PULMONARY MUCOUS EPITHELIAL HYPERPLASIA (PULMONARY ADENOMATOSIS)

A Report of Two Cases *

Edgar B. Taft, M.D., and Donald A. Nickerson, M.D.

(From the Mallory Institute of Pathology, Boston City Hospital, Boston, Mass., the Salem Hospital, Salem, Mass., and the Boston University School of Medicine, Boston, Mass.)

In the first article relative to pulmonary mucous epithelial hyperplasia (pulmonary adenomatosis) in man, Helly [1] remarked that it was a rare tumor which he described "to arouse interest because only the study of many similar cases will clear up the subject." In the past 4 years interest has again been aroused in this condition by the publication of reports of three similar cases by Bonne,[2] Richardson [3] and Sims.[4] In Sims' article, a most thorough and exhaustive review of the literature, the similarity of this condition to one seen in sheep was emphasized. This latter disease, variously known as jagsiekte, epizootic adenomatosis, and pulmonary adenomatosis, has a wide incidence in the sheep herds in South Africa, Iceland, Montana and Germany. Six human cases in all have been previously described.[1-6]

Report of Cases

Case 1

Clinical Course. The first case was that of a white male, 62 years of age, who was admitted to the Essex County Sanatorium on August 8, 1941, with a cough of 8 months' duration. About 1 month before developing his cough he began to notice undue fatigue. His cough became worse and during the winter of 1940-41 productive of 10 to 20 ounces of white, sticky, foamy sputum in 24 hours. In January, 1941, he began to notice loss of weight and strength. In March there was dyspnea on slight exertion. He consulted a doctor in June who sent him to the Sanatorium's Outpatient Department, after he had had to quit work. On July 20th he was advised to enter the Sanatorium.

His past history was negative except for "pleurisy" in the fall of 1940. One of his brothers was thought to have had tuberculosis in 1920.

He was a fairly well developed and well nourished man (height, 67¼ inches; weight, 145 pounds) who did not appear in acute distress. His temperature, pulse, respiration and blood pressure were not remarkable. Chest expansion was limited. There was no dullness to percussion and many coarse moist râles were heard over the chest on auscultation. Otherwise physical examination was negative.

The hemoglobin content of the patient's blood was 80 per cent (Sahli). The white cell count was 11,400 with 74 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 2 per cent large monocytes. There seemed to be a marked increase in platelets in the smear. The sedimentation rate was not increased. The urine was not remarkable. The sputum showed no tubercle bacilli on three examinations and but few leukocytes.

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Roentgenograms of the chest taken on July 24th and August 9th showed essentially similar findings (Fig. 1). They were read as follows: "There are diffuse mottled flocculent areas from apex to third rib on the right. There is a homogeneous shadow from the third to the fifth rib. This shadow covers the entire base, but is lighter toward the costophrenic angle. There is heavy infiltration on the left from the apex to the third rib. Below, the entire lung is obscured by a homogeneous shadow." This was interpreted as possibly a fungus infection or a tumor. On August 18th a Bucky plate was taken (Fig. 2) which did not reveal anything of further interest.

The patient's von Pirquet tuberculin test was very weakly positive. Bronchoscopy on August 21st revealed a profuse mucoid secretion in both major bronchi which apparently interfered with respiration. No localized lesion was found in the tracheobronchial tree. The secretion was interpreted as consistent with cardiac decompensation.

Three days prior to his death on the 19th hospital day the patient became markedly dyspneic and cyanotic and was placed in an oxygen tent with temporary relief. He became febrile at this time and remained so until his death on August 27th.

Autopsy Findings

At autopsy, 2 hours post-mortem, the body was that of a moderately well developed, somewhat thin white male. The dome of the diaphragm was at the 7th rib on the right and the 7th intercostal space on the left. There were numerous fresh fibrinous adhesions in both the right and left pleural cavities. The only other significantly abnormal findings were confined to the lungs.

The left lung weighed an estimated 900 gm. It was firm and consolidated. The pleura was covered with a thin coat of yellow fibrin. On section the upper lobe was gray-white with a glairy, mucoid appearance. On scraping with the section knife, a large amount of tenacious mucus was expressed from the cut surface. At the apex there was a gray-red, more granular zone, with several small areas of cavitation varying from 0.4 to 1.5 cm in diameter. The lower lobe presented the same glairy, mucoid appearance. The bronchi contained moderate amounts of mucoid material, and their mucosae were reddened and edematous. The pulmonary vessels were negative. The right lung weighed an estimated 850 gm. It showed almost complete consolidation of the entire lung with a few small peripheral zones of aeration. On section, it presented the same picture as the left lower lobe.

Microscopically, the lungs showed the only pathological changes of note. The alveoli were largely dilated. A few contained mucus, but for the most part they were filled with leukocytes and blood. The majority of the alveolar walls taken at random from various lobes of the lungs were covered by a simple columnar epithelium. In a few areas this epithelium showed a transition to a cuboidal type, but as a rule the change from the abnormal epithelium to the usual type was

abrupt, as if the alveoli were being invaded by the pathological cells. In some areas the columnar epithelium had formed small papillary processes.

The columnar cells were slender with pale cytoplasm and basally located nuclei. The cells were somewhat larger than the usual epithelial cells of the bronchial mucosa and were not ciliated. The nuclei occupied approximately one-sixth of the length of the cells and were for the most part round or oval with a pale network of chromatin. No mitoses were noted.

The alveolar walls were minimally thickened and contained an unusual number of lymphocytes. No abnormal epithelial cells were found in the lymphoid tissues of the lung. In one area there was marked increase in the fibrous connective tissue with loss of the usual architecture. The columnar epithelium in this area was arranged in small acinus-like structures.

The bronchiolar epithelium and that of the alveolar ducts did not seem to be affected by this process.

Case 2

Clinical Course. The second case was that of a white female, 79 years of age, who was admitted to the Boston City Hospital on the Fifth Medical Service on October 23, 1942. On a previous admission to the hospital in 1932 a diagnosis of primary anemia had been established. Since then she had had occasional injections of liver extract and had taken three liver capsules daily until about a month before her last admission. In the 2 months prior to admission the patient lost 20 pounds in weight. For 2 months she had severe anorexia and a dull pain in her epigastrium. She became pale and faintly yellow. She was bedridden for 1 month before entry. Her family history and past history were otherwise negative.

She was a markedly emaciated small woman (height, 56½ inches; weight at autopsy, 70 pounds) with lemon-tinted skin. Her tongue was pale and smooth with atrophic papillae. Her neck veins were distended, and her heart seemed to be enlarged to the left with systolic apical and aortic murmurs. Her lungs were clear to percussion and auscultation and no râles were heard. Her liver was just palpable. Her knee, ankle and abdominal reflexes could not be obtained.

Her red cell count was 860,000 with 4.5 gm. of hemoglobin per 100 cc. of blood. Her white cell count was 3,800 with 54 per cent neutrophilic leukocytes, 43 per cent lymphocytes, 1 per cent eosinophilic leukocytes, and 2 per cent basophilic leukocytes. A smear showed anisocytosis, hyperchromia, polychromasia, and basophilic stippling of the red cells. The platelets seemed to be decreased. The hematocrit reading was 12 mm. There were 1.2 per cent of reticulocytes. Examination of the urine and a Hinton test of the blood were negative. Her sputum was not examined. A roentgenogram taken on November 8th (Fig. 3) was interpreted as showing consolidation at the left base with focal pneumonia or encapsulated fluid in the region of the right middle lobe.

The patient was given three transfusions of 500 cc. each of citrated whole blood during the first week of her hospital stay. She also received daily injections of liver extract. Her reticulocyte count reached its maximum level of 13 per cent on the

5th hospital day. On the 14th hospital day the red cell count had increased to its maximum of 4,000,000. At this time her hematocrit reading was 42 mm.

On the 8th hospital day the patient developed a cough and consolidation of the left lower lobe was diagnosed. Signs and symptoms indicated increased infection, and the white blood cell count rose to 10,000. Three days prior to death the patient was stuporous and failing rapidly. Chemotherapy was not used. The patient died on the 27th hospital day.

Autopsy Findings

At autopsy, 7 hours post-mortem, the body was that of a well developed, emaciated white woman. Her abdominal panniculus was less than 0.5 cm. in thickness. There were about 300 cc. of clear yellow fluid in the right pleural cavity. The posterior portion of the left pleural cavity was completely obliterated by firm fibrous adhesions so that the lower lobe had to be cut away from the parietal pleura by sharp dissection. The heart weighed 280 gm. and was not remarkable. The gastric mucosa was markedly atrophic. Many diverticula were found in the sigmoid portion of the colon. These showed no surrounding reaction. The liver was small, weighing but 700 gm. It was somewhat browner than usual and cut with slightly increased resistance. It was not otherwise remarkable. The gallbladder contained a number of faceted stones, but its mucosa did not appear abnormal. The spleen weighed 120 gm. and was not remarkable. The kidneys weighed 190 gm. They showed a coarsely granular surface and, on section, a moderately thinned cortex which was well demarcated from the medulla. The bladder was dilated and contained 750 cc. of clear amber urine. The genital organs were markedly atrophic. There was moderate atheromatosis of the abdominal portion of the aorta. The lumbar, sternal, costal and femoral bone marrow was markedly soft, dark red and gelatinous.

The most significant findings were those in the lungs. The right weighed 700 gm. The lower and middle lobes were consolidated and showed no crepitation. The upper lobe was subcrepitant. On section the lower and middle lobes revealed a smooth cut surface which was dark red peripherally and gray in the central portions. The lower portion of the upper lobe was similar to the peripheral portion of the lower lobe. The rest of the upper lobe was dark red and yielded serosanguinous fluid on pressure. The consolidated portions of the lung yielded sanguinopurulent scrapings.

While the left lung was being removed, the upper and lower lobes were inadvertently separated. The lung weighed 420 gm. The lower lobe was ovoid and measured 8 by 6 by 4 cm. On section it was firm and pale gray, and had a gelatinous pink-gray, mulberry-like tumor process involving the central portion of the lobe. The bronchi were

small but unusually prominent. The left upper lobe resembled the right upper lobe except that the lingula contained several small spherical areas resembling the pink-gray gelatinous area described in the lower lobe. The trachea and bronchi of both lungs were congested and contained a moderate amount of mucoid secretion. The pulmonary vessels were not remarkable.

Culture of the heart's blood and of the right lower lobe revealed *Diplococcus pneumoniae,* type VIII. Culture of the left lower lobe revealed *D. pneumoniae,* type VIII, and hemolytic *Staphylococcus aureus.* A Ziehl-Neelsen stain of the lung revealed no acid-fast organisms.

On microscopical examination, the arterioles in most of the viscera showed a moderate amount of hyaline change. The perinuclear yellow pigment of the heart muscle cells was somewhat more prominent than usual. There were no changes of note in the liver. The kidneys showed occasional fibrosed glomeruli. No parietal (eosinophilic) cells could be found in the mucosa of the stomach. The bone marrow showed moderately active hematopoiesis as is seen in adequately treated primary anemias.

The lung sections showed the microscopical changes which were of interest. The majority of the sections showed merely a confluent bronchopneumonia. The unusual findings were confined to the left lower lobe, to the lingula of the left upper lobe, and to a small portion of the right upper lobe.

In scattered nodules in the upper lobes, the alveoli were lined with columnar epithelium. The epithelial cells were similar to those of the first case except that they were proportionately higher so that they almost obliterated the lumen of the alveoli in some areas. The surrounding alveoli were filled with mucoid secretion and desquamated cells, apparently of epithelial origin. Aniline blue stains revealed that the cells as well were filled with mucus. Cuboidal epithelium was not seen and no bronchioles could be identified with certainty. There was no invasion of the lymphoid tissues of the lungs.

The left lower lobe had been almost completely replaced by hyalinized collagenous fibrous tissue. There were islands of abnormal epithelium lining spaces as large as bronchioles. Areas of alveoli lined with abnormal epithelium also were seen. The bronchi and bronchioles appeared to be unaffected.

Elastic tissue stains revealed no change and aniline blue stains revealed a slight increase in the fibrous tissue of the alveolar septa in the areas involved by the process in question.

Discussion

The pathological picture as described in the two cases reported is essentially similar to that described in earlier articles. In both cases the disease picture was somewhat obscured by severe superimposed bacterial infections. The gross picture in this condition is very similar to that seen in Friedlander's pneumonia. Even microscopically the condition might easily be overlooked in cases with severe bacterial infections, so that it is not impossible that other cases of this nature have not been noticed in the past.

In the first case the clinical course can readily be correlated with the pathological findings, as in Helly's [1] case. The clinical course in both was similar to that of pulmonary tuberculosis. In the second case, however, the mucous epithelial hyperplasia was an incidental finding at autopsy which was not recognized until the microscopical sections were seen. The roentgenographic pictures in both cases were similar and an infectious process or a tumor was suspected in each.

The duration of the disease in these cases is problematical. In both of them there were areas of marked fibrosis in the lungs which seemed to indicate a protracted, chronic infection rather than an acute or neoplastic process. The most acute case in the literature, the second described by Oberndorfer,[6] was accompanied by an acute hemorrhagic pneumonitis of short duration in a 21-year-old male. In sheep, on the other hand, the course is not as acute. Sheep die, as a rule, within a few months after the infection is first noted, although some may live for more than a year.[7]

In the discussions of this and similar diseases in the literature, emphasis has been placed on the importance of such lesions in the consideration of the genesis of carcinomas of the lung. There are several phases of this problem upon which it is worth while to speculate. In the first place, where do these proliferating cells arise? Helly [1] favored the epithelium of the alveolar ducts for several reasons: (1) because the cells were nonciliated in contrast to those of the bronchioles; (2) because the cells could be seen extending from the alveoli to the bronchiolar mucosa but no farther; and (3) because there was a sudden transition from the abnormal cells to the usual alveolar lining. Oberndorfer,[6] on the other hand, was of the opinion that in his case, at least, the tumor arose from the lining cells of the alveoli which he believed have an epithelial origin. He felt that he could demonstrate gradual transitions between pathological cells and the usual alveolar lining cells.

In our opinion, a definite decision is difficult to arrive at; but because of their apparently peripheral and multicentric origin, it seems not unlikely that the abnormal cells arise from the alveolar lining cells (also the opinion of Dr. J. L. Bremer*), and provide further evidence for the epithelial nature of those cells. The changes are of a hyperplastic nature and there is also some metaplasia; for, although the cells are not ciliated, they are columnar and produce large quantities of mucus. In support of our contention, we note that this picture in no way resembles that seen in pulmonary adenomas of which the structure has been quite definitely established in recent years.[8] In that condition the hyperplastic nodules have ill-defined borders and are not encapsulated. They have no stroma other than that of the alveolar walls. Their cells frequently fail to fill more than a small portion of an alveolus. Their exact site of origin is somewhat more problematical.

It seems to us that Oberndorfer's [6] ideas are quite in accord with the picture presented in cases of the type which we have described. Helly's [1] ideas cannot be dismissed readily, however. In one of our cases intact alveolar duct epithelium was seen in several areas in which the alveoli were completely lined with abnormal cells. Thus in this case the microscopical picture is at variance with Helly's opinion. In sheep there are peculiar mucous glands in the walls of the respiratory bronchioles, and many authors believe that it is there that the proliferation starts. From the nature of these cells in man it is not impossible that they may arise from the occasional mucous goblet cells which occur in the mucosa of the bronchioles.

Are these tumor masses of infectious origin? There has been but one case in the literature in which the nature of this disease has been suspected at the autopsy table and confirmed by frozen section.[3] In that case attempts were made to produce a similar condition in experimental animals by the usual methods with no success. That the microscopically similar disease in sheep is of an infectious nature is undoubtedly true, but transmission of the disease from sheep to sheep or to any other laboratory animal has been almost universally unsuccessful. However, the disease has been proved to be infectious in nature, as is evident from a study of the epidemic which occurred in Iceland.[9] It seems that a virus is the most tenable cause for the hyperplasia, since no bacterial species has been recovered with any regularity from affected sheep.

A number of human cases with a more or less similar microscopical

* Personal communication.

picture have been described in which, however, metastases have been found—usually to the regional lymph nodes and occasionally to bone marrow and the brain. References to 10 or 11 such cases have come to our attention.[10-17] The published descriptions of all but 3 of these [15-17] have been examined by us. They all present a somewhat similar picture to the apparently nonmalignant cases described by other authors, although the production of mucus is not a constant finding in the malignant cases as in the nonmalignant condition.

Thus in respect to these few instances, on a histological basis and by analogy, it can be said that these carcinomas may be of an infectious origin. Aynaud is said to have seen metastases in one case of jagsiekte in a sheep (cited by Dungal [9]). However, in our opinion these tumors have but little significance in the consideration of the origin of carcinomas of the lung in general, because the large majority of pulmonary carcinomas obviously do not arise in such a manner but are bronchiogenic.

In a recent review of the case reports of such carcinomas, Neubuerger and Geever [18] agreed that this type of tumor was rare, with an incidence of less than 5 per cent of all carcinomas of the lungs. They feel, as we do, that mucous epithelial hyperplasia may not be as rare as the number of reports in the literature would indicate.

Summary

Two cases of pulmonary mucous epithelial hyperplasia (pulmonary adenomatosis) are described. After reviewing the available literature, the possibility of a viral etiology is considered. While a definite decision cannot be made, it seems probable that the abnormal cells arise from the alveolar lining. Origin from the goblet cells of bronchiolar mucosa cannot be excluded. This condition is of but little significance in a consideration of the genesis of pulmonary carcinoma in general.

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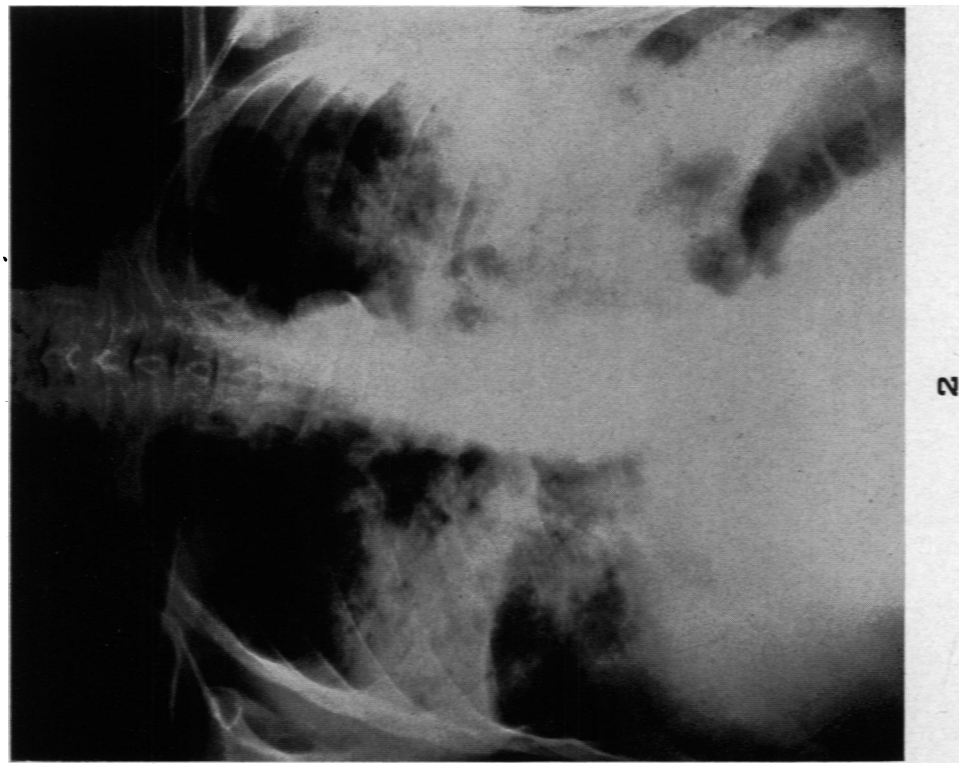
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 76

FIG. 1. Case 1. Roentgenogram taken on July 24, 1941.

FIG. 2. Case 1. Bucky plate roentgenogram taken on August 18, 1941.



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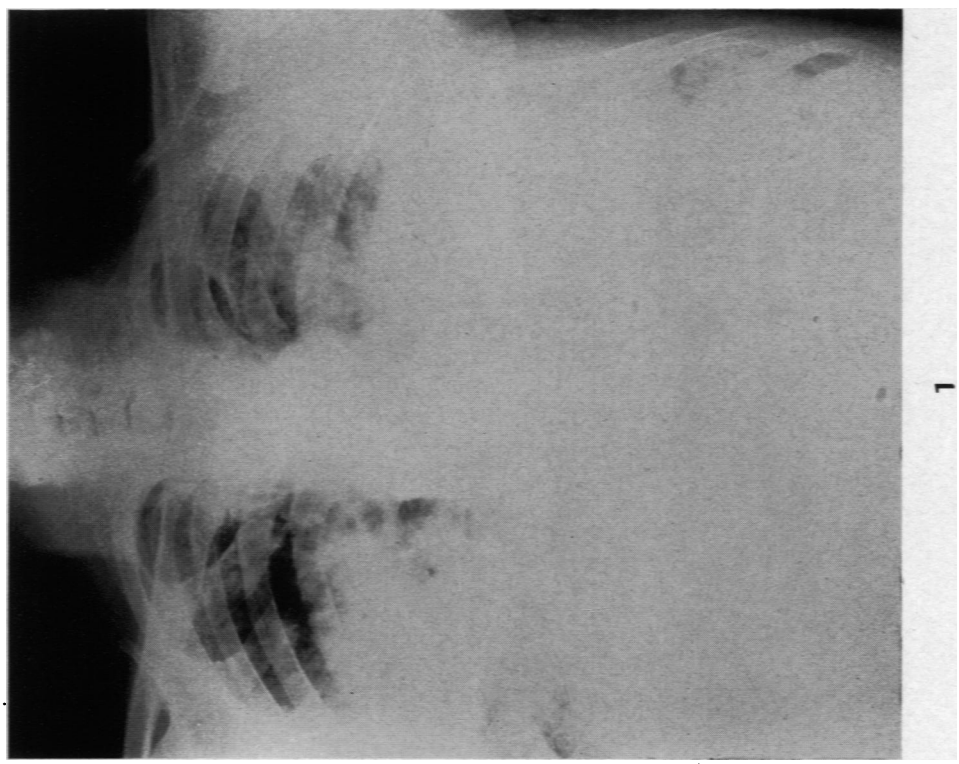

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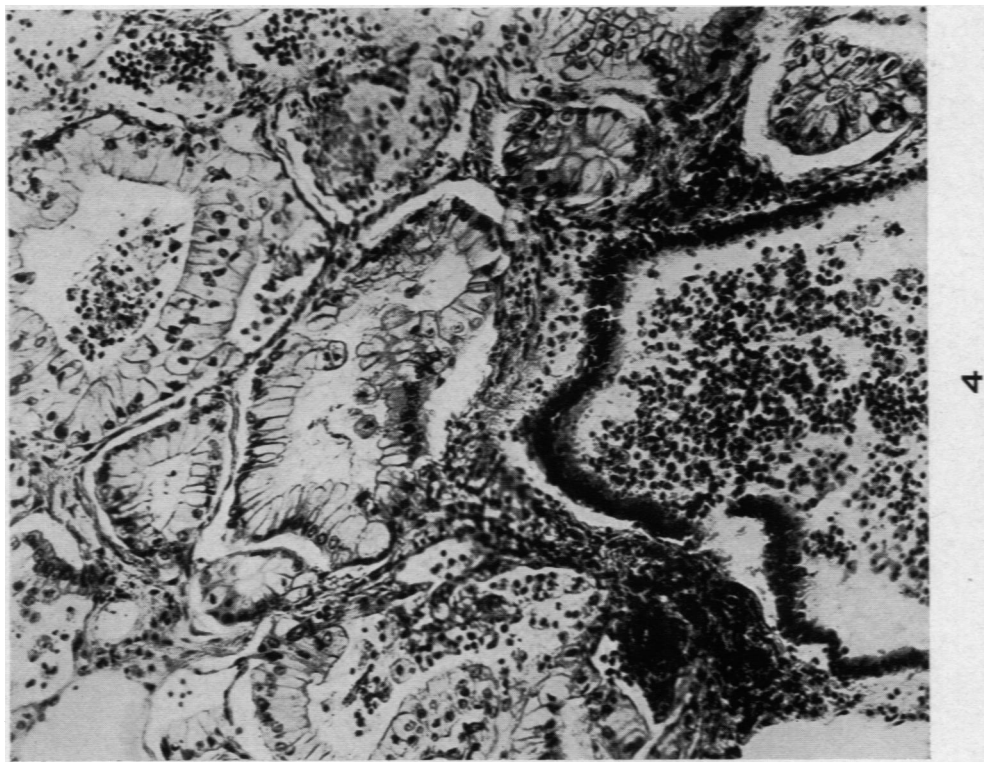
PLATE 77

FIG. 3. Case 2. Portable roentgenogram taken on November 18, 1942.

FIG. 4. Case 1. An uninvolved bronchiole with attached alveolar duct in an area with marked replacement of the usual alveolar lining by typical columnar, nonciliated epithelial cells. Hematoxylin and eosin stain. × 175.



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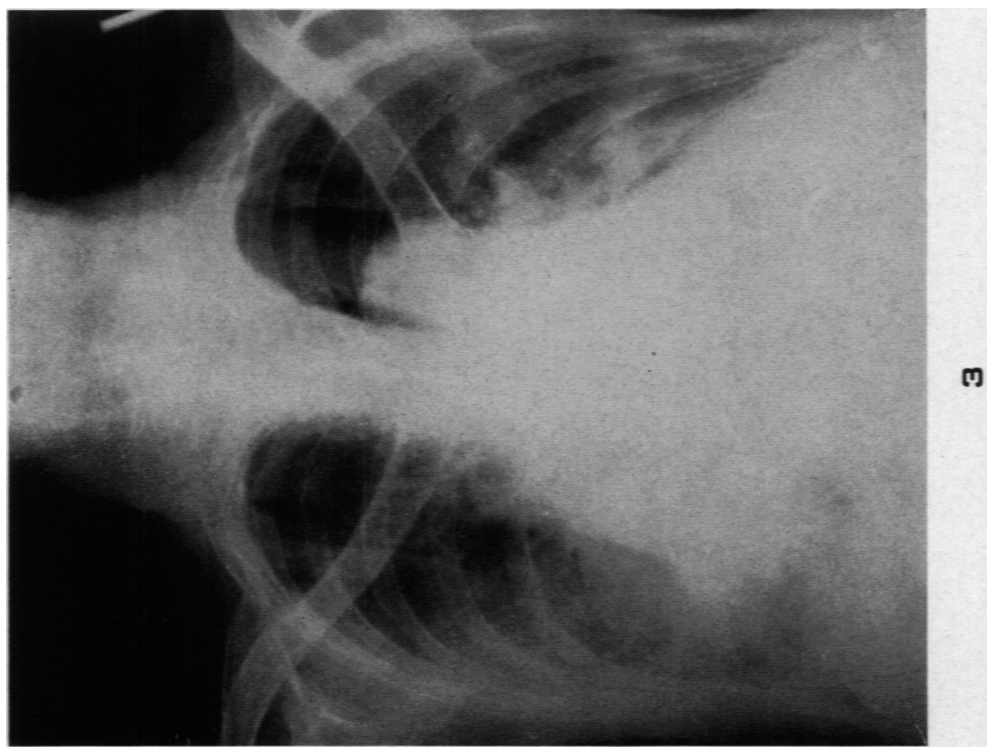

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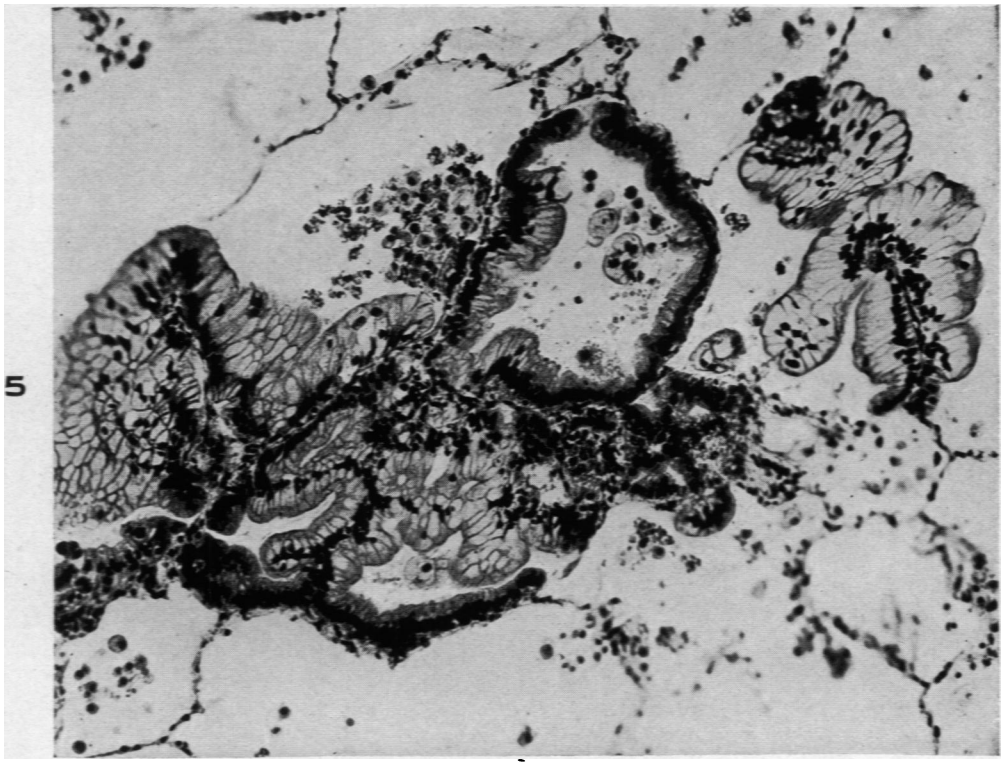
Taft and Nickerson Pulmonary Mucous Epithelial Hyperplasia

PLATE 78

FIG. 5. Case 1. A small cluster of abnormally lined alveoli in the midst of uninvolved alveoli. Hematoxylin and eosin stain. × 175.

FIG. 6. Case 2. A small collection of abnormal alveoli with the surrounding spaces filled with large quantities of intensely stained mucus which contains desquamated cells. Phloxine and methylene blue stain. × 175.



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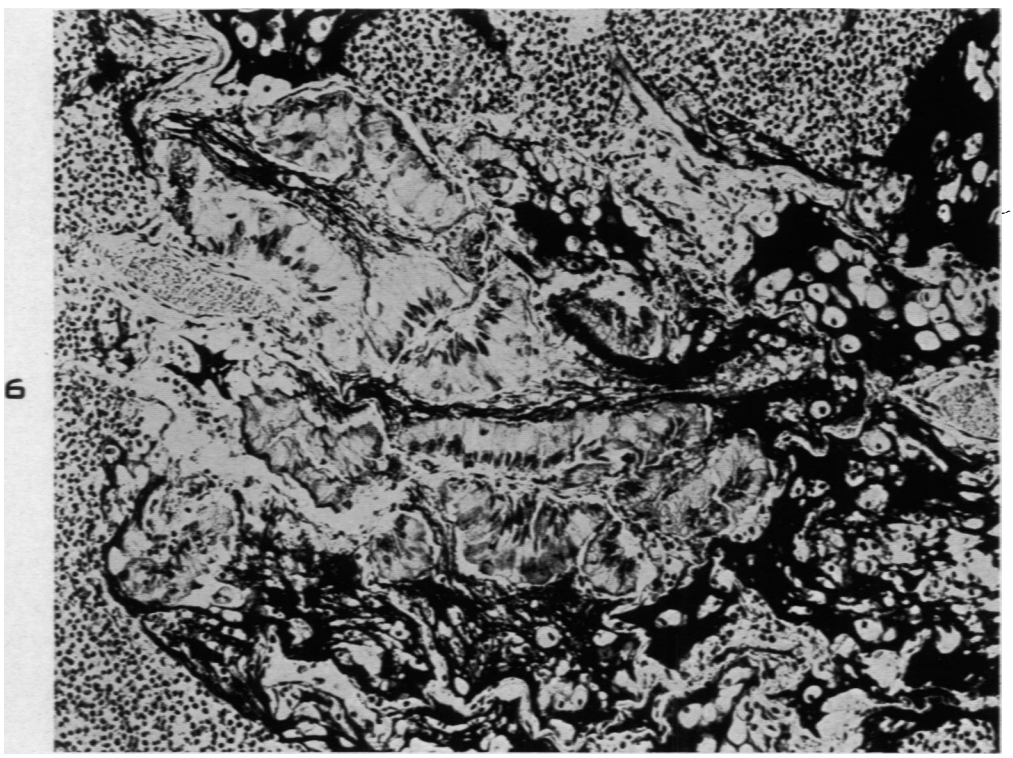

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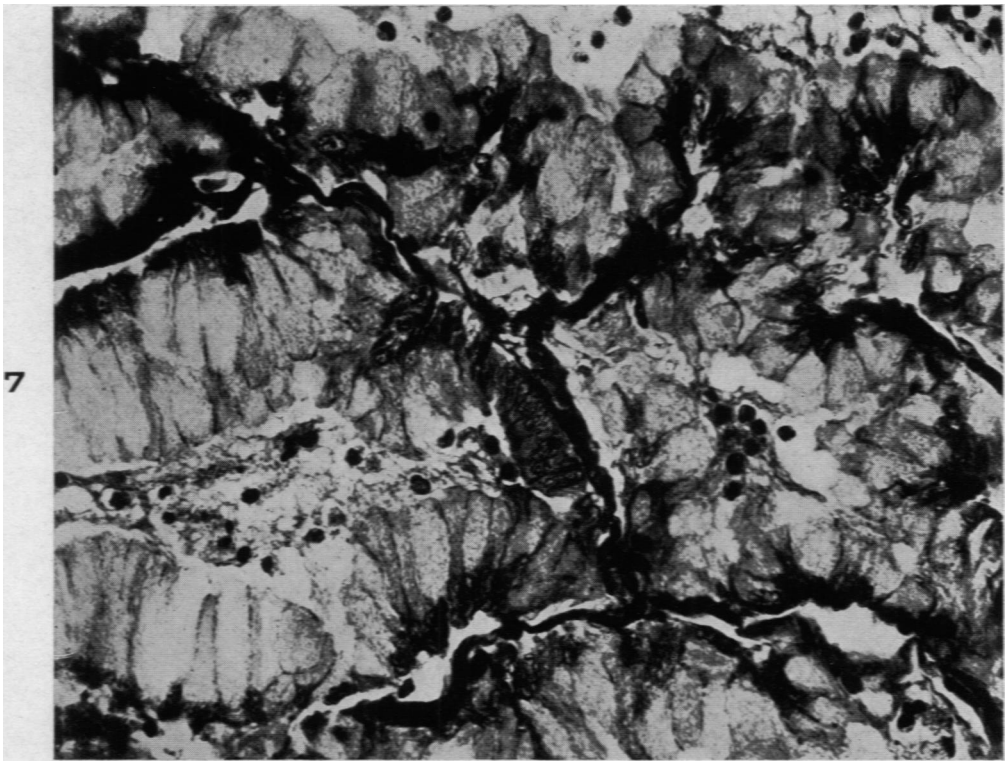
Taft and Nickerson Pulmonary Mucous Epithelial Hyperplasia

PLATE 79

FIG. 7. Case 2. Detail of the epithelial cells and alveolar walls to show that the latter are not involved or markedly changed by the hyperplastic process. Iron hematoxylin stain and Lee-Brown's modification of Mallory's aniline blue stain. × 390.

FIG. 8. Case 2. Photomicrograph of the left lower lobe, showing the marked fibrosis which the lobe has undergone. There is a central space lined with abnormal epithelium which shows moderately large papillary processes. Phloxine and methylene blue stain. × 175.



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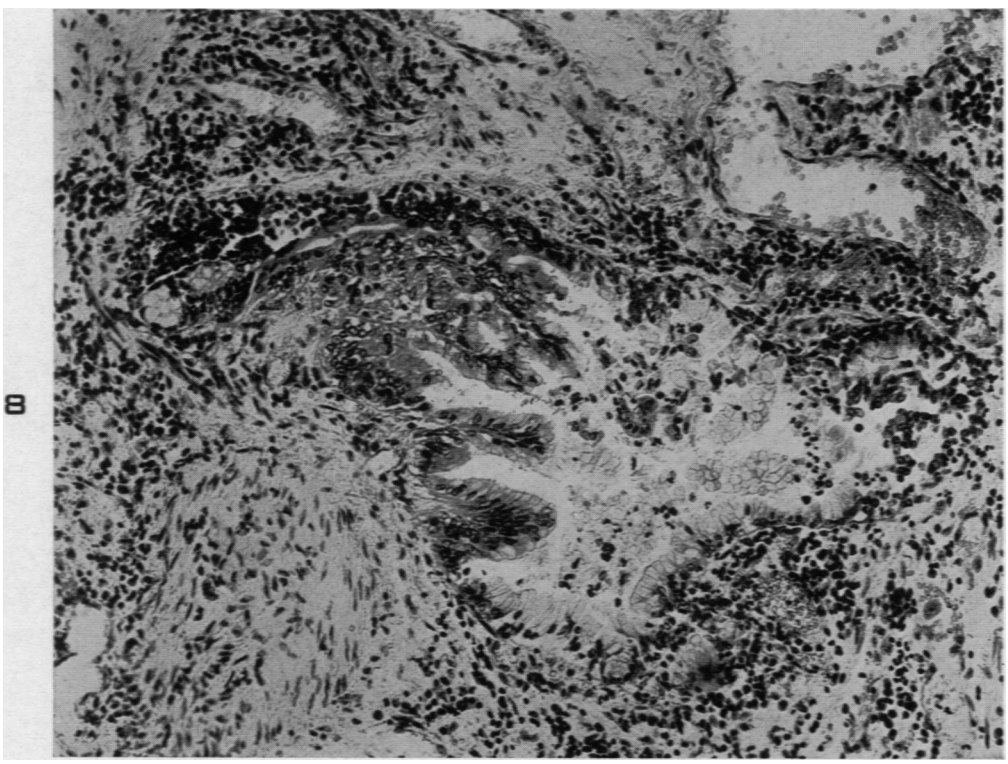

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