BRONCHIAL ADENOMAS ARISING IN MUCOUS GLANDS
ILLUSTRATIVE CASE *

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Bronchial adenoma was first reported in 1882 by Müller[1] as a pathologic entity separate from carcinoma of the lungs. Following this case, some thirty odd cases were reported until 1932, when Wessler and Rabin[2] reviewed the entire picture of bronchial adenomas and attempted to bring some order out of the confusion regarding origin and terminology. They believed that the adenomas of the bronchus originated in the duct epithelium of the mucous glands, and in support of this theory cited the facts that the tumors are invariably covered by an intact epithelium and lie on an uninterrupted basement membrane. This, in their opinion, eliminated bronchial epithelium as the site of origin. The cellular elements of the adenomas did not resemble the cellular elements of mucous glands, and no apparent transition from normal mucous glands to tumor could be seen. By exclusion, however, Wessler and Rabin reasoned that the only possible source was the gland duct epithelium. These authors believed that the term benign bronchial adenoma could adequately designate these tumors, even though there were histologic differences in various cases. This account of Wessler and Rabin marked the beginning of the clinical recognition and treatment of these lesions.

Hamperl[3] and Stout[4] believed that the tumors arose from the peculiar cells known as oncocytes or pyknocytes, which are found in mucous and serous glands and their ducts of adults. These cells are large and contain voluminous acidophilic cytoplasm and deeply stained pyknotic nuclei. The gland-like spaces formed by them do not secrete mucin.

Welt and Weinstein[5] and Edwards and Taylor[6] believed that these tumors were of endothelial origin. Most observers have considered them to be quite similar to the carcinoid tumors of the appendix. In the cases which resemble carcinoid tumors, argentaffin granules have rarely been demonstrated. Only one case reported by Holley[7] and one cited by Foot[8] contained argyrophilic granules.

Womack and Graham[9] postulated that the point of origin was from more than one type of cell in vestigial fetal lung buds. This concept of mixed cell origin, subsequently giving rise to the production of a

* Aided by a grant from the Sydney M. Cone Research Fund.
Received for publication, August 29, 1952.

tumor in which bone, cartilage, and various epithelial patterns are found, has not been wholly accepted, although the name is in wide usage. Allen,[10] Kramer and Som,[11] and Brunn and Goldman[12] argued that bone and cartilage formation is caused by dedifferentiation of adult epithelial cells as in adenomatous tumors arising from glands elsewhere in the body.

The widespread acceptance of the belief that these tumors arise from mucous and serous glands is founded on the reasons advanced by Wessler and Rabin,[2] namely, that bronchial adenomas apparently never arise from the smaller bronchioles in which serous and mucous glands are absent. Many of the tumors form definite acini, while others show an obscure alveolar arrangement. The substance found in the lumina generally has not been identified as mucin,[13] but Mallory cited one case in which he stated that the cells did produce mucin.[14] Although the various reasons form a somewhat unstable base for the theory of mucous and serous gland origin, this seems to be the most plausible view at the present time.

The names originally applied to bronchial adenomas were confusing because various pathologists reporting the histologic features of one or several cases drew the erroneous conclusion that *all* bronchial adenomas were of the types they had encountered. Later work with larger series showed varied architecture among the examples encountered and variation of cell forms in a single tumor. Before Wessler and Rabin[2] applied the term adenoma, various types had been called sarcoma of alveolar pattern,[15] cylindrical cell carcinoma,[16] basal cell carcinoma,[17] carcinoid and cylindroma,[3] benign glandular tumors,[18] vascular adenomas,[19] endotheliomas,[5] and mixed tumors.[9] More recently, McDonald,[13] Van Hazel, Holinger, and Jensik,[20] and Huizinga and Iwema[21] proposed a division of adenomas and cylindromas, with the distinction that the adenoma is distinctly benign and the cylindroma potentially malignant. Goldman and Conner[22] suggested a classification based on a decreasing order of malignancy and consisting of mixed tumor (cylindroma), carcinoid, myoblastoma, and benign glandular bronchial tumor.

The concensus of opinion is that the tumors should be termed adenomas with distinction between the (1) carcinoid and (2) the cylindromatous or mixed type.

Gross Description

The gross appearance of bronchial adenomas varies considerably. They may measure from 0.5 to 8 cm. in diameter. When seen bronchoscopically, they appear as pink, purplish, or sometimes pale spheri-

cal or ovoid masses. They may be attached by a broad base, or be distinctly polypoid with a definite pedicle. The surface is either smooth and shiny, or finely granular. Occasional ulcers may appear. By close inspection of the surface, many blood vessels may be seen. This accounts for the great tendency for bleeding to occur with manipulation during bronchoscopy. They are usually hard or firm, but very infrequently may be soft and friable. The size of the endobronchial portion tends to be deceptive, because extensions of the tumor into the bronchial wall and into the adjacent lung tissue beyond may constitute a large part of the tumor mass. The extramural portion is often of greater size than the intraluminal portion. Because of this, bronchial adenoma has been compared by McDonald[13] to an iceberg. Brunn and Goldman[12] illustrated in excellent cross-sectional drawings the endobronchial, intramural, and extrabronchial distribution of the tumors in their cases. Brock[23] cautioned that the expansion of the tumor external to the bronchial wall should not be mistaken for infiltration because epithelial structures, *i.e.*, mucous glands, are normally present outside the cartilaginous rings. The condition of the lung distal to the tumor will depend entirely upon the degree of bronchial obstruction. Emphysema, atelectasis, bronchiectasis, and pneumonitis may be present.

Histologic Findings

Histologically, these tumors have provided ground for much discussion and wide divergence of opinion as to their origin. Most pathologists agree on the type of cell, but there the agreement usually ends. The patterns have been of various types. Arrangement of cells in cords, small gland or gland-like spaces, the presence of bone and cartilage, and the types of secretion have evoked a wide range of opinion concerning their genesis.

In adenomas of the carcinoid type the cells approximate the size and shape of lymphocytes or plasma cells. Comparison has been made also to basal cell carcinoma, islet cell tumors of the pancreas, and parathyroid adenomas.[23] Variation in the size and shape of the cells is not usually marked, although in some cases they may be small cuboidal or tall columnar. The nuclei are round or ovoid, and normochromatic. The cells are arranged in groups or cords in which attempts at acinus formation are seen. In many cases, the cell groups and cords appear to be drawn away from their connective tissue framework. Among the collections of epithelial cells there is a thin stroma of supporting connective tissue which frequently contains vascular spaces lined by endothelium. In this respect morphologic characteristics similar to those of vascular tumors are presented. This group, which

resembles carcinoids of the appendix and ileum, differs in that argentaffin granules usually are not present in the cytoplasm of its cells.[7,8]

The cylindroma or mixed tumor type presents cells which are small and regular, and with indistinct borders. There is slight variability in the shape of their nuclei. There is a tendency for these nuclei to become hyperchromatic. Mitotic figures are rarely found in either this or the carcinoid type. There is more tendency in the cylindroma than in the carcinoid type to form tiny glandular spaces which very often contain secretion. Rosenblum and Klein[24] reported the case of an 11-year-old child with a bronchial tumor which presented a more distinctly glandular pattern. The glands were lined by tall cylindric cells whose cytoplasm was pale and frequently vacuolated. Mucoid material was present in many of the gland spaces. This secretion, which stains faintly with mucicarmine, has been called mucoid, for it apparently is not true mucus. McDonald[18] found that this substance, unlike mucus, stains red with polychrome methylene blue. At times the cylindromatous pattern presents ill defined spaces filled with secretion, and not true lumina. This type of bronchial tumor may resemble the mixed salivary gland tumor known as cylindroma. The stroma tends to be myxomatous in some examples and partially cartilaginous or osseous in others.

In attempting differentiation of these tumors from bronchogenic carcinoma, study of biopsy material is not without shortcomings. Occasionally, such material may not furnish a representative portion. Squamous metaplasia or distortion of the cells may falsely suggest bronchogenic carcinoma. In the differentiation of small-celled carcinoma, the distinction is not always made easily on the basis of cell structure. However, the presence of mitotic figures, the degeneration of the tumor cells, and the stromal infiltration with inflammatory cells usually are evidence of carcinoma.

The benign nature of bronchial adenomas themselves has been repeatedly questioned and in some instances vigorously opposed. Most observers agree that they are locally infiltrative, but that they do not exhibit the usual invasive tendencies of carcinomas. Castleman[25] reported that one case in twenty showed regional lymph node metastasis. Mallory[14] was of the opinion that adenomas should be classed as benign, although a few show regional lymph node involvement, and a very small proportion metastasize to distant points. Womack and Graham[9] believed that the majority of these tumors become malignant and that the identity of the original tumor becomes lost when full blown features of malignancy have developed. In this concept bronchial adenomas follow adenomas of breast, prostate, thyroid gland, and

rectum. Van Hazel *et al.*[20] reported one case with metastases to lymph nodes, liver, and kidney. McDonald[13] believed that the carcinoid type should be considered benign and that the cylindroma, because of its greater infiltrative tendency, should probably be considered potentially malignant. Moersch and McDonald,[26] in a recent series, reported 77 of 86 cases, 90 per cent, to be of the carcinoid type and 9 cases, 10 per cent, of the cylindroma type. Five of these 86 cases had definitely proved metastases in the regional lymph nodes and/or the liver. It was their opinion that adenomas of the cylindroma type possessed the greater malignant possibilities.

Report of Case Illustrative of Origin in Mucous Glands

T. P. S. was a white male, 54 years old, who was admitted to the University Hospital (chart no. 68941) on December 17, 1951. In October, 1951, he had complained of "generalized aching and feeling warm." His temperature was found to be 102° F. He was given aureomycin and returned to his work as a patrolman after 5 days. After 2 days his temperature rose to 104° F. He then complained of urinary frequency and dysuria. These symptoms responded to chloromycetin after several days. He again worked from November 9 to 13, and did not return to his physician. After November 13 the patient was entirely asymptomatic. There was no malaise, fever, cough, urinary symptoms, weight loss, or change in appetite. Roentgenographs done on November 14 and 27 showed infiltration of the right base.

Physical examination showed temperature, 99.2° F.; pulse, 90; respirations, 24; blood pressure, 130/78 mm. of Hg. The only positive findings were dullness and absence of breath sounds in the right lower lung.

Examination of gastric washings was negative for tubercle bacilli. Hemoglobin was 16.6 gm.; sedimentation rate, 10; hematocrit, 49; white blood cells, 9100 per cmm.; with polymorphonuclear leukocytes 69 per cent, lymphocytes 17 per cent, monocytes 0, eosinophils 14 per cent, basophils 0.

After admission to the hospital, roentgenologic examination confirmed previous findings of a lesion of the base of the right lung, interpreted as segmental atelectasis. Bronchoscopic examination revealed fixation and moderate narrowing of the right lower lobe bronchus. A spheroidal, apparently mucosa-covered mass, approximately 4 by 4 mm., was seen. This impinged upon the lumen of the anterior and cardiac basilar branches. The impression was that of a stenosing right lower lobe tumor, either adenoma or carcinoma. The biopsy specimen (no. 75117) showed many mucous glands, covered by ciliated pseudo-stratified columnar epithelium, in a fibrotic stroma in which there was a patchy lymphocytic infiltration. The section made from the aspirated secretions consisted of fibrin, red blood cells, leukocytes, and small groups of exfoliated epithelial cells which showed no evidence of carcinoma.

On December 27 a right posterolateral thoracotomy was done. An atelectatic area was not identified. After segmental resection of the right lower lobe, the patient made an uneventful recovery and was discharged on January 9, 1952.

The specimen comprised the posterior, anterior, and lateral basal segments with the attached right lower lobe bronchus. Projecting into the lumen of the bronchus was a rounded polypoid mass with a very short pedicle. This mass measured 1.3 cm. in diameter. The tumor was covered by intact mucosa. On section, it appeared composed of

many minute cystic areas filled with mucoid material. The lesion did not appear to invade the bronchial wall.

Histologically, the tumor was composed of closely approximated glandular spaces, each of which was filled with mucoid material. The cells lining the spaces were tall, cylindric, and mucus-bearing. The nuclei were situated at the bases of the cells and were generally round or oval. The lesion was well circumscribed. It was internal to the cartilage and was covered by cylindric-celled mucosa. A few inflammatory cells were scattered throughout the sparse stroma. A moderate number of vascular spaces were present, but these were not prominent, as one would expect in the usual bronchial adenoma. When stained with mucicarmine, the mucoid material in the gland spaces had a very faint pinkish tinge. The lining cells stained deep red. The intraluminal mucoid material probably was chemically altered mucoid material that arose in the cells.

This tumor presented none of the cord-like pattern or small gland-like spaces which are commonly seen in the carcinoid or cylindroma types. No bone, cartilage or precartilaginous tissue was present. The glandular structures were large faithful reproductions of the mucous glands present normally in the bronchial wall. The lining cells were tall and regular, in contrast to the somewhat irregular lining cells of the poorly formed acini of the usual cylindroma. The feeble staining with mucicarmine of the substance present in the acinar spaces was of but little help in proving mucous gland origin, even though the cells themselves did stain well and showed true mucus production.

The unusual histologic picture present in this case demonstrates the need for recognition of additional types for the classification of these tumors. It is obviously neither carcinoid nor cylindromatous. Actually it is more "adenomatous" than most bronchial adenomas, and clearly benign.

Summary

After reviewing the theories of origin of bronchial adenomas, their relationship to carcinoma, histology, and nomenclature, a report of a case is presented of which the history and gross appearance were commonplace, but the histologic structure quite unusual. Definite mucous gland reproduction denoted a distinctly benign adenoma having origin in mucous gland.

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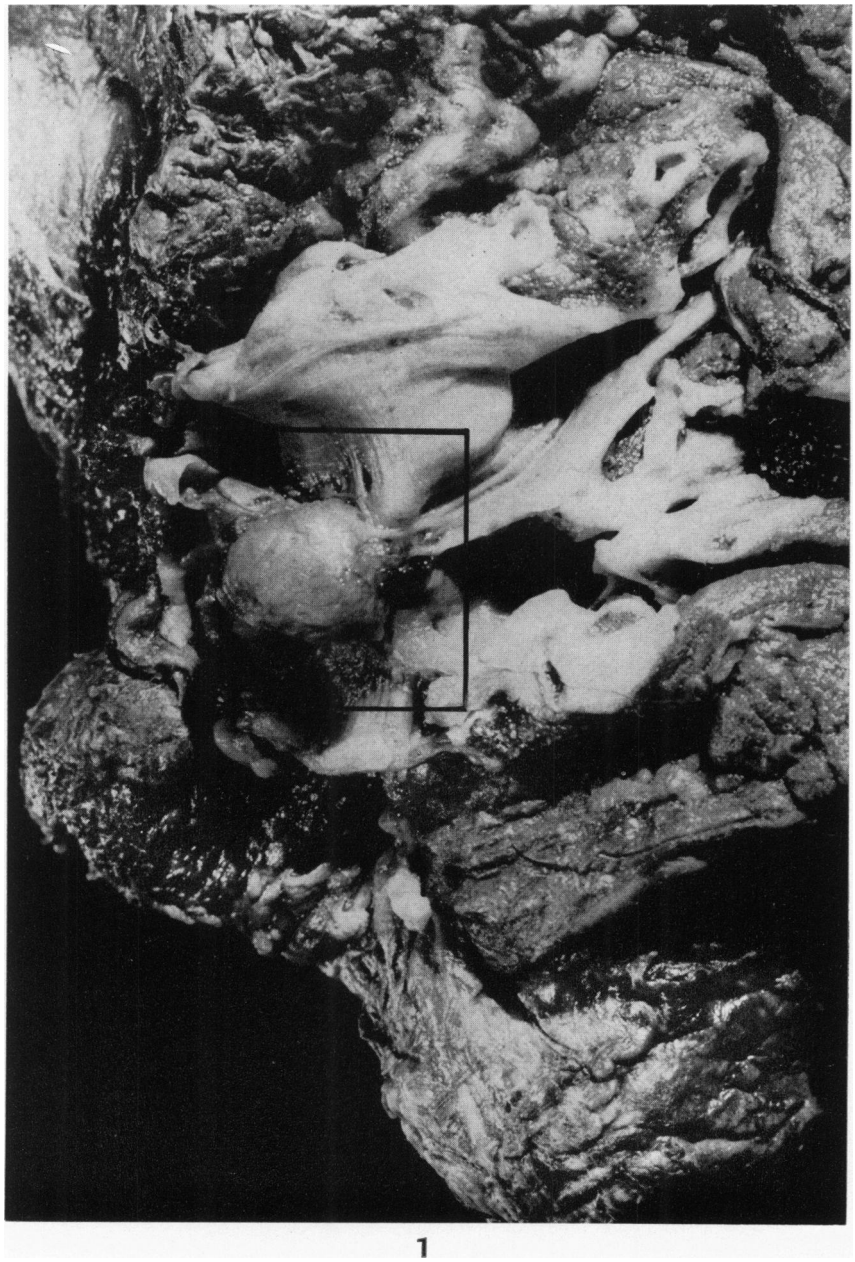
[*Illustrations follow*]

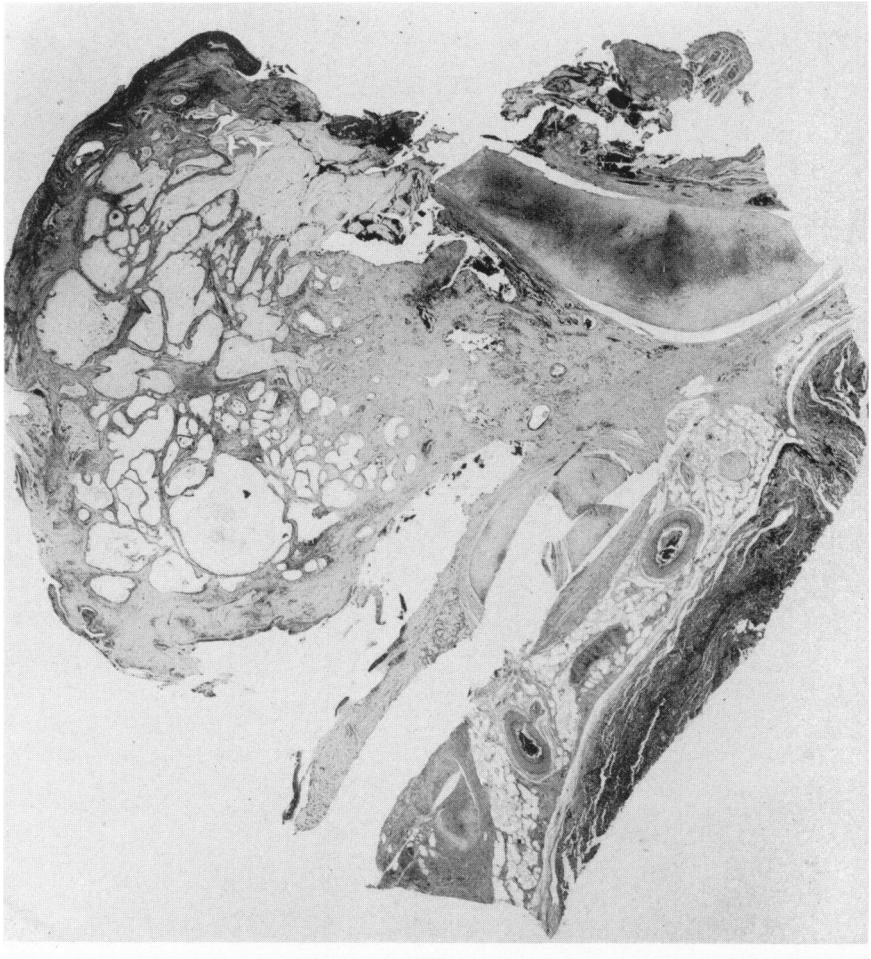
LEGENDS FOR FIGURES

FIG. 1. **Polypoid adenoma** projecting into the lumen of the right lower bronchus.



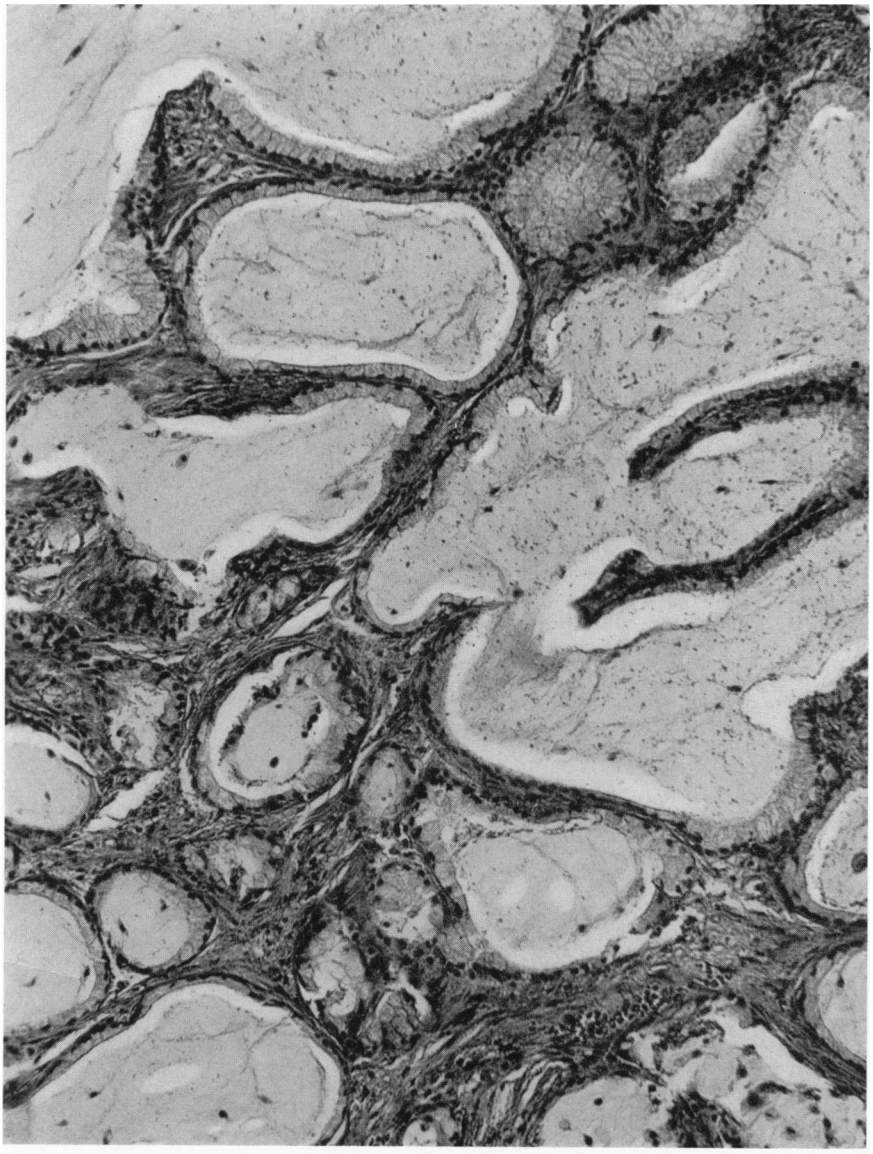
1

FIG. 2. Relationship of adenoma to layers of bronchial wall. Hematoxylin and eosin stain. × 50.



2

FIG. 3. Photomicrograph showing glandular structure and mucous epithelial lining. Hematoxylin and eosin stain. × 200.



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