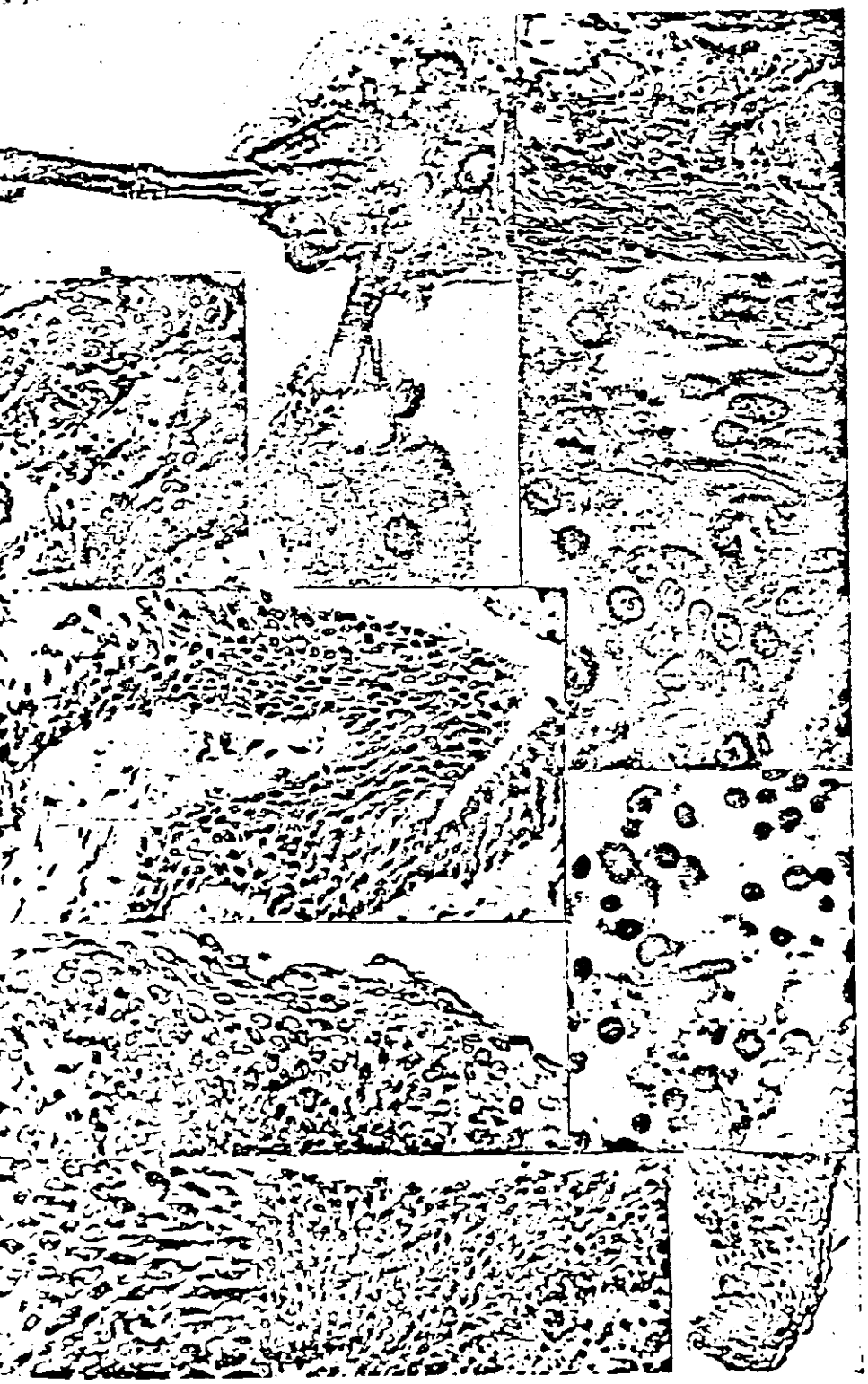
FIG. 9. White male, 66 years old (A. 5545). Pulmonary thrombo-arteritis, focal pneumonia. Bronchial metaplasia. × 220.

FIG. 10. White male, 43 years old (A. 5549). Chronic pulmonary abscesses, bronchiectasis, organizing pneumonia. (Questionable anthracosilicosis.) Bronchial metaplasia. × 220.



B

Hamburger



Pulmonary Asbestosis and Carcinoma