MUCO-EPIDERMOID TUMORS OF THE BRONCHUS ARISING FROM SURFACE EPITHELIUM*

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In a study of bronchial adenomas of the carcinoid and cylindromatous types,[1] 5 tumors were encountered which closely resembled these adenomas in behavior and gross appearance, but differed in microscopic structure. This report briefly outlines the clinical and roentgenologic findings in the 5 patients bearing these tumors, with notes on the pathologic observations, treatment, and course.

The symptoms experienced by these patients were quite similar and were characteristic of slowly developing bronchial obstruction; usually, the symptoms were intermittent and often absent for long periods of time. The commonest complaints were chronic productive cough, wheezing, and hemoptysis, and the illness was punctuated by episodes of acute pneumonitis. Occasionally there were dyspnea and chest pain. No patient lost weight, and indeed, 2 patients gained considerably during the course of the disease. The longest history was 30 years, characterized by repeated episodes of hemoptysis; the shortest was 3 months, heralded by a bout of pneumonia. Three of the patients were male, 2 female. Their average age at the onset of symptoms was 45 years, the youngest being 28 and the oldest 66; at the time of diagnosis and treatment, the average age had risen to 56 years, the youngest being 43 and the oldest 66. On physical examination there were no signs except those of pneumonitis to suggest the presence of a bronchial tumor.

The roentgenologic features were of considerable importance in the determination of the presence of a lesion, its localization, and the evaluation of its resectability. In those patients in whom serial roentgen examinations were made, one of the most striking findings was the leisurely growth of the tumors. They produced gradual change in the lungs, indicating bronchial obstruction, or showed slow but relentless growth of a mass. In other words, the principal observations were those indicative of bronchial obstruction or increase in the size of a mass. The former differed in no particular way from what might be found with other lesions which cause bronchial obstruction. The slowly

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growing lesion, as viewed by roentgenogram, was roughly spherical or slightly lobulated, homogeneous in density, and resembled a peripheral primary carcinoma or isolated metastatic neoplasm (Figs. 1 and 2). No lymph node involvement was demonstrated.

All patients were subjected to bronchoscopy for diagnostic purposes, and in one instance this procedure was utilized as a therapeutic measure. Although all of the lesions arose in major bronchi (3 in the right upper lobe, 1 in the right lower lobe, and 1 in the right main bronchus), 2 were not seen at the time of initial examinations. In one case this was carried out 7 and 6 years respectively before the time of ultimate resection, and in the other, repeated bronchoscopic examinations were performed. One tumor had no biopsy examination but was considered to be a bronchogenic carcinoma by the observer. In the remaining 2 patients, the tumors were visualized and biopsy specimens procured at the initial bronchoscopy. The lesion was classified as an "atypical adenoma" in one case (1935) and "consistent with adenoma" in the other (1948). At the time of later bronchoscopic examination, in 1946, of one of the patients whose tumor had not been visualized 6 years previously, a specimen was obtained which was termed "basal cell carcinoma."

The pertinent clinical data are given in Table I. The position of the tumors is illustrated in Text-figure 1.

TABLE I

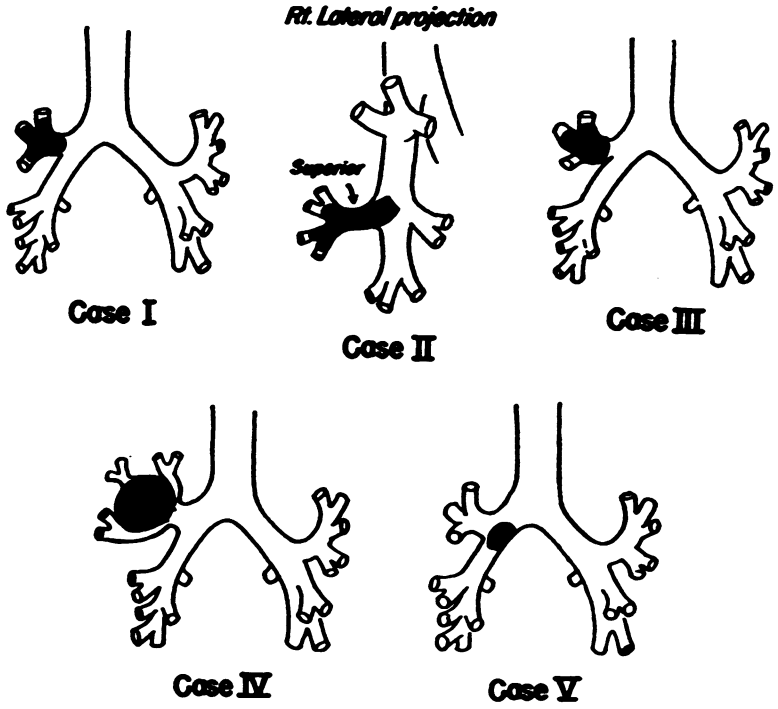
Clinical Data for Five Patients with Muco-epidermoid Tumors of the Bronchus

Case	Sex	Age at time of diagnosis	Duration of symptoms (yrs.)	Position of tumor	Treatment	Present condition	Length of follow-up (yrs.)
1	M	51	6	R. U. L.	Right pneumonectomy	Good	10
2	M	43	15	Main L. L. bronchus	Right middle and lower lobectomy	Good	8
3	M	66	3/12	R. U. L.	Right upper lobectomy	Good	6
4	F	62	30	R. U. L.	Right upper lobectomy	Good	4
5	F	59	1½	Right main bronchus	Transbronchoscopic eradication	Died during bronchoscopic resection	

Pathologic Observations

Case 1. Right Pneumonectomy

The tumor occluded the right upper lobe bronchus just proximal to its bifurcation and was attached to the mucosa at this point. Cylindrical ramifications of the tumor projected into and dilated the 3 segmental divisions of the bronchus for a distance of several centimeters. The ramifications were entirely intraluminal and were not attached to the bronchial wall. The surface of the lesion was smooth and white, its substance soft and rather friable. The bronchi beyond the tumor were ectatic; the parenchyma was collapsed and the seat of chronic pneumonitis. The middle and lower lobes were normal, and the 4 lymph nodes found in the specimen were negative grossly and microscopically.



Text-figure 1. Diagrams showing location of muco-epidermoid tumors in 5 patients.

Case 2. Right Middle and Lower Lobectomy

This 2 by 1 cm. tumor was attached over a small area to the mucosa of the main lower lobe bronchus at the origin of the superior segmental bronchus of this lobe (Fig. 3). It caused narrowing of the bronchus to the basal segments which distally showed mild ectasia. From the point of origin, the tumor projected into and caused dilatation of the superior segmental bronchus for a distance of 2.5 cm. and then branched with the bronchus, sending short cylinders of tissue into the primary divisions. The neoplasm was smooth, pale, and firm, entirely intraluminal, and attached to the mucosa only in the one area mentioned above. The projecting proximal tip of the tumor was 0.2 cm. from the resection margin of the bronchus. The middle lobe and the one lymph node included with the specimen were normal.

Case 3. Right Upper Lobectomy

The tumor was situated 1.5 cm. from the resection margin of the bronchus and formed a 1.5 cm. pale, firm mass that was attached to the mucosa at one point. Cylindrical extensions of the lesion entered and caused dilatation of the apical and posterior segmental bronchi and grew along these divisions for 1 cm.; the bronchi beyond the obstruction were dilated, and the parenchyma showed collapse and chronic pneumonitis. The neoplasm was entirely intraluminal, and there was no invasion of the bronchial wall at the point of attachment. The anterior segmental bronchus was free. The 2 lymph nodes with the specimen were essentially normal.

Case 4. Right Upper Lobectomy

The sharply circumscribed ovoid tumor measured 5.5 by 4 by 3 cm. and lay entirely within the lumen of the posterior segmental bronchus of the upper lobe. Its substance was pale and firm. The apical and anterior segmental bronchi were compressed by the expanding tumor and contained clear, tenacious, gelatinous material. The single lymph node found with the specimen was free of tumor.

Case 5. Tumor Visualized in Right Main Bronchus

This lesion was treated via the bronchoscope by means of a cutting forceps and diathermy.

Microscopic Examination

The microscopic structure of the 5 tumors was sufficiently similar to allow a composite description with the addenda of individual variations.

The tumors were composed of a series of anastomosing cellular columns and masses separated by thin sheaths of delicate connective tissue (Fig. 4). The epithelium in contact with these septa was supported on a distinct basement membrane (Fig. 5). In this position the cells were cylindrical and pseudostratified with clearly visible cytoplasmic membranes; the nuclei lay at different levels within adjacent cells. Further from the basement membrane and forming the core of the column there was a mosaic of polygonal cells with poorly defined cytoplasmic membranes. In general, the epithelial cytoplasm was eosinophilic and finely granular. The nuclei of the columnar cells were elongated and lay at right angles to the basement membrane, while nuclei of the polygonal cells were round or ovoid. The chromatin appeared as fine granules and large nucleoli were frequently present. No intercellular bridges or ciliated cells were found.

With the periodic acid-Schiff (PAS) reagent, each tumor was found to contain a number of cells with positive-staining granules or droplets (Fig. 6). All tumors showed individual cell necrosis, and in the two tumors that appeared to be the most highly organized, coagulation necrosis had occurred in multiple, sharply defined foci (Figs. 7 and 8). In these foci, measuring about 150 μ in diameter, the cytoplasm of the marginal cells was eosinophilic and the nuclei pyknotic, while the cen-

tral cells were reduced to anuclear granular masses. Often PAS-positive mucoid material had accumulated in varying quantity between the necrotic cells. Some of these areas contained a few cells with a relatively large amount of mucoid material. An extreme manifestation of this feature was the occurrence of cystic spaces containing mucoid material and lined by necrotic cells with PAS-positive cytoplasmic granules; a few of the cells were found to have desquamated into the lumens of the cysts (Fig. 9).

The description given is drawn largely from the 2 tumors that appeared to possess the highest degree of organization. The 3 other tumors adhered to the same basic pattern, but were less differentiated and consequently varied in microscopic structure. Certain characteristics remained constant qualitatively; namely, the pattern of the masses and anastomosing columns of tumor cells, the formation of basement membranes, the presence of PAS-positive granules in the cytoplasm of epithelial elements, and individual cell necrosis. The variations were probably reflections of cellular maturity. Thus, in several tumors the basal cells lying in contiguity with the basement membranes were not cylindrical but were polygonal or cuboidal in configuration and were intensely stained. Occasionally, there was crowding of the cells, associated with cytoplasmic and nuclear pleomorphism and moderate mitotic activity (Fig. 10); in the highly organized tumors, mitoses were difficult to find. Mucus production in the tumors varied from PAS-positive cytoplasmic granules and droplets to pools of mucus in cystic spaces.

Discussion

Both the gross and microscopic structure of the 5 tumors reported suggested that they were relatively benign neoplasms which had arisen in the mucosa of the bronchial tree. The growths were intrabronchial in location, and their sharply circumscribed deeper margins had not penetrated beyond the level of the cartilaginous rings. The tendency to grow along the bronchus, to expand it, and to branch with it was unusual; in several tumors a single point of attachment to the bronchial wall could be demonstrated.

In the more highly organized tumors, the microscopic appearance was distinctly reminiscent of respiratory epithelium. Pseudostratified columnar cells rested upon a basement membrane, while in the central portions of anastomosing cords of epithelium, the tumor cells became polygonal. As in respiratory epithelial elements, the tumor cells formed granules of mucoid material. Lack of a surface from which to discharge secretion or to desquamate resulted in foci of coagulation

necrosis with disintegration of the cells and release of the mucoid material. Thus, there developed minute cystlike areas filled with mucus and cellular debris. No ciliated epithelium was recognized. One fortuitous section which included the juncture of bronchial mucosa and tumor showed that the stunted ciliated cells of the pre-existing epithelium had been undermined by a layer of tumor cells (Fig. 11).

These tumors bore no microscopic resemblance to either the carcinoid or cylindromatous types of bronchial adenoma or to the bronchial adenomas arising in mucous glands as reported by Ramsey and Reimann.[2] There was a superficial resemblance of some components to epidermoid cells, but no attempt at keratinization or development of intercellular bridges was visible. In certain respects there was a resemblance to the muco-epidermoid tumors of salivary glands reported by Stewart, Foote, and Becker,[3] and by Rawson, Howard, Royster, and Horn.[4] Liebow[5] mentioned and illustrated a muco-epidermoid variant of the cylindroid form of bronchial adenoma "in which there is an intimate admixture of well differentiated mucous cells and sheets of cells suggesting squamous epithelium." In the tumors under discussion there were no well differentiated mucous glands, and intercellular bridges were not detected between the neoplastic cells. It was felt that the mucin originated in cells that stemmed from surface respiratory epithelium.

Dr. Liebow,[6] after reviewing these tumors, remarked on the necessity of further defining the interrelationships and potentialities of the group of bronchial neoplasms. These include muco-epidermoid neoplasms arising in mucous glands and surface epithelium, cylindromatous tumors, intrinsic papillomas of glandular nature, squamous papillomas, and squamous carcinomas that grow predominantly into the lumen of the bronchus.

Summary

Five intrabronchial neoplasms apparently arising from surface respiratory epithelium are described. The clinical courses of the patients, roentgenographic studies, and gross and microscopic structure of the tumors all suggest that they are relatively benign neoplasms comparable in activity to the carcinoid adenomas of the bronchus.

REFERENCES

1. Soutter, L.; Sniffen, R. C., and Robbins, L. L. A clinical survey of adenomas of the trachea and bronchus in a general hospital. *J. Thoracic Surg.*, 1954, **28**, 412–430.
2. Ramsey, J. H., and Reimann, D. L. Bronchial adenomas arising in mucous glands; illustrative case. *Am. J. Path.*, 1953, **29**, 339–351.
3. Stewart, F. W.; Foote, F. W., Jr., and Becker, W. F. Muco-epidermoid tumors of salivary glands. *Ann. Surg.*, 1945, **122**, 820–844.

4. Rawson, A. J.; Howard, J. M.; Royster, H. P., and Horn, R. C., Jr. Tumors of the salivary glands. A clinicopathological study of 160 cases. *Cancer*, 1950, 3, 445–458.
5. Liebow, A. A. Tumors of the Lower Respiratory Tract. In: Atlas of Tumor Pathology. Section V, Fascicle 17, p. 45, Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Armed Forces Institute of Pathology, Washington, D.C., 1952.
6. Liebow, A. A. Personal communication.

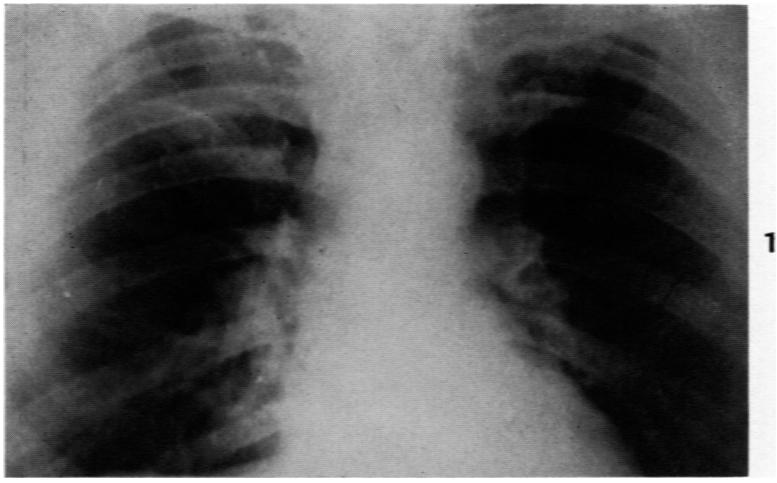
[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Case 1. Elevation of the lesser fissure of the right lung, indicating slight collapse of the upper lobe as the only evidence of abnormality.

FIG. 2. Case 1. Six years later. Extensive changes throughout the right lung with rounded areas of increased density and rarefaction. There is considerable reduction in size of this lung as shown by the displacement of the mediastinum to the right.

FIG. 3. Case 2. The pale, homogeneous tumor expands and ramifies within the superior segmental bronchus of the right lower lobe.



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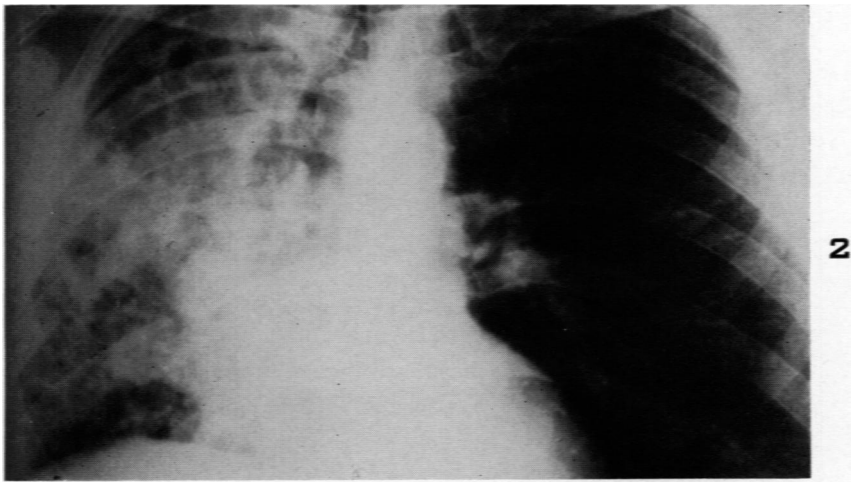

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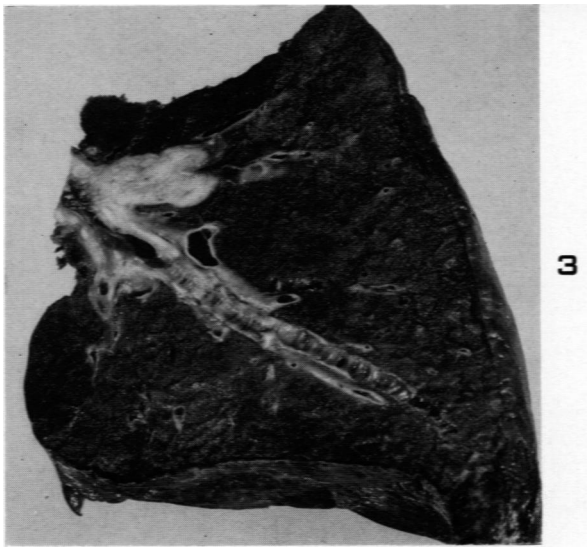

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FIG. 4. Low-power view of anastomosing cords of uniform cells. Hematoxylin and eosin stain. × 125.

FIG. 5. Pseudostratified cylindrical cells supported by a distinct basement membrane. The resemblance to respiratory epithelium is quite striking. The central polygonal cells have an indistinct outline and lack polarity. Periodic acid-Schiff stain. × 500.

FIG. 6. PAS-staining granules in the cytoplasm of the tumor cells. PAS stain. × 500.

FIG. 7. Neoplastic epithelial cells before obvious necrosis has taken place. No intercellular bridges are visible. Hematoxylin and eosin stain. × 250.

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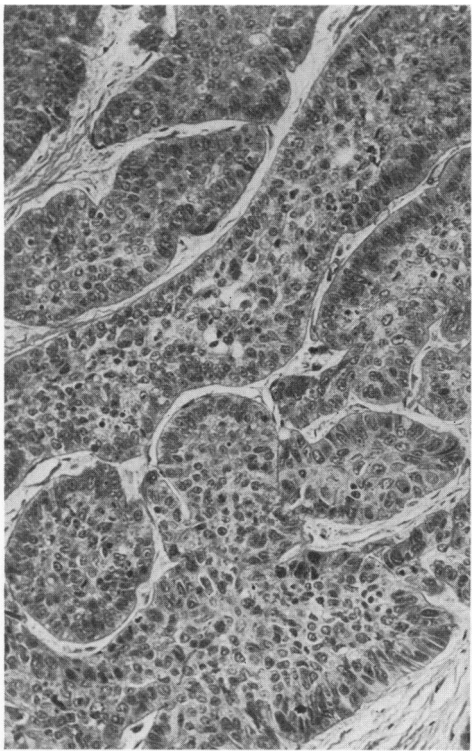

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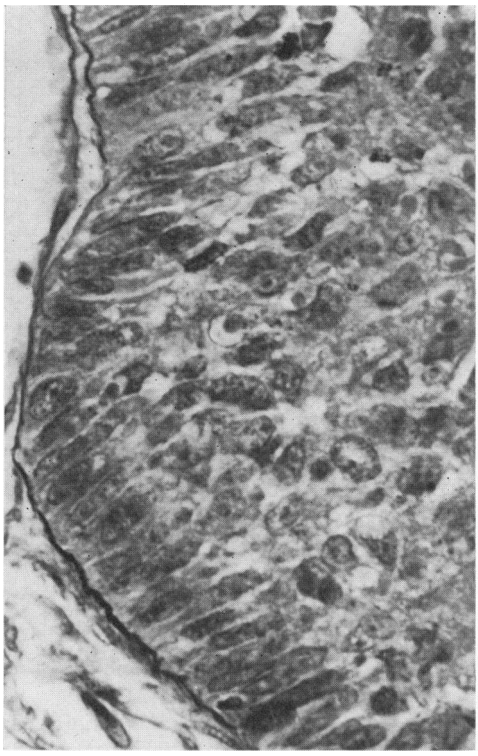

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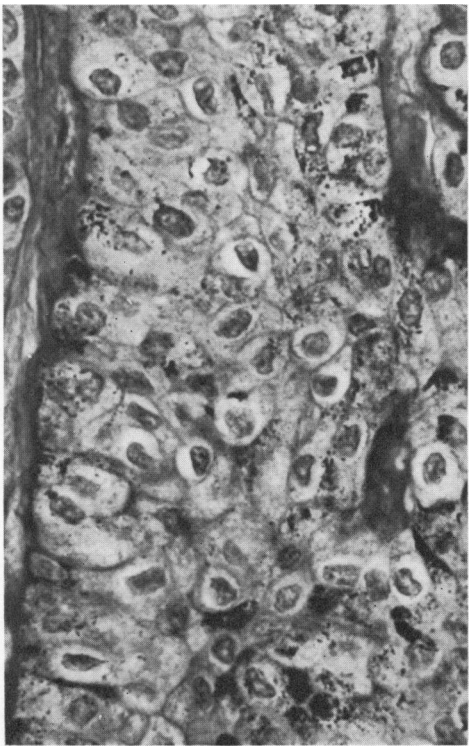

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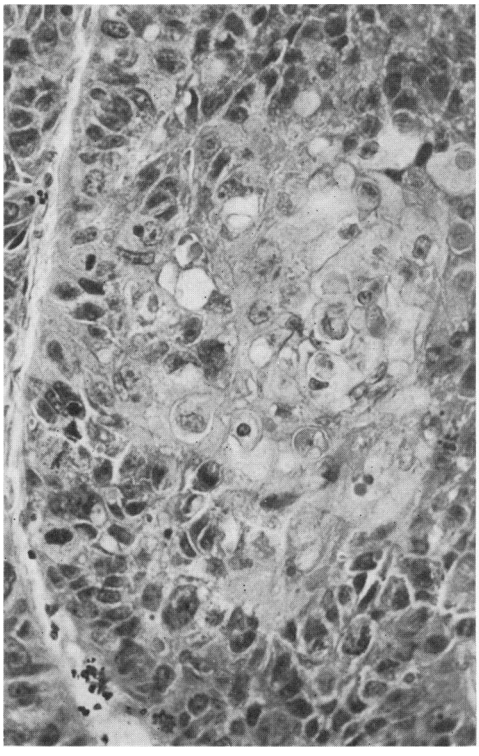
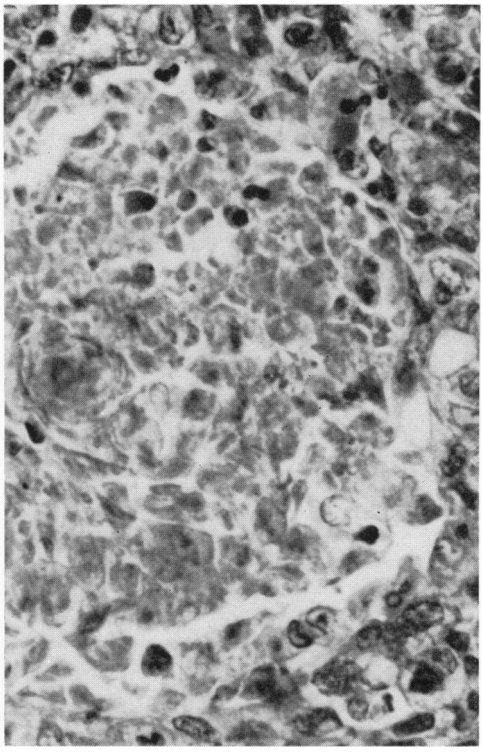


FIG. 8. Necrotic neoplastic epithelial cells. Hematoxylin and eosin stain. × 250.

FIG. 9. Cystic space containing shrunken mucoid material and a few necrotic cells. Note the cylindrical cells abutting upon the connective tissue septum. Hematoxylin and eosin stain. × 250.

FIG. 10. Loss of polarity and variation in nuclear shape and size in one of the less differentiated tumors. Hematoxylin and eosin stain. × 500.

FIG. 11. Tumor cells undermining bronchial epithelium which remains as a few stunted ciliated cells on the surface (arrows). Hematoxylin and eosin stain. × 500.



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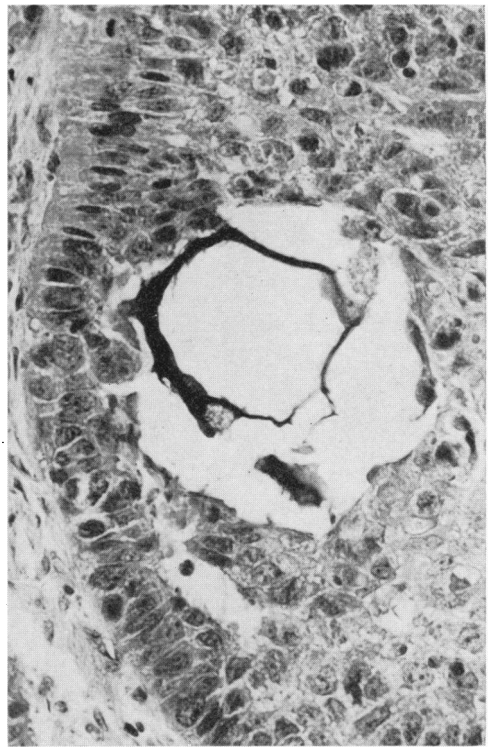

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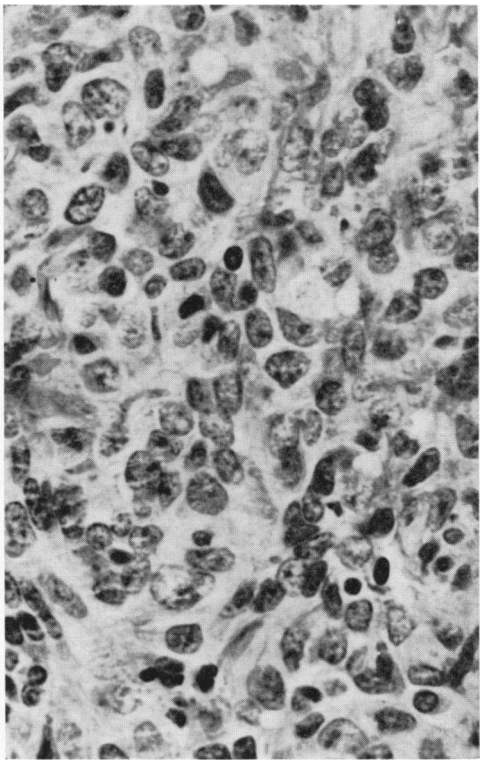

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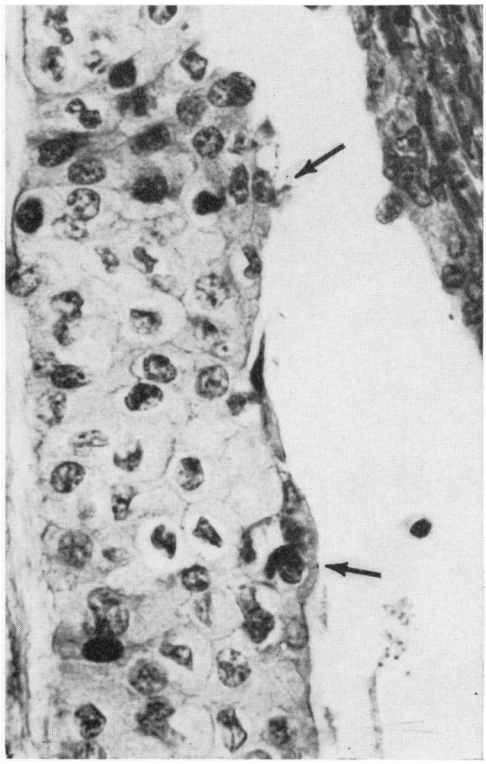

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