ANLAGEN AND REST TUMORS OF THE LUNG INCLUSIVE OF "MIXED TUMORS" (WOMACK AND GRAHAM) *

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It is quite apparent from perusal of the literature relative to the classification of tumors of the lung that there is but little agreement upon this subject. The greatest attention is, of course, focused upon the study of tumors of bronchiogenic origin because of their relative importance and comparative frequency. The possibility of treatment by surgical methods and the intrinsic malignant or benign character of the neoplasm are factors of vital consideration to the patient. For a comprehensive dissertation upon these phases of the subject the reader is referred to the paper by Goldman and Stephens [1] with the accompanying discussions.

Aside from the representative and basic studies of Fried [2-4] upon bronchiogenic carcinomata, wherein aberrant growth arising from the basal cell of mature tissue structure is discussed, the most significant observation relating to the pleomorphism of pulmonary neoplasms in respect to both cytology and histological pattern is that of Womack and Graham [5] upon mixed tumors. We [6] have, in a previous communication, discussed the intricate embryological mechanism of the lung and the likelihood of anlagen and rest alterations as a source of neoplastic formation. The intimacy of the laryngotracheal ridge and esophageal development serves to explain the entodermal anomalies of epithelial structures as emphasized by Rector and Connerley.[7] The mesenchymal defects are exemplified in congenital cystic disease, which topic, in general, is well set forth by Sellors.[8] Conceding such formative digressions as one source of tumor origin, the possibility of bizarre and diverse histological manifestations becomes apparent. It is not unlikely that these factors have led to the confused deductions and to the various names objectively applied in efforts at classification.

The designation "mixed tumors" of the lung by Womack and Graham [5] has had the salutary effects of emphasizing the embryological course of certain pulmonary tumors and of carrying a reasonable implication that some of these are benign. Strictly speaking, many such tumors may be unidermal, but with the intention of both confirming and stressing the observations of Womack and Graham, it appears to us that the terms "anlagen" or "rest" tumors serve more fully to em-

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phasize and encompass their objective. Naturally, the benignancy or malignancy of such neoplasms are dependent upon the same histological criteria regardless of origin.

Material Studied

The first two tumors which suggested to us origin from anlagen or rests occurred in newborn, full-term infants who had survived 7 and 5 days respectively. Such distinctive intrauterine tumor growths immediately indicated embryological aberrations. The case histories and clinical findings are not important. There were evident respiratory difficulties and congenital atelectasis seemed probable.

CASE I

In this infant surviving 7 days, it was found at necropsy that a tumor mass had replaced the entire lower lobe of the left lung. Upon sectioning, the mass was somewhat soft, and there were tubular structures, apparently dilated bronchi with thin walls, much like those noted in congenital cystic disease (Fig. 1). It is noteworthy that no irregular nodular formations were found except in that portion directed upward into the adjacent lobe. There had developed, for the greater part, a complete growth replacement of the normal structure of the lung. No other tumor masses and no metastasis were found.

Microscopical Examination

Sections prepared from various areas revealed, in general, the same histological picture. This consisted of irregularly distributed, tortuous branching tubules forming an apparently purposeless distribution of irregular alveolar spaces (Fig. 2). In many areas, infoldings or spur-like papillary invasions were noted. There was an occasional elongated tubular space having parallel sides and terminating in a simple bifurcation. These were suggestive of rudimentary bronchi. Tall, slender, columnar epithelial cells formed the linings for all the alveolar and tubular spaces. They revealed elongated, slender nuclei which were densely basophilic and presented a pale, slightly granular cytoplasm. In general these cells were arranged in a single layer, but occasionally they were stratified. The stromal structure was scant in amount and consisted of delicate, regularly arranged fibrous tissue. There was infrequently noted, in places where a larger amount of stroma was grouped, a more or less oval plaque of embryonal cartilage. Such plaques bore no direct relationship to the pseudobronchi and apparently were simple outgrowths of the mesenchymal development. Here and there in the stroma were found nutrient blood vessels.

CASE 2

This infant survived 5 days after full-term delivery. The upper lobe of the left lung presented two large, more or less rounded areas of ivory color which occupied the greater portion of its surface. Multiple radiating blood vessels, varying from approximately 1 mm. in diameter to minute dimensions, formed a cirsoid or telangiectatic arrangement over the surfaces (Fig. 3). Upon sectioning, these separate ivory-colored masses were found to merge beneath the surface. A structure of dense consistency was found to extend for a depth varying from approximately 1 mm. to 1 cm. It extended downward into a spongy reddish brown tissue which was less dense in character. The latter portion occupied approximately one-half of the upper lobe, the remaining tissue being crepitant and conforming to normal lung.

Microscopical Examination

In the pleural areas multiple blood-vascular sinuses were present within the connective tissue. These varied greatly in size and had thin walls. In many instances the lumen contained erythrocytes. Similar vessels appeared occasionally in the stromal projections within the underlying structure (Fig. 4). The nodules, as a whole, consisted of predominant young fibrous tissue. There were also numerous acinar spaces which were lined by low cuboidal epithelium and appeared in the aggregate as embryonal lung structure. Such, no doubt, had their origin from the entodermal layer of bronchial buds. A few irregularly shaped tubular spaces lined by columnar epithelium represented the more adult bronchiolar formations. It is probable that some of these latter spaces had certain continuity with the normally developed lung inasmuch as similar inflammatory cells were found scattered diffusely throughout spaces of both types.

CASE 3

A white male adult, 34 years of age, presented suggestive signs of an intrabronchial tumor, including hemoptysis. Specimens were obtained through bronchoscopic removal in 1935 and again in 1939. The interesting feature in this case is the dominance of one form of histological pattern in the primary biopsy specimen as compared to that removed 4 years later.

The specimen obtained in 1935 consisted of a small, rosette-shaped mass of tissue measuring approximately 6 by 5 by 4 mm. It was red, and soft. Upon removal, profuse bleeding occurred.

Microscopical Examinations

The sections presented a predominant mesenchymal derivative of cavernous hemangiomatous nature. There were numerous sinuses of irregular shape and size, lined with small rounded cells and containing numerous erythrocytes (Fig. 5). There were also similar spaces filled with cells resembling those present in embryonal bronchial glands.

The specimen removed in 1939 was an elongated oval portion of tissue of soft consistency and measuring 2 by 3 mm. in its greater diameters. Numerous more or less rounded acini were present. Many of these were lined with epithelium while others were completely filled with such cells. These cells presented comparatively large, deeply stained nuclei and only a small amount of light-staining protoplasm. They conformed to an embryonal or fetal gland type and were definitely of entodermal origin (Fig. 6). Only occasionally a sinus was seen containing blood, such as had been noted in the first specimen.

It seems evident that these two specimens were representative of mixed germinal layers. In the first a mesenchymal derivative was predominant while in the latter the tumor growth consisted to a great extent of elements of entodermal origin. This patient has just reported for observation. He is in excellent health and is free from all former signs and symptoms.

CASE 4

This individual was 19 years of age and had a history of occasional hemoptysis since the age of 7 years. Other clinical signs and symptoms were those usually present in a persistent intrabronchial polypoid growth wherein ball-valve action is present.

The specimen obtained through the bronchoscope was an irregularly shaped portion of tissue, of light pinkish red to pinkish gray color and somewhat firm in consistency. It measured approximately 7 by 5 mm.

Microscopical Examination

The sections revealed many more or less rounded acini with a lining of somewhat "ragged" epithelial cells with pale-staining nuclei and cytoplasm. These acini suggested a somewhat mature mucous gland structure; yet they were not of the fully developed adult type. In many of these spaces were found basophilic concretions of irregular shape, some of which resembled corpora amylacea (Fig. 7). While in portions the stromal structure showed nothing noteworthy, in other areas it formed very extensive plaques and presented extensive hyalinization (Fig. 8). In some of these hyalinized areas, cellular struc-

tures indicative of cartilage formation were seen. As has often been noted in growths in such locations, marked squamous-cell formation, metaplastic or aberrant, was present over the surface. The general characteristics of this tumor were indicative of mixed germinal origin inasmuch as both entodermal and mesenchymal structures appeared as participants in the neoplasm.

Summary

Four tumors of the lung, manifesting distinct evidences of origin either in anlagen or from more than one germinal layer, have been described. Two of these were of definite embryonal or anlagen origin, having developed during intrauterine life. In the first instance embryonal bronchial budding was perpetuated in a neoplastic mass. This was demonstrated by an aimless reduplication of tubular and immature alveolar structures indicative of a lack of orderly sequence of bud-branching. In the second case, evidence of both entodermal and mesodermal origin was revealed by areas of varied predominance of one or the other derivatives. In the third instance, less evidence of origin from mixed dermal layers was observed in each of two tissues removed for biopsy. Comparison, however, of the two specimens, between which there was an interval of 4 years, revealed a definite emphasis upon mesodermal structure in the first, while an entodermal character was clearly shown in the latter specimen. It is our opinion that the neoplasm in this second biopsy conformed closely in histological aspect to embryonal glands. The fourth example presented a neoplasm of mixed dermal components as revealed by the prevalence of elements of both layers.

It seems imperative, from the standpoint of the histological study of bronchiogenic tumors, that the embryological nature, as emphasized by Womack and Graham,[5] must receive serious consideration. In the study herein reported, bronchial anlagen origin is clearly established for certain of the tumors presented. Origin in an embryonal glandular rest is most probable in one instance.

While the biological characteristics of malignancy and benignancy are more or less constant regardless of the primary mature or embryonal origin of neoplasms, there are precedents for a benign nature for many tumors having the latter origin. Such serve to promote conservatism in the evaluation of the relative malignancy of the pulmonary growths which may belong to this group.

Note: We wish to express our appreciation to Dr. S. H. Colvin, through whose courtesy we obtained cases 3 and 4.

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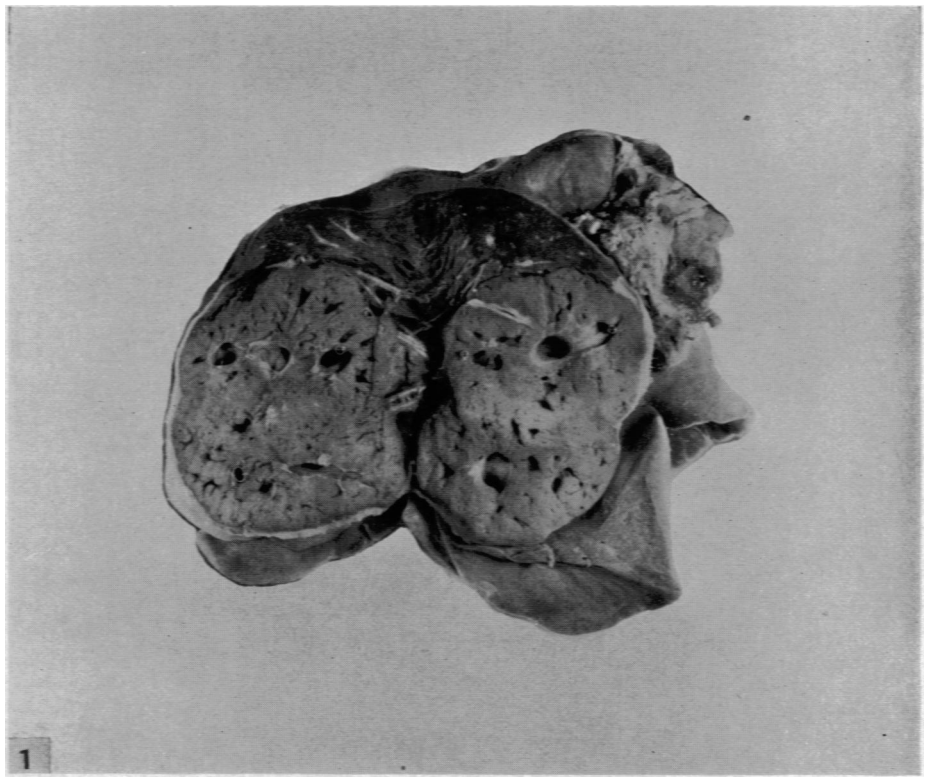
DESCRIPTION OF PLATES

PLATE 146

FIG. 1. Gross photograph of the left lung in case 1 showing a tumor mass replacing the entire lower lobe and compressing the upper lobe. The openings represent dilated tubules of apparently undeveloped bronchi analogous to those which occur in congenital cystic disease.

FIG. 2. Photomicrograph of the lung tumor in case 1 revealing branching tubules similar to those present in early embryonal lung structure. The lining consists of a single layer of columnar epithelium. × 300.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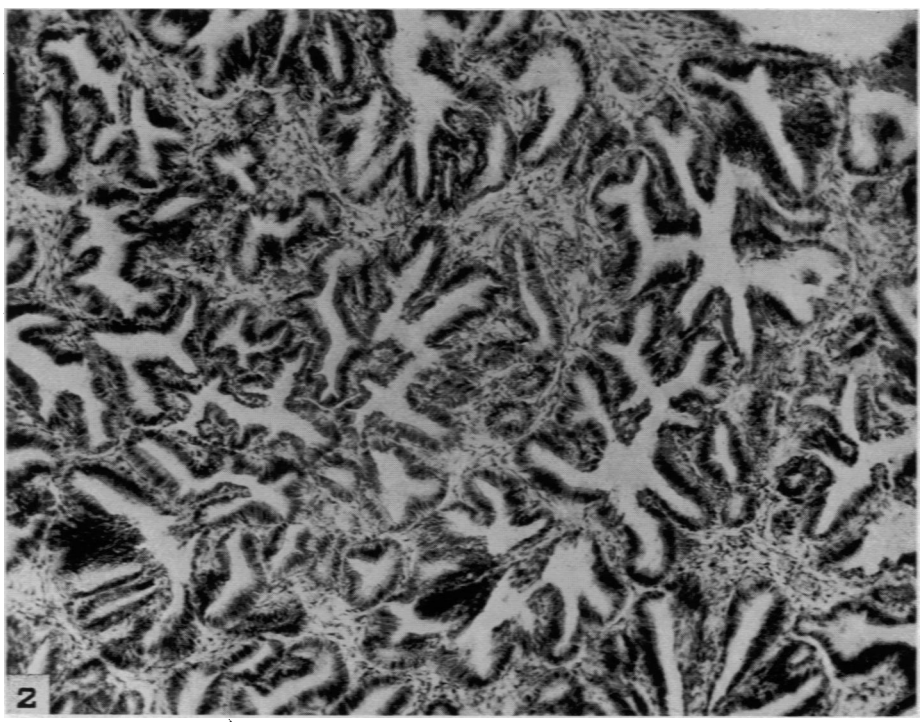
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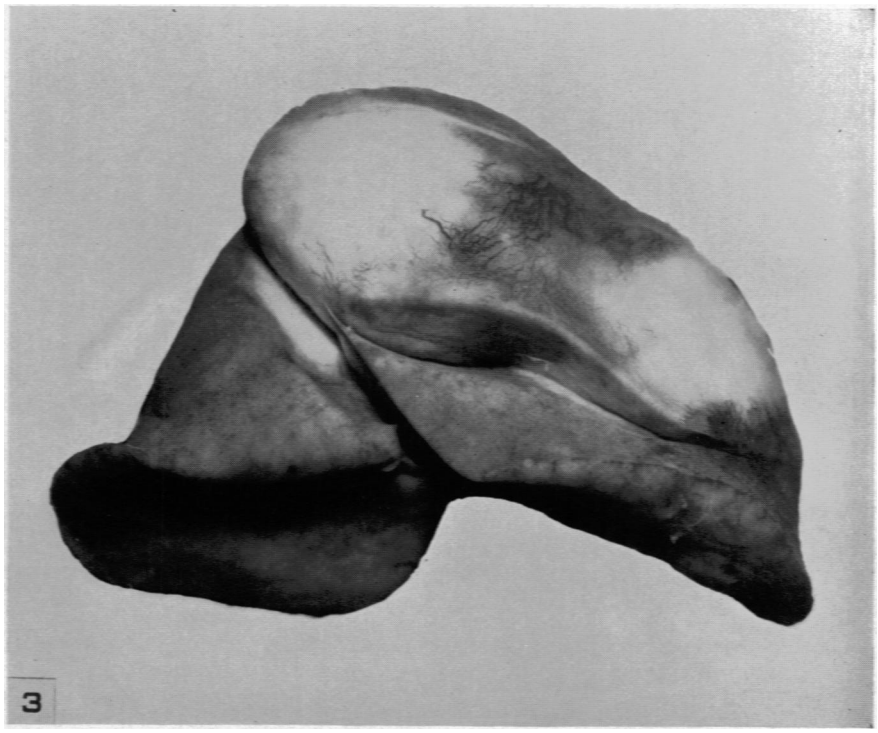
PLATE 147

FIG. 3. Gross photograph of the right lung of case 2. Large tumor masses are seen in the upper lobe of the right lung. Dilated vascular ramifications are present.

FIG. 4. Photomicrograph of a section of the tumor in case 2 wherein cavernous sinus formation and rudimentary alveolar arrangements of lung structure can be noted. × 200.



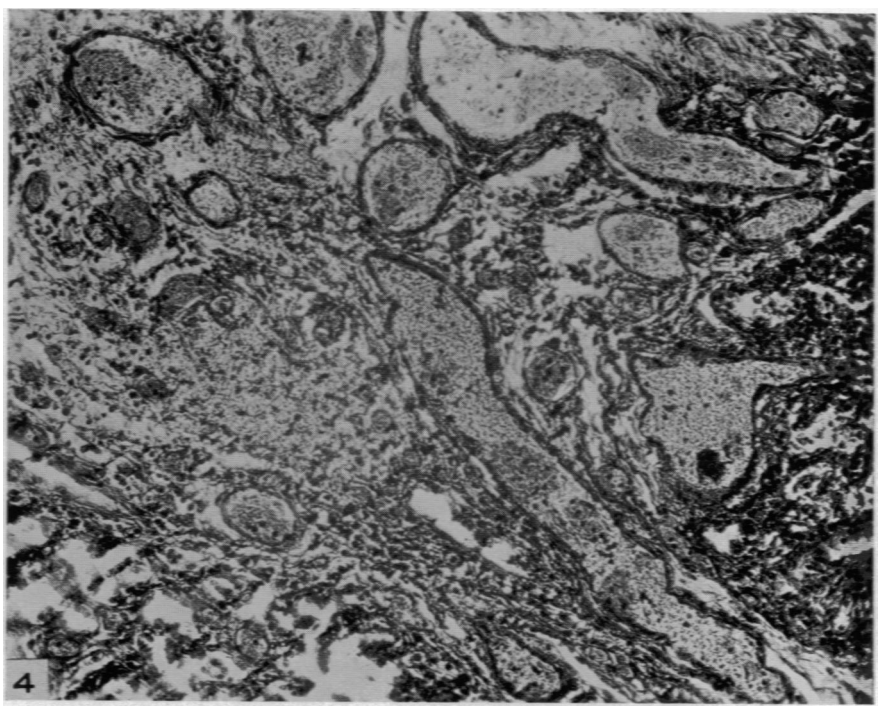


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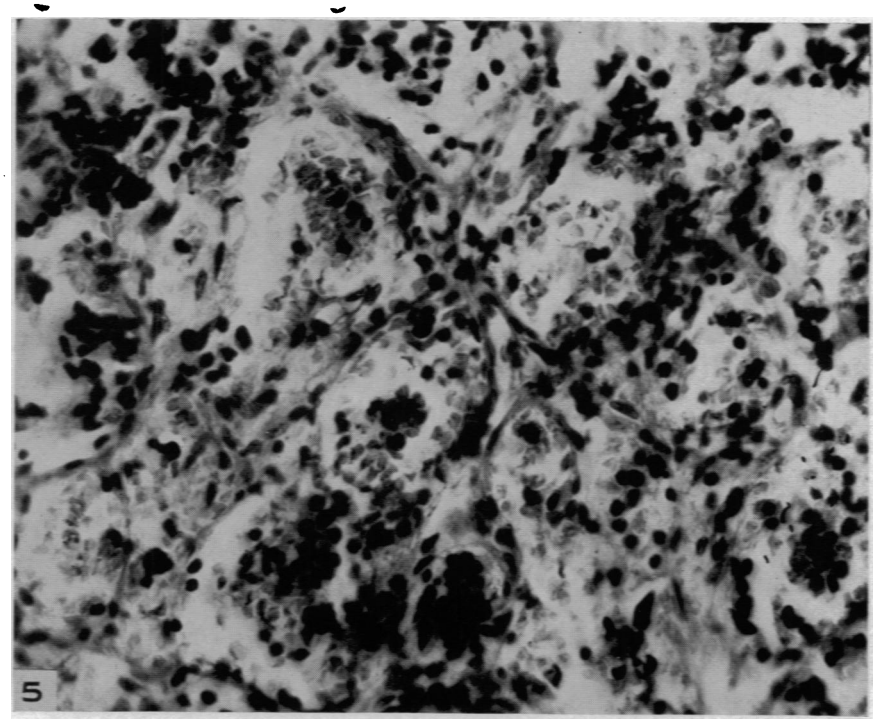
PLATE 148

FIG. 5. Photomicrograph of the biopsy specimen in case 3, obtained in 1935, in which angiomatous formation is predominant. Numerous vascular spaces containing erythrocytes are shown. × 500.

FIG. 6. Photomicrograph of the biopsy specimen of case 3, removed 4 years later (1939) in which embryonal glandular structure prevails. Numerous acini contain round and polyhedral cells with deep-staining nuclei and pale protoplasm. × 500.



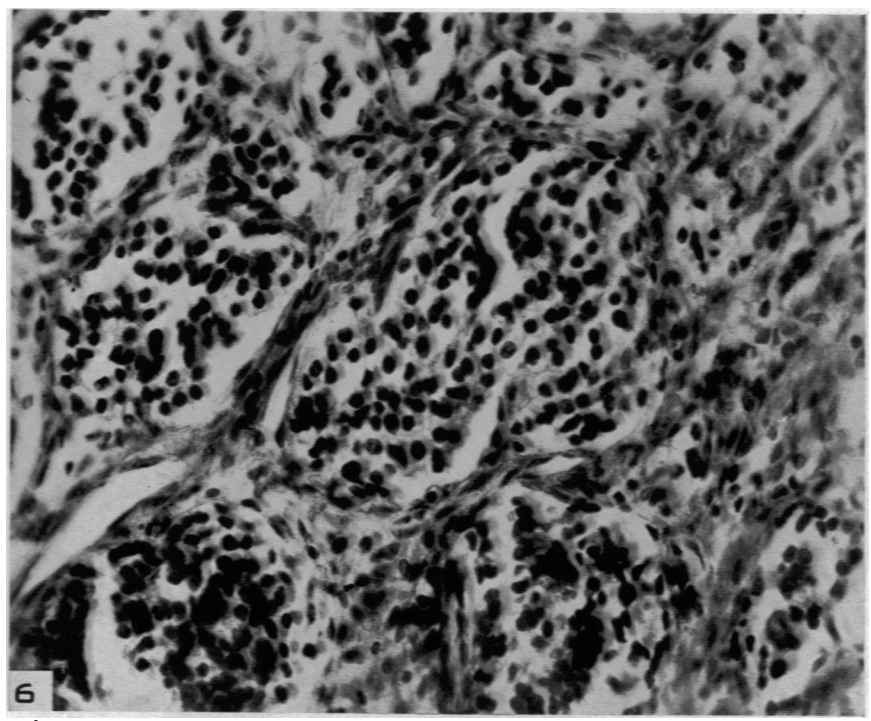


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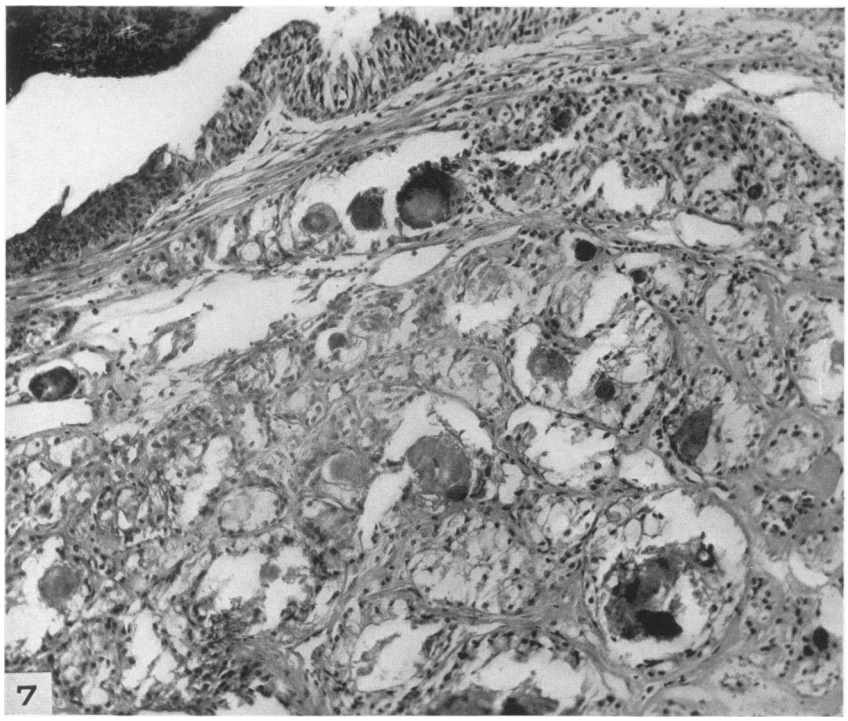
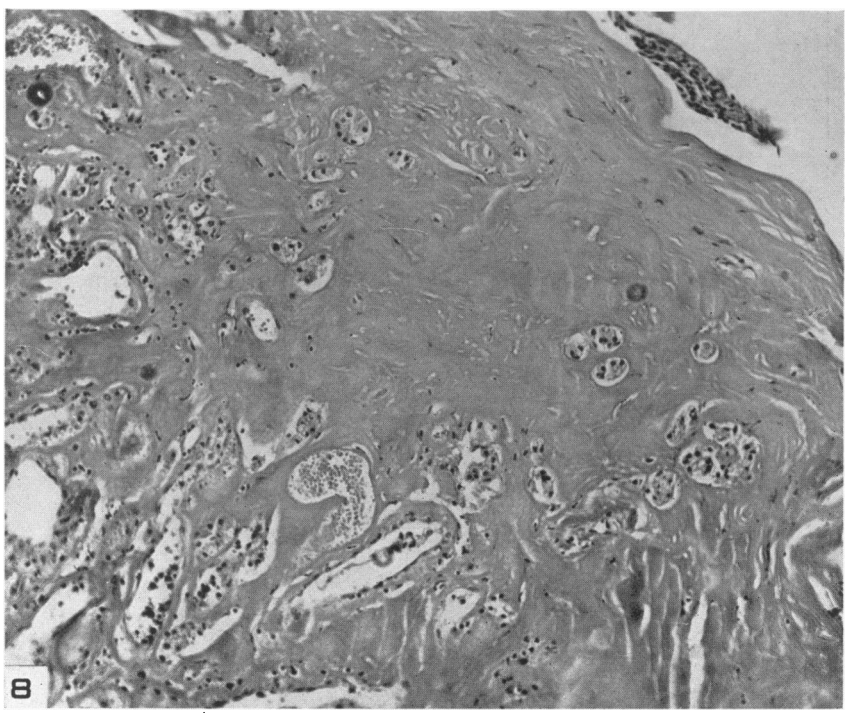
PLATE 149

FIG. 7. Photomicrograph of the biopsy specimen of case 4, revealing glandular acini, many of which contain concretions. The lining cells are pale and irregular in outline. The columnar epithelium of the bronchial lining above shows squamous cell metaplasia in the upper left portion of the field. × 250.

FIG. 8. Photomicrograph of the biopsy specimen of case 4, showing an area wherein extensive chondromatous structure prevailed. A few scattered glandular acini are present. × 250.





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