MIXED TUMORS OF THE LUNG: A RE-APPRAISAL

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THIRTEEN YEARS AGO Doctor Graham, with one of us, described a series of pulmonary tumors under the title of "Mixed Tumors of the Lung."[3] This study, being based on surgical specimens, represented the first total appraisal of the relatively early stages of this lesion, for at that time comparatively few of these tumors had been treated by complete surgical extirpation. As a matter of fact, experience with this tumor, which had previously been called adenoma of the bronchus, had been scant indeed until the advent of bronchoscopic examination a couple of decades previously. Following the use of this method of study, descriptions of the tumor in the surgical literature became much more abundant. A tumor extremely rare at necropsy began to be found not infrequently during life at bronchoscopy.

We called attention to this strange discrepancy, for certainly a benign lesion that is not too uncommon during life should neither be too uncommonly found at necropsy. We indulged in the speculation that perhaps these tumors did not disappear spontaneously, but rather changed their morphology as well as their clinical characteristics as they became invasive. Thus, at necropsy it would be difficult to differentiate them from ordinary forms of bronchiogenic cancer. Such a concept would be in keeping with prototypes elsewhere in the body.

While many of these tumors in times past had been diagnosed as adenoma of the bronchus, we felt such a term misleading, for it suggested a benign and purely epithelial tumor. In our experience, certainly this was an invasive lesion that could and did metastasize, and it at times was not purely epithelial. With us, the passage of time and the observation of many more patients has tended to substantiate this attitude. It has also been the experience of others. Nevertheless, it is the consensus of most of the authors of recent texts of pathology that these tumors are either completely benign, or that they show malignant propensities rarely.

Because this subject is an important one on both theoretical and practical grounds, we have felt it would be worthwhile to reopen the discussion in the light of additional experience. In so doing, we shall describe a recent series of patients seen at the State University of Iowa Hospitals with tumors that seem to fall in this category.

CASE REPORTS

Case 1.—M. K., a 65-year-old lady, entered the hospital on November 21, 1949, with a history of having had her right breast removed 20 years previously for a non-malignant lesion. In the autumn of 1943 she had sustained a vertebral fracture which healed without difficulty and without any residual. Two and a half years before admission she suffered an attack of acute appendicitis which subsided without operative interference. The patient had lost from 130 to 115 pounds in the last 2 to 3 years. On routine roentgenogram examination of her chest it was known that she possessed a circumscribed mass in the left lower lung field which had been present for many years and which had not changed in size. Ten days before admission to the hospital she experienced nausea, followed by chills and fever and vomiting. She was seen by her family physician, who noted a large mass in the right side of the abdomen, and it was because

of this that she was admitted to the hospital. There was additional history of intermittent diarrhea during the past year.

Except for the mass present in the lower left lung field on roentgen ray examination, further studies of the lung were unrevealing. The heart was normal, the blood pressure 150/90. On palpation of the abdomen, a mass was felt which filled the entire right side from the costal margin to the brim of the pelvis. It was hard, smooth, movable on respiration and ballottable. It was not tender. Rectal and pelvic examination revealed nothing abnormal. Pyelograms were normal and the blood urea nitrogen and creatinine were within normal limits. Examination of the stool was negative for parasites or blood. Roentgen ray examination of the esophagus, stomach, small and large bowel was normal. Liver function tests were normal. With the exception of a slight amount of albumin, the urine examination was normal. The hemoglobin level was 13 Gm. per 100 cc. The red blood cell count was 4,000,000 and the white blood cell count was 8200. The differential count was normal.

The liver was examined surgically on November 26, 1949, by Dr. Robert Tidrick, at which time it was found to be involved by obviously metastatic neoplasm. There were numerous masses of discrete tumor tissue. A small portion of this was removed from the left lobe of the liver. Microscopic examination of the tissue showed it to be a poorly differentiated cancer, obviously metastatic to the liver. The cellular pattern is compatible with metastasis from a primary bronchial tumor, more than likely that often spoken of as bronchial adenoma.

While the postoperative convalescence was uneventful, the patient expired 1 year later due to the metastatic lesion. It is important to note that during the performance of the liver biopsy, extensive exploration of the abdomen and the abdominal viscera was carried out and no primary lesion was found at that time. The subsequent course of the patient revealed no other evidence of primary lesions than the mass apparent in the lung.

The fact that there was no necropsy performed and the fact that there was no biopsy done on the primary tumor in the lung makes the diagnosis here a presumptive one. We have seen on other occasions long-standing primary lesions metastasize without apparent gross change in the physical appearance of the primary growth.

Case 2.—P. McF., a 24-year-old unmarried white woman, was admitted to the hospital on September 9, 1949, with a complaint of intermittent hemoptysis since March, 1948, and a period of severe hemoptysis between February and June, 1949. There was pain, pleuritic in type, and there had been repeated attacks of pneumonia in the left lung since March, 1948, intermittent coughing for 2 years and a weight loss of about 15 pounds during the same length of time. The patient stated that she had been in good health until March, 1948, at which time she was attending college. She then developed the hemoptysis and cough and a diagnosis of tuberculosis was made even though no organisms could be found. The patient treated herself by intermittent bed rest, but her pulmonary symptoms continued. In June, 1949, she returned to her home and started bed rest at home without improvement. She was referred to the hospital by her local physician.

Physical examination on admission revealed a well-developed 24-year-old girl, and examination of her chest showed a definite retraction of the left lower chest cage and slight scoliosis with a convexity to the right. There was dullness to percussion in the lower half of the left hemithorax. The breath sounds were high pitched. There were no wheezes. Percussion over the left lower chest was dull. The trachea and mediastinum were shifted slightly to the left. The heart was normal. The blood pressure was 118/72. The remaining physical examination, as well as the rest of her past history, was negative. Laboratory examination showed 14 Gm. of hemoglobin per 100 cc., a red blood cell count of 4,200,000, white blood cell count of 8900. There were no unusual findings in the urine. The electrocardiogram was normal. Roentgen ray film of the chest revealed atelectasis of the left lower lobe with shift of the mediastinum and heart to the left. Esophagrams and upper gastro-intestinal roentgen ray examination were both normal. Several examinations of sputa for tuberculous organisms were negative and the skin tuberculin was negative.

On September 16, 1949, bronchoscopic examination was carried out and just opposite the left upper lobe orifice a smooth, round, bluish tumor was visible which nearly completely obstructed the left main bronchus. Only a slit-like crescentic orifice remained. Biopsies were taken and they showed glandular elements of a mixed tumor of the lung. Accordingly, on September 29, 1949, a pneumonectomy was carried out on the left side and at the same time a partial thoracoplasty was done. At the time of pneumonectomy no hilar lymph nodes could be palpated which seemed to have been involved with the tumor. On palpation of the tumor the mass could be felt in the left main bronchus and it was easily movable and resection

was carried out at a safe distance proximal to this tumor mass. Pathologic examination of the specimen showed the characteristic picture of mixed tumor. Beneath a thin layer of stratified squamous epithelium in the bronchus there was an area of collagen and connective tissue, beneath which one encountered infiltrating cords and masses of small epithelial cells with scant cytoplasm of the sort encountered in fetal lung tissue. These cords of epithelial cells surrounded large blood spaces and it was easily obvious why ulceration would result in considerable hemorrhage. In some areas of the tumor there was evidence of an increased amount of stroma, and when these areas were stained for reticulin huge amounts were seen. There was no evidence of distant invasion into the regional lymph nodes, although there was a moderate amount of hyperplasia of the reticular structures. There was hemorrhage and bronchiectasis in the lung distal to the tumor.

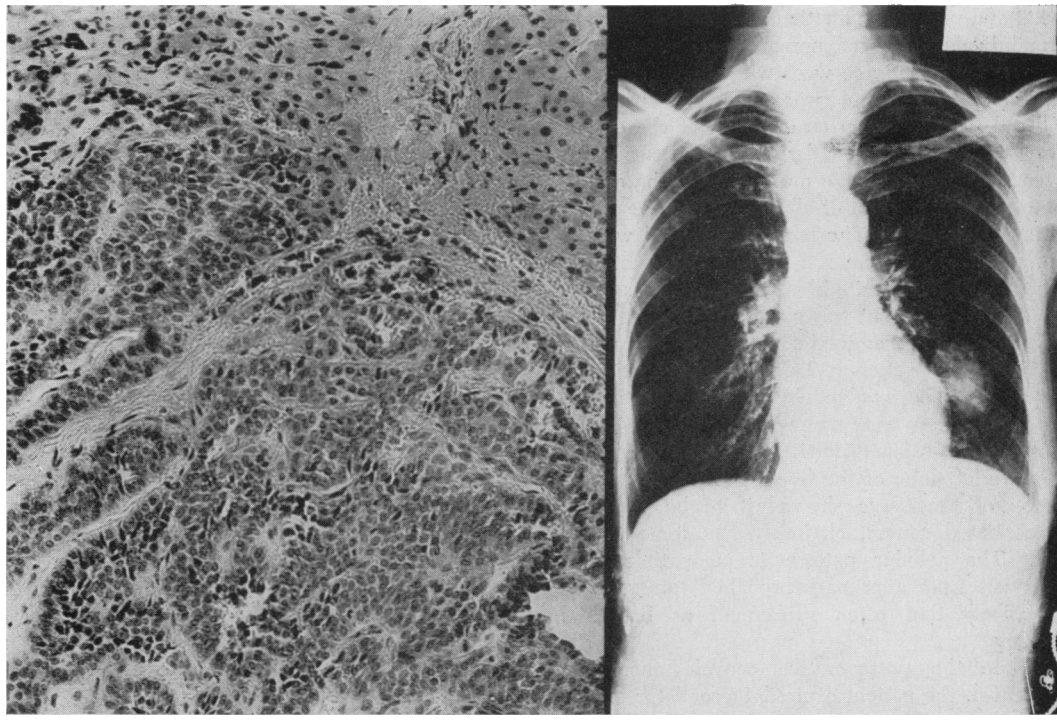


FIG. 1.—(Case 1) Photomicrograph demonstrating the cellular pattern of the metastatic tumor in liver. The pattern is compatible with metastasis from a primary bronchial tumor, spoken of as bronchial adenoma. Roentgenogram of the chest demonstrates the primary tumor in the left lung field.

The patient's postoperative course has been entirely uneventful and at the present time she has returned to her college studies. The symptomatology presented by this patient can be explained on the basis of the vascularity of the tumor and the intermittent obstruction that would occur when inflammation and edema of the tumor and surrounding bronchial structures took place. While there is no evidence of distant invasion, local infiltration of the tumor was apparent throughout its entire periphery. Of interest to us pathologically were the variations in tissue relationships in the growth. In some places epithelial overgrowth was predominant, while in others marked vascularity was present. In still other areas the considerable reticulin already described would be most abundant, apparently replacing much of the epithelial tissue and also possessing evidence of collagen formation.

Case 3.—K. O.'B. This patient, a 53-year-old woman, was first seen at our hospital in 1949, where a diagnosis of acute cystitis was made. During the

same time she was treated for a dull aching pain in the low back region. No orthopedic diagnosis was made at that time, however. Cystoscopy revealed generalized fairly acute cystitis. This subsided under treatment. At that time there was no history of pulmonary disease. She returned on March 7, 1950, at which time the complaint of having had fever and chills every night for the previous 3 weeks was given. She had developed a slight hacking cough. There was no chest pain or other pulmonary symptoms. The white blood cell count at that time was 25,000. She was treated by antibiotic therapy and a diagnosis was established of pneumonia of the right lower lobe of the lung. The roentgen ray diagnosis at that time was likewise one of pneumonia. The picture was an atypical one and numerous agglutination tests were performed, all of which were negative. The pneumonic infiltrate cleared during an observation of several days, and the patient was discharged.

FIG. 2

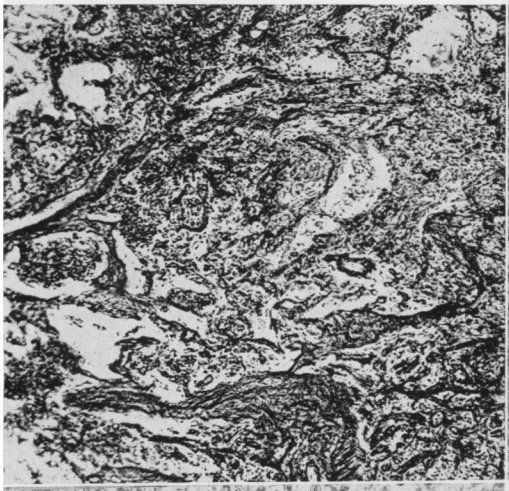
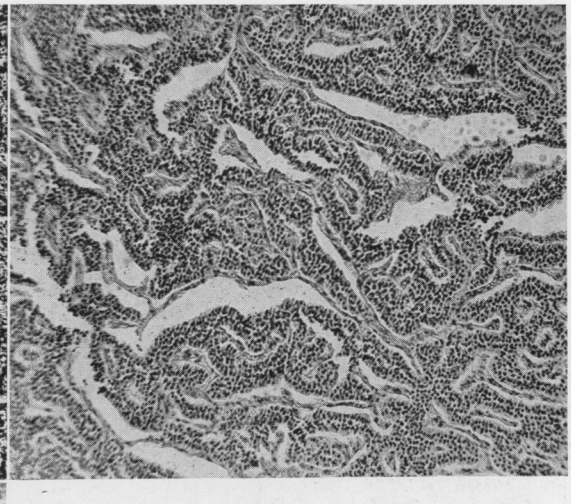


FIG. 3



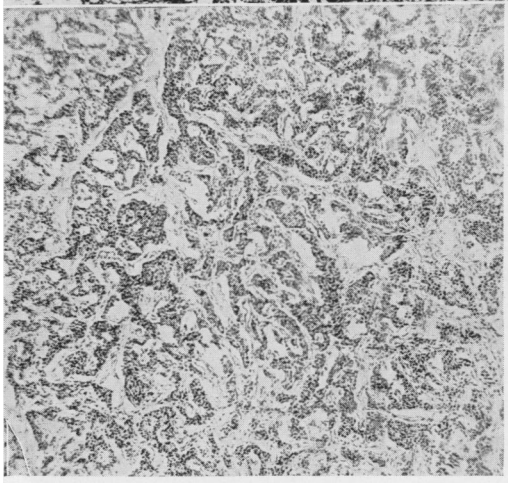


FIG. 4

FIG. 2.—(Case 2) Photomicrograph—reticulum stain. Section through portion of the tumor showing the large amount of stroma and reticulum.

FIG. 3.—(Case 3) Photomicrograph of central portion of tumor showing architectural structure suggesting duct systems and budding of bronchi.

FIG. 4.—(Case 4) Photomicrograph of section in center of tumor. Cords and nests of tumor cells fairly consistent in architecture growing in relatively dense stroma are seen.

She returned again on June 10, 1950, approximately 3 months later. She stated that in the interval she had felt well until 6 days before this present admission. At that time she developed a sudden tickling in her throat and had an episode of massive hemoptysis. There had been no fever. Since then she had had blood-streaked sputum. Physical examination at the time of this last admission revealed a well-developed 53-year-old woman. There was moderate dullness to percussion over the lower one-third of the right lung field posteriorly. Breath sounds were present over both sides of her chest, but those over the right side were definitely prolonged and high pitched. The blood pressure was 140/80. The heart was apparently normal. The skin tuberculin test was negative. Numerous sputa studies were negative for tubercle bacilli or other pathogens. The electrocardiogram was normal.

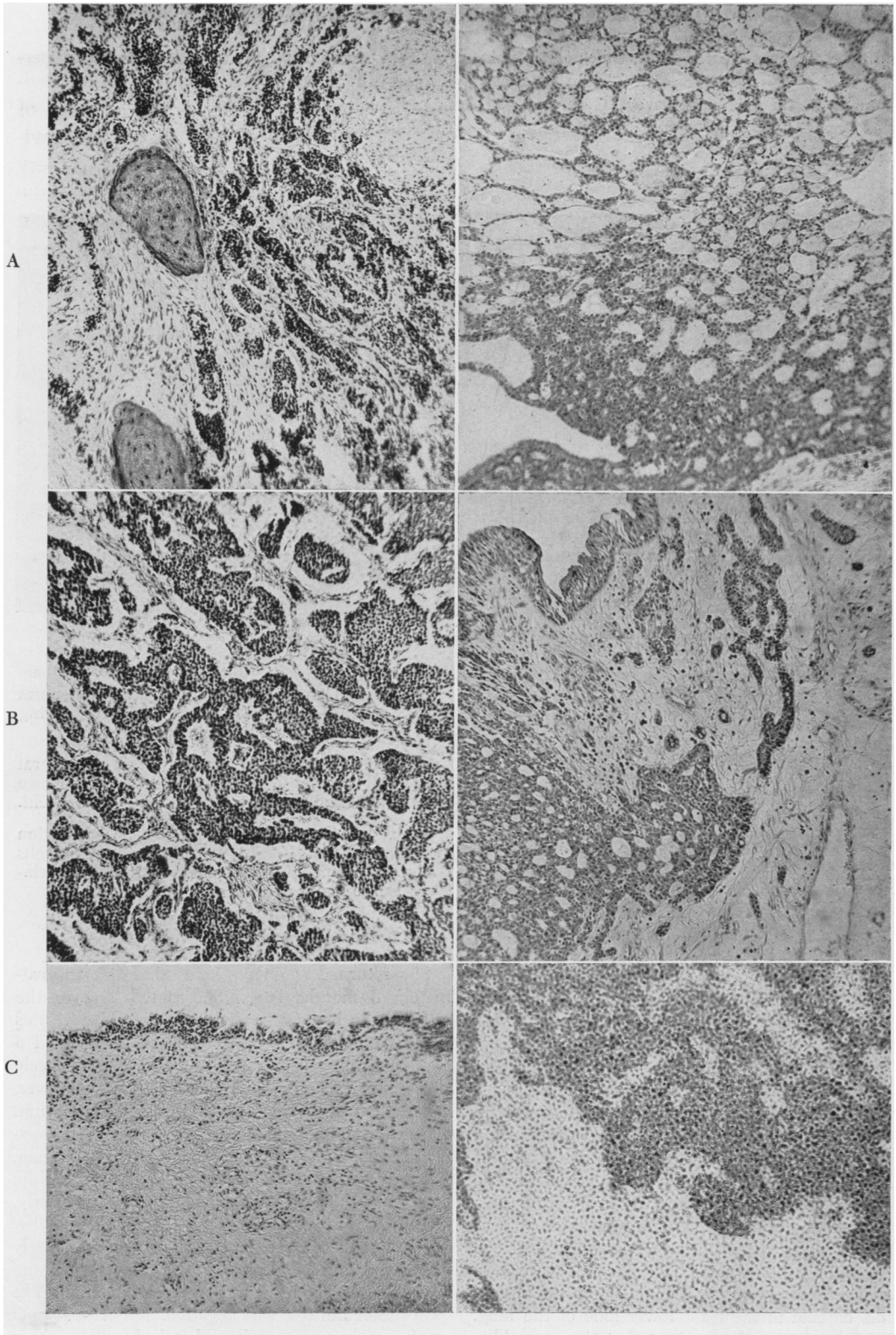


FIG. 5. FIG. 6

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Examination of the blood showed 14 Gm. hemoglobin per 100 cc., the red blood cell count was 5,150,000, white blood cell count 7500, and the urine showed nothing abnormal. A roentgenogram of the chest revealed an infiltrative lesion, possibly due to atelectasis and pneumonitis in the right lung field. Bronchoscopic examination was carried out on June 14, 1950, and at that time a round, smooth tumor was noted in the right intermediate bronchus. Bronchograms were carried out which showed a complete block in the region of the right intermediate bronchus. The diagnosis of a mixed tumor of the lung was made. Sputum examinations for abnormal cells revealed none.

On June 17, 1950, a right pneumonectomy was carried out. At the time of operation a large mass was palpable in the right lung hilum. On gross inspection there were no enlarged hilar lymph nodes present that would give a suspicion of metastatic involvement. The operative procedure and the postoperative course of the patient was uneventful.

When the lung was sectioned the mass was seen to be unusually large. A considerable portion of the neoplasm was outside of the bronchial lumen, invading diffusely into the lung parenchyma as well as through the bronchial wall. Numerous lymph nodes around the hilum and peribronchial nodes were dissected out and all of them showed no evidence of metastasis or malignant involvement. Microscopically, the picture was one of a mixed tumor of the bronchus. There was no ulceration present underneath the bronchial mucosa. There was also a considerable dearth of supporting stroma in the tumor. In many areas the tumor had the architectural structure seen where duct systems are undergoing budding and the microscopic picture was highly suggestive of the budding of bronchi.

Six weeks following the pneumonectomy the patient had a thoracoplasty. This also was an uneventful procedure and the postoperative course has been smooth. The patient has had no further difficulties.

Because of its huge size and lack of recent active growth, this tumor had obviously been present in the patient for a very long time. One is impressed again with the suddenness with which symptoms began and how when they had started they persisted. Here again from the pathologic standpoint, while there was no distant invasion, there was diffuse local infiltration.

Case 4.—E. B., a 56-year-old Negro woman, was first seen in our hospital in February, 1938, at which time, at the age of 46, she complained of irregular menstrual periods. Following curettage of the endometrium a diagnosis of functional metrorrhagia was established and the patient received 2500 mg. of radium therapy. Following this she got along well until about 1940, at which time she aspirated a small piece of popcorn which she was able to cough up after a prolonged period of time. At that time she raised a large amount of bright red blood. From then on she has had intermittent spells of coughing and occasionally hemoptysis. These attacks would occur every 2 to 3 months. She developed an oppressive, heavy feeling in the right chest and gradually started to have a wheeze in the right chest. The patient thinks she coughed up a piece of tissue in 1946. At that time she was examined bronchoscopically and was told that an area of inflammation was visible in the right bronchus. Studies were made to exclude tuberculosis and these, along with roentgenograms of the chest, were said to be negative at that time. In January, 1948, she developed pneumonia in her right chest and since then has shown a progressive shortness of breath, necessitating 2 to 3 pillows at night to sleep on. From 6 months before admission to the present time she lost about 10 pounds in weight.

Physical examination at the time of admission, April 18, 1948, revealed her heart to be slightly enlarged, with a regular rhythm and blood pressure of 200/110. The chest was thick and examination of the lung revealed a few ronchi and some dullness in the right base. The urinalysis on admission was normal, the hemoglobin level was 11.5 Gm. per 100 cc., the red blood cell count was 4,020,000, white blood cell count 7100, and the differential count was normal. All other blood studies were likewise normal, which included prothrombin time. The sedimentation rate was increased to 51 mm. per hour. The Wassermann reaction was negative. A roentgenogram of the

FIG. 5.—Case 5. (A) Section through tumor showing heterotopic bone formation, infiltrating cords of tumor cells and abundance of connective tissue stroma. (B) Section through a regional lymph node involved by metastatic tumor. The neoplastic cells are strikingly uniform in shape, size and staining characteristics, and are similar to the ones in the primary tumor. (C) Section through one of the cyst walls of the right upper lobe. The cystic space is lined by bronchial-type epithelium.

FIG. 6.—Case 6. (A and B) Photomicrographs of sections of the tumor demonstrating a pattern of growth often encountered in basal cell carcinoma of dermal appendages (adenocystic basal cell carcinoma of bronchus). (C) Photomicrograph of the metastatic brain lesion. Note absence of cystic architecture.

chest showed a shadow of increased density in the right hilar region which at first appeared to be mediastinal in position. Further films revealed slight evidence of right middle and lower lobe obstruction necessitating a diagnosis of primary bronchogenic tumor. Sputum examination failed to reveal any evidence of tubercle bacilli. Bronchoscopic examination revealed a smooth tumor in the region of the right intermediate bronchus. A biopsy from this lesion, however, showed essentially normal bronchial tissue. Bronchograms done before the patient was admitted to the hospital showed the right intermediate bronchus to be completely blocked. Roentgen ray examination of the stomach and intestines was normal and gastroscopic examination was normal. Roentgen ray examination of the colon was normal. Intravenous pyleograms were normal.

There being no evidence of primary lesion elsewhere, on June 15, 1948, a right thoracotomy was carried out and at that time a 4 x 6 x 6 cm. tumor was found, intrapulmonary in location, just below the level of the origin of the bronchus to the upper lobe. There was no evidence of any mediastinal gland enlargement or direct extension of the tumor into the mediastinal area. The carina was free and movable. The right middle and lower lobes of the lung were removed.

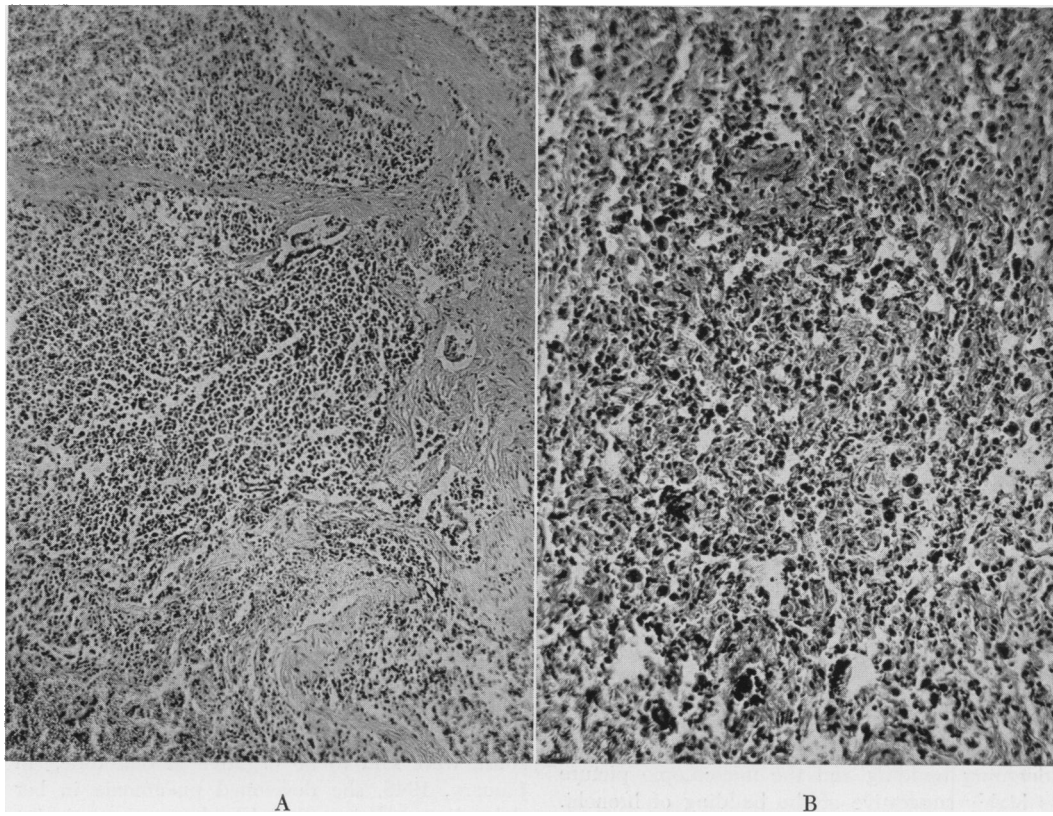


FIG. 7.—Case 7. (A) Photomicrograph showing solid sheet-like growth of cells resembling the picture of oat-cell carcinoma of the lung. However, the local invasion at margin is minimal. (B) Photomicrograph showing pleomorphism in other portions of the tumor mass. Note the presence of endothelial-lined spaces, multinucleated cells and cells resembling myeloblasts.

Examination of the specimen showed a large mass of homogenous, apparently well encapsulated tumor tissue. On microscopic section there could be seen nests and cords of cells fairly consistent in architecture growing in a relatively dense stroma. While a moderate amount of hemorrhage and necrosis could be demonstrated in some areas, there was a relatively small amount of sinusoidal vascularity, as is so often seen in this type of tumor. Microscopically the capsule surrounding the tumor was a dense one. In spite of this the tumor had extensively involved the wall of the bronchus, where it seemed to invade freely. The surrounding lung tissue was collapsed and there was a moderate

amount of bronchiectatic formation distal to the tumor area. There was no local lymph node involvement.

The patient's postoperative course was entirely uneventful and she has been followed since her operation. She remains in good health.

The history of this patient, with the subsequent pathologic findings, illustrates how large such a tumor can become before producing symptoms and how often an accident, such as the aspiration of a small foreign body with the consequent inflammation, may produce a chain of events which persists until the tumor is removed. The tumor was known to have been present for eight years, and the intrapulmonary encapsulation is of interest in this light. Where this type of encapsulation is not present, we have rarely seen a tumor exist for so long without evidence of distant metastasis.

Case 5.—J. S., a 27-year-old white woman, was first seen in the Oakdale Sanitorium on June 4, 1945. At that time she stated that she had had a productive cough for 7 months, pain in her right chest for 2 months, a 20-pound weight loss during this period of time, and night sweats for 2 months. She thought that she had been relatively well until about December, 1944, at which time she had suffered a massive sudden hemoptysis. She believed that blood came from her right side. During that same month she had had 3 more episodes of severe bleeding and had developed a persistent cough. She became bedridden due to increased weakness around February, 1945, and at that time she began to cough approximately one half a cup of purulent material per day. She was seen by her local physician, who felt that she had an attack of pneumonia and treated her with sulfa drugs.

On admission to the Oakdale Sanitorium the patient had a large amount of sputum. On one occasion the sputum showed tubercle organisms, and for this reason the patient was admitted to the Sanatorium. It was felt that her primary diagnosis was one of tuberculosis on the basis of the roentgen ray films and the single positive sputum examination. Accordingly, pneumothorax therapy was instituted. However, she quickly developed fluid in the pleural space, atelectasis of the right upper lobe and fever. For this reason the pneumothorax was immediately abandoned. From then on the patient was observed on conservative treatment. Subsequent roentgenograms taken at the Oakdale Sanatorium showed her left lung field to be perfectly clear. All the sputum examinations, following the initial one, were negative for tubercle organisms. Bronchograms carried out on April 19, 1946, revealed a block in the region of the right upper lobe bronchus. Culture for tubercle organisms was negative. The patient received repeated bronchoscopic examinations between May and August, 1946, and finally a diagnosis of mixed tumor of the bronchus was established as a result of a positive biopsy. It was felt by some that the lesion was probably malignant because of the numerous mitotic figures that could be seen in some of the biopsies. Laboratory examination at that time showed the urine to be normal, hemoglobin to be 12 Gm. per 100 cc., red blood cell count 4,200,000, white blood cell count 9750. The serum albumin was 3.10 Gm. and the serum globulin 3.50 Gm. The total plasma protein was 6.60 Gm., the Wassermann was negative.

On October 14, 1946, the right lung was removed surgically. At the time of exploration it was found that the tumor was about 1 cm. distant from the carina but it was possible to transect the right main bronchus proximal to the mass. The patient's postoperative course was entirely uneventful.

The examination of the removed lung was of considerable interest to us. There was a large mass of firm yellow tissue adherent to the external surface of the bronchus near the hilum. Grossly, this tissue had an irregular structure in which there was evidence of bone present. The upper lobe of the lung showed numerous large cystic cavities, in no way unlike that seen in congenital cystic disease. Directly distal to the tumor one encountered bronchiectasis similar to that often seen following bronchial obstruction. There was one large hilar lymph node present that seemed to be involved grossly by tumor.

Microscopic examination of the tissue confirmed most of the gross findings. There was relatively a preponderance of epithelial overgrowth, although the stroma was most abundant. The epithelium grew in cords interlacing in type and very thick and extended outward around the cartilaginous rings of the bronchus and into the lung. More commonly near the bronchial wall, but extending out into the pulmonary area, there was seen heterotopic bone formation, apparently of a membranous type. Nowhere could we find cartilage. The neoplastic cells were strikingly uniform in shape, size, and staining characteristics. There were a few mitotic figures present. The lymph nodes examined showed masses of metastatic neoplastic cells which were similar to the primary tumor. Interestingly enough, several tubercles were also seen in some of the lymph nodes. Microscopic examination of the cystic spaces in the upper lobe showed them to

Fig. 8

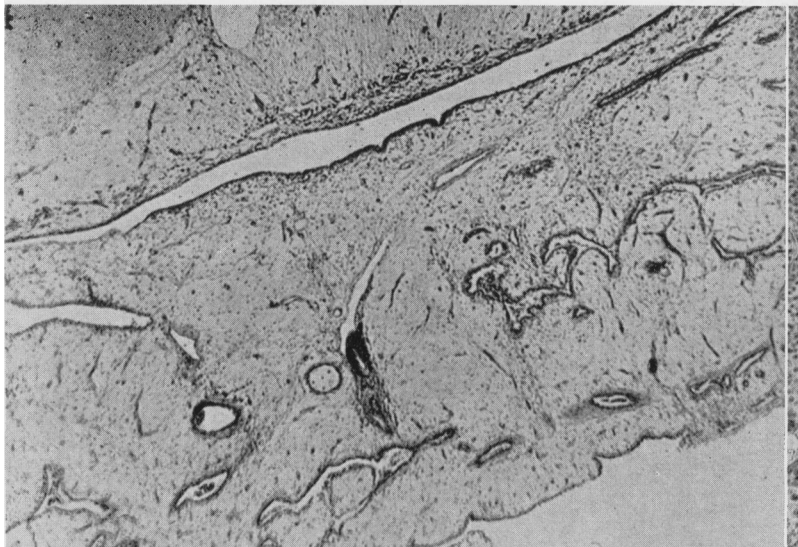
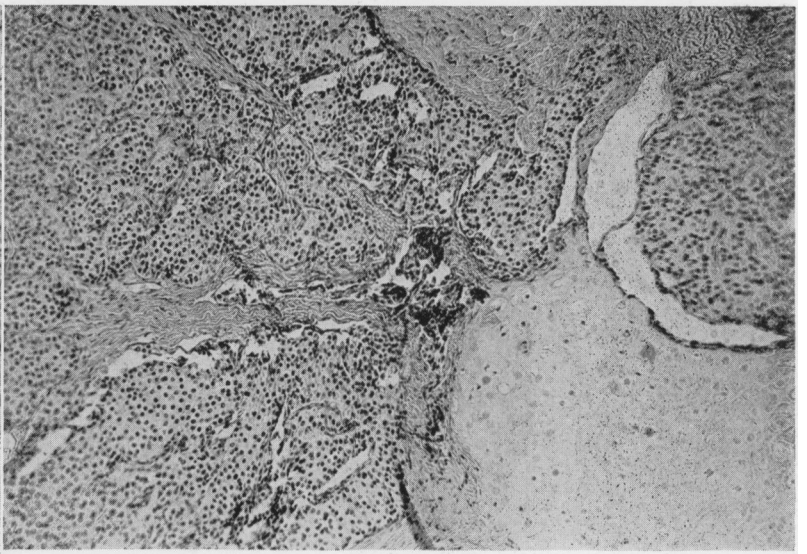


Fig. 9



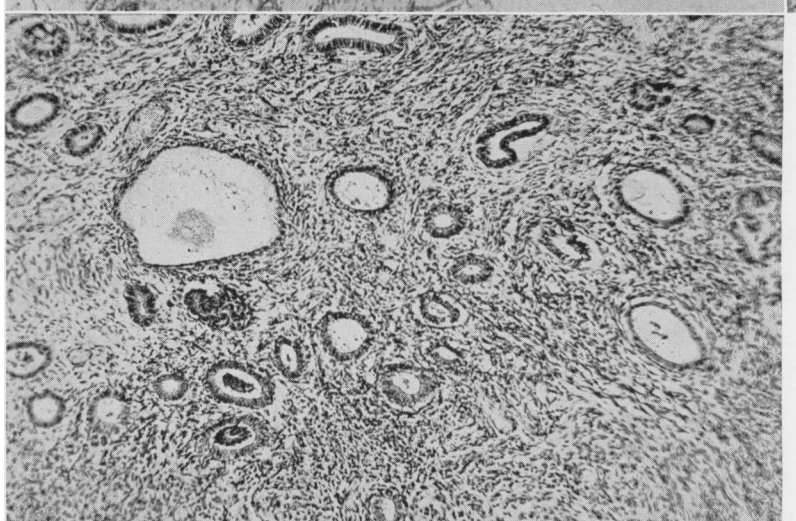


Fig. 10

Fig. 8.—(Case 8) Photomicrograph showing the chondromatous nature of the tumor. There is much fibroblastic activity. Many slit-like spaces are present lined by bronchial epithelium.

Fig. 9.—(Case 9) Photomicrograph showing locally invasive tumor. Well developed cartilage, mature collagen fibers, normally formed vascular spaces and masses of epithelial cells of consistent configuration are seen. Note the multiplicity of types of tissue present.

Fig. 10.—(Case 10) Photomicrograph through the tumor shows tubular structures cut in cross section, varying in diameter and lined by columnar and cuboidal epithelium. These structures are surrounded by a stroma of fibrocytes. The picture resembles the one seen in adenofibroma of the female breast.

be lined by bronchial epithelium with remnants of smooth muscle and occasional bits of cartilage in their wall. There was also hyperplasia of the alveolar epithelium in this area. The microscopic examination then was typical of the usual findings in cystic disease of the lung.

The patient was discharged in good condition, but was re-admitted on December 10, 1946, for tubal ligation and sterilization. Following this she has been in excellent condition.

In spite of the fact that this patient has apparently survived her cancer, there can be no doubt in our mind that this was cancer. The lymph nodes were involved and this was not by direct extension but by metastasis.

The presence of the isolated areas of bone and collagenous stroma is of interest. Such structure does not represent areas of epithelial modulation. Bone can never become epithelium nor can epithelium become bone. We are, therefore, dealing obviously with two types of tissue.

The presence of cystic disease in the upper lobe is also a fact of great interest to us. In 1941, Doctor Graham and one of us[4] called attention to the frequent finding of areas of epithelial metaplasia in lungs that had been removed for congenital cystic disease. In the cases that we reported at that time there was no classical picture of the mixed tumor. In our discussion of this type of metaplasia seen in cystic disease of the lung in that contribution, the following paragraph can well be quoted at present:

"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, 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."

Case 6.—F. K. This 65-year-old white male was first admitted to the hospital on April 17, 1946, with a history of having had a cough from 4 to 5 months. There also had been some slight pain in the left chest. Eight days prior to admission the patient had a bronchoscopic examination which revealed a tumor in the left main bronchus very close to the carina. There had been no history of hemoptysis. The sputum, however, had been purulent and quite large in amount, up to one-half cup a day for the past 4 months. There had been a 10-pound weight loss. The patient stated that he had had several attacks of what had been diagnosed pneumonia during the past 5 months, always on the left side. Other than this the past medical history was irrelevant to the present condition.

On physical examination the heart was normal to percussion and auscultation; the blood pressure was 120/70. There was dullness over the left chest with decreased breath sounds and many râles. The remainder of the physical examination was normal except for the presence of a right indirect inguinal hernia. The laboratory findings revealed the urine to be normal and the hemoglobin level 13 Gm. per 100 cc. The white blood cell count was 12,400; vital capacity 2000 cc. The electrocardiogram was normal. All blood chemical studies were normal, which included the blood sugar and plasma protein estimation. The blood serology was negative. Examination of tissue removed by biopsy at the previous bronchoscopic examination showed the tumor to be in the mixed tumor group.

At operation on April 22, 1946, the left lung was completely atelectatic, with areas of bronchiectasis. The tumor could be felt in the left main bronchus very close to the carina. It was impossible at that time to resect the left main bronchus proximal to the tumor and still close the trachea. For this reason the left main bronchus was transected distal to the tumor and the latter was removed through the bronchial stump by curettage after the lung had been taken out. Although this was an unsatisfactory procedure, at the end of the operation it was apparent that all tumor tissue had been removed. No local lymph nodes were felt to be involved in the process. The patient's postoperative course was entirely uneventful and he was discharged from the hospital on May 11, 1946. Pathologic examination of the lung revealed widespread atelectasis and bronchiectasis, along with chronic pneumonitis such as had been anticipated at operation. There was no gross involvement, nor was there microscopic involvement of the regional

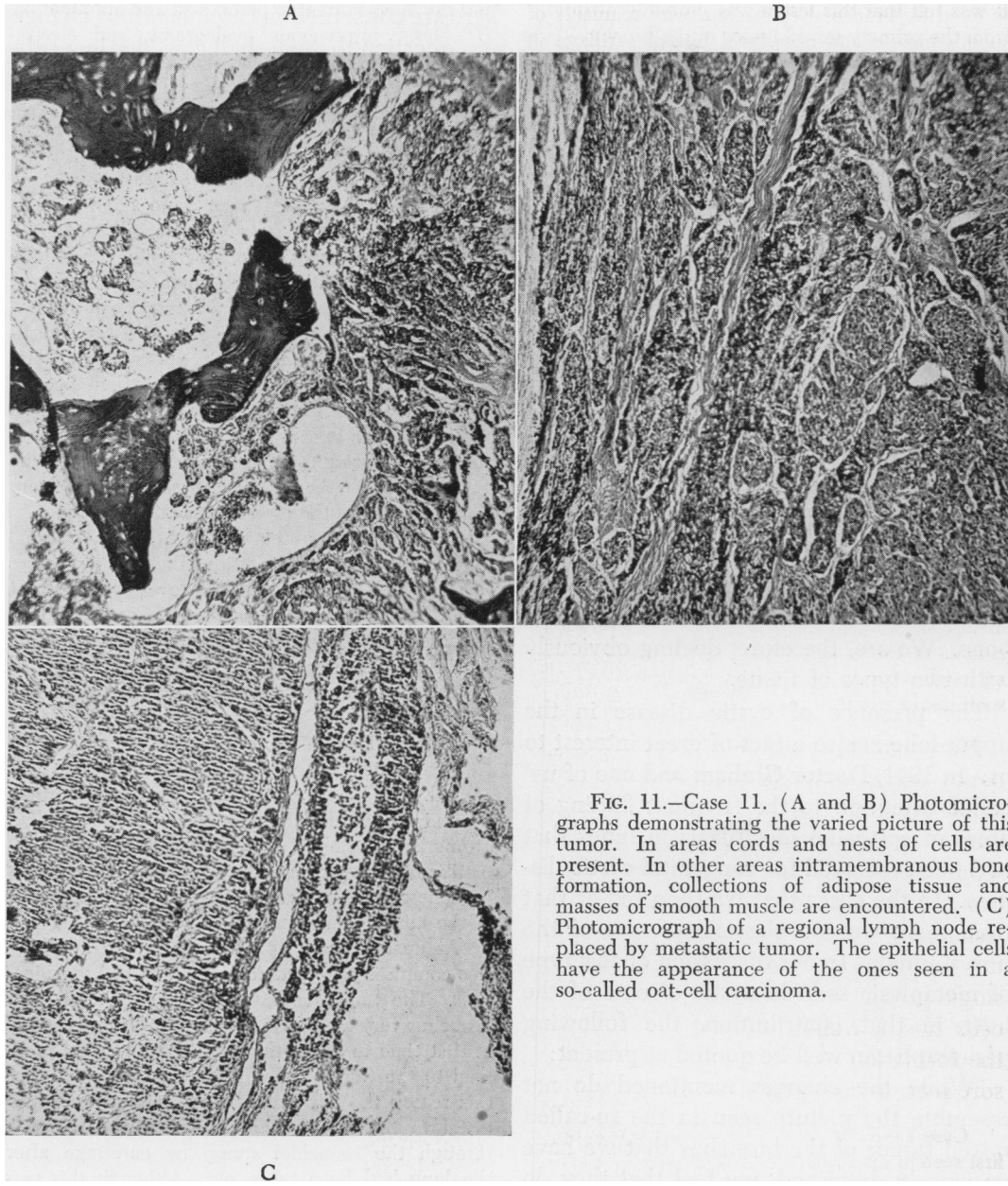


FIG. 11.—Case 11. (A and B) Photomicrographs demonstrating the varied picture of this tumor. In areas cords and nests of cells are present. In other areas intramembranous bone formation, collections of adipose tissue and masses of smooth muscle are encountered. (C) Photomicrograph of a regional lymph node replaced by metastatic tumor. The epithelial cells have the appearance of the ones seen in a so-called oat-cell carcinoma.

lymph nodes. The microscopic appearance of the tumor was interesting. Not only was it unencapsulated, but when the bronchial wall was studied carefully it seemed to arise in several different areas. The cells seemed to form a pattern so often encountered in certain types of basal cell carcinoma of the dermal appendages, and this type of tumor has been referred to by some as adenocystic basal cell carcinoma of the bronchus. Studies in other areas of the tumor were remarkable in their resemblance to atelectatic lung, and the small cystic areas of tumor architecture mimicked to a considerable degree respiratory bronchioles.

In November, 1946, the patient started having frontal headaches, occipital headaches, and vomiting which became projectile. At about that time he also developed diplopia. He was re-admitted to the University Hospitals on January 27, 1947. It was thought that this patient had a rapidly expanding intracranial lesion, probably of the cerebellum.

It was felt that this lesion was probably metastatic from the primary mixed tumor of the bronchus. On January 31, 1947, a ventriculogram was carried out which revealed a space-occupying lesion in the right occipital horn. A right occipitoparietal craniotomy was carried out on the same day and a moderately well-encapsulated tumor was encountered which was of an estimated size of about 5 x 5 cm. The right occipital lobe was amputated which contained the tumor mass. It was the operator's impression that at that time this neoplasm was most likely a metastatic tumor. The patient's postoperative course was uneventful, and he was discharged on February 9, 1947. He was able to walk for short distances at this time. The last communication we have regarding this patient is dated April 24, 1948, in which it is stated that the patient had expired at home prior to this date, but the exact time was not given.

Microscopic examination of the tissue removed from the brain reveals an entirely different picture from that seen in the primary lesion. The cystic architecture is no longer present, the cells growing as a confluent mass. It is of interest that the metastasis is much more like that of the banal carcinoma of the bronchus than is the primary lesion, although a study of the individual cells shows no such marked difference.

Here again is obvious evidence of malignancy on the part of one of these tumors. What seemed to be a benign lesion at the time of operation metastasized with a microscopic morphology resembling that of bronchiogenic cancer. Study of the primary lesion also calls attention to the fact that this tumor began in an area rather than in a single group of cells and that the epithelial cells had a well-developed potentiality to the formation of a tubular structure of the sort seen in the terminal bronchiole.

Case 7.—E. W., a 45-year-old white female, was first seen in the Department of Otolaryngology complaining of roaring in her left ear with an unusual sensation in her nose. During routine examination roentgenogram of her chest was made. This revealed a peripheral sharply circumscribed mass located in the left midlung field. The past medical history was without significance with the exception of an operation for suspension of the uterus and appendectomy in 1941. She also gave a history of vague digestive disturbances, but further study of her gallbladder, stomach, and intestines revealed no abnormalities. On physical examination the heart was of normal size, the blood pressure 128/84, and the lungs normal to percussion and auscultation. Urinalysis, intravenous pyelograms, and electrocardiogram were normal, and bronchoscopic examination showed a normal endobronchial tree. Pelvic examination revealed a small leiomyoma in the uterus but an otherwise normal pelvis. The hemoglobin level was 13 Gm. per 100 cc., the red blood cell count 4,050,000, and the white blood cell count 5800. Because the skin tuberculin test was strongly positive after 48 hours, the preoperative impression was that this patient had a tuberculoma of the left midlung field.

At operation on February 19, 1951, a tumor mass was noted located in the left lower lobe and was found to pulsate synchronously with the heartbeat. There were no hilar nodes palpable. The left upper lobe was normal. Due to the location of this mass and the fact that it was pulsating in nature, a left lower lobectomy was carried out without any difficulty. The specimen removed revealed a well circumscribed round lesion which appeared to be highly vascular and had many large vessels entering it giving the gross appearance of a hemangioma.

On microscopic examination the architecture varied in different portions of the lesion. In some areas there was a solid sheet-like growth of cells resembling the picture of oat-cell carcinoma of the lung. In other areas there were multi-nucleated cells and cells resembling myoblasts. There were also many endothelial-lined spaces, some of which contained blood. While the histologic picture was pleomorphic and resembled that of an immature neoplasm, there was definite lack of aggressiveness in its invasive characteristics. Extending through the tumor in many areas, there were cyst-like dilatations of the bronchial structures. There was not a great deal of local invasion and the lymph nodes examined showed no evidence of tumor.

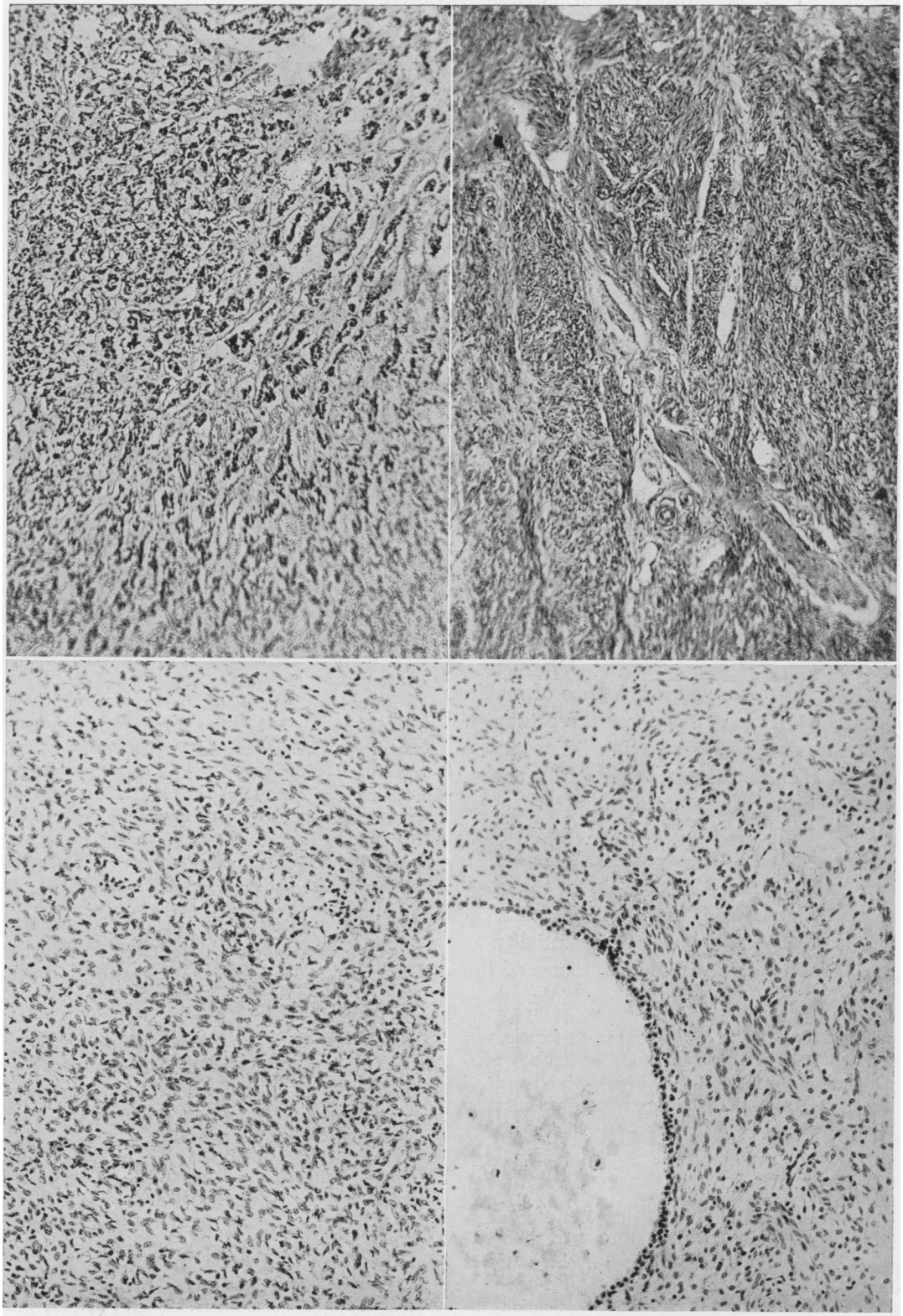
As has so often been the case when the tumor has been discovered accidentally by a routine chest film, pathologic study of the lesion showed but little evidence of invasiveness. On the other hand, the potencies of the tissues involved here are quite striking. There is a mixture of epithelial and mesenchymal cells that could easily lead one to give a compound classification to this type of tumor if he so wished. Fundamentally it seems to be composed of primitive angioblastic, myoblastic and epithelial cells.

Case 8.—A. S. About 3 months before this patient was admitted into the hospital he fell, sustaining a fracture of a rib on his left side. He was a white male, 50 years of age, somewhat obese in

FIG. 12

A

B



A

B

FIG. 13

See opposite page for legends.

body habitus. A roentgenogram of his chest showed, in addition to the fracture, a round tumor in the periphery of the lower left lung field. Following the fracture the patient stated he had developed a mild cough. There had been no hemoptysis and no other chest symptoms. There had been no weight loss, no night sweats, or any other symptom consistent with pulmonary disease. His past medical history was not contributory to the present complaint.

On physical examination it was noted that his blood pressure was 180/110, and while the heart appeared to be normal in size, more extensive cardiac evaluation gave the impression that the patient had hypertensive vascular disease which was at present time well compensated. The electrocardiogram was normal. Preoperative intracutaneous tuberculin reactions were mildly positive. Intravenous pyelograms were normal, the urine was normal, the hemoglobin level was 16 Gm. per 100 cc., the red blood cell count was 4,950,000, the white blood cell count 11,800; the vital capacity was 3200 cc.; the Wassermann reaction was negative. Further roentgen ray examination of the chest showed a sharply circumscribed round shadow of increased density about 3.5 cm. in diameter lying in the lower half of the left lung field anteriorly.

On April 1, 1951, a segmental resection of that portion of the left upper lobe containing the tumor was carried out. The postoperative course was uneventful.

The gross appearance of the lesion was one of chondroma. On microscopic section, however, this chondromatous tumor was seen to be filled with small slit-like cavities lined by bronchial epithelium. In other areas there was considerable fibroblastic proliferation.

Although this type of lesion is undoubtedly benign, here again one sees the combination of mesenchymal and epithelial tissues.

Case 9.—L. S. This 45-year-old white woman was admitted to the surgical service on May 15, 1947, with the complaint of chronic cough and hemoptysis of 2 months duration, a weight loss of 15 pounds in the previous 4 months and a loss of strength for the same length of time. She stated that for the past 3 to 4 years before admission she developed many colds and would have a chronic hacking cough for a long time following them. In March, 1947, she developed a severe attack of influenza with pain in her right chest. There was a history elicited of one episode of hemoptysis 4 years before admission, however. At that time she coughed up bright blood for about 1 week. Tuberculosis studies had been made at that time and were all negative. During March, 1947, she had a chest roentgenogram taken. It showed some abnormality in her right lung field. About this time she again had episodes of hemoptysis, sometimes as much as a cupful of blood per day. There had been no pain in her chest nor had there been wheezing. The remainder of her past medical history was of no consequence to the present illness.

On physical examination the blood pressure was 108/70, the heart of normal size and the rhythm regular. Electrocardiogram was normal. Physical examination of the lung fields showed full and equal expansion and on auscultation no abnormalities were heard. The patient was subjected to two bronchoscopic examinations. The first one was on May 9, 1947, at which time a large amount of bleeding was encountered and a questionable mass visualized in the right lower lobe bronchus. Because of the hemorrhage certainty was not obtained. Accordingly, the procedure was repeated on May 13, 1947, at which time a definite tumor mass was found in the region of the middle lobe orifice. Again, the mass bled extremely easily and no biopsy could be obtained. All of the laboratory studies were normal. Sputum examinations were negative for tubercle bacilli. The hemoglobin was 13.5 Gm. per 100 cc., and the white blood cell count 8200.

On May 19, 1947, a right pneumonectomy was performed. At the time of dissection in the lung hilum no metastases to lymph nodes were apparent. The tumor was palpable in the right main and intermediate bronchi. Examination of the specimen showed the right lung to weigh 420 Gm. In the main bronchus to the right lower lobe there was a nodular mass arising from the bronchial wall. It measured 2 x 1.8 x 1 cm. and had a thin intact mucosal covering. On section it could be seen invading through the bronchial wall at its point of attachment into the pulmonary tissue. The superior portion was mottled and hemorrhagic in appearance and the basilar portion was soft and yellow and homogenous. There was extensive bronchiectasis distal to the obstructing mass. The bronchi were filled with purulent material. On microscopic examination cells were easily demonstrated invading the fibrous stroma. This stroma for the most part

FIG. 12.—Case 12. (A) Photomicrograph of the portion of tumor demonstrating the epithelial cells growing in clumps. Cells have scant amount of cytoplasm. (B) Photomicrograph (trichrome stain) of portion of tumor showing interlacing bundles of spindle cells, and smooth muscle. No epithelial cells are encountered in this area.

FIG. 13.—Case 13. (A) Photomicrograph showing the dense stroma myxomatous in some areas and giving the picture of leiomyoma in others. (B) Photomicrograph through one of the cystic spaces lined by cuboidal epithelial cells.

was coarse and collagenous, interrupted here and there by large areas of hyaline cartilage. The epithelial cells were growing as solid tubes with fairly large nuclei and clear cytoplasm. Examination of the lymph nodes removed at operation showed no evidence of extension.

Here again one has a tumor that is locally invasive and is composed of well-developed cartilage, apparently adult collagen, normally formed vascular spaces, and masses of epithelial cells showing a fairly consistent configuration. Here again is a multiplicity of tissues, neither one of which ordinarily reverts to the other.

Case 10.—R. A. This patient, a 15-year-old boy, apparently enjoyed good health until January, 1944, at which time he developed bronchopneumonia. This was treated with sulfa drugs. He had a productive cough producing about one-half cup of yellow thick sputum per day following this episode. The cough was most common in the morning. There were no pleurisy pains, but he thinks that he had fever intermittently. There was a weight loss of 15 pounds between January and September, 1944. He was admitted to the hospital on October 2, 1944. Tuberculin skin tests at that time were negative. There was a history of occasionally blood-streaked sputum but no massive hemoptysis. His past medical history was unrevealing.

On physical examination there was noted decreased expansion of the right chest, impairment to percussion all over the right lung except the apex, reduced breath sounds in the lower portions of the right chest, and definite râles in the right base. The left lung was clear and normal to percussion and auscultation. The blood pressure was 110/64. The heart was normal. Urine examination was normal. The hemoglobin was 12 Gm. per 100 cc. of blood and the red blood cell count 4,540,000. The white blood cell count was 1450. Bronchoscopic examination revealed a tumor obstructing the right main bronchus and biopsy of this revealed the histologic pattern of a mixed tumor of the bronchus.

On October 6, 1944, a right pneumonectomy was carried out. At the time of pneumonectomy the tumor was felt in the right main bronchus and was freely movable, giving a ball-valve action. It was attached to the right main bronchus by a stalk with a broad base. The postoperative course was uneventful and the patient has been followed in the tumor clinic repeatedly since operation. The last report some 7 years later shows him to be perfectly well, pursuing the occupation of a watchmaker and repair man. This patient never had a post-pneumonectomy thoracoplasty on the side of the pneumonectomy.

The microscopic appearance of the tumor tissue differs from the common types of so-called mixed tumors that we have described. One sees clusters of tubular structures cut in cross sections, varying in diameter and lined by cuboidal or low cuboidal cells similar to those seen in the smaller bronchi. These tubes are surrounded by a stroma of fibroblasts chiefly, in which there are wandering cells, occasional collections of lymphocytes and a considerable amount of edema. The picture resembles very much the lesion called adenofibroma found in the female breast. That portion of the tumor adjacent the normal bronchial mucosa is interesting in the sense that the mucosa is extremely thin and beneath it one sees abnormal collections of smooth muscle and occasional masses of epithelial cells growing at random.

Here again is a picture of tissue disorganization so that even tissue differentiation has been markedly interfered with by cells that do not look particularly neoplastic in type.

Case 11.—M. R., a 44-year-old white woman, was admitted to the hospital complaining of wheezing in her left chest for 18 years, hemoptysis, increasing shortness of breath, and frequent attacks of pneumonia in her left lung for the past 12 years. The respiratory difficulties had become increasingly more severe during the past 12 years, especially when she was lying down. There had been innumerable attacks of intermittent hemoptysis, some of which were quite severe. There had been left chest pain, mostly over the anterior chest radiating to the axilla and back. Her cough became productive during the last 2 years, up to 2 cups of sputum per day. She had had 3 episodes of pneumonia during the past 6 years, the last severe episode one and one-half years ago. Two weeks before admission the patient consulted Doctor Randall in Waterloo, who performed a bronchoscopic examination and a diagnosis of mixed tumor of the bronchus was established.

On admission to the University Hospital there was noted definite limitation of expansion of the left chest. The left chest appeared smaller than the right. The lungs were resonant on both sides but the breath sounds on the left were harsh. There were a few râles in the left base. Bronchograms carried out showed a lesion constricting the lumen of the left main bronchus at the area of the bifurcation of the left upper and lower lobe bronchus. The heart was of normal size but the mediastinum was definitely shifted to the left. The blood pressure was 130/80. The hemoglobin was

13 Gm. per 100 cc. on admission and the red blood cell count 4,240,000; white blood cell count 4500; the Wassermann was negative; the urine was normal and the differential blood count was normal. Sputum was examined for abnormal cells and none were found. No acid-fast organisms were present in the sputum. The skin tuberculin test was negative. Roentgenograms of the chest revealed evidence of left lower lobe atelectasis. A large extensive shadow of an apparent mass was also visible on one of the roentgenograms. The electrocardiogram was normal. Bronchoscopic examination was carried out on June 20, 1951, at which time a tumor was seen. However, biopsies obtained at this time revealed only normal endobronchial mucosa and some scarring. Apparently the tissue had not been removed deep enough to obtain the tumor tissue proper.

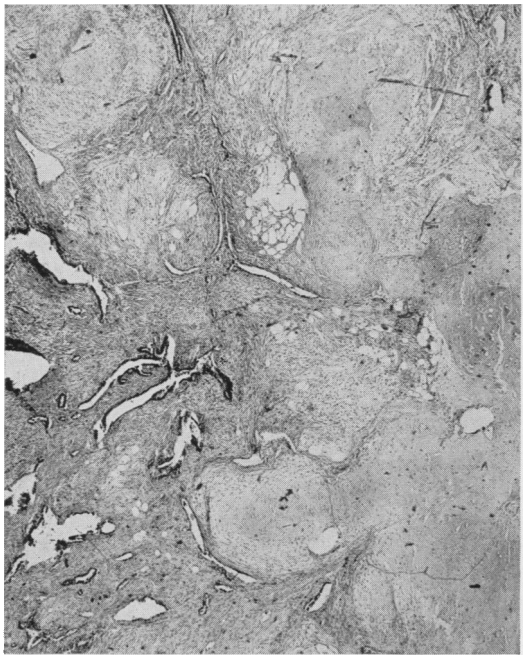


FIG. 14.—Case 14. Photomicrograph showing the complexity of this tumor. Fibrillary connective tissue, abnormal hyaline cartilage, adipose and fibrous tissue are present. The tumor is lobulated and separated by spaces lined by pseudostratified columnar epithelium.

On June 24, 1951, left pneumonectomy was carried out. At the time of operation, the mass was apparently extrinsic to the lumen of the left main bronchus. At the time of resection it became also evident that at least 1 or 2 of the regional lymph nodes had become involved by the neoplasm and all of the lymph nodes in this area were resected. The operative procedure and the postoperative course was uneventful.

Microscopic examination of the tumor showed a varied picture. There were nests and cords of cells in a fairly classical pattern so often seen in mixed tumors. Here and there, scattered diffusely throughout the tumor, however, one encountered areas of bone, both membranous and endochondral in type. There seemed to be no relationship between the position of this bone and the bronchial wall. In many areas adjacent to the bone one encountered collections of fat. Other portions of the tumor showed chaotic conglomerate masses of smooth muscle. This muscle tissue apparently was well differentiated, as was the bone. Examination of the lymph nodes showed extension of the tumor as cancer and, interestingly enough, here the epithelial cells were growing in sheet formation identical to that picture seen in so-called oat-cell cancer of the lung.

This patient illustrates a type of lesion that we think is safe to call malignant because it invaded locally and metastasized to regional lymph nodes. The morphology of the metastasis is not that of a benign tumor but that of cancer. Here again one sees illustrated numerous adult tissues, not of epithelial origin, present within the tumor mass.

Case 12.—B. A. This 66-year-old white woman was admitted to the hospital with the complaints of attacks of shortness of breath, pain in the chest, weakness, fatigue, and swelling of the legs of one and one-half years duration. She stated that she was in quite good health until December, 1943, and she had first had attacks of dyspnea and pain in her chest, coming on mostly at night. These attacks lasted for about 2 hours. The attacks of pain were localized to the left side of the chest and did not radiate. She also noted some cardiac hyperactivity. These attacks occurred about once a month. She was seen by her local physician, who placed her on digitalis. There was definite nocturnal dyspnea and coronary pain at that time. One month before she was admitted to the hospital she noted swelling of her legs which extended up to the lower part of her thighs. She also noted some swelling in the abdomen and some pain in the right upper portion of the abdomen. She denied any cough or hemoptysis.

On physical examination she was found to be a poorly nourished woman who seemed acutely ill as well as having suffered for a long time from chronic distress. She was unable to be out of bed

with comfort. Examination of the chest revealed it to be symmetrical, there were no masses noted, there were no râles in either lung field. The mediastinum was in midline. There were no abnormal breath sounds. The heart was definitely enlarged. There was a blowing systolic murmur heard over the entire precordium. There was auricular fibrillation present with a rate of about 104. The blood pressure was 160/90. The abdomen was large and rotund with ascites present. The liver was enlarged approximately 3 finger breadths below the costal margin. The rest of the examination was essentially negative to the present complaint. The impression was gained of arteriosclerotic heart disease and auricular fibrillation with congestive failure. The electrocardiogram revealed auricular fibrillation, but all other laboratory findings were within normal limits with the exception of a mild secondary anemia and a low plasma protein level, the total being 4.10 Gm. per 100 cc., with the albumin of 2 and globulin of 1.9 Gm. per 100 cc. The patient's course was rapidly downhill and she expired on July 13, 1945.

At the time of necropsy a tumor was found in the lung as an incidental finding. It was located in one of the smaller bronchi in the periphery of the right lung. The tumor was about 1 cm. in diameter and well circumscribed. On section the neoplasm had a firm gray homogenous appearance. There was no gross invasion and there was no evidence of any other similar lesions at the time of autopsy. The microscopic appearance of this lesion was that of a mixed tumor of the lung peripheral in location. The cells were small and symmetrical, with a scant amount of cytoplasm and hyperchromatic nuclei. They grew in cords and small clumps. In many areas of the tumor there were foci in which no epithelium could be encountered at all, but instead, interlacing bundles of spindle cells, chiefly fibroblasts, although the presence of smooth muscle could not be completely excluded.

This finding of mixed tumor was apparently incidental, as the cause of death was obviously one of congestive heart failure from hypertensive heart disease with arteriosclerotic damage of the kidneys, chronic passive congestion of the viscera, a pulmonary embolus and lobular pneumonia.

Although, as we said earlier, it is questionable whether such a tumor as we are describing can completely disappear leaving no residual scar, there seems to be but little doubt about the fact that many of them can remain in a dormant innocuous stage for years. The above is such an example. Those factors that determine when such a tumor or, for that matter, any tumor, shall become clinically invasive are yet not known.

Case 13.—D. M., a 30-year-old man, had an entrance complaint of a tumor in the right lung which he had known to be present for the past two and one-half months. Although the patient stated that in retrospect he could recall on several occasions during the past year a slight sharp stabbing pain over the right lower chest and behind the sternum, he had considered himself completely well until a routine chest roentgenogram had been taken by a mobile tuberculosis unit in June, 1951. When he was admitted to the hospital, roentgenograms of his chest verified the previous findings of a large shadow occupying the right mid- and lower lung field. Because of its extreme size and relatively symptom-free existence, the impression gained when he first was seen was that of a neurofibroma of the posterior mediastinum. The patient had lost about 16 pounds during the past 7 or 8 years but he had been actively working and had no other complaints to offer. His past medical history was unrevealing.

On physical examination a normal and well-developed, strong, young man was noted. Examination of the chest showed decreased and absent breath sounds over the right lower chest posteriorly and laterally. This was in the region of the shadow noted on roentgenogram examination. Bronchograms carried out revealed the right main bronchus to be displaced but not blocked. Esophagrams revealed displacement of the mid- and distal thirds of the esophagus to the left and anteriorly without any roentgen ray evidence of intrinsic involvement. The plasma protein level was 7.35 Gm. per 100 cc., of which 4.83 Gm. per 100 cc. was albumin and 2.52 globulin. The urine was normal, the Wassermann reaction was negative, the hemoglobin level was 14 Gm. per 100 cc. of blood, and the red blood count was 6,000,000, the white blood count being 10,000.

At operation on August 17, 1951, a mass approximately 15 cm. in diameter was found firmly attached to and apparently having its origin from the right lower lobe of the lung. This mass was also densely adherent to the parietes of the right lateral chest wall, and posteriorly it extended also between the descending aorta and the esophagus, displacing it into the left chest and anteriorly. The resection was moderately difficult and a right lower lobectomy with resection of this large mass had to be carried out. His postoperative course was entirely uneventful and the patient is now back at work.

When the tumor was sectioned it tended to exude from its capsule, very much like a leiomyoma of the uterus. It was firm, slightly edematous and could be separated in slit-like areas very much as

is seen in a fibro-adenoma of the breast. It had a definite adventitious capsule. On microscopic examination there was dense stroma in some areas, myxomatous in type; in other areas there was fibroblastic proliferation with collagen, and in still other areas the picture was that of leiomyoma. Of great interest were the numerous small cystic areas scattered throughout the tumor. These small cysts which ranged from several microns to several millimeters in diameter, were lined with epithelial cells, some of which were cuboidal and some of which were columnar. Here and there one encountered brush borders with definite ciliation. There was no evidence of masses of epithelial cells, nor did we encounter bone or cartilage.

The pathologic picture here is one in which there is both epithelial and mesenchymay tissue, the latter of which has taken on more abundant growth. The epithelial tissue tends to differentiate fairly well into tubular structures and it would be most difficult indeed for us to anticipate that these structures have their origin from the tissue that goes to make up the stroma. In so far as morphology and function of the cells is concerned, one seems obligated here to recognize the presence of several types of different tissues.

Case 14.—D. W., a woman of 54 years, was admitted to the hospital on October 29, 1951, with multiple complaints, none of which seemed to be significant. Outstanding in the patient's mind was the complaint of burning in the neck and tickling in the throat which had been present for two years. There was also chronic fatigue and constipation.

On physical examination a marked scoliosis with kyphosis was noted. The patient was a thin, nervous, unhappy woman. There was marked bulging of the right hemithorax posteriorly with elevation of the right shoulder. Percussion and auscultation were unrevealing. The abdomen showed nothing abnormal. Examination of the heart showed a harsh systolic murmur over the precordium. The blood pressure was 130/85. The Wassermann reaction was negative and the urine was normal, as was examination of the sputum. The electrocardiogram was normal. The red blood cell count was 3,600,000, the white count 10,650, and the hemoglobin level 12 Gm. per 100 cc.

A roentgenogram of the chest revealed a sharply circumscribed mass in the left upper lung field. This lesion was found by bronchography to be located in the left upper lobe. Intravenous pyelography and genito-urinary studies revealed the kidneys to be normal. Gastro-intestinal roentgenogram examinations revealed the entire intestinal tract to be normal.

At operation on October 31, 1951, a hard tumor was encountered in the left upper lobe which was removed by resection of the anterior pectoral segment of the left upper lobe. The postoperative course was entirely uneventful and the patient was discharged on November 7, 1951.

Examination of the specimen removed showed it to be a sharply circumscribed mass 3 x 2 x 3 cm. It was hard, lobular, and white in color. There were small slit-like spaces between some of the lobules, and these were filled with mucus, which was clear except where it was stained slightly with blood. In no part of the mass was there calcification.

On microscopic examination the tissue was found to be made up of a tangled mass of fibrillary connective tissue with abnormal hyaline cartilage, along with adipose and fibrous tissue. These structures were mixed at random in the lobules and at times separated by epithelial-lined spaces. This epithelium was for the most part pseudostratified columnar ciliated epithelium resembling that of the respiratory tract. The picture was in keeping with that of a mixed tumor of the lung.

This specimen demonstrates again the complexity of the so-called chondromas of the lung and illustrates well the potentiality of the mesenchymal tissues in this area.

DISCUSSION

These patients exhibit in many respects the same clinical features that we noted in our earlier paper and which we feel important enough to bear repetition. While the age limit is most variable, we have never encountered these tumors before puberty. They more commonly occurred in individuals somewhat younger than was found in squamous cancer of the bronchus. Neither is there seen the large preponderance of males, such as is true in squamous cancer, for in our experience the mixed tumor has been found more frequently in females.

Symptoms are produced by mechanical obstruction of the bronchus, these most frequently being atelectasis with subsequent infection that is mistakenly called pneumonia. There are times in the presence of suppuration when there may be bronchiec-

tasis. Such bronchial obstruction may appear in episodes, probably due to inflammation in the tumor with edema. The tumor may ulcerate and there will be hemoptysis because of the extreme vascularity of the tumor. Apparently such a tumor may be present for a long time, undergoing slow growth and presenting no symptoms until such inflammation or ulceration occurs, brought on by the accidental aspiration of a foreign body or brought on by respiratory infection. At such times there is the appearance of sudden onset.

When the tumor is not protruding into the major bronchus there may be no symptoms at all and we have had several such lesions discovered accidentally when a chest film was taken for other reasons.

In spite of the fact that once such symptoms begin they reappear with increasing frequency, many patients have allowed them to persist for a long time — long enough for us to be able to say that the greater the time that has lapsed since the first symptom and the larger the size of the tumor, the more likely the chance of regional and distant metastases.

From the above analysis of symptoms it is apparent that physical examination of the chest can reveal only those signs that are the result of bronchial obstruction. Except for the round, solitary, peripheral lesion, this is also true of the roentgen ray findings. Where a major bronchus is involved, and this is the most frequent site, the instillation of iodized oil into the bronchus rarely fails to show occlusion. At such times it is unusual not to have bronchoscopic verification of the tumor.

Here again the examination of the sputum for tumor cells has been disappointing. We have as yet been unable to recognize such a tumor by this procedure, even though the tumors be large and have metastasized.

Because, in spite of early local invasion, distant metastasis is usually late, extirpative surgery frequently gives a good result. We need not discuss here whether this tumor should be called an adenoma, signifying benignancy, or carcinoma, signifying malignancy. One would find it difficult to define these two categories in tissues that are basically neoplastic. Any uncontrolled growth that has the potentiality to invade could hardly be considered benign under crude clinical criteria regardless of the factors of size and time.

The malignancy of a lesion will vary from the point of view from which it is considered. From the standpoint of the biologist, the difference between a benign growth of neoplastic cells and a malignant growth composed of similar cell types is by no means clear cut. There may be but little apparent difference between the enzyme systems, the mineral metabolism and the utilization of protein and sugar, and that difference be only quantitative.

Clinically, because of the need in therapy, the difference is artificially but more clearly defined. Malignancy always denotes the presence of invasive characteristics. If a lymph vessel or a blood vessel is fortuitously entered by the malignant cells, there may be embolic phenomena, with regional or distant metastases. There must always, however, be the fundamental factor of invasion, and for that reason it has by consent become the criterion for clinical malignancy. The greater the aggressiveness of this invasion, or the richer the lymphatic and vascular beds in which the tumor cells are growing, the more frequent will these cells become embolic. The same relation holds with the size and the duration of the tumor. These clinical observations are now for the most part subject to experimental proof.

In these lesions that we have described we have demonstrated local invasion in many of them. Regional lymph node extension has also occurred, as have distant blood stream metastases. It is of interest that while such metastases may resemble the architecture of the parent tumor, they also often are identical to the more classical pulmonary cancer forms. At such times a pri-

mary lesion may give but little indication of the presence of distant extension.

For the most part, these lesions grow slowly and we have never seen metastases in a young person. Neither have we seen the stromal element metastasize. Nevertheless, the ultimate fate of these tumors seems inexorable if they persist long enough.

We have then, in this lesion, groups of cells usually epithelial in type and showing marked resemblance to each other but growing in odd architectural patterns and tending to permeate or invade. Ordinarily, one notes a mesenchymal framework in these tumors composed of reticulum and lined with cells resembling and functioning as endothelium. These endothelial cells line huge sinusoidal spaces filled with blood into which the epithelial cells project. Again, this mesenchymal tissue may be much denser, showing collagen formation, or there may be bone or cartilage or even smooth muscle. Such mesenchymal tumors have been called chondromas or hamartomas. Never in our experience have they been composed purely of the classical mesenchymal structures, however, for they always contain epithelium.

In our previous report it was our contention that these tumors had their origin in areas of improperly developed lung tissue because so often the tumor gave the structural appearance of fetal lung. Since various tissue patterns were so frequently present we felt that the term "mixed tumor" was an applicable one here. Where cells behave differently in the same tumor under identical conditions, there must be some intrinsic difference between these cells. In such a tumor as we have described, the host, the site, the vascularity, nutrition, and environment are identical. The cells therefore, having different functions and as a result forming different tissues, must themselves be different.

This in no way predicates that such tumors must be formed from at least two germ layers as was once our belief. There is much known now that tends to refute our former concept of the rigidity of the three germ layers in terms of the subsequent structures that they produce. Recent work by Waddell[2] is of interest in this respect in so far as the lung is concerned. By utilizing observations on the fetus in utero and in fetal pulmonary transplants, he found evi dence that the epithelium of the bronchi and the lining of the alveoli originate from mesoderm rather than endoderm, as has been previously supposed. He was able to observe intracytoplasmic accumulation of glycogen in the cells of the mesenchyme which preceded and correlated nicely with the differentiation of bronchi and alveoli. The alteration of the environment of the pulmonary tissue by transplantation with subsequent change in its nutrition and blood supply resulted in structural changes resembling considerably some of the morphologic features we have noted in the above tumors.

The formation of an organ, such as the lung, is not a predestined event, but is the result of a sequence of chemical reactions properly timed, in which the genic structure, the enzyme systems, hormones, nutrition, minerals and so on play their part. Interference with this sequence of events in any of many ways will result in the type of structural change we call malformation. Realizing that the lung is undergoing development at least until puberty, this concept is of great help in interpreting pulmonary abnormalities other than the lesion we are describing.

It has been demonstrated that there is a tendency on the part of some tissues in malformed areas to retain to a considerable degree their embryonic, enzymatic activity. It is of interest to find, therefore, that embryonic tissue is more sensitive to the experimental induction of cancer than is its adult counterpart.[1] This is important in understanding the frequency in which these areas

we have described become malignant tumors.

Because, therefore, there does exist a different clinical picture than that seen in the more common type of bronchiogenic cancer, and because, morphologically, these tumors are so often composed of a mixture of tissues that apparently represent differentiation rather than modulation, we still find it of value to give such lesions the separate classification of "mixed tumors."

SUMMARY

An additional series of mixed tumors of the lungs is described. These tumors are shown to possess invasive characteristics, with a tendency to metastasize, and therefore should be considered malignant growths in spite of the fact that many of them will persist for many years without dissemination. The idea that these tumors fundamentally are composed of a mixture of different functioning tissues is discussed and the concept retained that these lesions result from a failure of proper tissue coordination in pulmonary development.

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