NEURILEMMOBLASTOSIS

The Influence of Intrinsic Factors in Disease When Development of the Body Is Abnormal*

Keith Inglis, M.D.

(From the Department of Pathology, University of Sydney, Sydney, Australia)

In a paper on subdural hemorrhage, cysts, and false membranes (Inglis[1]), changes were described which were thought to illustrate the influence of intrinsic factors in disease when development of the body is normal. The present contribution is concerned with the influence of intrinsic factors in disease when development of the body is abnormal.

The opinions expressed in this paper are submitted as a hypothesis. It is recognized that the evidence presented in their support is not conclusive, but it is thought that it provides a reasonable explanation of the relationship to one another of the various lesions that may be met with in patients suffering from "tuberous sclerosis" of the brain, and also of such lesions occurring in patients who present no clinical evidence of cerebral disease.

It is suggested that specific nerve sheath tissue is of outstanding importance to the subject under discussion. Opinions still differ as to the nature of nerve sheath tissue, but in the present paper the terms specific nerve sheath tissue, neurilemma, and sheath of Schwann are used synonymously.

Definitions

Neurilemmoblastosis is used to describe a condition characterized by lesions, many of which are distinguished by the presence of cells (some of them primitive) regarded as akin to those that form the neurilemma or sheath of Schwann. In some of the lesions of neurilemmoblastosis distinctive cell groups cannot be identified; nevertheless, it is suggested that in the causation of such lesions the neural intrinsic factor of neurilemmoblastosis plays an essential part.

Glioneurilemmoblastosis is suggested as a suitable name when the brain is affected as well as other parts of the body.

Neurilemmoblastoma is used when the specific tissue of neurilemmoblastosis forms a tumor mass. Such a tumor is benign.

Liponeurilemmoblastoma is the name given to a tumor composed of a mixture of neurilemmoblastic tissue and lipomatous (adipose) tissue. This tumor also is benign.

Neural intrinsic factor is used to mean a specific factor, of intrinsic nature and neural origin; this factor is considered to underlie all of the

* Received for publication, July 6, 1949.

lesions of neurilemmoblastosis. Neurilemmoblastosis is looked upon as a visible, recognizable, demonstrable manifestation of neural intrinsic factor. Neural intrinsic factor is considered to underlie other conditions, including neurofibromatosis with which neurilemmoblastosis has features in common; there are, however, important differences between these two conditions.

Basic intrinsic factor requires further explanation. The laws of growth and development operate through intrinsic factors from the time of fertilization of the ovum, and it is only after neural tissue appears in the developing embryo that neural intrinsic factor as such can come into play. For the more fundamental operation of intrinsic factors the term basic intrinsic factor is employed. Basic intrinsic factor is not regarded as apart from neural intrinsic factor, but as more primitive and comprehensive, and as embracing a potential neural intrinsic factor component. Neural intrinsic factor, on its more primitive side, merges into basic intrinsic factor; the line of distinction between them is indefinite, and it is often a matter of doubt as to whether the link between certain related pathologic conditions is at the level of neural intrinsic factor or of basic intrinsic factor.

CASE I

The patient (P.U.S. 110), a married woman, 41 years of age, had consulted a doctor for "asthma" 8 years prior to her death. She had suffered from attacks of breathlessness during the last 3 years of her life. A nodular rash on the nose and cheeks had been present since the age of 3 months. No mention of fits or of mental abnormality was made in the notes. She had had 4 children. Five days before death there was severe pain in the chest.

Dyspnea and cyanosis were found on examination. "Adenoma sebaceum" was present on the nose and cheeks. The left nipple was retracted and fluid was draining from it. The Wassermann reaction was negative; red blood cells, 6,850,000; hemoglobin, 141 per cent. The urine was acid and the specific gravity 1016; albumin, granular casts, and a few leukocytes and red blood cells were present; blood culture was sterile. Roentgenologic examination showed the right lung to be about half collapsed; the left lung showed mottling; the pulmonary artery was enlarged. The provisional diagnosis was Ayerza's disease.

Autopsy Report

At gross examination, the *thymus* was not recognizable. The *right lung* was collapsed as the result of pneumothorax due to rupture of an emphysematous bulla. Most of the collapsed lung was solid with blood, but the apex presented a striking picture of bullous emphysema. Dotted throughout the substance of the lung were white nodules about 1 mm. in diameter. The entire *left lung* was emphysematous. White nodules 1 to 2 mm. in diameter were present in the lung tissue. The most strik-

ing feature in the *heart* was enlargement of the pulmonary artery; it was larger than the aorta. The *liver* was enlarged and showed chronic venous congestion; in the right lobe were a few small whitish nodules about 1 mm. in diameter. The *spleen* showed no special changes. The *right kidney* weighed 515 gm. The capsular surface was studded with raised yellowish tumors. A large thin-walled cyst was present near the lower pole. In the small amount of capsular surface free from tumors a few small cysts could be seen. The cut surface showed small amounts of kidney substance free from tumors. The tumors involved medulla as well as cortex. Cysts were inconspicuous on the cut surface. The pelvis and ureter were not dilated. Most of the tumors were yellow, some were white, some were a mixture of yellow and white. The *left kidney* weighed 320 gm. (with adrenal attached). It was very similar to the right, but was slightly less involved by tumors. On the capsular surface, in the areas free from tumorous tissue, a few cysts were to be seen. The cut surface showed an appreciably larger amount of kidney substance free from tumors than did that of the right kidney. In the left kidney also, yellowish and whitish tumors were present, but for the most part the two types were blended. The pelvis was not dilated. In the portions of kidney which were free from tumors the capsular surface was smooth, and the cut surface showed that the cortex was not diminished in amount in relation to the medulla. The *uterus,* when cut into, was seen to contain small nodules similar to those found in the liver and lungs. The *esophagus, stomach, intestines, adrenal glands, pancreas,* and *ovaries* appeared normal. The *brain* and *spinal cord* were not examined.

Histologic Findings

The term malformation might be applied, perhaps more correctly, to some of the lesions referred to in this paper as tumors or neoplasms, but it has been found impossible to draw a line of demarcation between the different stages of the pathologic process, because areas of abnormal tissue which appear to show malformation merge insensibly into others which appear to be tumorous or neoplastic.

Kidneys. Three varieties of renal lesions call for special comment: white tumors, yellow tumors, and cysts. Histologically, it was found that the white tumors were composed mostly of elongated and round cells, and that at least a few fat cells were present in most of them. The yellow tumors, though composed mainly of adipose tissue, contained scattered areas of elongated and round cells.

White Tumors. The tissue composing the white tumors is considered to provide a key to the interpretation of many of the changes in the organs and tissues of the body outside the central nervous system in patients suffering from "tuberous sclerosis" of the brain. A common appearance of this cellular tissue is to be seen in Figure 1 in which the picture is thought to resemble that seen when neurilemmal cells proliferate after division of a nerve, or that to be seen in a spontaneous schwannoma (neurilemmoma). A striking feature of the cellular tissue in these renal tumors was the great variation in the size and shape of the cells. In Figure 1, leashes of spindle cells are to be seen passing in various directions; the nuclei tend to be elongated and to have rounded ends. Speaking generally there was little tendency to "palisading" in the cellular tumors, no more than is to be seen in Figure 1. Another appearance is to be seen in Figure 2 in which some of the nuclei are elongated and have more or less parallel sides, their ends being blunt and sometimes almost square. In many situations the cells were rounded rather than elongated, and sometimes were much smaller than the elongated cells (Fig. 3). Parts of the cellular growths were very vascular (Fig. 4). Here the vascular channels were large and their walls varied in thickness; some of the walls were hyaline and continuous with similar hyaline bands in the main tumor masses. The hyaline material stained green with Masson's trichrome stain. Spindle cells passed between the vessels and sometimes had a "perithelial" arrangement. Fat cells were often scattered among the spindle cells. This angiomatous appearance is thought to be due to the effect of the neural tissue on the blood vessels.

Yellow Tumors. The yellow tumors were composed for the most part of adipose tissue (Fig. 5) and large portions of them were composed solely of adipose tissue. The cells of the adipose tissue were indistinguishable from those of ordinary lipomata or of normal subcutaneous adipose tissue. Many of the fatty tumors were not clearly defined at the periphery; indeed, a striking feature was the way in which single fat cells, or clusters of fat cells, appeared isolated, either in the cellular tumors or between renal tubules where no other neoplastic tissue was to be seen. In most of the fatty tumors there were collections of tumor cells like those which formed the white tumors.

Cysts. The large cyst in the right kidney was probably of the same nature as the smaller ones in the parts of both kidneys which were free from tumors. In Figure 6 one of these cysts is to be seen. It may well be related to congenital polycystic disease of the kidneys, but Figure 6

does not provide in itself convincing evidence of this relationship. Stronger evidence that the renal cysts found associated with neurilemmoblastosis are part of the polycystic disease complex is provided by case 2.

Uterus. A general impression of the structure of the uterus in case 1 is given by Figure 7, which shows the cut surface of a portion of the myometrium, including part of the peritoneal surface. The myometrium is dark, the tumor nodules pale. On the left there is a large wedge-shaped tumor nodule (A) with base at the peritoneal surface, at the top of the figure a rather broken-up nodule, and in the lower part of the figure several smaller nodules, one indicated by the letter B. The structure of the largest nodule (A) is to be seen under higher magnification in Figure 8. Here the lower third (which is dark) represents myometrium, and the upper two-thirds (pale by contrast) is composed of ill defined spindle-shaped cells and many small structureless, somewhat homogeneous areas which stained green with Masson's trichrome stain and are thought to be akin to similar areas in some of the renal tumors (cf. Fig. 8 with Figs. 1 and 4). The tumor shown in Figure 8 is thought to be of neural origin like those in kidneys and lungs, and to be part of the widespread condition of neurilemmoblastosis. Even the smallest neoplastic foci in the uterus were pale by comparison with the adjacent myometrium, whereas very small myomata (in sections stained by hematoxylin and eosin) are usually darker than the adjacent myometrium because of their large number of involuntary muscle cells with blue-stained nuclei closely packed together. Another point of interest was that the small neoplastic foci in the uterus of case 1 (like many neoplastic foci in other organs in this case) showed blurred cellular definition, whereas in very small uterine myomata the cells were generally clearly defined.

Liver. The liver showed conspicuous venous congestion and a few small tumor nodules. One of the nodules is illustrated in Figure 9. It was in the substance of the liver, but not far beneath the capsule. The nodule was composed of adipose tissue, and apparently of adipose tissue alone. No fat was present in the epithelial cells of the hepatic parenchyma. The lipoma was not encapsulated or circumscribed. The isolation of fat cells is thought to be due, not to infiltration from the main mass, but to transformation of ordinary connective tissue cells into fat cells *in situ.* Similar appearances were seen in the kidney. Likewise when so-called congenital rhabdomyoma forms in the heart, the tumor is not encapsulated or circumscribed, but shows cardiac muscle cells, separate from the main tumor mass, presenting an early stage of the characteristic changes *in situ.* Figure 10 shows interesting changes in

a portal tract. A bile duct, indicated by the letter A, is seen in the lower part of the portal tract, and a portion of a dilated branch of the portal vein in the upper part; below, and to the left, hepatic parenchyma surrounds the portal tract. The enlargement of the portal tract is due to a mixture of two elements, ill defined spindle-celled tissue and adipose tissue in which the fat spaces are of different sizes. This composite picture is regarded as similar to the mixture of neural cellular tissue and adipose tissue to be seen in many of the renal tumors. In Figure 11 changes similar to those shown in Figure 10 are seen, but at a somewhat earlier stage. The abnormal zone in the center is surrounded by parenchymatous tissue, only slightly engorged, and therefore probably peripheral so far as lobular arrangement is concerned. The central abnormal zone is therefore probably an enlarged portal tract with a dilated branch of the portal vein in the center. The rounded spaces are thought to indicate fat cells, and the rest of the ill defined tissue partly cellular tissue of neural origin. The central area (Fig. 12) taken alone would be difficult to interpret, but, in the light of evidence revealed by Figures 10 and 11, it is regarded as a group of cells of neural origin akin to the spindle cells shown in the portal tract included in Figure 10, and of the same order as the cellular nodules in other parts (cf. Fig. 12 with Figs. 13 and 15).

Lung. The sections taken from solid portions of lung were especially interesting because they showed two outstanding appearances: the more or less circumscribed areas which were almost free from pigment, and the intervening zones in which pigment was abundant. The pigment gave the reactions for free iron, and was regarded as hemosiderin. The pigment-free areas were thought to be composed largely of neurilemmoblastic tissue; the pigment-containing areas were thought to be areas of collapsed lung, the hemosiderin in the lumina of the compressed air sacs being due to polycythemia and chronic venous congestion. This interpretation is thought to be in keeping with the appearances to be seen in Figure 13 which reveals in the lower part collapsed air sacs with thickened walls and blood pigment (hemosiderin) in the lumina, and in the upper part a nodule of tumorous tissue with somewhat blurred histologic detail, such as is common not only in the tumors of the lung but also in tumors elsewhere in the body (cf. Fig. 13 with Figs. 12 and 15). Another pulmonary tumor nodule is seen in Figure 14. The irregularly distributed hyaline bands in this nodule resemble those in some of the renal tumors (cf. Fig. 14 with Fig. 4).

Lymph Node. Several lymph nodes situated near the trachea were saved for histologic examination; these were slightly larger than normal

and contained collections of cells (some elongated, some rounded) considered to be essentially the same as those in tumor nodules in kidney, lung, and liver. One of these collections of cells (of the rounded variety) is included in Figure 15 (cf. Fig. 15 with Figs. 12 and 13).

Skin of Face. One of the nodules of the skin of the face was examined microscopically. No special changes were observed in the sebaceous glands, except for slight hyperplasia, but deviation from the normal was seen in the dermis where dilated vessels with thin walls were conspicuous and collections of lymphocytes also were present. The feature of the dermis, however, to which special significance is attached, was the presence, near the dilated vessels, of ill defined tissue in which spindle-shaped nuclei and structureless material were seen. This cutaneous lesion is thought to have a neural basis and to link with the nodules in kidney, lung, and other parts.

Breast. Sections of the breast showed an intraductal papilloma, the processes of which had a connective tissue core and an epithelial covering, the appearances corresponding with those commonly seen in hyperplastic cystic disease of the breast. This lesion may have been a chance accompaniment, but since Batchelor and Maun[2] mentioned tumors of the breast as among the many conditions that may be found in patients with congenital rhabdomyoma (congenital glycogenic tumor) of the heart, and since these cardiac tumors are commonly associated with tuberous sclerosis of the brain, the possibility of neural intrinsic factor (or basic intrinsic factor) having influenced the development of the mammary lesion in case 1 seems worth bearing in mind.

Congenital rhabdomyoma (congenital glycogenic tumor) of the heart, which is commonly associated with tuberous sclerosis of the brain, was not present in case 1, but it was present along with tuberous sclerosis of the brain and congenital polycystic disease of the kidneys in case 2.

CASE 2

The patient (P.U.S. 5083), a male child, 4 months old, was said to have appeared normal at birth, but to have suffered from occasional screaming attacks. A week prior to admission he began to have twitching and rolling of the eyes.

Autopsy Report

There were no external abnormalities. The *brain* showed the characteristic changes of "tuberous sclerosis" (Dr. R. D. K. Reye). In the *heart,* numerous small, pale yellowish, opaque areas were seen beneath the pericardium and endocardium, and larger, pale yellowish, firm tumors projected from the pericardial surface and into the cavities of the heart. The largest of these measured 2.7 by 2.1 by 0.7 cm. The *right*

kidney weighed 50 gm. and was composed, for the greater part, of large thin-walled cysts filled with clear fluid. A small portion of more solid tissue, honeycombed by cysts, occupied the lower pole. The *left kidney* closely resembled the right in appearance, and weighed 48 gm. No lesions were found in other organs.

Histologic Findings

Kidneys. Cysts were present in both renal cortex and medulla. There was no significant increase in connective tissue. In Figure 16, microscopic cysts, into which glomeruli project, constitute a striking feature. This is commonly seen in polycystic disease of the kidney. Other cysts were larger and had no glomeruli projecting into them.

Heart. There were many separate nodules in the heart, which were not circumscribed. The cells composing the nodules were large, and in the cytoplasm of many of them conspicuous spaces were present. Near the main nodules an early stage of the process was revealed by the presence of small spaces in cardiac muscle fibers, the appearance resembling that seen in sections of fetal heart muscle at an early stage of development. The congenital rhabdomyomas of the heart are interpreted as due to an anomaly of growth and differentiation, the heart muscle fibers growing large but presenting an undifferentiated appearance. The small isolated lesions separate from the main nodules in the heart of case 2 are thought to be due to change *in situ* and not to extension from the main nodules.

Localized Neurilemmoblastosis

Neurilemmoblastosis is regarded as a systemic disease which may manifest itself in many lesions in many organs, as in case 1. On the other hand, it is suggested that essentially the same disease may be in play when only one organ is affected, and two such examples of localized neurilemmoblastosis will now be described, namely, case 3 (liponeurilemmoblastoma of the kidney) and case 4 ("honeycomb lung," "cystic disease of the lung").

LIPONEURILEMMOBLASTOMA OF THE KIDNEY

CASE 3

The patient (P.U.S. 4929), a woman, 56 years of age, complained of a lump in the left lumbar region, which was increasing in size. There were no urinary symptoms, and kidney function on the left side was good according to dye excretion. The tumor mass, together with the kidney in which it was growing, was removed surgically.

The specimen showed that an almost spherical tumor, approximately 13 cm. in average diameter, apparently had grown in the middle zone of

the kidney, leaving intact only the upper and lower poles, which appeared normal (Fig. 17). The tumor was circumscribed and appeared to be encapsulated. The cut surface presented a mottled appearance, yellow, white, and red areas being present.

Histologic Findings

The yellow areas consisted predominantly of adipose tissue, but collections of elongated cells were present to some extent. The white areas were predominantly cellular, but some of them contained a little adipose tissue. The great majority of the cells in the white areas were elongated and ran in bundles or strands (Fig. 18). These cells had elongated nuclei, and the outlines of their cytoplasm were very ill defined. In some situations the cells were much smaller and less elongated; these were regarded as developmentally younger cells but otherwise as of the same nature as those illustrated in Figure 18. Those portions of the tumor which appeared red to the naked eye showed an angiomatous appearance microscopically (Fig. 19). The walls of the vascular channels seemed somewhat hyaline. The elongated cells of the tumor tended to merge insensibly in the walls of the large vessels (Fig. 20). In some situations the dilated vascular channels formed the bulk of the tissue (Fig. 19). The close histologic resemblance that this tumor bore to the renal tumors of case 1 is made clear by comparing Figures 18 and 20 with Figures 2 and 4, respectively. If the arguments in support of a neural origin for the renal tumors of case 1 are valid, then it is thought they give strength to the opinion that neurilemmoblastosis is the essential condition in the renal tumor in case 3.

"HONEYCOMB LUNG," "CYSTIC DISEASE OF THE LUNG"

The occurrence of cystic disease of the lung and tuberous sclerosis of the brain in the same patient has been recorded by Berg and Vejlens[3] and by Warren and Warvi.[4] It is suggested that the emphysematous lungs in case 1 come under the same category. Pneumothorax occurred in the case recorded by Berg and Vejlens, in the case described by Warren and Warvi, and in cases 1 and 4 of the present series.

It seems important to determine whether cystic disease of the lung, occurring apart from tuberous sclerosis of the brain and its more common accompanying lesions, may present histologic changes like those found in cystic disease of the lung which forms part of the tuberous sclerosis complex in the one individual. Case 4 appears to be an example of cystic disease of the lung occurring apart from tuberous sclerosis of the brain; the brain, however, was not examined at autopsy, and it is

recognized that there may be lesions of tuberous sclerosis in the brain, without clinical evidence of its presence.

CASE 4

The patient (P.U.S. 3326) was a woman, 32 years of age. Her father's brother suffered from "epileptic fits." The patient herself had had no serious illnesses, and had had no previous mental disorders. For 4 years prior to death she had suffered from breathlessness on the least exertion. About 2 or 3 years before death she had "spat up blood." Shortly before death she became cyanosed and dyspneic.

Autopsy Report

At autopsy, there was a small right pneumothorax. The left *lung* weighed 400 gm.; the right, 710 gm.; when the lungs were cut no normal pulmonary tissue could be seen; the whole of each lung appeared to consist of small communicating cavities varying from 2 mm. to 1 cm. in diameter, giving a sponge-like appearance to the organ. There was much blood in the right lung. The hilar lymph nodes were not enlarged. The *heart* weighed 300 gm. The right ventricle was somewhat hypertrophied. In the peritoneal cavity were about 5 pints of turbid fluid. The *liver* was small and fatty; the *kidneys* were dark red due to venous congestion. The *brain* was not examined.

Histologic Findings

Lungs. Figure 21 shows a cyst-like area immediately beneath the visceral pleura. Figure 22 shows portions of several cystic spaces, some of them partly collapsed; the thick walls of the cystic spaces are composed of spindle-shaped and elongated cells. This cellular tissue did not extend throughout the entire lung; indeed its distribution was patchy and scattered. Occasionally a small nodule of elongated cells was seen. Part of such a nodule is illustrated in Figure 23, and here the elongated cells, with their elongated nuclei and ill defined cytoplasm, run parallel with one another and give an appearance closely resembling that of the renal tumors of cases 1 and 3 (Figs. 2 and 18). The changes in the lungs in case 4 are somewhat different from those in case 1, but in both cases the pulmonary lesions are thought to be essentially neurilemmoblastic.

Lymph Nodes. Figure 24 shows the structure of a hilar lymph node from case 4. Lymphoid tissue is seen, but the outstanding feature is presented by the strands of elongated cells, which bear a close resemblance to those in the pulmonary tissue (Figs. 22 and 23). The neurilemmoblastic tissue in the lymph nodes varied somewhat in its structure. In this case another lymph node, certainly hilar or mediastinal, showed in addition to broad bundles of elongated cells like those in Figure

24, clusters of smaller, irregularly rounded or oval cells that are thought to be akin to those in the lymph node in case 1 (Fig. 15).

Comment

The pulmonary changes in case 4 seem to correspond grossly and histologically to those of the case described by Rosendal[5] in which the alveoli and bronchioles were transformed into small cysts, and involuntary muscle was present in the interstitial tissue in the lungs and in the hilar and mediastinal lymph nodes. Also, the pulmonary changes in case 4 seem to correspond grossly and histologically to those of the case described by Berg and Vejlens[3] in which cystic disease of the lung, spontaneous pneumothorax, and tuberous sclerosis of the brain were present in the same patient; these authors said that in the connective tissue forming the walls of the pulmonary cysts there were smooth muscle cells forming groups with tumor-like appearance and a structure resembling that of myomas. It seems likely that the changes in the lungs and lymph nodes in cases 1 and 4 in the present series are essentially of the same nature as those in the lungs and lymph nodes in the case described by Rosendal and in the lungs in the case recorded by Berg and Vejlens, and that it is only the interpretations of histologic appearances that differ.

Discussion

General

In cases 1 and 2 many of the common extracerebral lesions to be met with in the tuberous sclerosis complex are present. The hypothesis submitted in this paper is that neural intrinsic factor underlies all of them. Neural intrinsic factor is conceived of as having several potentialities. One of these potentialities is in the direction of neurofibromatosis in which the abnormal specific nerve sheath tissue is relatively mature, is closely related to nerve fibers, and is associated with changes of a distinctive kind in various organs and tissues.

A second potentiality is in the direction of neurilemmoblastosis in which the abnormal specific nerve sheath tissue is relatively immature, is unrelated to nerve fibers, and is associated with changes in organs and tissues of a distinctive kind, but different from those met with in association with neurofibromatosis. The induced changes in neurilemmoblastosis and those in neurofibromatosis may overlap, especially in the skin. By virtue of the second potentiality (in the direction of neurilemmoblastosis), neural intrinsic factor may influence the development and behavior of various tissues or organs, and such tissues or organs may show (a) conspicuous evidence of neurilemmoblastosis, (b) slight evi-

dence of neurilemmoblastosis, or (c) no distinctive evidence of neurilemmoblastosis. It is therefore considered that neurilemmoblastosis and its underlying neural intrinsic factor should be regarded as parts of the one concept.

In relation to the preceding case reports there are four suggestions which are regarded as of outstanding importance: (1) That neural tissue, and not involuntary muscle, is the essential component of the cellular tumors in cases 1, 3, and 4; (2) that the fatty tumors in the liver in case 1 are due to the influence of neural tissue on neighboring connective tissue cells; (3) that the kidneys in case 2 show changes characteristic of congenital polycystic disease of the kidneys; (4) that the distinctive lesions of neurilemmoblastosis are dynamic and not static. Cutaneous lesions, for example, usually appear after birth, and often can be observed to increase in size. Static lesions, however, may also occur. The fourth observation means that at least some of the lesions of neurilemmoblastosis cannot be due to extrinsic factors causing sudden injury to, or disease of, a part of the fetus during gestation, but that such lesions may reasonably be accounted for by some intrinsic factor carried in the germ plasm predisposing certain parts of the body to the disease, the actual manifestation of the disease being delayed for even many years after birth. Extrinsic factors theoretically might cause changes in the fetus which would predispose the tissue to lesions appearing later in life, but, at least in the majority of cases, the delayed appearance of such lesions is associated with evidence suggesting germinal transmission of the predisposition to them.

Points in Favor of Regarding the Cellular Tumors of Cases 1, 3, and 4 as Part of a Systemic Disease (Neurilemmoblastosis) Due to Abnormal Development of Specific Nerve Sheath Tissue (Neurilemma)

(1). Tuberous sclerosis of the brain is commonly associated with fatty tumors in the kidney like those in case 1. (2). Tuberous sclerosis of the brain is due to distinctive proliferation of developmentally abnormal cerebral glia, and is thus of neural (epiblastic) origin. (3). In the lipomatous tumors of the kidney in case 1 there are cellular portions presenting the same features as the white renal tumors, which are predominantly cellular and contain very little adipose tissue. (4). In case 1 cellular tumors like those in the kidney were present in liver, lungs, uterus, and lymph nodes, so that the condition is widespread and probably of the nature of a systemic disease. (5). The association of the cellular tumors of the kidney in case 1 with adipose tissue is in keeping with a neural affinity of the cellular tissue since lipomata are commonly

associated with neurofibromatosis which is thought to have a neural basis. (6). Parts of the cellular tumors in case 1, especially those in the uterus, are thought to be morphologically different from involuntary muscle. (7). Tumors of involuntary muscle are not commonly associated with overgrowth of adipose tissue. (8). There is a close morphologic resemblance between the elongated-celled tissue of the cellular renal tumors of case 1, the renal tumor of case 3, and certain affected areas in the lungs of case 4, on the one hand, and the tissue of traumatic and spontaneous schwannomas (neurilemmomas), on the other. (9). If the elongated-celled tissue in the lesions of cases 1, 3, and 4 was composed of involuntary muscle (of mesoblastic origin), these lesions would be quite different from the cerebral lesions of tuberous sclerosis which are of epiblastic origin, whereas in the present hypothesis the cerebral and extracerebral lesions are regarded as all of the same order, that is, as parts of a systemic disease of epiblastic origin.

Causation and Origin of the Lipomata

In case 1 the relation of the cellular tissue to the adipose tissue would seem to be the same in the kidneys as in the liver. The interpretation placed on the appearances illustrated in Figures 9 to 12 inclusive is that abnormal cells of neural origin have influenced normal cells of connective tissue origin to store fat, even though such cells never store fat in normal conditions, no matter how obese the subject. This is the more remarkable because a liver may show extensive fatty change of the hepatic parenchyma although the connective tissue cells in the liver framework (*e.g.*, portal tracts) remain quite free from lipids. In some lipomata a hemangiomatous element is present. The overgrowth of adipose tissue in such tumors is probably not due to the extra blood supply, because neural abnormality with little alteration to vessels may be associated with overgrowth of adipose tissue, as is to be seen in certain lesions in both neurilemmoblastosis and neurofibromatosis. It is suggested that in angiomatous lipomata neural intrinsic factor may underlie both the angiomatous element and the lipomatous element of the growth.

Pathogenesis of Polycystic Disease of the Kidneys and Associated Conditions

The renal cysts of case 1 are regarded as probably due to congenital polycystic disease, and the lung changes in case 1 are regarded as essentially of the same nature as those in the cystic lungs associated with tuberous sclerosis described by Berg and Vejlens.[8] The renal cysts in case 2 are regarded as definitely due to congenital polycystic disease, and tuberous sclerosis of the brain and congenital rhabdomyoma (congeni-

tal glycogenic tumor) of the heart were present in the same patient. It would seem that the renal cysts described by Batchelor and Maun[2] as commonly associated with congenital glycogenic tumor of the heart may come into the category of congenital polycystic disease of the kidney. These authors wrote that the majority of congenital glycogenic tumors of the heart are associated with tuberous sclerosis of the brain.

Madonick, Savitsky, and Hochfeld[6] added 2 cases to the 12 already described in the literature of association between intracranial aneurysm and polycystic disease of the kidney. They believed the association is more than coincidental. Their first patient, a man 52 years of age, had a congenital aneurysm of the anterior cerebral artery associated with cysts of the lungs, liver, and kidneys. This is in keeping with the opinion that a relationship exists between congenital polycystic disease of the kidney and faulty development of the circulatory system. The association with cysts of the lungs is in keeping with the suggestion that both congenital polycystic disease of the kidney and developmental abnormalities of vessels at the base of the brain are predisposed to by neural intrinsic factor (or basic intrinsic factor), because evidence is submitted in this paper in support of the opinion that neurilemmoblastosis and its underlying neural intrinsic factor are related to cystic disease of the lung and to developmental abnormalities in the circulatory system. In view of the above statements it is suggested that neural intrinsic factor (or basic intrinsic factor) may underlie congenital polycystic disease of the kidney.

The Significance of the Abnormalities of the Circulatory System Associated with Neurilemmoblastosis

It is thought that in case 1 of the present series the large size of the pulmonary artery, in association with widespread emphysema (honeycomb lung or cystic disease of the lung) and neurilemmoblastosis, was due to abnormal development. In the case of epiloia (tuberous sclerosis of the brain) described by Norman and Taylor,[7] there was a large congenital diverticulum of the left ventricle; in the wall of the diverticulum there was tissue like that of the wall of the aorta (heterotopia of aortic tissue). Madonick, Savitsky, and Hochfeld[6] found a congenital aneurysm in the wall of the anterior cerebral artery associated with cysts of the lungs, liver, and kidneys. It would seem, therefore, that developmental abnormalities of the circulatory system occur in association with neurilemmoblastosis or with some of the lesions which, although they may show no distinctive neurilemmoblastic tissue, are possibly part of the neurilemmoblastic complex; these occurrences are in keep-

ing with the suggestion that neural intrinsic factor (or basic intrinsic factor) may influence the development of abnormalities of the circulatory system on these occasions.

Congenital Rhabdomyoma (Congenital Glycogenic Tumor) of the Heart

Batchelor and Maun[2] stressed the importance of the glycogenic content of the tumor cells. They said that although their review of the literature revealed that tuberous sclerosis had been observed in 50 per cent of cases of congenital glycogenic tumor of the heart, the co-existence of the two lesions actually was much higher. In the present study, congenital rhabdomyoma (congenital glycogenic tumor) of the heart was present only in case 2. This tumor presented the usual histologic features. It is suggested that neural intrinsic factor (or basic intrinsic factor) may have predisposed to the development of this tumor, which is regarded as an anomaly of growth and differentiation. The fact that in Wolbach's[8] case of cardiac rhabdomyoma there was evidence of faulty development of neural tissue as revealed by the presence of nests of neuroglial tissue in the meninges of the spinal cord is thought to be consistent with this opinion. The histologic resemblance between the heart muscle of the normal human fetus at an early stage of development and congenital rhabdomyoma (congenital glycogenic tumor) of the heart is also thought to be in keeping with this interpretation.

Norman and Taylor[7] described a congenital diverticulum of the heart (heterotopia of aortic tissue) in association with epiloia (tuberous sclerosis). Intervening between the diverticulum and the muscular wall of the ventricle was an irregular mass of adipose tissue microscopically showing a very meager stroma. A remarkable feature of this stroma was the presence of scattered cells of large size presenting features which the authors said left little doubt that they are the same as the primitive muscle cells which form the so-called rhabdomyoma of the heart.

In the present paper, evidence has been submitted in support of the opinion that neural intrinsic factor underlies lipomatous overgrowth (Figures 9 to 12), and it has been suggested that neural intrinsic factor (or basic intrinsic factor) may influence the development of congenital aneurysm or dilatation of vessels. Therefore it is thought that the association of heterotopic aortic tissue (in the wall of a congenital cardiac diverticulum) with heterotopic adipose tissue containing primitive cardiac muscle fibers, may be significant in this regard, and may support the suggestion that neural intrinsic factor (or basic intrinsic factor) may influence the development of congenital glycogenic tumor of the heart.

Miscellaneous Lesions

In keeping with the hypothesis submitted in this paper, it is suggested that neural intrinsic factor (or basic intrinsic factor) may influence the development of various other lesions sometimes found in patients suffering from tuberous sclerosis, such as cutaneous fibromata and bony lesions, including melorheostosis as in the case reported by Hall.[9]

Conclusions

The hypothesis submitted in this paper is that there is a common factor underlying all of the extracerebral lesions comprised in the tuberous sclerosis complex.

It is suggested that this common factor is intrinsic in nature and neural in origin, and to it the name neural intrinsic factor is applied.

Cellular tissue in renal tumors associated with tuberous sclerosis and cellular tissue found in cystic disease of the lung, widely regarded as involuntary muscle, is interpreted as being akin to specific nerve sheath tissue (neurilemma, sheath of Schwann) and as constituting part of a systemic disease for which the name neurilemmoblastosis is used.

Congenital polycystic disease of the kidneys, cystic disease of the lung, and certain developmental abnormalities of the circulatory system are thought to link up with neurilemmoblastosis, possibly at the basic intrinsic factor level.

I wish to thank Drs. A. C. Telfer, R. D. K. Reye, A. H. Tebbutt, and Jean Armytage for providing specimens and notes, Mr. S. Woodward-Smith for taking the photographs and photomicrographs, and Mr. L. Findlayson for technical assistance.

REFERENCES

1. Inglis, K. Subdural haemorrhage, cysts and false membranes: illustrating the influence of intrinsic factors in disease when development of the body is normal. *Brain*, 1946, **69**, 157–194.
2. Batchelor, T. M., and Maun, M. E. Congenital glycogenic tumors of the heart. *Arch. Path.*, 1945, **39**, 67–73.
3. Berg, G., and Vejlens, G. Maladie kystique du poumon et sclérose tubéreuse du cerveau. *Acta paediat.*, 1939, **26**, 16–30.
4. Warren, S., and Warvi, W. N. Tumors of sebaceous glands. *Am. J. Path.*, 1943, **19**, 441–459.
5. Rosendal, T. A case of diffuse myomatosis and cyst formation in the lung. *Acta radiol.*, 1942, **23**, 138–146.
6. Madonick, M. J., Savitsky, N., and Hochfeld, L. Intracranial aneurysm and polycystic kidneys. *J. Nerv. & Ment. Dis.*, 1946, **103**, 509–513.
7. Norman, R. M., and Taylor, A. L. Congenital diverticulum of the left ventricle of the heart in a case of epiloia. *J. Path. & Bact.*, 1940, **50**, 61–68.
8. Wolbach, S. B. Congenital rhabdomyoma of the heart. Report of a case associated with multiple nests of neuroglia tissue in the meninges of the spinal cord. *J. M. Research*, 1907, **16**, 495–519.
9. Hall, G. S. Tuberose sclerosis, rheostosis, and neurofibromatosis. *Quart. J. Med.*, 1940, n.s. **9**, 1–10.

[*Illustrations follow*]

DESCRIPTION OF PLATES

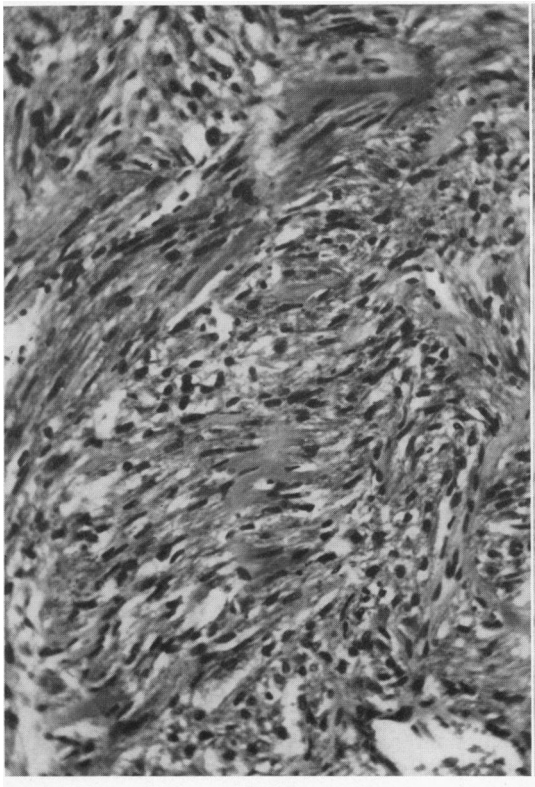
PLATE 75

FIG. 1. Case 1. Kidney, showing an appearance commonly found in the cellular tumors. × 200.

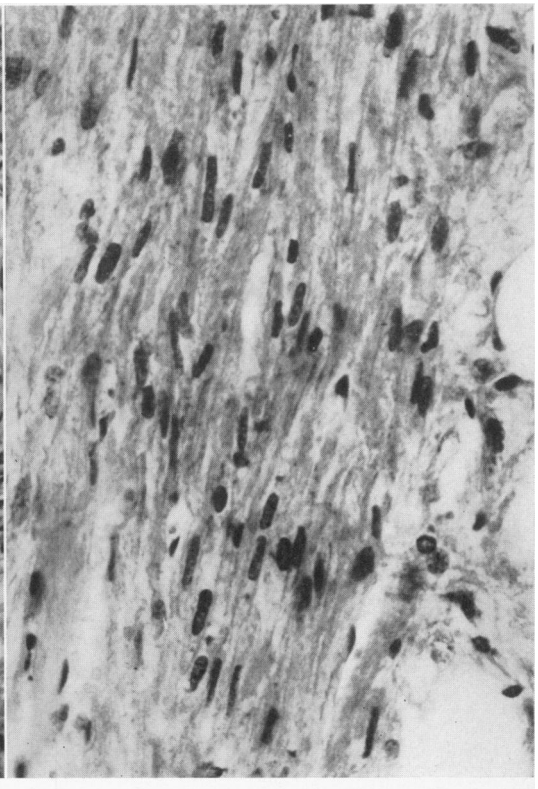
FIG. 2. Case 1. Kidney: many of the nuclei are long, have parallel sides, and rounded or almost square ends. This figure may be compared with Figure 18, case 3 (kidney), and Figure 23, case 4 (lung). × 400.

FIG. 3. Case 1. Kidney: in this portion of the cellular tissue the individual cells are small, rounded or irregular, and their cytoplasm is ill defined. × 200.

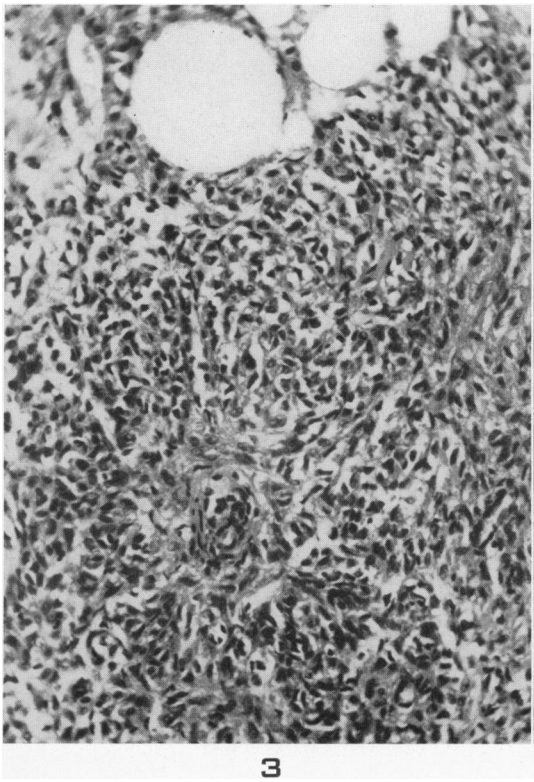
FIG. 4. Case 1. Kidney: small spindle cells are abundant; irregular homogeneous bands are conspicuous. The walls of some blood vessels are composed of homogeneous material; the walls of others show fairly good histologic detail. Dilated vascular channels are conspicuous in this field, but in some fields they are much more prominent and give an angiomatous appearance. This figure may be compared with Figures 19 and 20, case 3 (kidney). A few fat cells are included. × 100.



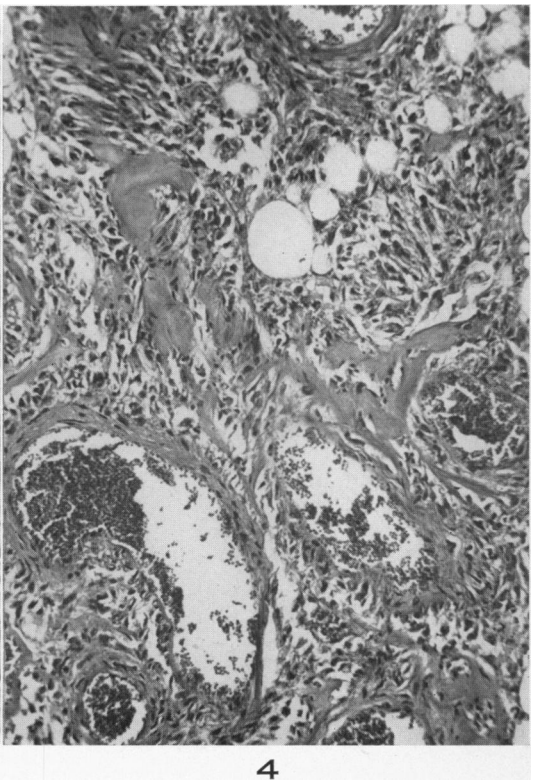
1



2



3



4

Inglis Neurilemmoblastosis

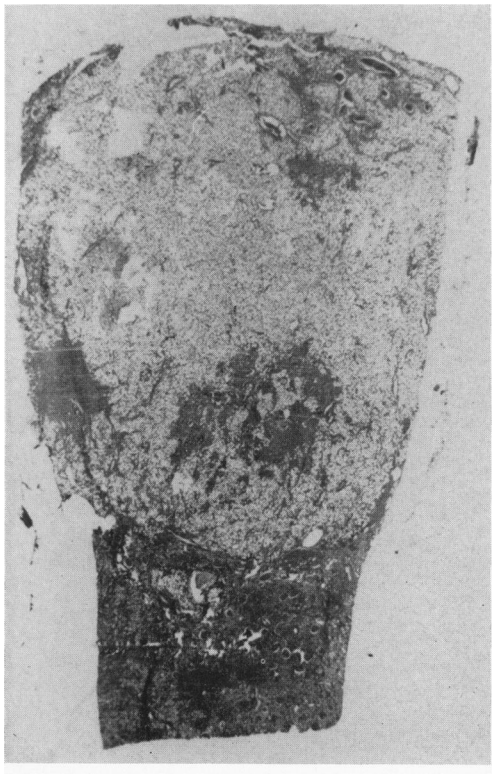
PLATE 76

FIG. 5. Case 1. Kidney: a lipomatous tumor is shown; the dark areas in its substance are due to the presence of cellular tissue like that which forms the white tumors. × 4.25.

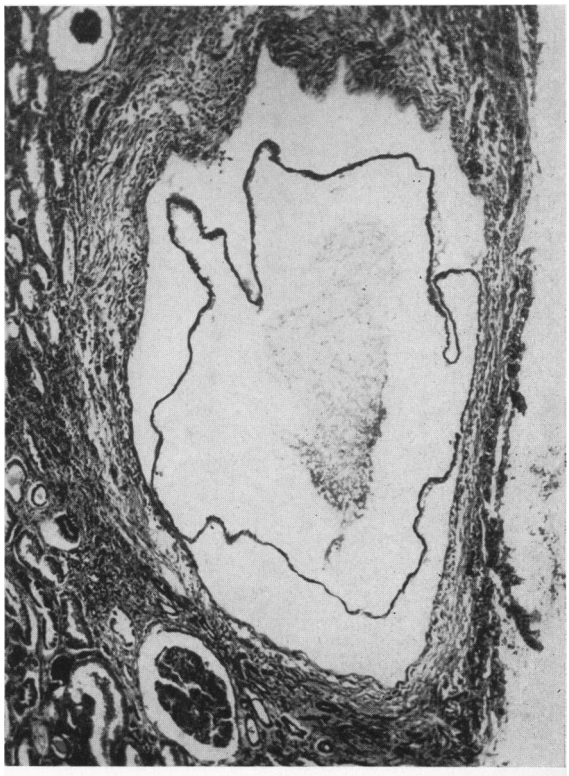
FIG. 6. Case 1. Kidney: a cyst is seen with epithelial lining (detached in preparing the section), and a thick wall. Appearances like this may be seen in congenital polycystic disease of the kidney. × 50.

FIG. 7. Case 1. Uterus: numerous pale tumor nodules contrast with the dark myometrium. The nodule indicated by the letter A is shown under higher magnification in Figure 8. The letter B points to one of several smaller nodules. × 15.

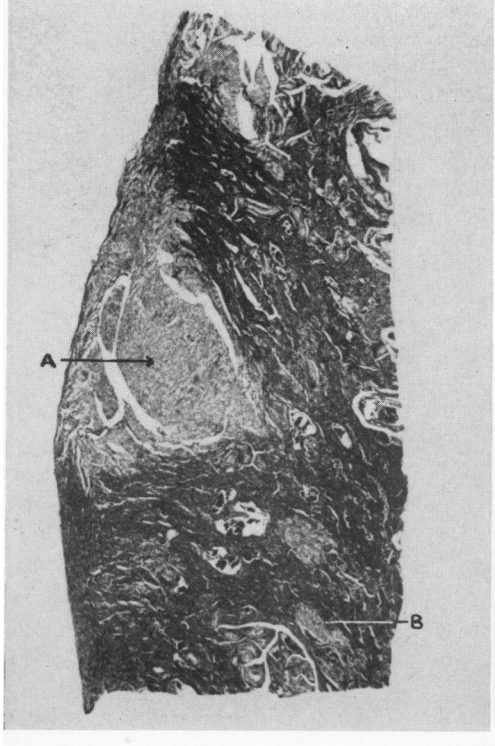
FIG. 8. Case 1. Uterus: the nodule indicated by the letter A in Figure 7 is here shown more highly magnified. A small portion of the myometrium (dark) is included in this illustration. The tumor (pale) resembles tumors in other organs; for comparison with Figure 1 (kidney). × 100.



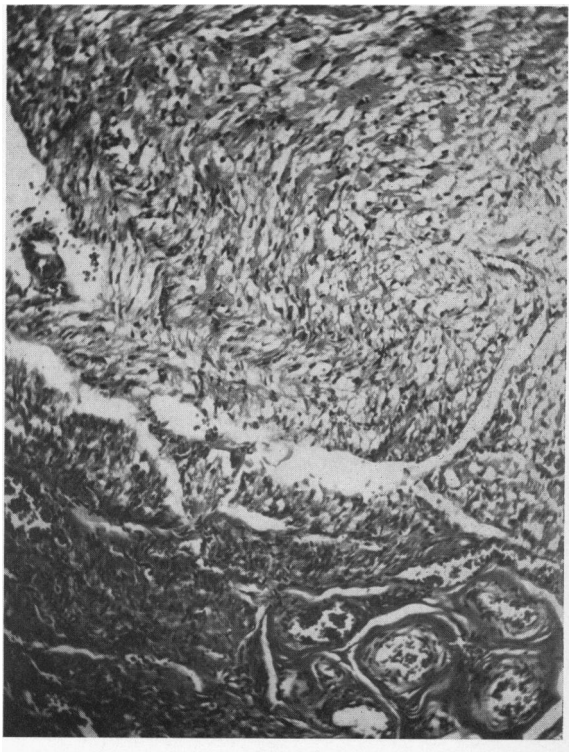
5



6



7



8

Inglis

Neurilemmoblastosis

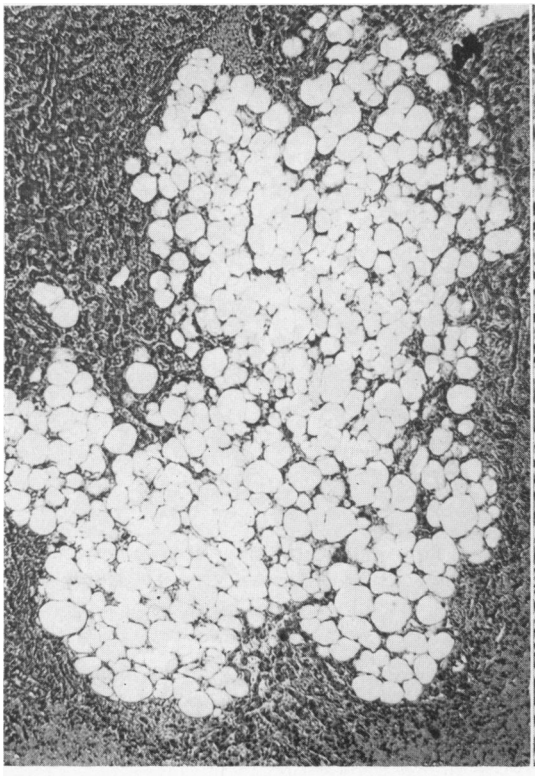
PLATE 77

FIG. 9. Case 1. Liver: lipomatous tissue is present in congested hepatic parenchyma. The lipoma is ill defined at the periphery, and isolated fat cells are present nearby. × 60.

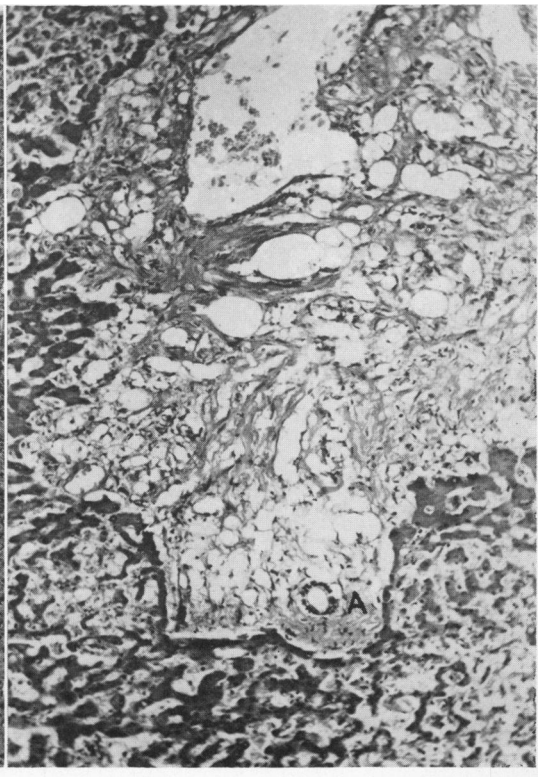
FIG. 10. Case 1. Liver: abnormal tissue is seen in a portal tract. A bile duct (A) is present below and a part of a branch of the portal vein above. Most of the tissue is composed of spindle cells and structureless material. Fat cells are distributed irregularly throughout this abnormal tissue which is thought to be of the same nature as the tumors in the kidneys and elsewhere. × 100.

FIG. 11. Case 1. Liver: a portal tract is seen surrounded by a zone of relatively normal hepatic parenchyma; the more distant parenchyma shows retrograde change due to venous engorgement. In the center of the portal tract is a dilated branch of the portal vein; bile ducts are small and barely recognizable. The specially significant features are the ill defined, loosely arranged tissue and the fat cells. It is thought that the changes in this portal tract are essentially the same as those in the portal tract illustrated in Figure 10. × 100.

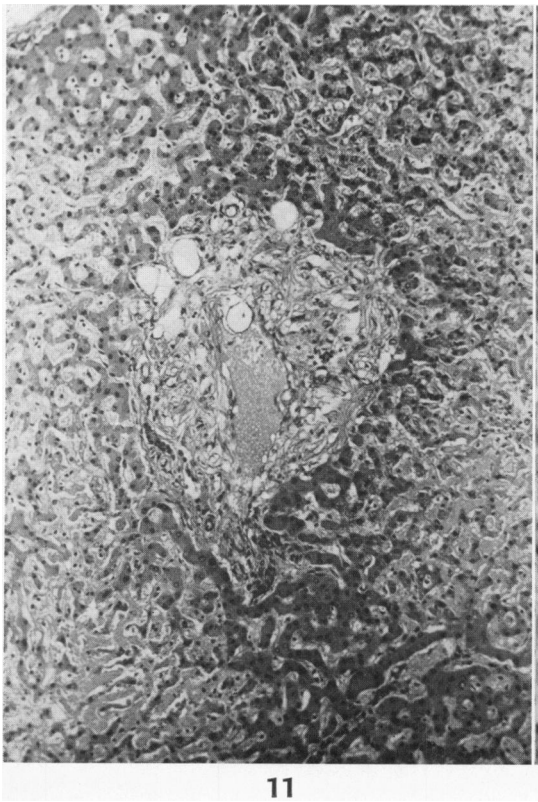
FIG. 12. Case 1. Liver: the cellular lesion in the central part of this illustration is regarded as a tumor nodule like those found in other organs. This figure may be compared with Figure 13 (lung) and Figure 15 (lymph node). × 200.



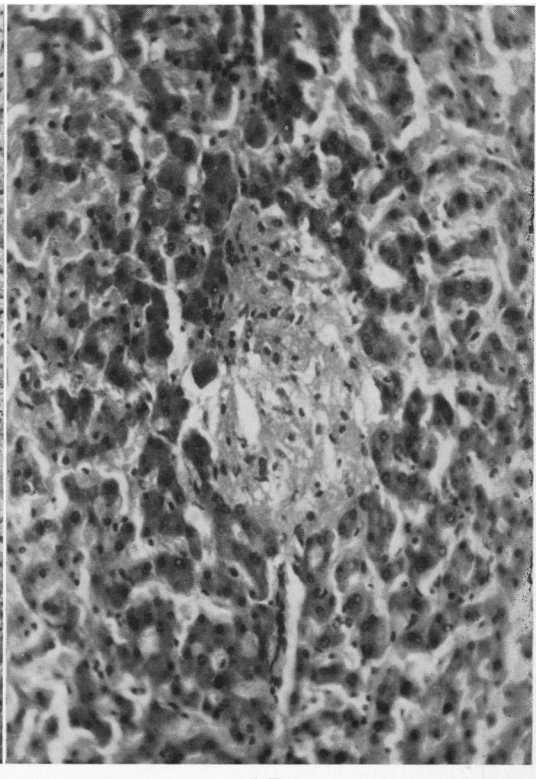
9



10



11



12

Inglis

Neurilemmoblastosis

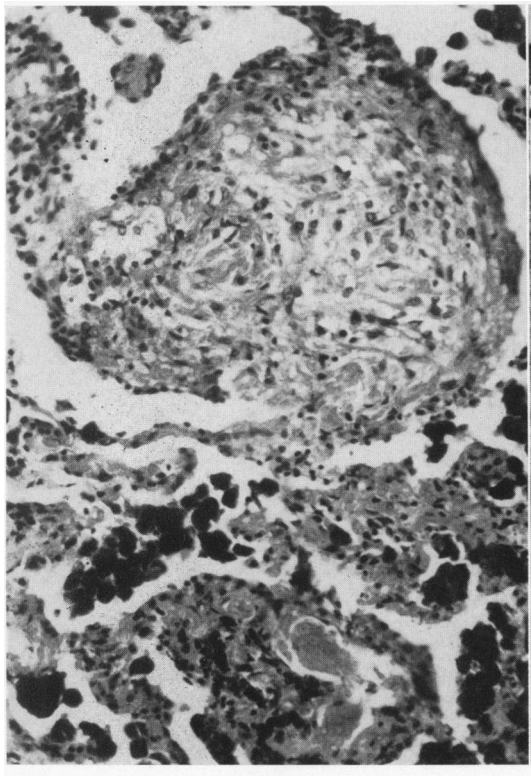
PLATE 78

FIG. 13. Case 1. Lung: the lower part of the illustration shows somewhat collapsed air sacs, the lumina of which contain cells laden with hemosiderin; the upper part shows a tumor nodule in which the cells are ill defined. This figure may be compared with Figure 12 (liver) and Figure 15 (lymph node). × 200.

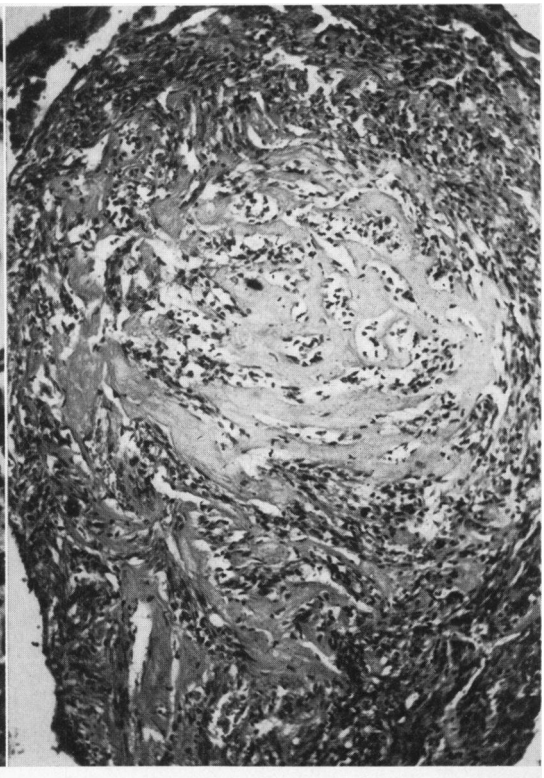
FIG. 14. Case 1. Lung: a tumor nodule is seen in which irregular homogeneous bands are conspicuous, for comparison with Figure 4 (kidney). × 100.

FIG. 15. Case 1. Lymph node: a small tumor nodule is present. This figure may be compared with Figure 12 (liver) and Figure 13 (lung). × 200.

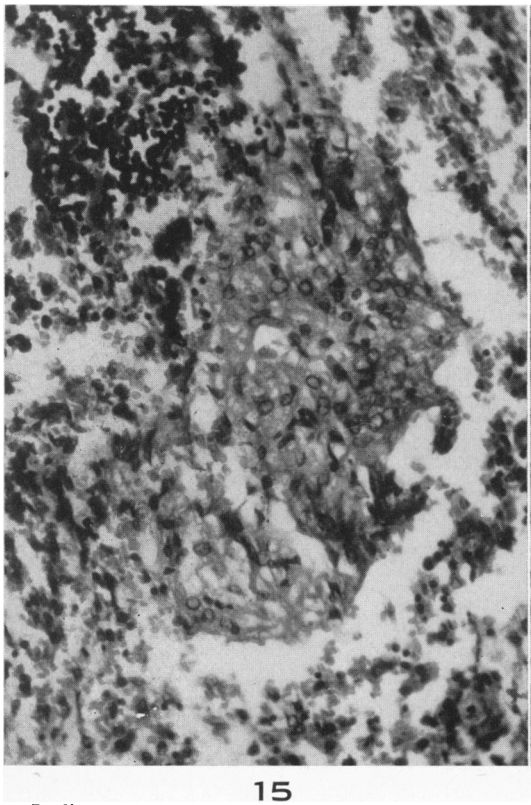
FIG. 16. Case 2. Kidney: cysts are present into which glomerular tufts project. × 100.



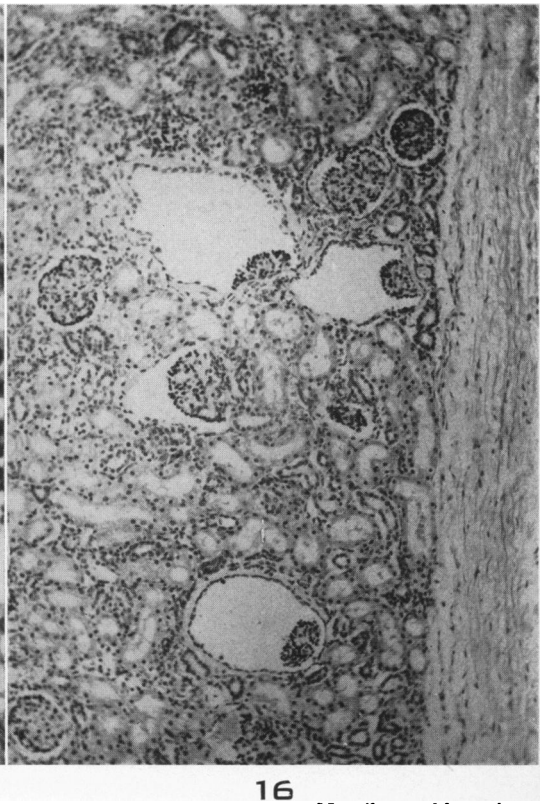
13



14



15



16

PLATE 79

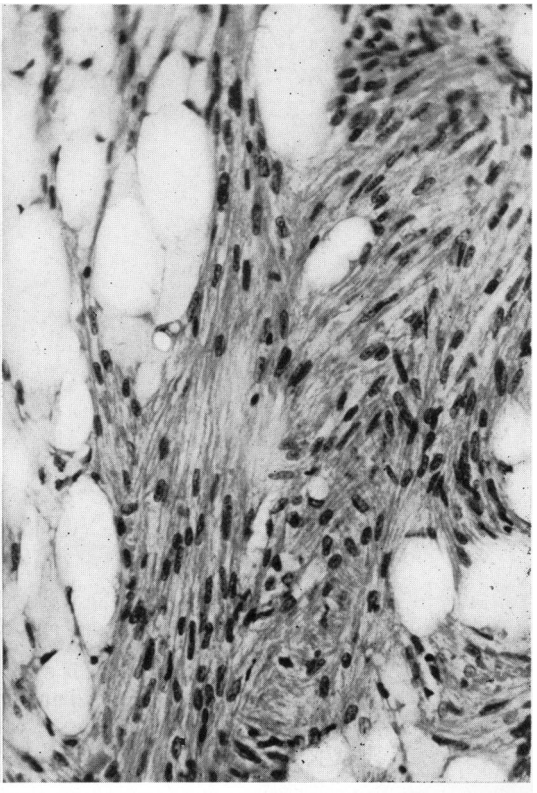
FIG. 17. Case 3. Kidney: the photograph shows the gross appearance and size of the tumor.

FIG. 18. Case 3. Kidney: adipose tissue is included, but the most striking feature is presented by the elongated cells which have ill defined outlines and conspicuous nuclei with parallel sides and rounded ends; this may be compared with Figure 2, case 1 (kidney), and Figure 23, case 4 (lung). × 200.

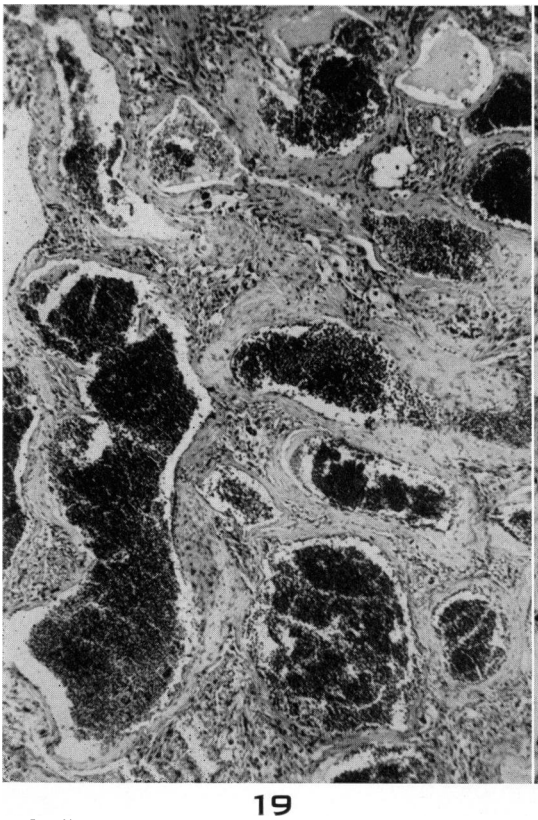
FIG. 19. Case 3. Kidney: this portion of the tumor has an angiomatous appearance. × 50.

FIG. 20. Case 3. Kidney: the tumor cells are seen to merge in the walls of the vascular channels. Some lipomatous tissue is included. × 100.

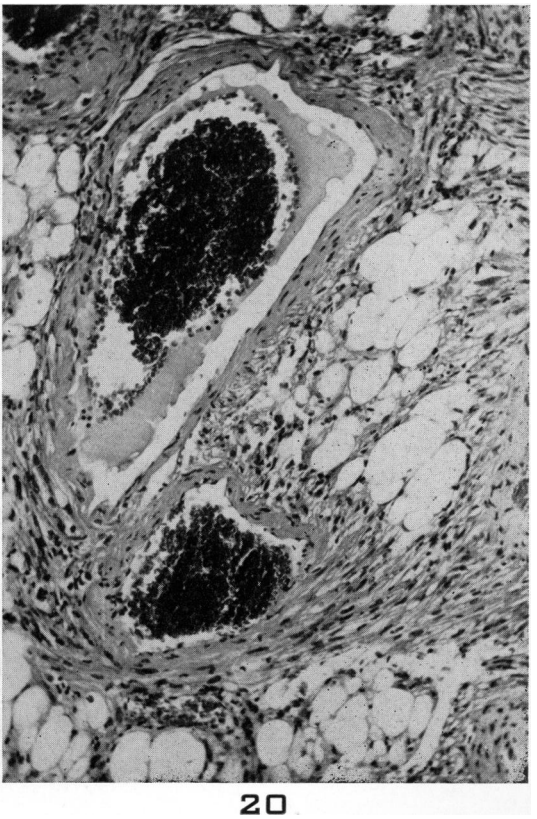
17



18



19



20

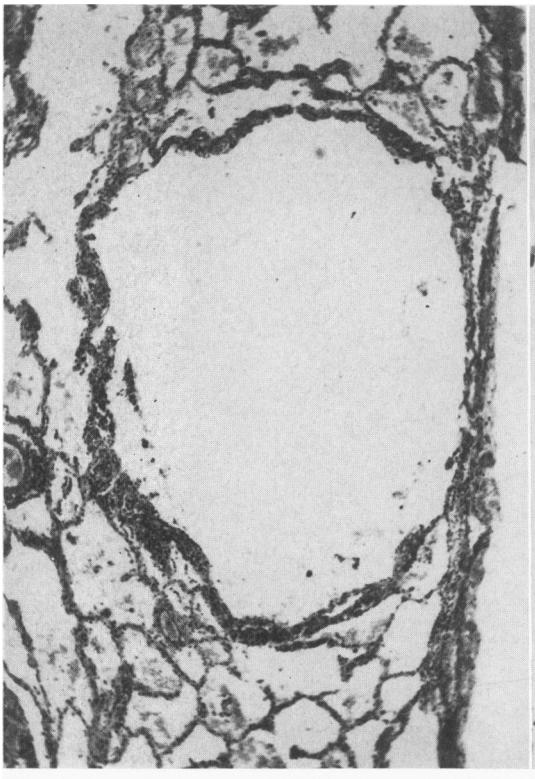
PLATE 80

FIG. 21. Case 4. Lung: a cyst-like area is seen immediately beneath the visceral pleura. × 50.

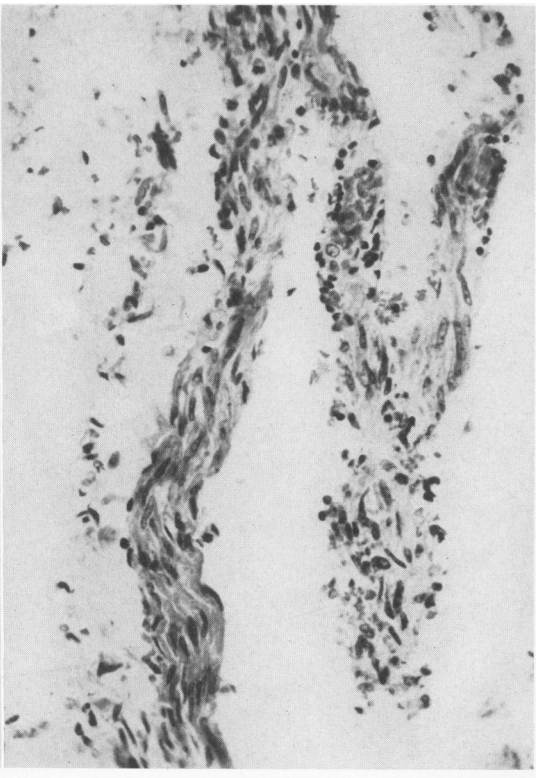
FIG. 22. Case 4. Lung: the walls of partly collapsed cyst-like spaces are composed largely of spindle-shaped and elongated cells. × 200.

FIG. 23. Case 4. Lung: this is a portion of a small nodule composed largely of elongated cells with elongated nuclei having parallel sides and rounded ends; this may be compared with Figure 2, case 1 (kidney), and Figure 18, case 3 (kidney). × 400.

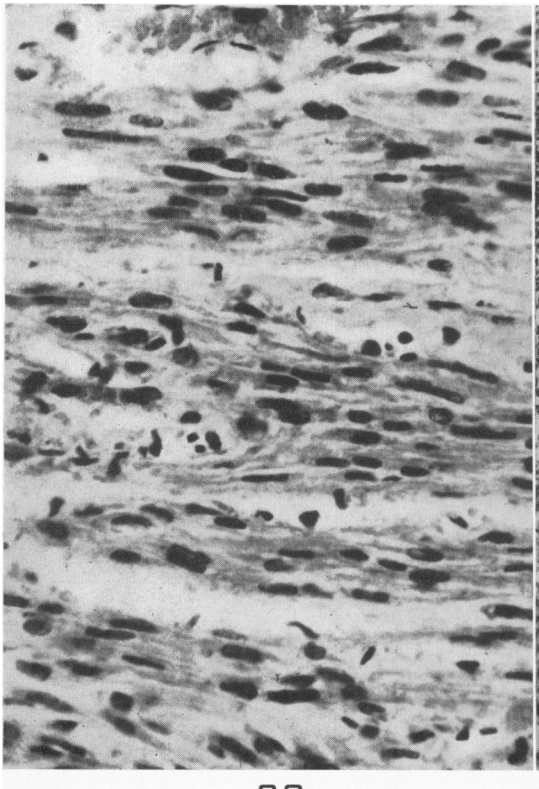
FIG. 24. Case 4. Lymph node: the illustration shows the structure of a portion of a hilar lymph node; bundles of elongated cells are conspicuous. × 100.



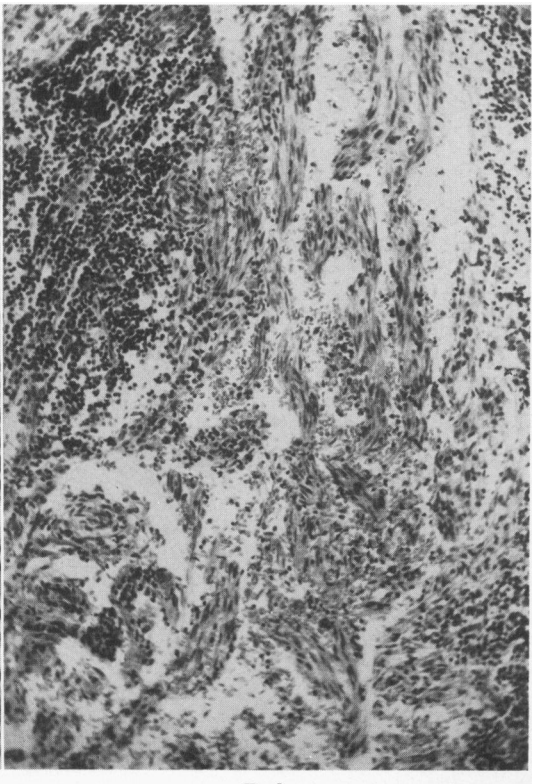
21



22



23



24

Inglis Neurilemmoblastosis