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NESIDIOBLASTOMA, THE ISLET TUMOR OF THE PANCREAS *

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This is a microscopic study of 9 "adenomas of the islets of Langerhans" removed surgically from 6 patients at the Presbyterian Hospital, New York City. It is a supplement to the report on these tumors published by Whipple and Frantz in 1935. The operations were performed for the relief of hypoglycemia with severe and long continued collateral symptoms of from 1 to 12 years duration. All patients recovered from the operation. In 5 patients the blood sugar rose and the collateral symptoms disappeared promptly. In Case 3, after removal of Tumor 3, there was no improvement. At a second operation, 1 month later, Tumor 4 was found and removed, together with 6 cm. of the tail of the pancreas, this time with prompt recovery.

The tumors were small, from 4 mm. to 2 cm. in diameter. In the tumors 2 cm. in diameter there was extensive fibrosis and calcification. In none of the tumors was there sufficient material for chemical or biological assay. The conclusions in this paper are based solely on histological staining, including specific staining of the cytoplasmic granules.

TUMOR PATTERNS

Structurally these tumors are nothing but gigantic islets of Langerhans, of which we have an excellent example in Tumor 1.

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Figure 1 shows how faithfully this tumor copies the structure of the normal islet. It reproduces the rich capillary network bordered by rows of columnar and cuboidal cells. As in normal islets, some of the capillaries have an endothelial lining, but many have none, the tumor cells seemingly being in direct contact with the blood. The tumor cells measure the same as cells of normal islets and are packed with fine granules which stain like the granules of the normal islet cells. As in normal islets, there is a minimum of fibrous connective tissue limited to a few strands along the capillaries and a delicate meshwork of argyrophil reticulin around the capillaries. Large areas of the tumor have no reticulin framework. Even with the highest magnifications and with a variety of stains, this tumor is indistinguishable from a normal islet except at the border where the adjoining acini are entangled and compressed in an incomplete fibrous capsule. The balance between tumor growth and blood supply is well maintained for all the cells appear healthy and there is no sign of necrosis or fatty degeneration.

Tumor 2, illustrated in Figure 2, is another gigantic islet of healthy cells. The figure shows the tendency of these tumors to exaggerate and repeat over and over some structural feature of a normal islet, in this instance the rosette arrangement of the cells around a capillary.

Figure 3 illustrates Tumors 5 and 6, removed at the same operation. This is an unusual pattern consisting of long ribbons of columnar cells with centrally placed nuclei. Each ribbon is a single row of cells lying between two capillaries. At many points no endothelial lining is visible and there is no fibrous connective tissue or argyrophil reticulin interposed between the tumor cells and the blood stream. The cells are packed with the specific islet cell granules. The cells of this tumor give an illusion of being abnormally large. By actual measurement they are quite uniformly the size of many normal islet cells.

Unusual as this pattern is, it is merely another instance of exaggeration and repetition of an ordinary islet figure. Short ribbons of this type occur in normal islets but the true prototype of the long ribbon is found in islet hypertrophy. MacCallum's picture of the ribbons in islet hypertrophy would serve as an excellent illustration of Tumors 5 and 6. Despite its resemblance to an embryonic structure, this ribbon pattern is not an embryonic or

undifferentiated form. Embryonic islets are more like the compact short ribbon type pictured in Figure 1.

As far as we know, no other islet tumor of the long ribbon type has been recorded, but the long ribbons of hypertrophy have been described by MacCallum, Cecil, and Weichselbaum and Stangl and regarded, mistakenly we believe, as an undifferentiated or regenerating form.

Hydropic Degeneration

Hydropic degeneration was not observed in any of our tumors. In the absence of exact knowledge we refrain from speculation on the possible relation to excess production of insulin.

Fibrosis

Pursuing our thought that the islet tumors are gigantic islets, we arrive at Tumors 3, 4, 5, 6, 8 and 9, all of which show more or less extensive fibrosis, hyaline degeneration and calcification. Here again the tumors are merely reproducing islet lesions on a grand scale; for non-tumoral islets are subject to precisely these changes — fibrosis, hyaline degeneration and calcification. The size of the tumors renders these lesions more impressive than when they occur in the tiny islets.

Fibrosis seems to be the common fate of these tumors. Of our 9 tumors, 6 present broad areas of fibrous connective tissue dotted with small groups of surviving tumor cells. In 1 of the 3 remaining tumors fibrosis is beginning in one sector. In most of the reports of islet tumors more or less extensive fibrosis has been recorded.

Figure 4 shows the fibrosis beginning in one sector of Tumor 1 as a thickening of the capillary wall studded with small blocks of collagen.

Figure 5 shows an advanced fibrosis, only a few tumor cells remaining; but these tumor cells are packed with the specific granules and they must have been active to judge by the prompt relief from the hypoglycemia after operative removal.

Hyaline Degeneration

In some of our fibrosed tumors much of the newly formed fibrous connective tissue has been converted into a clear glassy

substance which, in the negative outcome of amyloid and mucin reactions, we must be content to call hyalin. With Mallory's aniline blue collagen stain, or with its variants — Masson's trichrome and Heidenhain's azocarmine — the hyaline substance stains pale blue, much paler than the fibrous connective tissue. Many tumor cells contain similar pale blue patches in their cytoplasms. Studying these patches and the apparent conversion of entire cells to pale blue blocks, we are convinced that the tumor cells themselves undergo the hyaline as well as the fibrous connective tissue change, settling, in our own minds at least, the long-standing controversy as to whether the hyaline metamorphosis is restricted to the collagen or to the cytoplasm. It affects both.

This hyaline metamorphosis of the tumor cells has nothing to do with Bloom's D cells which stain with aniline blue.

Calcification

Three of our tumors are extensively calcified, which is not surprising considering the extent of the hyaline degeneration. As Mallory observes, hyaline material calcifies readily everywhere in the body.

Spontaneous Cure

On viewing the extensive destruction of tumor cells by fibrosis and hyaline metamorphosis, one surmises that this process might proceed to total obliteration of the tumor cells and a spontaneous cure (Bensley, O'Leary). Against this conclusion is the fact that tumors of several years duration and with extensive destruction of cells are still capable of producing hypoglycemia, as shown by the prompt relief of this condition after their removal.

The situation reminds one of chronic tuberculosis where, despite extensive healing by fibrosis and calcification, the healing process never quite overtakes the advance of the tuberculosis. Among islet tumors there is no authentic instance of spontaneous cure.

Nuclei

A word should be said about nuclei. Those pioneers in the study of islet cells, Lane and Bensley, described characteristic features of the nuclei of A and B cells and acinus cells, and their descriptions have been copied from one writer to another ever since with-

out adequate criticism. With the acid fuchsin-methyl green stain it is a simple matter to bring A cells, B cells and acinus cells into the same field for comparison. After a careful study of human and animal pancreas, and of the tumors, all fixed promptly in Zenker's or Bouin's fluid and properly stained, my conclusion is that there is nothing characteristic about the nuclei which distinguishes one of these cells from the other. When put to the practical test of diagnosis these meticulous nuclear distinctions break down, as they did with one experienced cytologist and student of the pancreas (O'Leary), who studied the 5 St. Louis tumors under the most favorable conditions — immediate fixation and expert staining — and concluded that "these characteristics are hardly sufficient to distinguish one type of cell from another." We agree with him.

Specific Granules

Islet cells and the cells of the islet tumors differ from most cells in the body by being packed with fine granules. These are probably secretion granules (O'Leary). They are not artefacts for they are visible in fresh islets (Laguesse, Bensley, Covell, O'Leary). Laguesse stained these granules with safranine; Lane with gentian violet and orange G; Martin with ethyl violet and orange G; Bowie with ethyl violet and Biebrich scarlet; and Bensley with a variety of methods, including acid fuchsin and methyl green. These stains were devised for the pancreas in the lower animals. In our hands, when applied to human pancreas and human tumors, these stains with one exception proved to be exasperatingly capricious. The exception was Bensley's acid fuchsin-methyl green, which we found to be simple, accurate and constant in all kinds of islets, normal and pathological, and in islet tumors.

If normal pancreas is fixed in Zenker's fluid and paraffin sections are stained with acid fuchsin and differentiated in methyl green, the acinus cells are green with green nuclei, the zymogen granules red, and the basal filaments and mitochondria red. In contrast with the green acinus cells the islet cells are packed with fine red granules. With a slight modification of the technique the granules of Lane's A cells hold the red, while the granules of the B cells turn purple. The tumor cells react to this stain exactly like islet cells. In most of the tumor cells the granules take the

purple color of B cells with here and there a red A cell. It should be noted that to get good differentiation of islet cells, human pancreas requires stronger and longer staining than the pancreas in the lower animals. In the tumors we have not found Bensley's granule-free C cells and we agree with O'Leary in failing to find any of Bloom's D cells that stain with aniline blue. D cells are supposedly brought out best by fixation in Helly's fluid (Zenker-formol), in which some of our tumor tissue was fixed.

Origin of the Tumors

In the pancreas, the duct epithelium is the source of all growth and repair (Bensley, Norbert, Grauer). In the embryo, epithelial buds from the duodenum grow toward the spleen as branching pancreatic ducts. This duct epithelium is totipotent, as Bensley calls it, for at one point it differentiates into acinus cells, at another point into islet cells, and at still other points it pushes forward as branching ducts. The duct epithelium retains this totipotency throughout life, as shown by the remarkable instances of regeneration of the pancreas from the ducts, reproducing the pancreatic structure complete, with acini, islets and ducts, amounting in several instances to regeneration of the entire pancreas of the adult rabbit (Grauer). Once differentiated out of the duct epithelium the islets grow by proliferation of their own cells (Bensley).

Curiously enough a stimulus that calls forth the duct-building and islet-building potency of the pancreas, while leaving the acinus-building potency in abeyance, is known. After ligature of the ducts both acini and islets degenerate and disappear, or nearly disappear (Bensley). If ligation is continued the islets regenerate from the ducts but the acini do not. If, on the other hand, the ligature is removed and free drainage of the duct system reestablished, the acini regenerate as well (Bensley, Harvey, Grauer).

The islet tumors may be regarded as a reaction of the duct epithelium to a stimulus that has called forth its duct-building and islet-building potencies, leaving the acinus-building potency in abeyance. Figure 6 from Tumor 3 shows the process in full swing. Throughout the tumor, ducts are so numerous that most of them must be accepted as newly formed. In the center of the figure a duct is seen, easily recognizable by the terminal bars or

"Schlussleisten" which fill the chinks between the epithelium. The epithelium of the duct is continuous with a group of tumor cells, as if the tumor cells were differentiating out of the duct epithelium.

Similar abundance of ducts and continuity of duct epithelium with tumor cells is found in every one of our tumors. O'Leary observed similar figures in 4 out of 5 of the St. Louis tumors, and interprets them in the same way. O'Leary observes justly that the mitotic figures in some of the tumors show that once differentiated out of the duct epithelium the tumor cells possess the power of independent proliferation.

In the normal pancreas such continuity of duct epithelium and islet cells is a matter of common observation (Laguesse, Bensley, and others). It is even asserted, on the evidence of serial sections, that the islets of the adult pancreas never lose their original continuity with the duct epithelium. The formation of the islet tumors, then, is merely an exaggeration of a normal procedure — differentiation of islet cells out of duct epithelium and subsequent independent growth.

Concerning mitoses and infiltration, we quote from Whipple and Frantz: "We have classified these eight tumors as adenomata, for the present at least, and only in the fifth, sixth, and eighth have we seen any evidence of what might be considered an infiltrating tendency. Marked variation in the size and shape of cells, mitotic figures in any appreciable number and blood vessel invasion are nowhere present."

NESIDIOBLASTOMA

There is need for a short and accurate name for these tumors. Adenoma of the islets of Langerhans is long and cumbersome. Adenoma itself is vague, for we have already two kinds of adenoma, the benign epithelial tumor and lymphadenoma, quite different from each other. To add still another adenoma, an endocrine variety, merely adds to the confusion. We have followed current custom of suffixing "oma" to the Greek name of the cells of origin of the tumor. Selecting *νησίδιον* as the Greek word for islet, the cells that differentiate out of the duct epithelium to build islets may be called nesidioblasts — islet builders. When these islet builders, or nesidioblasts, form tumors, the tumor is a nesidioblastoma. The name has another application. In contrast with

the concentration of excess islet tissue in a tumor there is some evidence pointing to a diffuse or disseminated proliferation of islet cells as a possible cause of hypoglycemia. Such a diffuse proliferation of nesidioblasts would be a nesidioblastosis.

Summary

Microscopically the chief feature of most of the tumors is their exact duplication of the pattern of normal islets. They also resemble islet hypertrophies in their tendency to exaggerate some features of the normal islet pattern. Just as the tumors duplicate the structure of normal and hypertrophied islets, so they are subject to the same pathological vicissitudes such as fibrosis, hyaline degeneration and calcification. The origin of the tumor cells is indicated by the abundance of figures showing the epithelial lining of the duct continuous with a group of tumor cells.

The origin of the name "nesidioblastoma" is explained.

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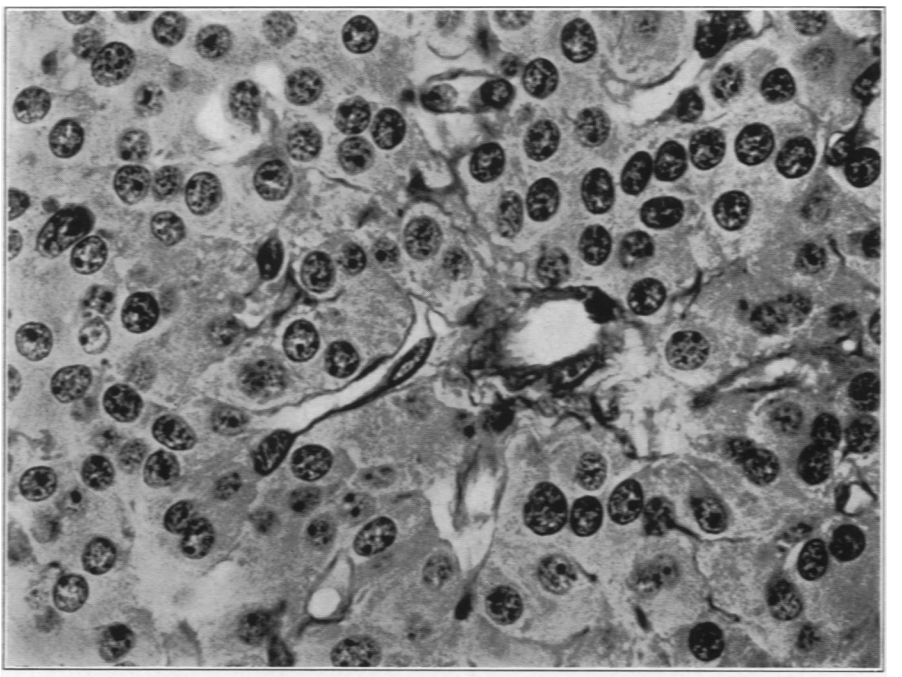
DESCRIPTION OF PLATES

PLATE 27

FIG. 1. Tumor 1. The photomicrograph shows how the tumor faithfully reproduces the structure of the normal islet with its rich capillary network bordered by rows of columnar and cuboidal cells. Azocarmine stain. × 730.

FIG. 2. Tumor 2. In this tumor there is a rosette arrangement of the cells around capillaries. This reproduces one feature of normal islets. Azocarmine stain. × 730.



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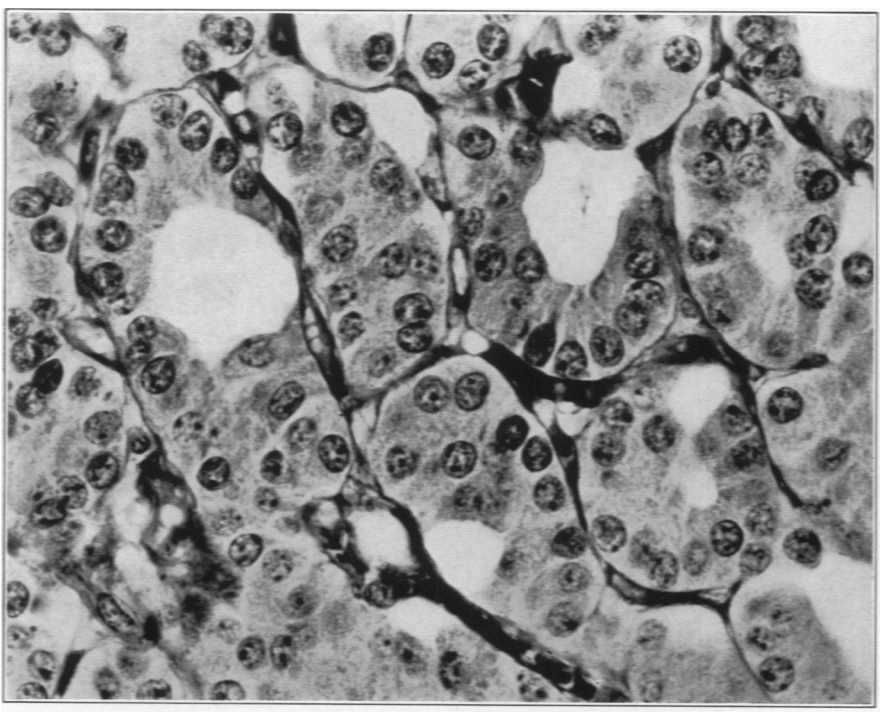

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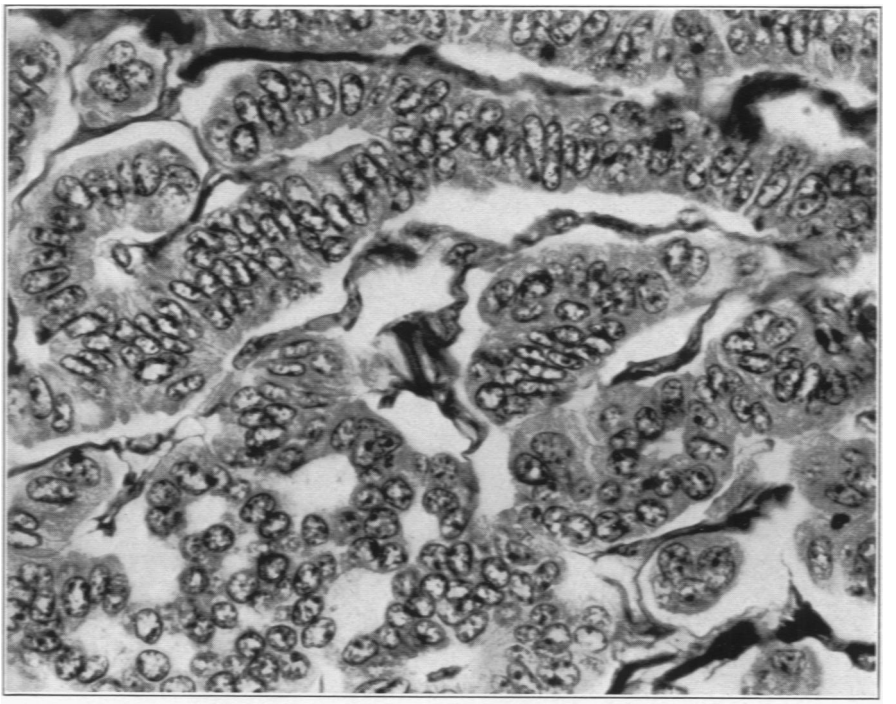
PLATE 28

FIG. 3. The photomicrograph shows the pattern of Tumors 5 and 6; long ribbons of columnar cells with centrally placed nuclei, each ribbon a single row of cells lying between capillaries. Azocarmine stain. × 730.

FIG. 4. This section of Tumor 4 shows fibrosis beginning as thickening of the capillary walls studded with small blocks of collagen. At A is shown the lumen of a capillary and at B a small block of collagen in its wall. Other collagen masses may be distinguished by the absence of granules. Masson's aniline blue-acid fuchsin-ponceau stain. × 730.



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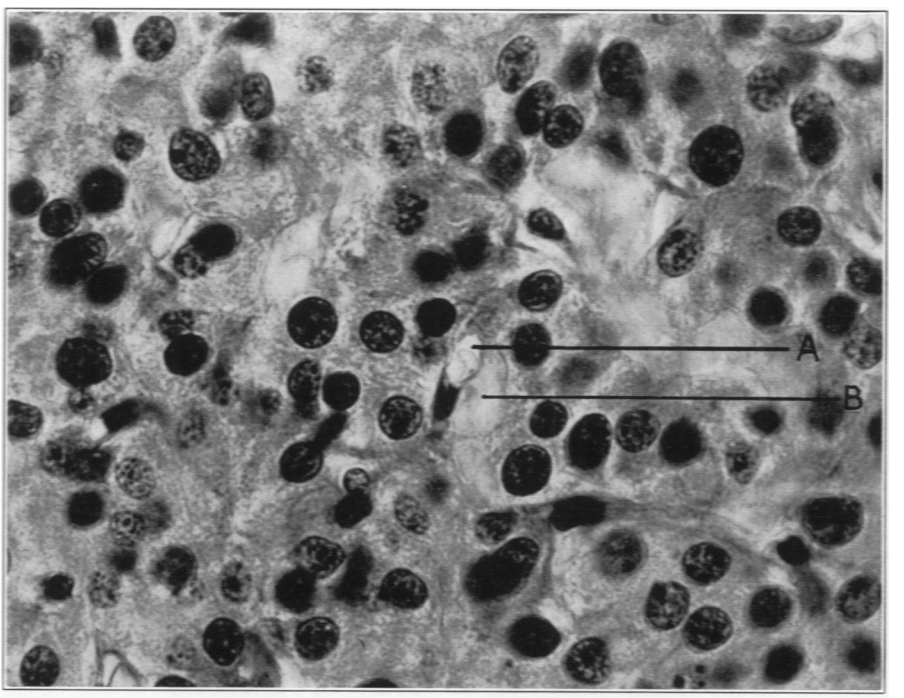

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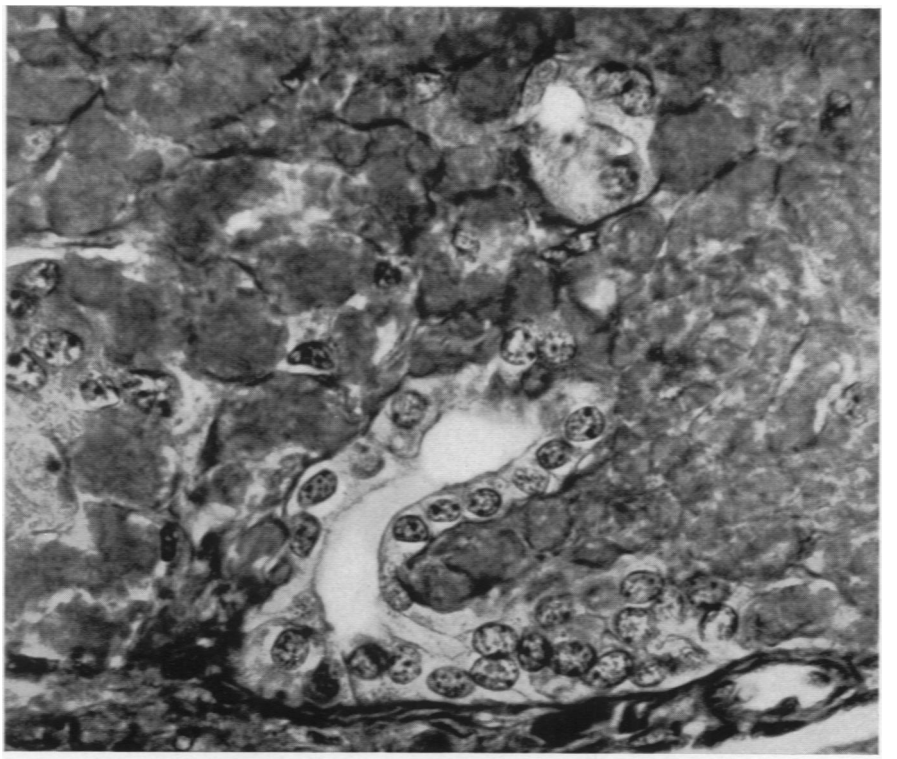
Laidlaw Nesidioblastoma

PLATE 29

FIG. 5. Tumor 3. An example of advanced fibrosis; only a few tumor cells remain but they are apparently active, judging by the presence of granules and the prompt relief of hypoglycemia after their surgical removal. Azocarmine stain. × 730.

FIG. 6. Tumor 3. This shows the epithelium of the duct in continuity with a group of tumor cells, as though the tumor cells were differentiating out of the duct epithelium. The Schlussleisten are shown as black dashes between the cells lining the lumen and radiating from it. Masson's aniline blue-acid fuchsin-ponceau stain. × 1600.



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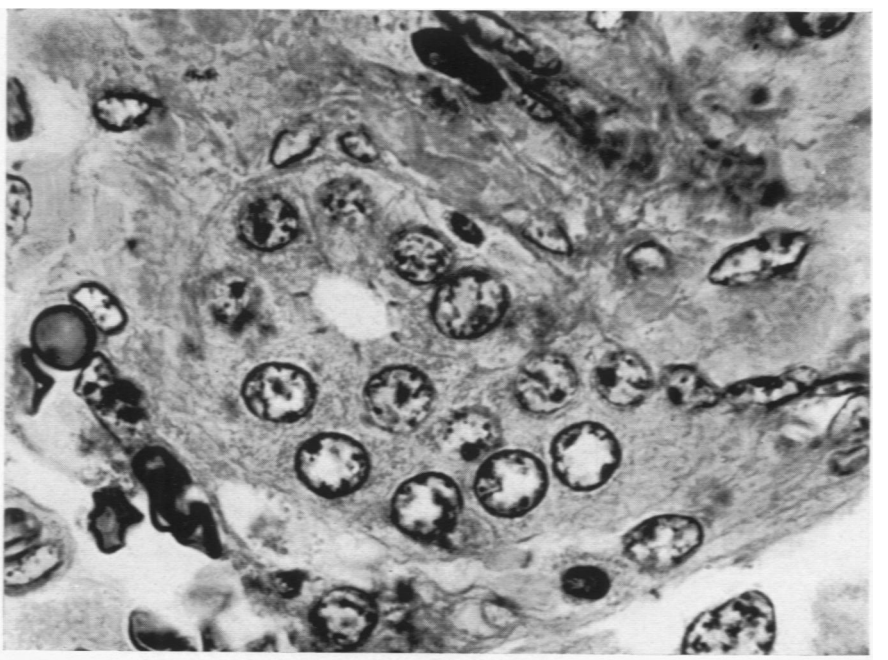

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