EPITHELIAL METAPLASIA IN CONGENITAL CYSTIC DISEASE OF THE LUNG *

Its Possible Relation to Carcinoma of the Bronchus

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As primary cancer of the lung is becoming more and more frequently an operable lesion, opportunities to observe earlier growths are likewise becoming more frequent. This is of greatest importance for it affords a chance to correlate the microscopic picture, as determined from bronchoscopic biopsy, with the gross pathological findings in the early stages of the disease. In such a way a confident understanding of the clinical picture may be reached. Before this understanding can be brought about, however, such a correlation between the microscopic and clinical picture must be established.

As was suggested several years ago,[1] forms of classification based on the microscopic picture as seen in far advanced lesions have but little to offer the clinician. Many of the tumors, by the time they have become widespread, exhibit a marked degree of pleomorphism producing different phases of cellular differentiation depending upon the site from which the section was taken. However, this does not always occur, for at times widespread tumor growths will be seen in which sections taken from many areas will show the same phase of cellular configuration.

There seems to be but little correlation between the amount of cellular differentiation and the extent of the growth. Squamous cell cancer of the bronchus offers a good example of this. It is not unusual to find a very well differentiated squamous type of tissue in an early lesion; nor is it unusual to find a similarly well differentiated type of squamous epithelium in a far advanced lesion. The same lack of correlation between the amount of cellular differentiation and extent of growth holds true in squamous cell cancer that shows even poor differentiation. We have on numerous occasions seen relatively poorly differentiated squamous epithelium in lesions definitely operable. In view of the fact that normal bronchial epithelium under certain conditions possesses the ability to form keratin, it is difficult to interpret

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the meaning of keratinization in carcinoma of the bronchus and the relationship to its ability to spread. Until such an interpretation is forthcoming its clinical significance must remain vague. It seemed to us, therefore, that any correlation between a particular microscopic picture and the extent, and therefore the operability, of the lesion is so often hazardous that various morphological classifications based on the microscopic picture of the lesion are all of but little clinical value.

Recently we had reason to modify the foregoing conceptions somewhat.[2] As our experience with early lesions increased we began to encounter a type of tumor that could be set apart from the more classical type of bronchiogenic carcinoma. It was associated with a very definite clinical picture. It was seen in females just as often, if not oftener, than in males. It usually occurred in younger people and often was characterized by rather long-standing clinical features, many of the patients giving symptoms dating back a number of years before more active growth had occurred. The pathologic picture was different from the usual type of carcinoma in the sense that the lesion protruded into the bronchus as a nodule covered with epithelium. This epithelium was generally squamous and overlay an area of fibrous tissue distal to which tumor cells were seen. These tumor cells were often arranged in cords and alveoli resembling unaërated fetal lung tissue. Not infrequently there also was found evidence of mesodermal tissue such as cartilage, bone, muscle and often an extreme vascularity. When the specimen along with the entire lung or lobe was removed surgically it was noted that the tumor was often collar-button-shaped. The larger portion of it was frequently outside the lumen of the bronchus extending into the lung parenchyma. The fact that only a minor portion was evident and the major portion invisible suggested the analogy to an iceberg. It may or may not have metastasized. Almost universally there was some type of congenital abnormality of the lung tissue. This was present most frequently as an abnormal number of lobes. Other pulmonary malformations were observed. Because of the resemblance to fetal lung tissue, its association with congenital abnormalities of the lung and the mixed tissue elements present, it occurred to us that this lesion was probably one intimately connected with congenital malformation of the lung.

This conception then would recognize two main types of bronchial tumors. One of these arises in apparently adult epithelium, is much more frequent in the male after middle age, usually possesses some tendency on the part of the epithelium to form keratin and generally spreads fairly rapidly. The other type probably arises in tissue of embryonic type, is generally associated with congenital pulmonary disorganization, does not favor either sex and may remain in the same site for many years before invading other tissue. Each of these types, therefore, presents features both morphologic and clinical that make it distinguishable in most instances. Such a classification has been of the greatest value to us from the standpoint of both therapy and prognosis. The latter type includes the tumor which in the literature is commonly designated as bronchial adenoma. In our opinion this tumor should be regarded as potentially malignant, although in many instances it may show no tendency to invade other tissues for many years and doubtless occasionally has been successfully removed through the bronchoscope.

We have been particularly interested in those tumors often associated with developmental defects in the lung.

If such a conception is true, in all probability one should occasionally be able to find evidence of epithelial overgrowth in pulmonary tissues which are the site of congenital malformation. The following report is concerned with efforts to identify such evidence of overgrowth in the epithelial elements of disorganized pulmonary tissue before such overgrowth was evident clinically.

Observations

Because of the availability of surgical material, congenital cystic disease of the lung was taken as a lesion evidencing abnormal pulmonary formation. All of this material presented severe secondary infection with concomitant distortion of the anatomical picture. Accordingly, only those cases were used in which adequate, careful studies could be made. There were 9 such patients, 6 of whom were treated by total pneumonectomy and 3 by lobectomy.

Immediately after the surgical removal of the lung or lobe the specimen was distended by the injection of Kaiserling's solution into the patent bronchi, care being used not to produce over-

distention and distortion. After fixation for 24 hours the specimen was sectioned along the axis of the major bronchi. A longitudinal slab of the entire lung or lobe, as the case might be, approximately 1 cm. thick, was then made and this was cut into smaller blocks which were then fixed in formaldehyde for 24 hours and sectioned after paraffin embedding. The sections were stained with hematoxylin and eosin, phosphotungstic acid and hematoxylin, and, in instances where indicated, with Mallory's aniline blue and orange G stain. The sections were studied particularly in relation to the normal architecture of the bronchi and bronchioles with attention to the relative amount and type of tissue going into the formation of these structures.

Of the 9 specimens submitted to such study, in 3 there was evidence of epithelial overgrowth found microscopically which upon subsequent examination of the gross specimen was not apparent with the naked eye. In none of the specimens was any gross evidence of tumor formation seen. It must be assumed, therefore, that the structures to be described are entirely local in their growth.

Reports of Cases

Case 1

A. V., male, age 34. Five years before admission to the hospital the patient had suffered an attack of bilateral bronchopneumonia. He was in bed 1½ months and spent an additional 2 months in convalescence. Two years before admission to the hospital he developed a cough which became progressively worse and was productive of white, foul sputum, particularly in the morning. There was a gradual development of dyspnea. Occasionally the sputum was blood-tinged and occasionally there was slight pain in the left chest. Upon admission to the hospital he was found to have numerous cavities throughout the entire left lung which upon bronchoscopic examination were found to be filled with pus. There was no evidence of bronchial obstruction nor of tumor formation. The right lung was normal. Accordingly, on April 3, 1939, the entire left lung was removed by Dr. Brian Blades.

Gross Pathology. Figure 1 shows the gross appearance of the lung. The visceral pleura was covered by firm, fibrous adhesions. Palpation of the lung revealed atelectasis in the lower lobe with many spotty, cystic areas more noticeable in the upper lobe. On sectioning the lung, the pleura was found to be thickened to the extent of about 4 mm. The bronchi and bronchioles, particularly of the upper lobe, extended to large cavities lined by

walls of varying thickness depending upon the amount of inflammation present. Within these cysts there was found a great deal of pus. The lower lobe for the most part was atelectatic although here and there one could see fairly large cysts.

Microscopic Pathology. Very little lung parenchyma was encountered. The interalveolar septa were markedly thickened, presumably as the result of chronic inflammatory change. The alveoli all seemed to be considerably dilated. The cystic cavities were lined by bronchial epithelium, some of which was ciliated and beneath which one found a chronic inflammatory reaction, nonspecific in type, with complete absence of many other bronchial structures. Very seldom was cartilage found. Smooth muscle for the most part was absent. There were no mucous glands. Whether these structures were never formed or whether they had been destroyed by inflammation cannot be determined; the latter would be most unusual. In one area there were noted masses of epithelial cells tending to be squamous in type which had delimited external borders and which were normally differentiated and showed no evidence of mitotic figures. Figure 2 is taken through this area. These cells had their origin well away from bronchial tissue. Although the cell masses were not encapsulated, they gave the appearance of very slow growth.

In the larger bronchi the structures were for the most part normal. Sections through the lymph nodes showed only chronic inflammatory change. The picture throughout all of these sections was that of a congenital lesion of the lung in which the bronchi and bronchioles were enormously dilated into cyst formation. Because of the size of the cysts and because they were lined by perfectly normal bronchial epithelium and showed rather minimal inflammatory change as compared to an unquestioned case of bronchiectasis, one is justified in calling this congenital cystic disease of the lung rather than a marked bronchiectatic change.

Case 2

L. F., male, age 48. Fifteen years before admission to the hospital the patient developed a productive cough which persisted for 2 years and which came on spontaneously. There was gradual improvement. About 2 years before admission to the hospital the patient developed influenza and following his recovery there was a return of the cough, which has remained constant and productive. The sputum was purulent and foul and was much

more profuse in the morning. During these 2 years he had lost approximately 15 lbs. Upon admission to the hospital he was found to have numerous saccular dilatations involving the entire left lung, which upon bronchoscopic examination were found for the most part to be filled with pus. The right lung was relatively normal. There was no evidence of bronchial obstruction of any sort. On April 27, 1939, the entire left lung was removed (E. A. G.).

Gross Pathology. The material examined consisted of the entire left lung. There were many adhesions involving the pleura which were unusually firm. On cut section the bronchi were seen to be tremendously dilated and extended into large cystic cavities which were filled with pus. The lingula was the only portion of the upper lobe involved in the cystic process. The lower lobe was markedly involved and in many areas presented atelectasis.

Microscopic Pathology. Microscopic study showed the bronchi to be markedly dilated. The lining epithelium was everywhere intact and in some places changed to a squamous type. The bronchi in many places were dilated and in most areas presented a notable absence of some of the normal mesodermal elements of the bronchial wall, notably cartilage and smooth muscle. In other areas, however, there was an overabundance of smooth muscle. There was very little scarring or fibroplasia of the bronchial wall and a relatively small amount of infiltration by inflammatory cells. These for the most part were lymphocytes and plasma cells. In the lumen of the bronchi, however, there was considerable pus. Upon studying the extension of the bronchi into the periphery of the lung, cystlike structures lined by bronchial epithelium were encountered. The air sacs were often markedly dilated while in other areas considerable atelectasis was present. An interesting feature around some of the bronchial walls was an ingrowth of the epithelium of the air sacs into the wall itself forming small cystlike cavities. In several areas nests of epithelial cells were observed in the bronchial wall just beneath the epithelium. For the most part these cells were cuboidal, although here and there they showed a tendency to become spindle-shaped, apparently growing at random (Figs. 3 and 4). There was no encapsulation. The nuclei for the most part were vesicular and relatively symmetrical. There was only a scant cytoplasm in many of the cells, which was vesicular. Mitotic figures were not apparent. The size of the cystic cavities, the

absence of normal bronchial elements in the wall and the relatively slight amount of inflammatory reaction present in the wall all suggest that the lesion present here is one of congenital cystic disease rather than that resulting from an acquired infection.

Case 3

W. T., male, age 39. At 3 years of age the patient had a suppurative lymphadenitis and osteomyelitis which healed in approximately 3 years. At 9 years of age he developed pneumonia, following which he had a productive cough with foul sputum which had since been constant. There had been no hemoptysis nor had there been any great change in his condition. One year before his admission to the hospital the patient developed influenza, at which time signs suggestive of pulmonary tuberculosis were found and he was sent to a tuberculosis sanitarium. Here he was thought to have bronchiectasis of the right lower lobe and was referred to the Barnes Hospital where he was found to have large saccular dilatations chiefly confined to the right lower lobe. On bronchoscopic examination these cavities were found to be filled with pus. There was no evidence of obstruction to the bronchi nor was there any evidence of pulmonary tuberculosis. Accordingly, on August 27, 1940, the right lower lobe was removed by Dr. Brian Blades. Because no evidence of an interlobar fissure was seen at the time of operation it was necessary to make a resection of that portion rather than to perform an ordinary lobectomy.

Gross Pathology. Examination of the gross specimen showed the entire surface to be covered by irregular patches of fibrous tissue representing adhesions which had been divided at the time of operation. Landmarks on the specimen were rather difficult to identify. The posterior inferior portion of the lobe was dense and of a firmer consistency than the anterior portion of the specimen. On cut section it was found that many of the larger bronchi were markedly dilated. The walls of these bronchi were considerably thickened. The entire posterior portion of the lobe was almost completely consolidated and the anterior portion fairly well aërated. In the posterior portion near the base there was a large cyst measuring 1.5 by 2.5 cm.

Microscopic Pathology. The features of chief microscopical interest were limited to the bronchi. The markedly dilated walls showed considerable irregularity, there being many infoldings with the production of an irregular lumen. The epithelium was intact over a good portion of the bronchi. However, in certain areas the mucosa was lost, leaving a connective tissue base. In other areas the columnar epithelium lining the dilated bronchi

was thickened and there was a suggestion of a change to a squamous type. On the whole, however, there was a small amount of inflammatory exudate to be found in these dilated bronchi. There was almost complete absence of cartilage throughout the smaller bronchi and bronchioles. In several areas there was marked metaplasia of epithelial elements. These areas were often found in regions normally occupied by mucous glands and presented as large islands of cellular material, fairly well differentiated and showing only a few mitotic figures (Figs. 5 and 6). There was a striking tendency for growth along the subintimal portion of the pulmonary vein. Often the epithelium would project into the vein, giving the appearance of a thrombus of tumor tissue. In most instances, however, it was possible to see that the endothelium was intact overlying the metaplastic tissue. Adjacent to these areas of epithelial hyperplasia there could also be seen areas of new muscle formation without any appreciable relation to the normal architecture. This muscle was of the smooth type and was not associated with any bronchus. Examination of the lymph nodes showed chiefly sinus hyperplasia with epithelial elements. Other portions of the lung showed various phases of atelectasis and pneumonitis such as one would expect from the gross picture. Because of the obvious evidence of malformation presented in this lobe it was felt that the inflammatory process here was probably secondary and that the nature of the lesion was one of congenital cystic disease.

Discussion

It is possible that objections might be raised to the consideration of these pathological processes as congenital cystic disease rather than as bronchiectasis. We have classified these lesions as congenital cystic disease because the lungs have shown evidence of developmental malformation. The fact that clinical symptoms in these three individuals did not develop until relatively late is of no significance. Frequently, clinical symptoms in congenital cystic disease of the lung do not occur until the development of an infectious process. Where cysts are not infected it is not unusual to find them symptomless.

The epithelial changes described in the three cases were not apparent to the naked eye. The blocks were examined for such

changes before sectioning. In no instance was there any evidence of extension to contiguous structures such as the mediastinum, nor was there any evidence of distant metastasis. These lesions were found only after careful search, requiring in some instances as many as fifteen separate blocks of tissue. While the process described obviously represents abnormal cellular growth, because of its local situation we have not felt justified in considering it malignant from a clinical standpoint.

While the changes mentioned do not resemble the picture seen in the so-called mixed tumor of the bronchus that we have previously described, we feel that they do represent a similar process; namely, a disturbance in the fundamental structural tissue growth so often seen in areas of abnormal tissue organization. Where this situation is encountered in other parts of the body it is not unusual to find malignant manifestations following environmental stresses and strains. Whether such abnormal epithelial proliferations as described here are concerned in carcinomatous change is a question that we shall consider in a subsequent publication.

Conclusions

Studies were undertaken to determine the presence of abnormal epithelial overgrowth in congenital malformation of the lung. In 3 of 9 patients operated upon for congenital cystic disease of the lung, evidence was found of such overgrowth which consisted for the most part of masses of poorly differentiated epithelial cells tending to appear as spindle cells or cuboidal cells showing a definite tendency toward invasion but nowhere presenting any evidence of metastasis. In none of these specimens was the lesion apparent to the naked eye.

REFERENCES

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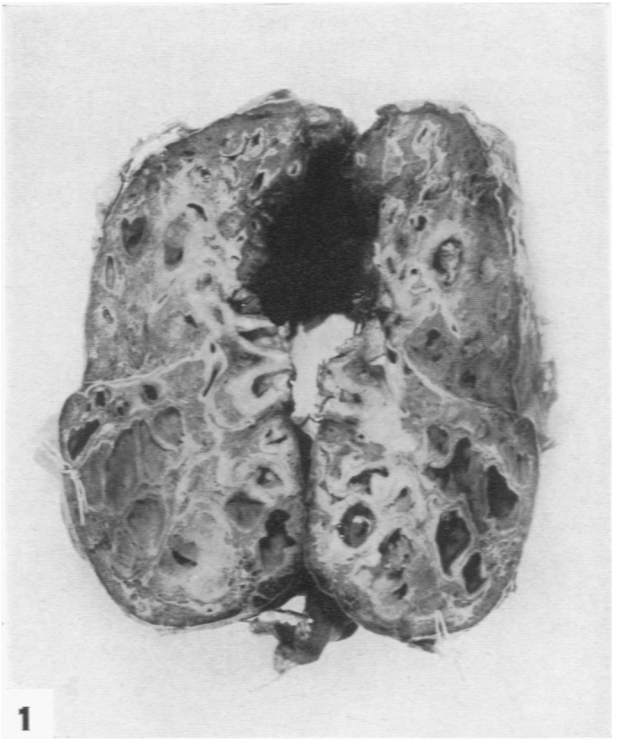
2. Womack, N. A., and Graham, E. A. Mixed tumors of the lung. So-called bronchial or pulmonary adenoma. *Arch. Path.*, 1938, **26**, 165–206.

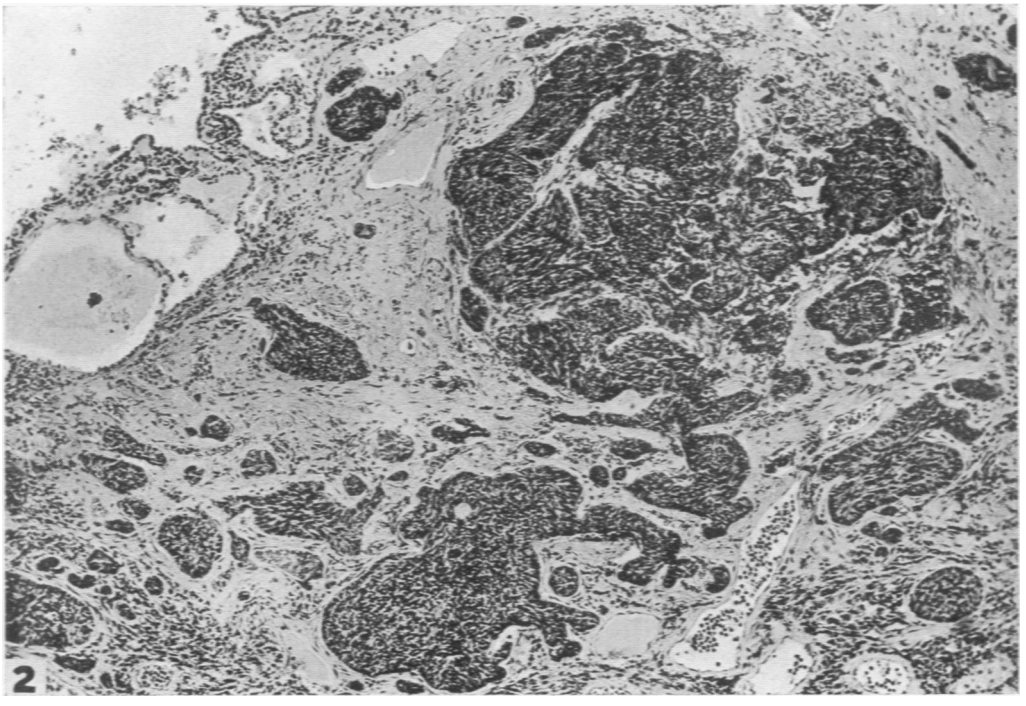
DESCRIPTION OF PLATES

PLATE 107

FIG. 1. Sagittal section through entire lung. The lower lobe presents numerous large cysts, the walls are moderately fibrosed and there is very little normal lung tissue present.

FIG. 2. An area of metaplastic epithelium in which the cells are for the most part spindle-shaped and the margins of the cellular areas are often clearly demarcated by palisading of the nuclei. There is no evidence of encapsulation. × 250.



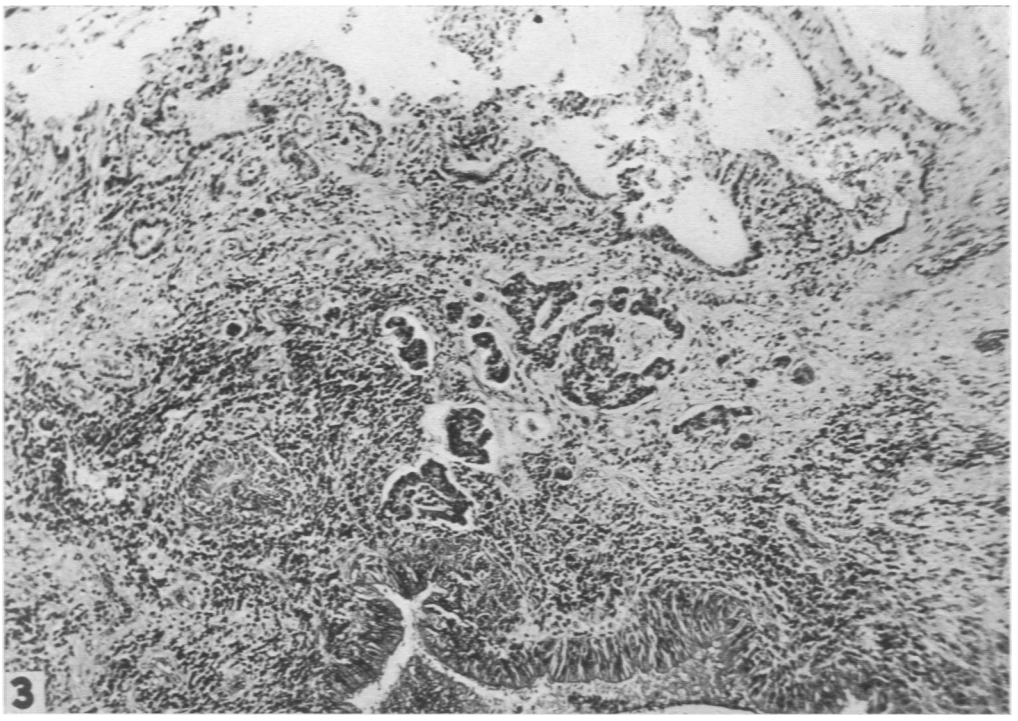


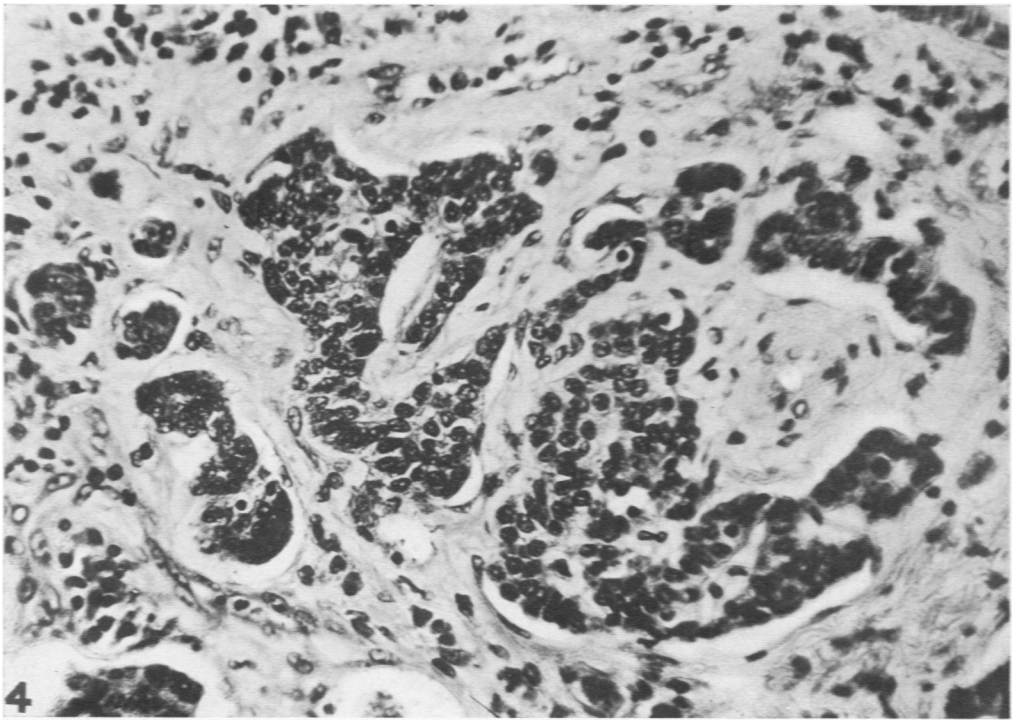
Womack and Graham Metaplasia in Cystic Disease of Lung

PLATE 108

FIG. 3. A low power view of epithelial overgrowth showing relationship to the bronchial epithelium. There is a moderate round cell reaction throughout the wall of the bronchus. No cartilage is visible. The epithelium lining those air sacs adjacent to the bronchus is of cuboidal type. × 300.

FIG. 4. Another area similar to that described in Figure 3 is shown. The epithelial masses give the appearance of having invaded lymph vessels. × 600.



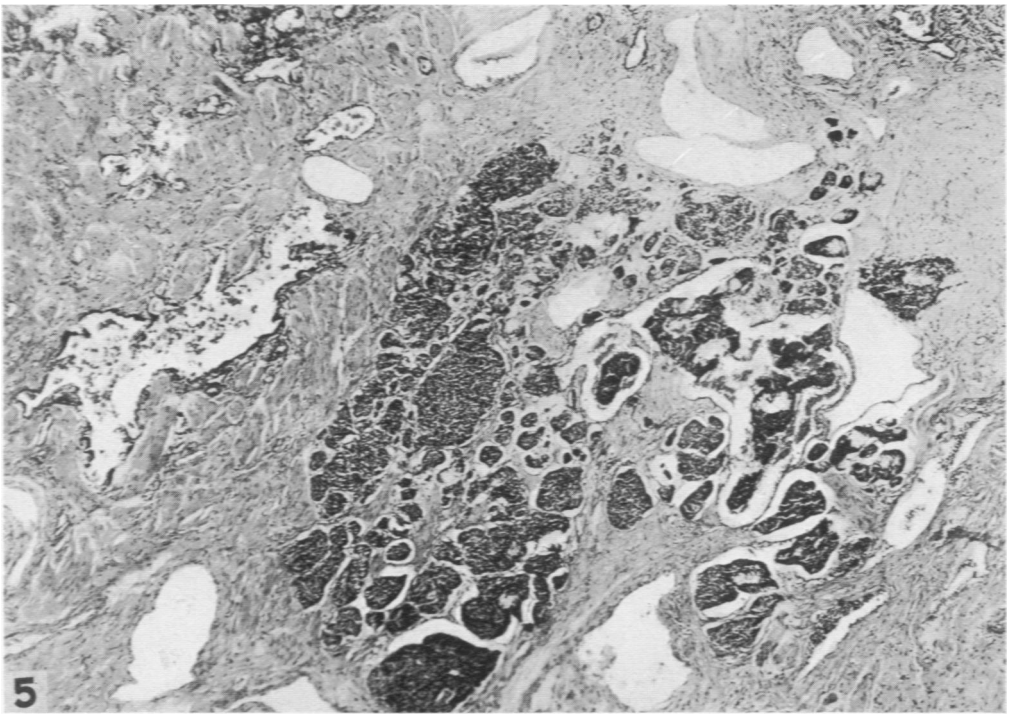


Womack and Graham Metaplasia in Cystic Disease of Lung

PLATE 109

FIG. 5. Low power view of an area of epithelial hyperplasia found well away from any bronchial wall. There are numerous small cavities and a large amount of smooth muscle is found in the stroma. These masses of cells are growing without any evidence of encapsulation. × 250.

FIG. 6. Groups of epithelial masses segregated in a dense area of smooth muscle and fibroblasts. The cells tend to be spindle-shaped, although the margins of the masses evidence palisading of the nuclei. × 250.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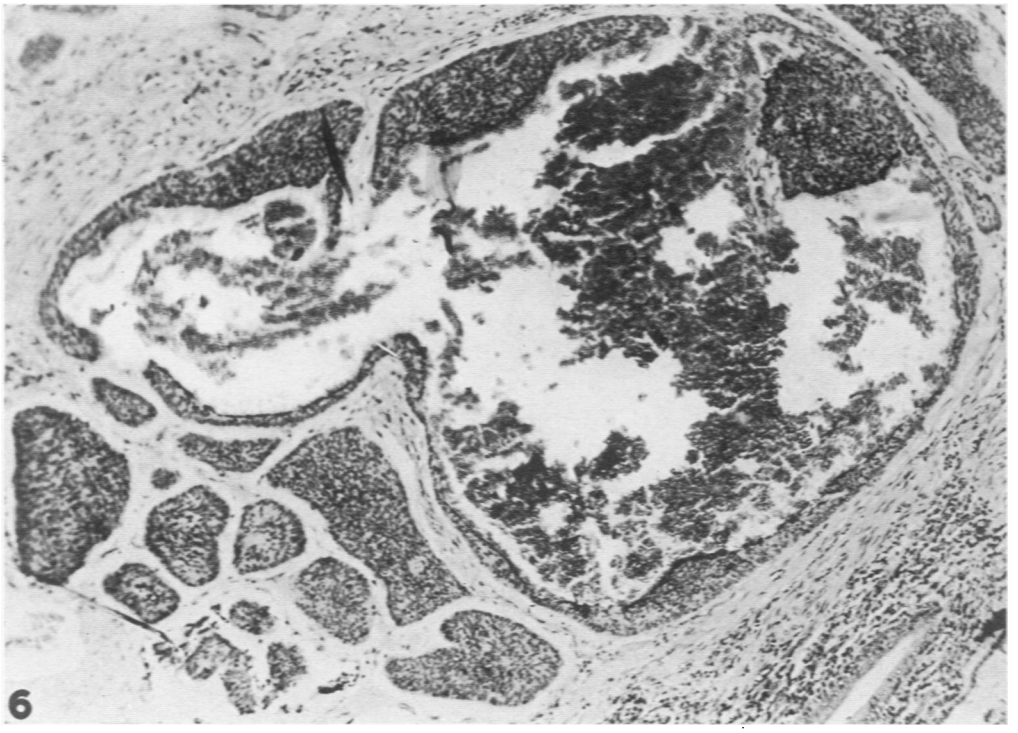
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