Y. M.

Report

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Edmund Joseph Horgan for the degree of Master of Science in Surgery. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

C. H. Mayo
Chairman

Christopher Graham

W. Carpenter MacCarty

THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Edmund Joseph Horgan final oral examination for the degree of Master of Science in Surgery. We recommend that the degree of Master of Science in Surgery be conferred upon the candidate.

Minneapolis, Minnesota

May 30 1919

Horace B. Balfour
Chairman

C. M. Jackson

F. C. Mann

Wm. Carpenter MacCarty.

THE UNIVERSITY OF MINNESOTA

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Chairman

May 16 1919

THESIS

THE HISTOGENESIS OF CARCINOMA IN THE ISLETS OF THE PANCREAS

Edmund Joseph Horgan

Submitted to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Degree of Master of Science in Surgery

May, 1919.

THE HISTOGENESIS OF CARCINOMA IN THE ISLETS OF THE PANCREAS

Introduction

The earliest stages of carcinoma have been found in association with chronic inflammatory changes in many organs of the body; therefore it seemed theoretically possible that similar neoplastic changes might be found in association with chronic pancreatitis. With this idea in mind I examined two hundred and sixty-two pancreases which were removed at necropsy between Jan. 1, 1910 and Jan. 1, 1919 in the Mayo Clinic from patients who died with ulcer of the stomach, ulcer of the duodenum, cholecystitis with and without stones, cholangitis with and without stones, and carcinoma of the stomach, liver, gallbladder and bile ducts. In no case in this series was a definite advanced carcinoma of the pancreas studied, although comparison was made of thirty-six specimens of tissue from late carcinoma with the tissue showing early changes.

In the cases available for study the pathologic conditions of the pancreas found in association with those chronic upper abdominal lesions mentioned were acute and chronic pancreatisis, stages of fat necrosis, simple cysts, cyst adenomas, papillary cystadenomas, hypertrophy and hyperplasia in the Islets of Langerhans. Of these conditions, hypertrophy and hyperplasia in the islets in chronic pancreatitis have been the objects of this special investigation. In order to obtain more accurate knowledge which might throw light on the histogenesis of carcinoma of the pancreas, a detailed study of pathologic specimens, grossly and microscopically was made. This was supplemented by the study of the normal development and of the structure of the pancreas.

Embryology

The pancreas in man develops from two anlagen which appear in the embryo of three to four millimeters in length. The dorsal pancreatic anlage begins as an outpouching on the duodenum, the ventral pancreatic anlage as a grooved bud arising from the common bile duct (Fig. 1). The growth of the dorsal pancreas is more rapid than that of the ventral. The anlagen grow separately until they meet posterior to the duodenum where they coalesce and continue development in one mass in the dorsal mesentery. In one embryo* , 26 mm., the dorsal and ventral anlagen are fused. The body and tail grow upward and to the left to lie in the dorsal mesogastrium posterior to the stomach. As the stomach and dorsal mesogastrium change position the pancreas moves within the dorsal mesogastrium until its position is transverse when it becomes firmly fixed to the parietal peritoneum of the posterior abdominal wall (Fig. 2).

The primitive outpouchings are lined with a columnar epithelium similar to that in the duodenum. As the buds grow the epithelium develops branching ducts ramifying the connective tissue. The main duct of the dorsal pancreas opens into the duodenum while the main duct of the ventral pancreas opens into the common bile duct at the ampulla. When the dorsal and ventral anlagen unite the main duct of the ventral pancreas makes a lateral anastomosis into the main duct of the dorsal pancreas. In this way the main duct of the ventral pancreas with the distal half of the duct of the dorsal pancreas form the duct of Wirsung, and the proximal half of the duct of the dorsal pancreas is the duct of Santorini. When the embryo is from 26 to 33 mm. in length, and the tail of the pancreas extends well out into the dorsal mesogastrium, branching tubules can be seen throughout the gland. No acini nor islets are to be seen at this stage and there is no evidence of lobulations. The connective tissue forms the major portion of the

* University of Minnesota No. H. 29.

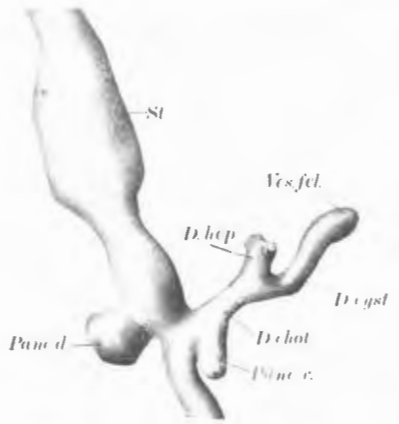

FIG. 5. Reconstruction from a human embryo of 7.5 mm. (H. E. C. 256). × 55 diams. *D. chol.*, ductus choledochus. *D. cyst.*, ductus cysticus. *D. hep.*, ductus hepaticus. *Panc. d.*, pancreas dorsale. *Panc. v.*, pancreas ventrale. *St.*, stomach. *Ves. fel.*, vesica fellea.

Fig. 1. Photograph from Thyng.

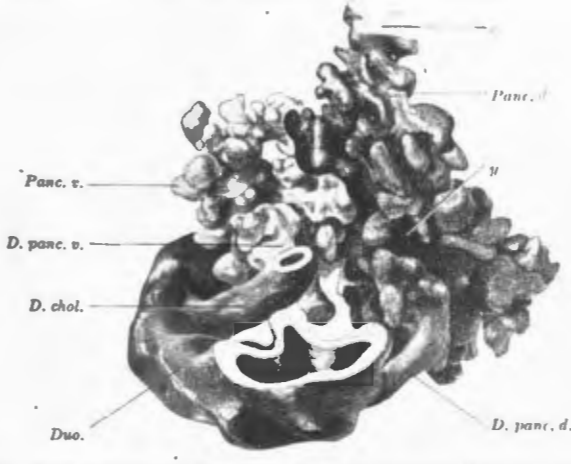

FIG. 309.—Model of the head of the pancreas of a 22.8 mm. embryo (Harvard Collection, Series 871). × 50 diam. *D. chol.*, common bile-duct; *D. panc. d.*, duct of the dorsal pancreas; *D. panc. v.*, duct of the ventral pancreas; *Duo.* duodenum; *Panc. d.*, dorsal pancreas; *Panc. v.* ventral pancreas; *x* and *y* are explained in the text.

Fig. 2. Photograph from Thyng.

organ. At the end of the branches of the main duct the tubules have an enlarged bud. This bud branches and forms new tubules until the acini begin to form by several buds at the tip of each tubule. After the acini have begun to form throughout the gland the islet cells appear in the connective tissue along the small ducts. Pearce found masses of cells which he identified as islet cells in an embryo of 54 mm. In the section of one embryo*, 158 mm. in length, in which I examined the ducts, acini and islets were well developed. The islets stand out clearly in the loose connective tissue near the ducts. They are circular masses, the cells of which are not well differentiated. As the glandular tissue grows into the connective tissue it envelops the islets. The connective tissue is derived from the mesodermal tissue of the dorsal mesentery (Figs. 3 and 4).

Histology

The embryology of the pancreas has been sufficiently studied in man and in species of lower vertebrates to establish the fact that all the histologic units develop from the same anlagen.

The pancreas is a "mixed" epithelial gland composed of three separate and distinct histologic units each made up of differentiated, specialized epithelial cells:

1. The pancreatic ducts (of Wirsung, Santorini, the interlobar and intralobular ducts, and the anastomosisng tubules of Bensley).
2. The alveolar glands.
3. The islets of Langerhans (Fig.5).

The pancreatic duct system.- The duct system in the pancreas is made up of one large duct, the duct of Wirsung, and an accessory duct, the duct of

* University of Minnesota, Col. No. H187.

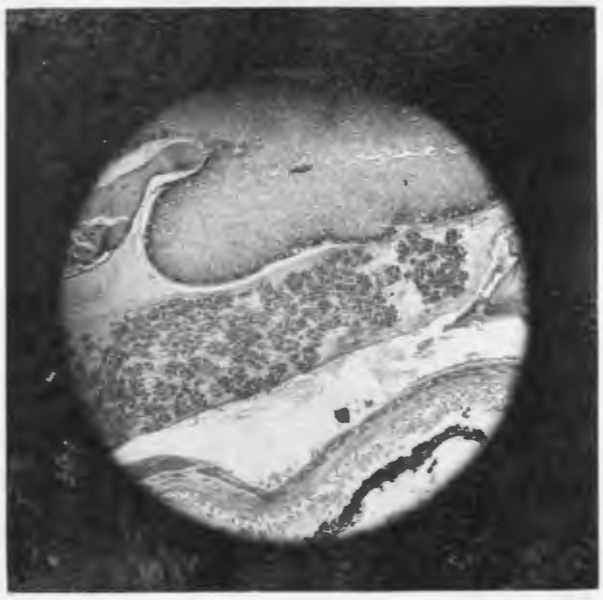

Fig. 3. (H.187 Univ. of Minn. Collection)Microphotograph of pancreas in embryo (158 mm. C.R.Length) showing relation to stomach and left adrenal.

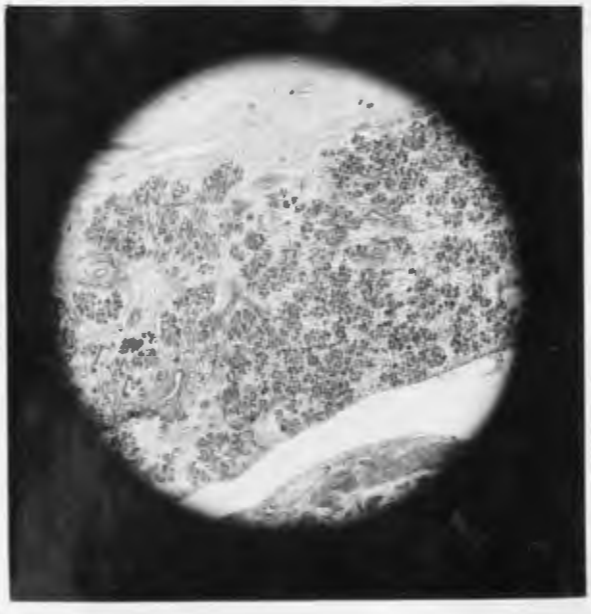

Fig. 4. (H.187 Univ. of Minn. Collection) Microphotograph of pancreas in embryo (158 mm. C.R.Length) developing in mesogastrium. Pancreatic ducts, acini, and islets may be seen.

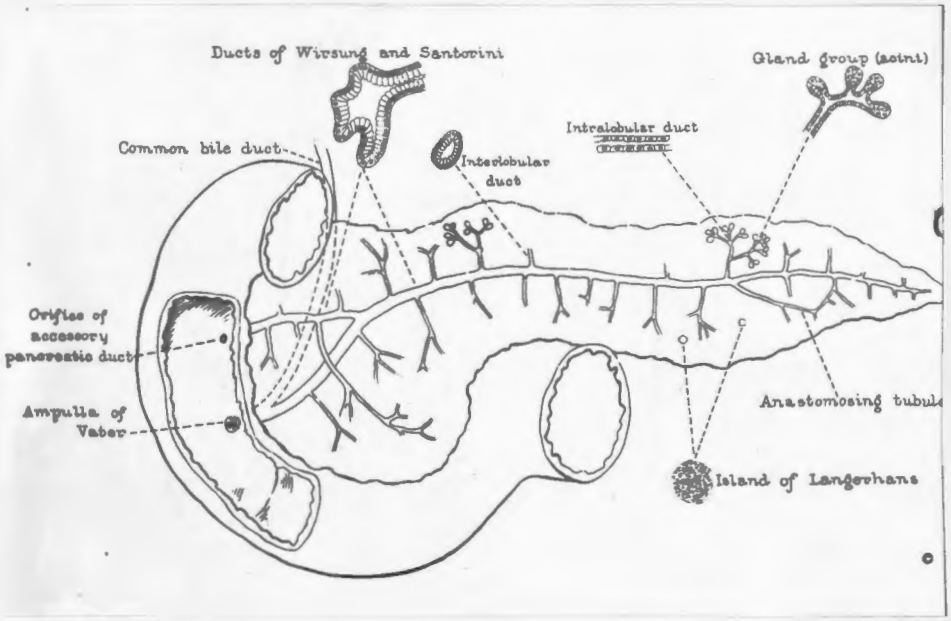

Fig. 5. Diagram of pancreas showing its histologic units.

Santorini. From these ducts numerous highly branched tubules ramify the organ. The duct of Wirsung passes from the duodenal portion of the organ, where it opens into the ampulla of Vater, to the splenic portion. Throughout its entire length the first division of the tubules open into it. These primary branches do not enter directly; they pass through the connective tissue of the duct of Wirsung for a short distance. The terminal branches are rather tortuous; Bensley has shown that they have many anastomosing tubules (Fig. 6). The main ducts (Wirsung and Santorini) are lined with a single layer of high columnar epithelium on a fine membrana propria; in some sections it is thrown up into folds (Fig. 7). In the interlobular and intralobular and anastomosing tubules the epithelium is a single layer of columnar cells, gradually diminishing in height in the terminal branches (Fig. 5).

The alveolar glands.- Projecting out from the terminal ends of the tubules are the alveolar glands. These are branched tubular glands lined with a single layer of large secreting cells, pyramidal in shape, the apex of which points into the lumen of the acinus with the base, near which is a large circular nucleus, lying on a membrana propria. The cytoplasm is divided into two zones, granular and homogenous; the granular zone at the apex is made up of the zymogen granules in a faintly staining protoplasm; the homogenous zone is in the basal portion of the cell. The zymogen granules in the granular layer and the mitochondrial filaments in the homogenous layer may be studied only by the use of special fixation and staining. The secreting acinic cells receive their blood supply from a capillary network in the membrana propria (Fig. 8).

The Islets of Langerhans.- These islets are small, circumscribed masses of epithelial cells distributed throughout the entire organ although they are more numerous in the splenic portion. Most of the islets are spherical, from 0.2 to 0.3 mm. in diameter, but they may be oval in shape (Fig. 9). They

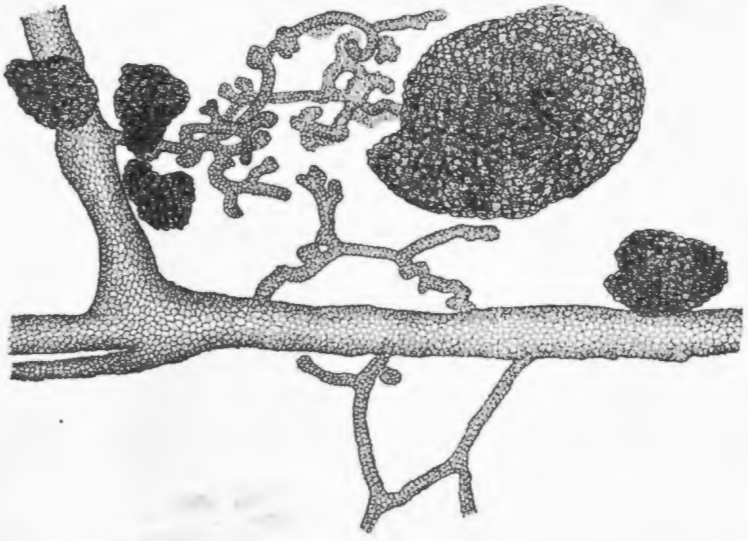

Fig. 5 Duct with branches showing the highly branched tubules connected with the duct and with an islet. Intra vitam staining with pyronin and neutral red. × 77.

Fig. 6. Photograph from Bensley.

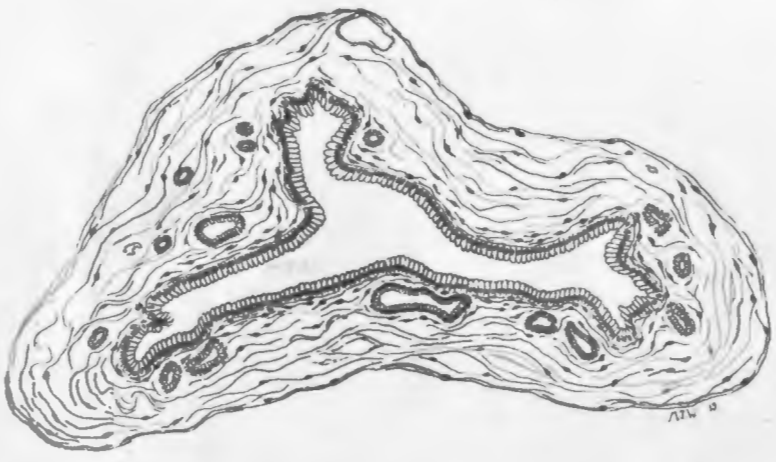

Fig. 7. Diagram of cross section of pancreatic duct with primary branches passing through its wall.

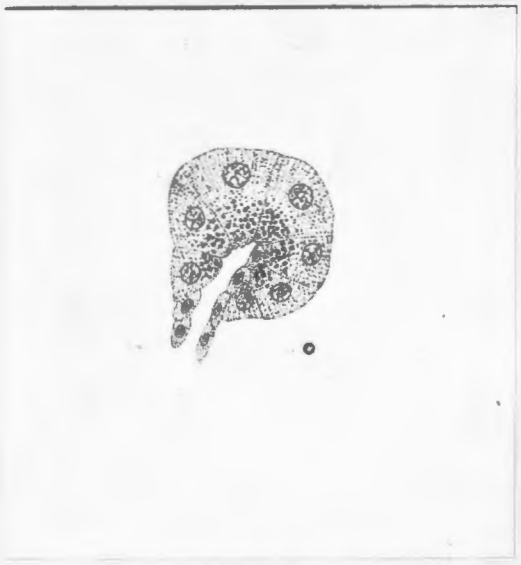

Fig. 8. Diagram of secreting cells in pancreatic acinus.

Fig. 9. Diagram of islet.

have no duct connection, either with the pancreatic tubules or with each other, but lie in close relationship to the tubules. The texture of the connective tissue separating them from the acini is very delicate. The arteries supplying the islets form a rich capillary cluster. The vessels do not enter through a hilus. Each islet has a number of small capillaries which pass in from the connective tissue at different points on the surface. The arrangement of the efferent blood stream is the reverse (Fig. 10).

The islet cells are of two varieties, A and B. The A cells are the larger; they have a large elliptical nucleus with the chromatin in one or two round clumps. In the cytoplasm there are many small granules. The smaller B cells are more numerous; they have a central nucleus which is circular and contains a larger amount of chromatin. Their cytoplasm is packed with small granules. These cells may be differentiated from one another and the granules stained only by the fixation and staining methods of Lane. In the sections the cells are seen in irregular masses, in single, or in double cords. They lie in a delicate connective tissue among the loops of the capillary cluster (Figs. 11, 12,13,14,15,16,17,18, and 19).

Blood vessels.- The blood supply to the pancreas is through the splenic, hepatic, and superior mesenteric arteries. The main trunk of the splenic and hepatic each send a number of branches. The superior pancreaticoduodenal and the inferior pancreaticoduodenal supply the head with a number of branches. The veins which are tributaries of the portal system follow the arteries.

Lymphatics.- The lymphatics drain into the splenic, anterior, and posterior pancreaticoduodenal groups (Fig.20).

Pathology

Technic.- The pancreatic tissue was examined grossly; blocks

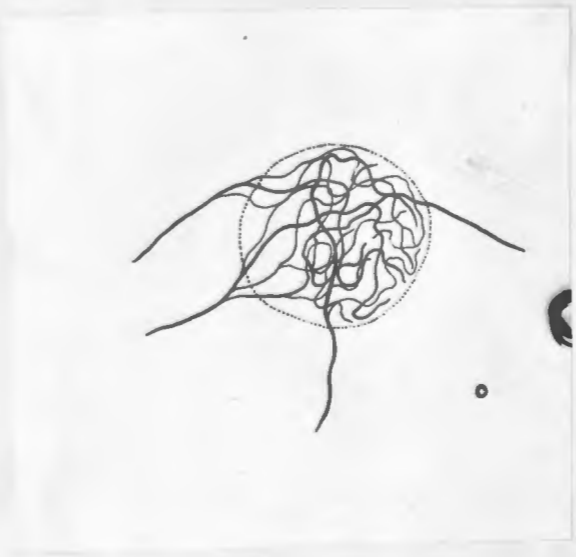

Fig. 10. Diagram of capillary cluster of islet of pancreas

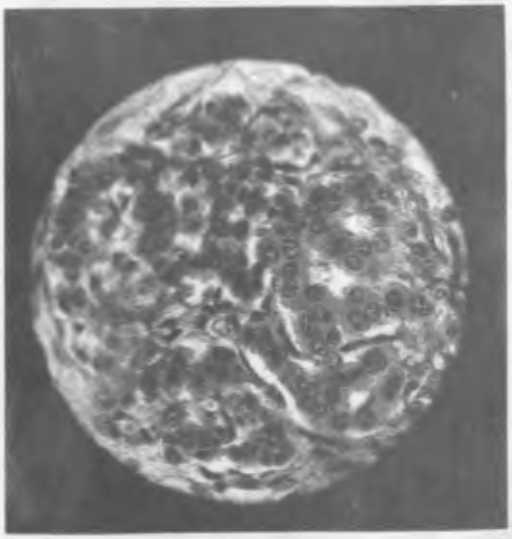

Fig. 11. (H.187. Univ. of Minn. Collection) Microphotograph of islet in embryo pancreas (X250).

Fig. 12. (H.187. Univ. of Minn. Collection) Microphotograph of islet in the pancreas of an embryo (158 mm. in C.R. length) (X250).

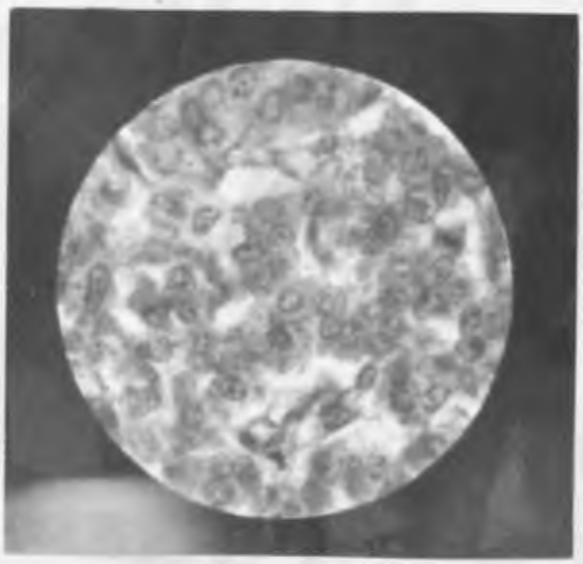

Fig. 13. (H.187. Univ. of Minn. Collection) Oil immersion Microphotograph of islet cells in embryo 158 mm. pancreas (X500).

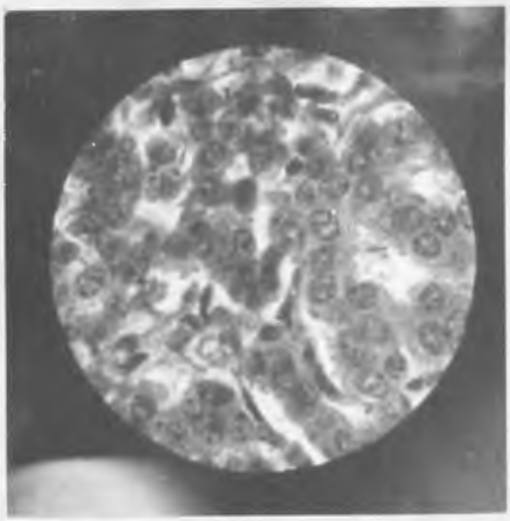

Fig. 14. (H.187. Univ. of Minn. Collection) Oil immersion microphotograph of islet cells embryo 158 mm. (X500).

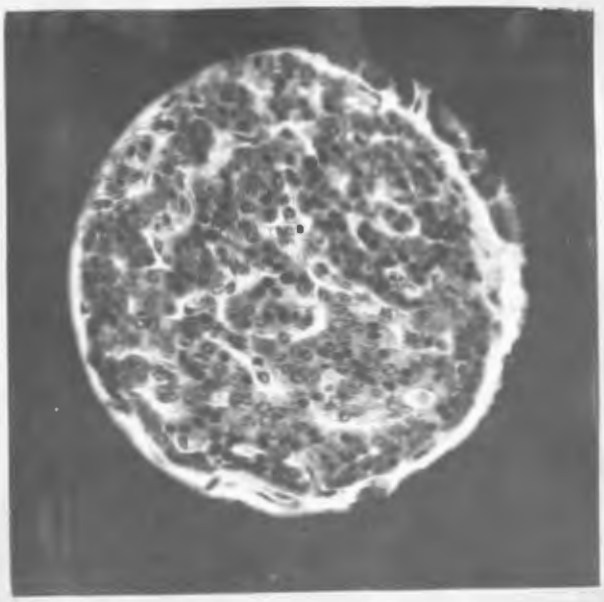

Fig. 15. (A135776). Microphotograph of islet in infant aged eight months (X250).

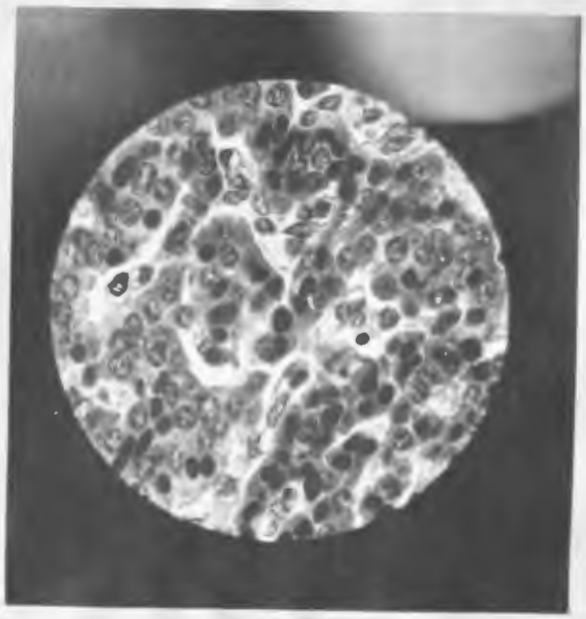

Fig. 16. (A135776). Oil immersion microphotograph of islet cells in an infant aged eight months (X500).

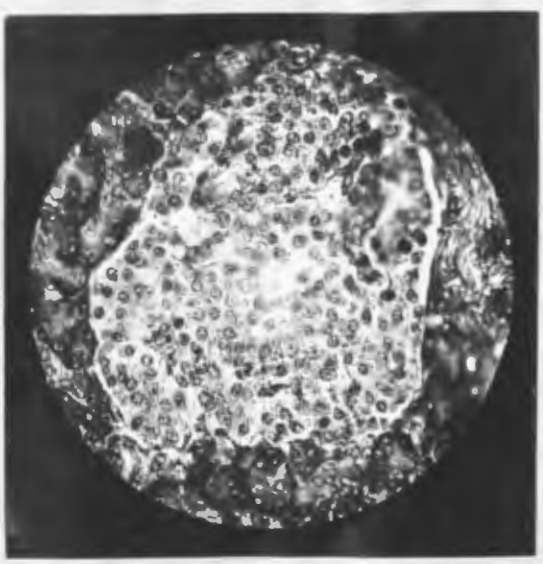

Fig. 17. (A122722) Microphotograph of islet in pancreas of adult (X230).

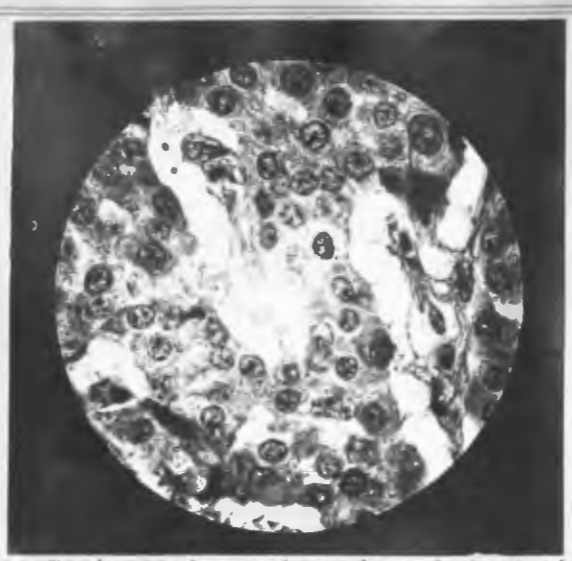

Fig. 18. (A122722) Oil immersion microphotograph of islet in pancreas of adult (X500).

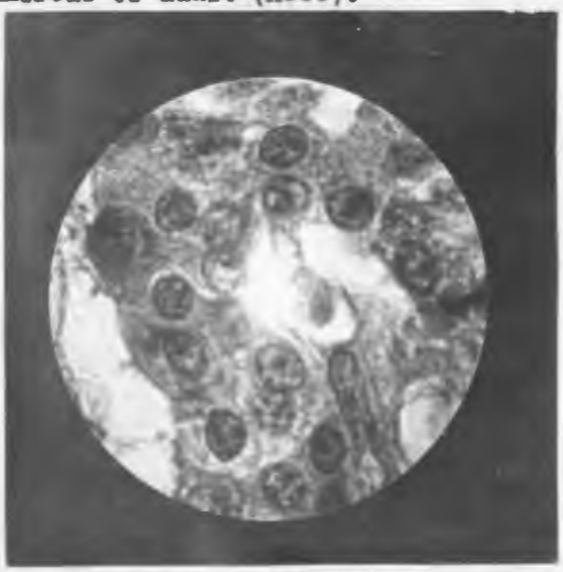

Fig. 19. (A122722) Oil immersion microphotograph of islet in pancreas of adult (X1000).

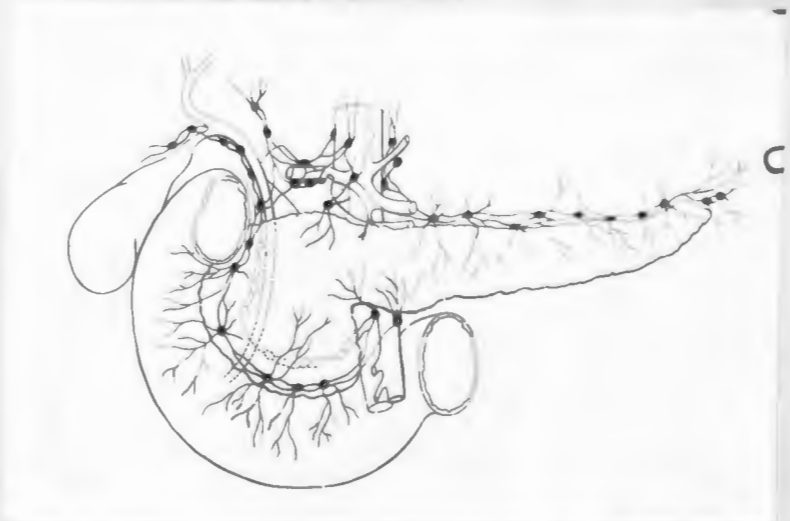

Fig. 20. Diagram of peripancreatic lymphatic glands.

cut from the duodenal, central, and splenic portions of the pancreas were sectioned and stained for microscopic study. The gross specimens had been preserved in neutral 10 per cent formalin solution. Blocks for microscopic study are preserved in 10 per cent formalin solution, Zenker's fluid with acetic acid, and Bensley's formalin - Zenker solution. Blocks from all the specimens which are preserved in formaldehyde solution were placed in a weak aqueous solution of ammonia for twenty-four hours and a few drops of strong ammonia added to the weaker alcohols when the tissues were being dehydrated; those preserved in Zenker's fluid with acetic acid and Bensley's formalin-Zenker were dehydrated in the usual manner. The blocks were embedded in paraffin and several slides from each block were cut in series for the routine microscopic examination. Additional blocks and sections were cut when needed. A few frozen sections were made. Some sections were stained with Ehrlich's hematoxylin and eosin and Goodpasture's acid polychrome-methylene blue and eosin. Others were stained with phosphotungstic acid hematoxylin and Bensley's brasalin water blue to differentiate the islet epithelium from the acinic epithelium. The blocks of tissue which had been preserved in formaldehyde and treated with ammonia could be differentiated by these stains also.

Chronic pancreatitis.- Chronic pancreatitis is an almost if not a constant finding in association with gastric and duodenal ulcer; it is most marked, however, in the duodenal portion of the organ. The amount of pancreatic involvement and the degree of inflammatory reaction are dependent on the location and duration of the ulcer and the severity of the acute exacerbations. When the gastric or duodenal ulcer perforates onto the pancreas and an area of the pancreas becomes the base of the ulcer the marked local pancreatitis which develops gradually changes from an acute to a chronic form (Fig. 21). In

Fig. 21. (A36163). Microphotograph of duodenal ulcer perforated onto pancreas showing marked connective tissue reaction in area of localised pancreatitis.

addition there is usually a diffuse pancreatitis (Figs. 22, and 23). The pancreatitis is manifested either by a lymphocytic infiltration or by fibrosis extending into the interlobular, interacinar and periductal connective tissue.

Hypertrophy of the islets observed in the series of cases studied.- In the microscopic examination of sections of the pancreas from the 263 cases that were selected for this study, hypertrophy of the islets in connection with a chronic pancreatitis was found in forty-eight cases. When the histories of these forty-eight cases were examined, two important discoveries were made; first, none of them showed glycosuria in any of the uminalyses of twenty-four hour specimens made while the patients were under observation and examination; second, 79.3 per cent of these were found to be cases in which a gastric or duodenal ulcer was found at operation or at necropsy. In the series of 262 cases which was selected for this study gastric ulcer was found in 71; in seventeen (25 per cent) the islets showed hypertrophy. Duodenal ulcer was found in 61 cases; in nineteen (31 per cent) the islets showed hypertrophy. Gastric and duodenal ulcer were found associated in 11 cases; in two (18.1 per cent) the islets showed hypertrophy. Hypertrophy of the islets was also observed in six cases of gastric carcinoma, two cases of carcinoma of the rectum, one case of carcinoma of the sigmoid, and one case of cyst of the pancreas.

Hypertrophy of the islets was observed grossly and in section from all portions of the gland. Grossly the largest ones appeared as creamy white bodies. Microscopically the close relationship of these hypertrophic islets to the ducts was very noticeable. They varied from slightly above normal to twenty times their normal size, the largest islet measuring 6 mm. in its greatest diameter.

Microscopic pathology of hypertrophic islets.- There is a great variation in the size of the hypertrophic islets; they vary from .5 mm. to 6 mm.

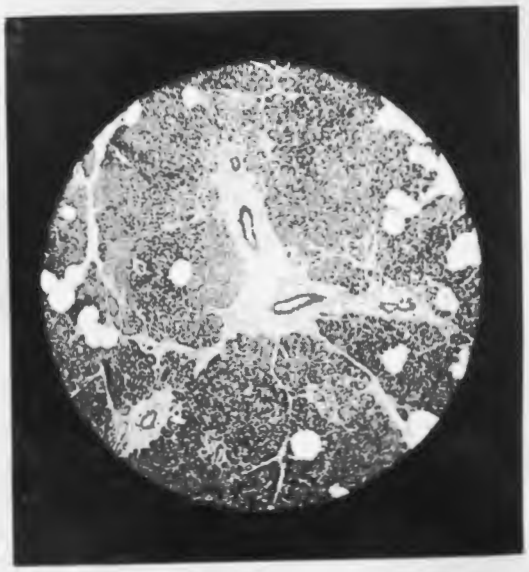

Fig. 22. (A61333). Microphotograph. Chronic pancreatitis. Interlobular fibrosis most marked.

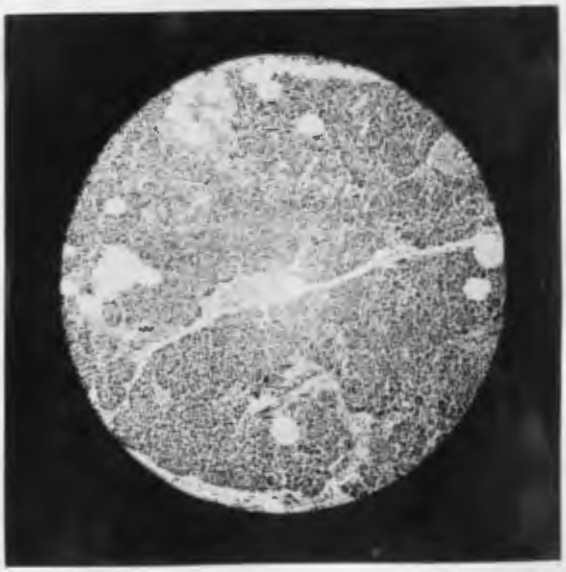

Fig. 23. (A61333). Microphotograph. Chronic pancreatitis. Interacinar fibrosis most marked.

in diameter. Most of them are round or oval, on section, although many do not conform to this shape. In a few cases examination of all the sections showed only a few hypertrophic islets in each case; usually they were found in greater numbers. They are found in sections from all portions of the pancreas but in a few cases all which were observed were in the duodenal portion. Connective tissue in the islets is always increased and the capsule surrounding the islet is always thickened (Figs. 24, and 25). Hypertrophic and hyperplastic epithelial cells are found in these islets and in a few migration of these hyperplastic epithelial cells takes place; they pass through the three successive stages of neoplasia.

Primary cytoplasia*.- The arrangement of the cells in the islets in short single and double cordons and masses between the capillary loops is similar to the normal. Most of the epithelial cells of these islets are differentiated; some are hypertrophic and the outline of the cytoplasm in these is not well defined (Figs. 26, 27, 28). These islets have a thickened connective tissue capsule and a diffuse fibrosis throughout. They are .5 mm. to 1 mm. in diameter. The capillary blood vessels have slightly thickened walls. No leukocytes or lymphocytes are to be seen nor is there any other evidence of an inflammatory process of the islets except a fibrosis.

Secondary cytoplasia.- The cordons formed by the epithelial cells are more marked than in the normal islet. Most of the cordons are formed by single rows of epithelial cells, a few by double rows. In the sections these cordons

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* MacCarty's terminology of stages of neoplasia:

Primary cytoplasia = Hypertrophy of regenerative cells plus presence of differentiated cells.

Secondary " = Hyperplasia of regenerative cells plus absence of differentiated cells, with or without pratial regeneration.

Tertiary " = Hyperplasia of regenerative cells plus migration, with or without partial differentiation.

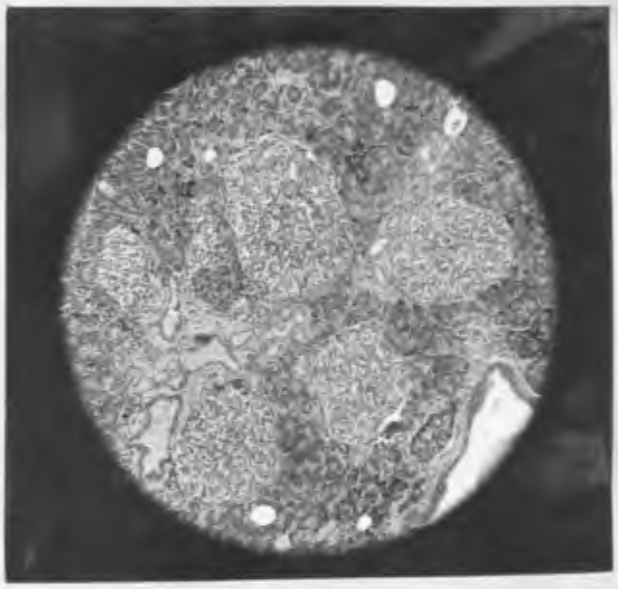

Fig. 24. (A58947). Microphotograph of hypertrophic islets (X35). Stage of pancreatico-primary-adenocytoplasia.

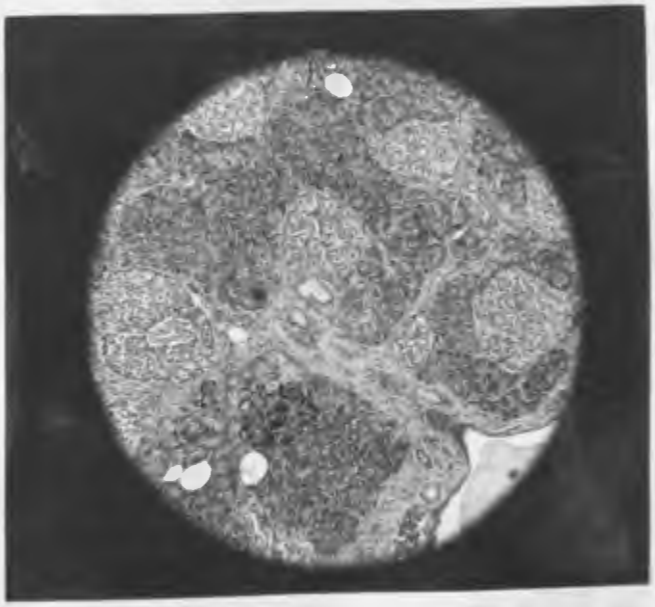

Fig. 25. (A58947). Microphtoograph of hypertrophic islets (35). Stage of pancreatico-primary-adenocytoplasia.

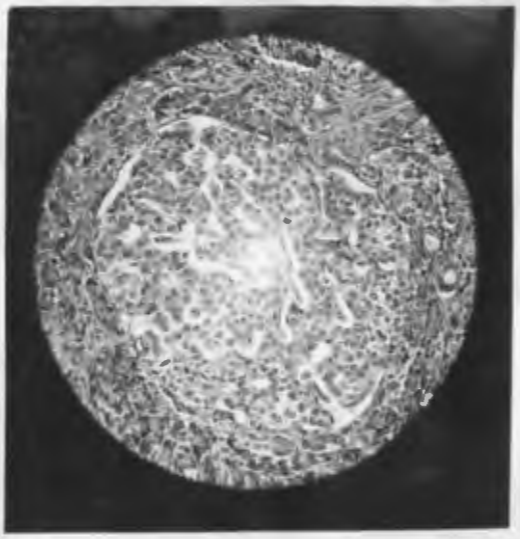

Fig. 26. (A78507). Microphotograph of hypertrophic islets (X250) Stage of pancreatico-primary-adenocytoplasia.

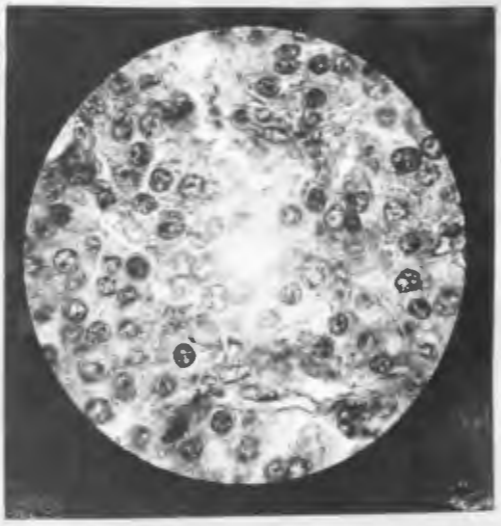

Fig. 27. (A78507). Oil immersion microphotograph of hypertrophic islet (X500). Stage of pancreatico-primary adenocytoplasia.

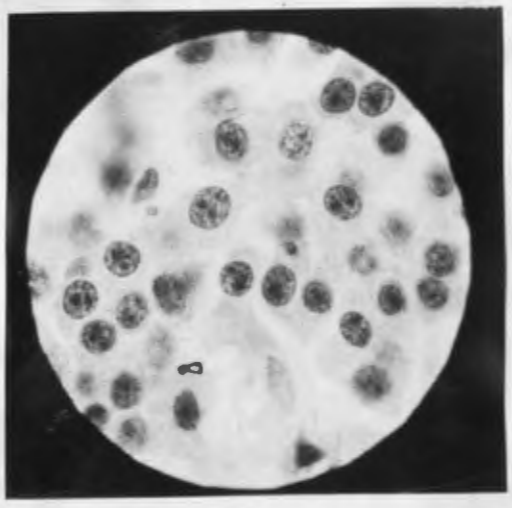

Fig. 28. (A116521). Oil immersion microphotograph of hypertrophic islet (X1000). Stage of pancreatico-primary-adenocytoplasia.

follow the contour of the blood vessels and where the vessels are sectioned transversely the cordons encircle them. The epithelial cells are undifferentiated or partially differentiated. Some of the undifferentiated cells are hypertrophic. The number of epithelial cells has increased markedly but the cells are all confined within the connective tissue capsule (Figs. 29,30,31,32,33,and 34). Some of these hypertrophic islets with hyperplasia of the epithelial cells are very large (.6 mm. to 1.5 mm.). The capsule is of dense fibrous connective tissue and fibrosis is diffuse throughout the islet. The capillary blood vessels have increased in proportion to the size of the islets and the vessel wall is thickened. There is no evidence of inflammation except fibrosis.

Tertiary cytoplasia.- The cordons are not well defined; most of the cells are in masses. The epithelial cells are undifferentiated; some, however, in some islets show partial differentiation. They are hypertrophic and hyperplastic, there being a marked increase in the size and number. In the center of some of the islets there is an area of cellular debris as the result of cellular disintergration; a few nuclei can be identified in this area. Migration of the epithelial cells through the connective tissue may be seen at the periphery. This migration of the epithelial cells is evidence of a carcinoma (Figs. 35-46). These islets are very large, the largest being 4 mm. by 6 mm. Proliferation of the connective tissue is very marked throughout the islet and the capsule is thick and densely fibrous. Bands of fibrous tissue pass out from the capsule of the islet into the interacinar and interlobular connective tissue. The blood vessels are very large, but their size is in proportion to the size of the islet, and their walls are thickened.

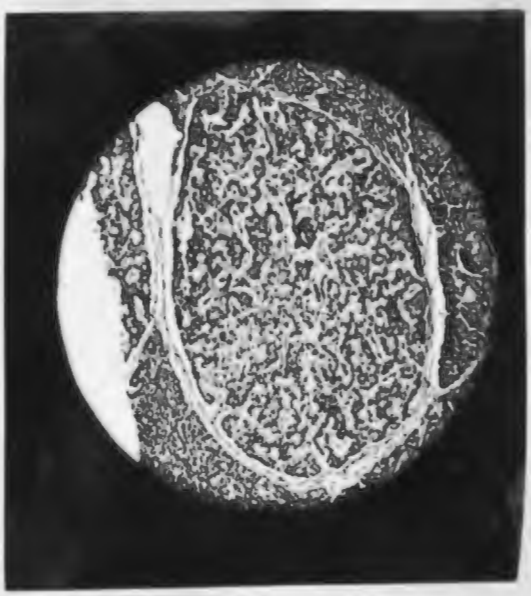

Fig. 29. (A50276). Microphotograph of hypertrophic islet (X60). Atage of pancreatico-secondary-adenocytoplasia.

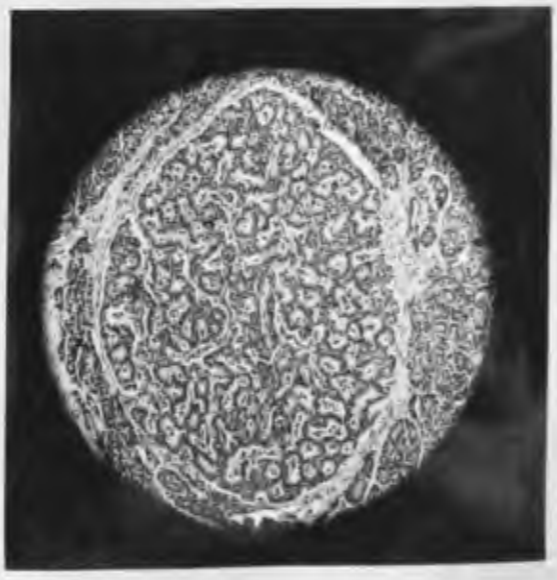

Fig. 30. (A50276). Microphotograph of hypertrophic islet.(X60). Stage of pancreatico-secondary-adenocytoplasia.

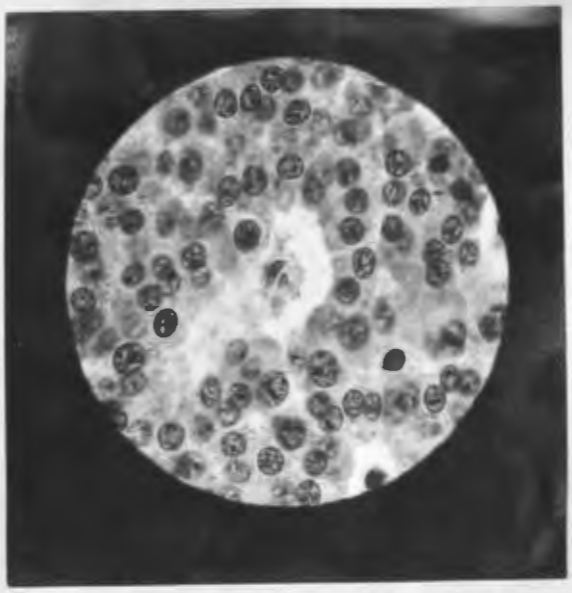

Fig. 31. (A50276). Oil immersion microphotograph of epithelial cells in hypertrophic islet (X500). Stage of pancreatico-secondary-adenocytoplasia.

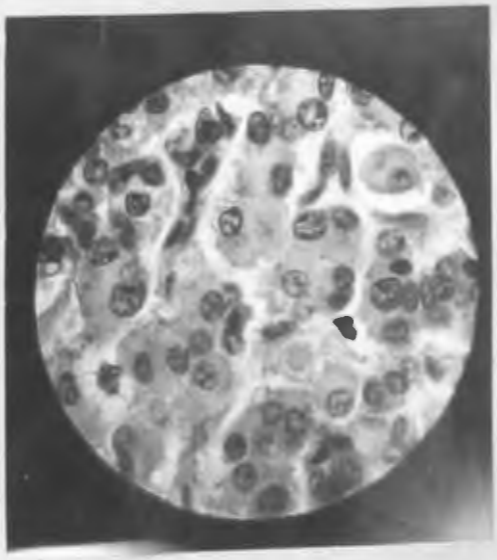

Fig. 32. (A50276). Oil immersion microphotograph of epithelial cells in hypertrophic islet.(X500). Stage of pancreatico-secondary-adenocytoplasia.

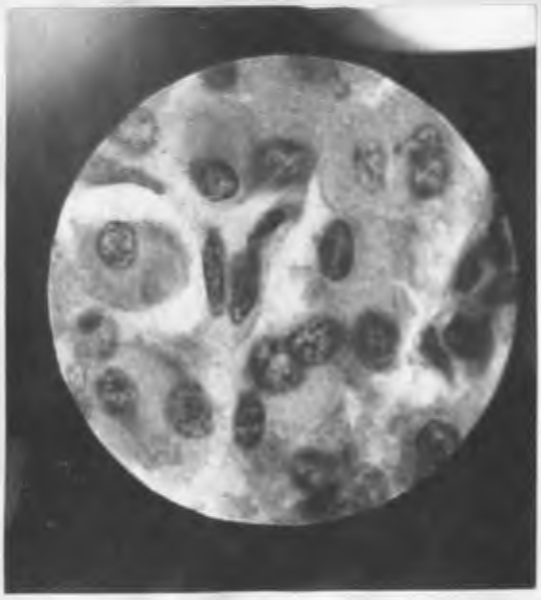

Fig. 33. (A50276). Oil immersion microphotograph of epithelial cells in hypertrophic islet (X1000). Stage of pancreatico-secondary-adenocytoplasia.

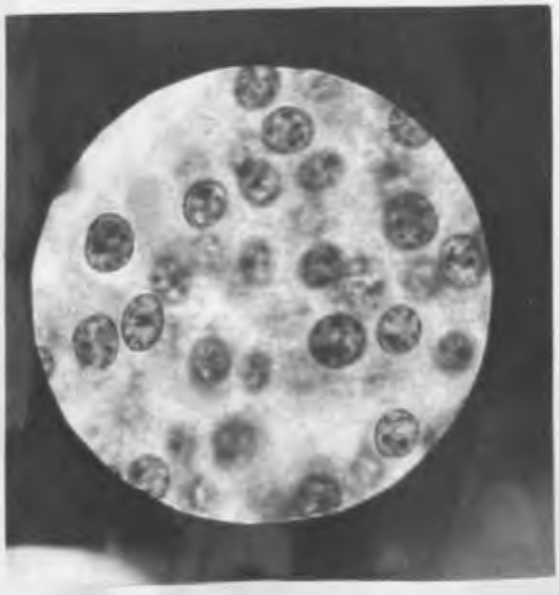

Fig. 34. (A50276). Oil immersion microphotograph of epithelial cells in hypertrophic islet (X1000). Stage of pancreatico-secondary-adenocytoplasia.

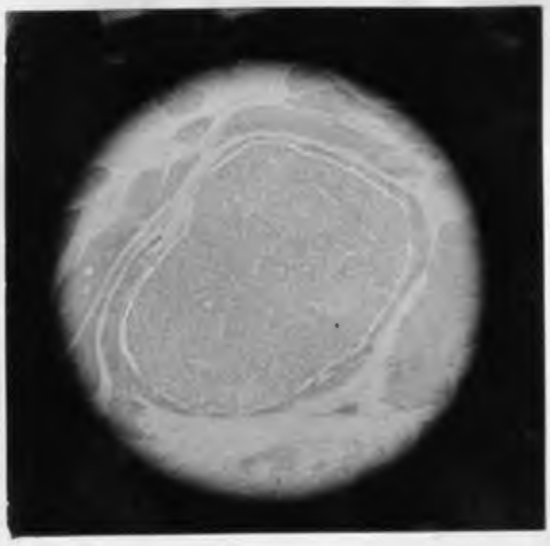

Fig. 35. (A26398). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule (X8). Stage of Pancreatico-tertiary-Adenocytoplasia.

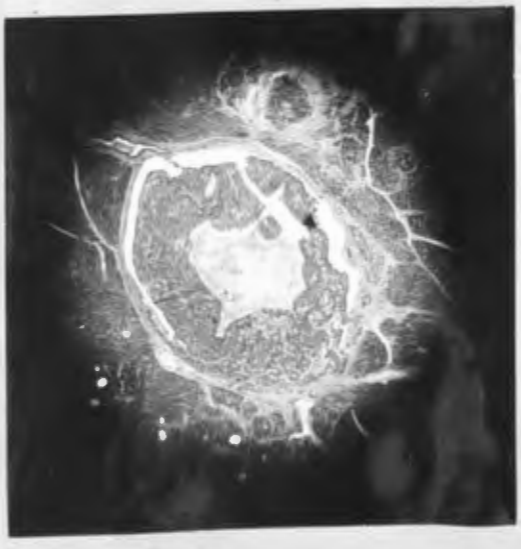

Fig. 36. (A26276). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule (X20). Stage of pancreatico-tertiary-adenocytoplasia.

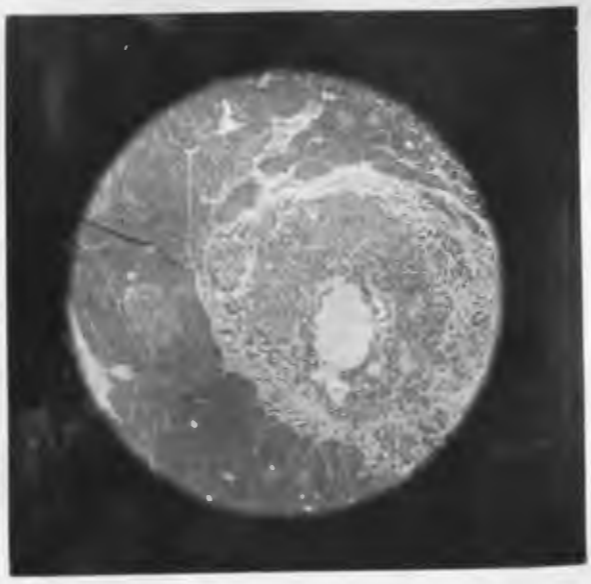

Fig. 37. (A50276). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule (X12). Stage of pancreatico-tertiary-adenocytoplasia.

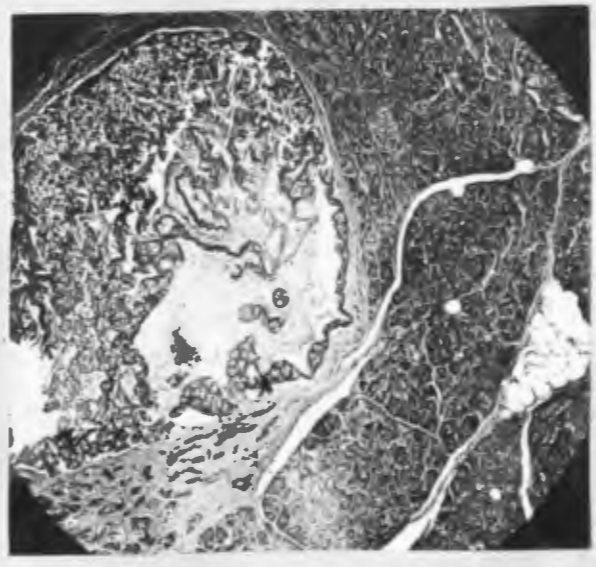

Fig. 38. (A50276). Microphotograph of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule (X8). Stage of pancreatico-tertiary-adenocytoplasia.

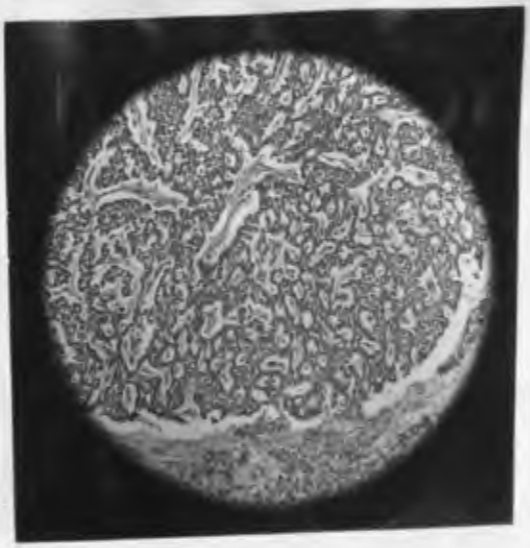

Fig. 39. (A26398). Microphotograph of periphery of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule (X50). Stage of pancreatico-tertiary-adenocytoplasia.

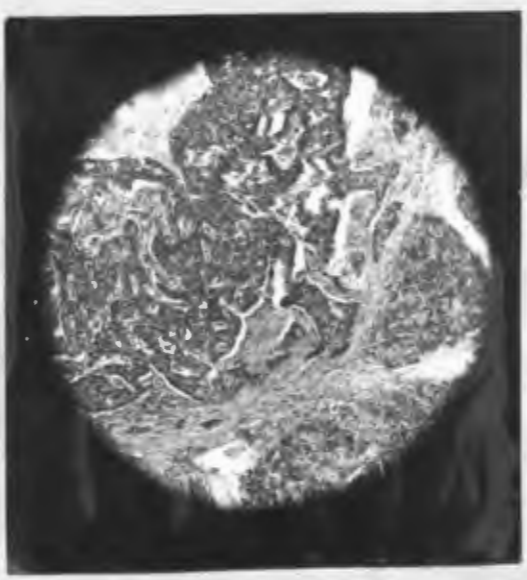

Fig. 40. (A50276). Microphotograph of periphery of islet showing hypertrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule (X50). Stage of pancreatico-tertiary-adenocytoplasia.

Fig. 41. (A50276). Microphotograph of periphery of islet showing hyperjrophic, hyperplastic epithelial cells with migration of these cells through connective tissue capsule(X50). Stage of pancreatico-tertiary-adenocytoplasia.

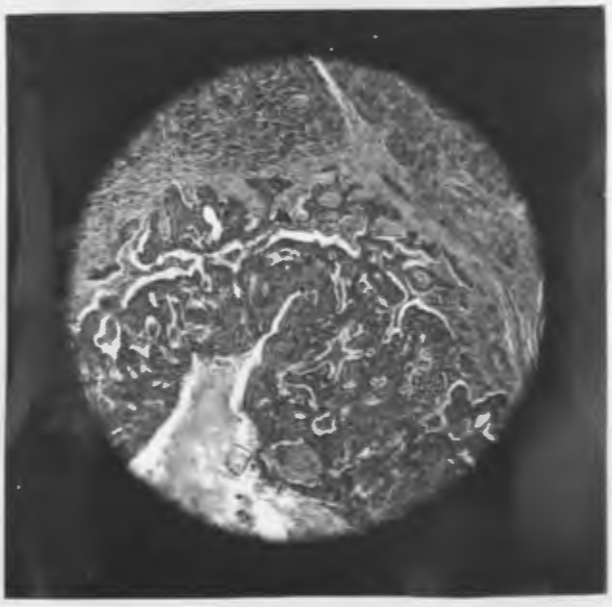

Fig. 42. (A50276) Microphotograph of periphery of islet showing hypertrophic, hyperplastic epithelial cells with migration of the cells through connective tissue capsule (X50). Stage of pancreatico-tertiary-adenocytoplasia.

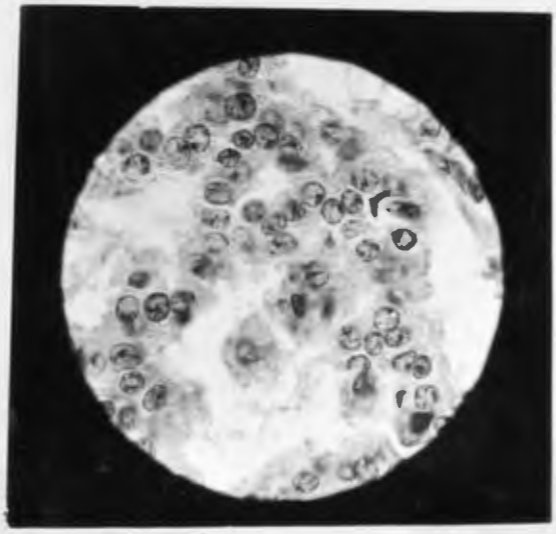

Fig. 43. (A26398). Microphotograph of islet cells showing hypertrophic, hyperplastic epithelial cells (X500). Stage of pancreatico-tertiary-adenocytoplasia.

Fig. 44. (A26398). Oil immersion microphotograph of islet cells showing hypertrophic, hyperplastic epithelial cells (X1000). Stage of pancreatico-tertiary-adenocytophasia.

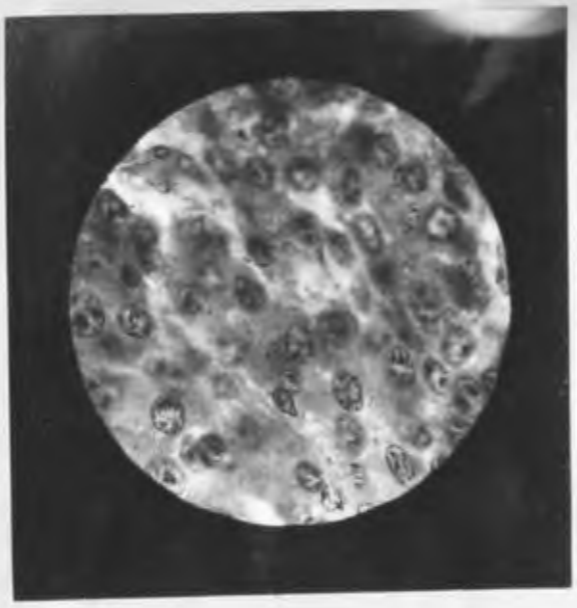

Fig. 45. (A50276). Microphotograph of islet cells showing hypertrophic, hyperplastic epithelial cells (X500). Stage of pancreatico-tertiary-adenocytoplasia.

Fig. 46. (A50276). Microphotograph of islet cells showing Hypertrophic, hyperplastic epithelial cells (X500). Stage of pancreatico-tertiary-adenocytoplasia.

Discussion

The islet areas in the pancreas were first described by Langerhans, who considered them to be nerve fibers. From the collective embryologic, cytologic, and histologic studies of later workers, foremost among them Renaut (quoted by Lane and Opie) Laguesse, Opie, Lane, Lewis, Thyng, Dewitt, and Bensley, it has been well established that the islets are, histologically, a definite epithelial unit of the pancreas developed from the epithelium of the primitive anlagen, without duct connection, with a rich capillary blood supply, and a hormone secreting function.

Hypertrophy of the islets, and adenomas of the islets, are the only precancerous conditions reported in the literature. Hypertrophy has been reported mostly in connection with diabetes. It is not characteristic of diabetes, however, nor is it to be found in all cases of diabetes. Nichols, Helmholtz, and Cecil have reported cases of a single hypertrophied islet in the pancreas. Nichols and Helmholtz each considers his case to be an adenoma while Cecil reports his case an an hypertrophy of the islet.

After reviewing the literature I find that most writers classify carcinoma of the pancreas either as alveolar or canalicular.

In 1903, Fabozzi reported his study of the pancreatic tissue taken from five patients who had died from carcinoma of the pancreas and tried to establish from these the histogenesis of carcinoma of the pancreas. His deduction is that all carcinomas of the pancreas have their origin in the islets. His illustrations are diagrammatic, and his descriptions are not sufficiently conclusive to be accepted by later writers.

It is not reasonable to assume that all neoplasms in a mixed gland, like the pancreas, originate in one only of its three epithelial units.

It is more logical to assume that a neoplasm may originate in any one of the epithelial units, the ducts, the acini, or the islets. From a biopathologic point of view the histogenesis of neoplasia of the pancreas should be studied in each of these. Under suitable pathologic conditions, each epithelial unit could be expected to produce undifferentiated cells from its germinative tissue; but the study must be made from the tissues which show the changes antecedent to carcinoma. When neoplasia is well advanced or has caused death, it is impossible to establish the site of origin or the successive pathologic changes from the tissue removed at operation or at necropsy; it is because pathologists have tried to prove the histogenesis from tissue removed at necropsy, after malignancy has caused death, that the histogenesis of carcinoma of the pancreas has not been established (Fig. 47). In a microscopic study of advanced carcinoma of the pancreas we find small masses of cells in the dense fibrous connective tissue. In their form and arrangement they may resemble small ducts, or acini, but if carefully scrutinized they will prove to be groups of degenerating cells. They are epithelial cells, but whether they are degenerating acinic cells or degenerating cells of neoplasia cannot be determined (Figs. 48 and 49).

The histogenesis of carcinoma of the pancreas must be studied from portions of the pancreas which are too small to be recognized in the gross specimen as carcinoma. For this reason I selected for the study of the early neoplastic changes a series of cases which show chronic inflammation. In the course of the investigation I found a definite hypertrophy and hyperplasia of the islets of Langerhans. This condition was found in about 25 per cent of the cases of chronic interacinar and interlobular pancreatitis which was associated with chronic gastric and chronic duodenal ulcer. In these hypertrophic islets hypertrophy, hyperplasia, and migration of the cells were observed.

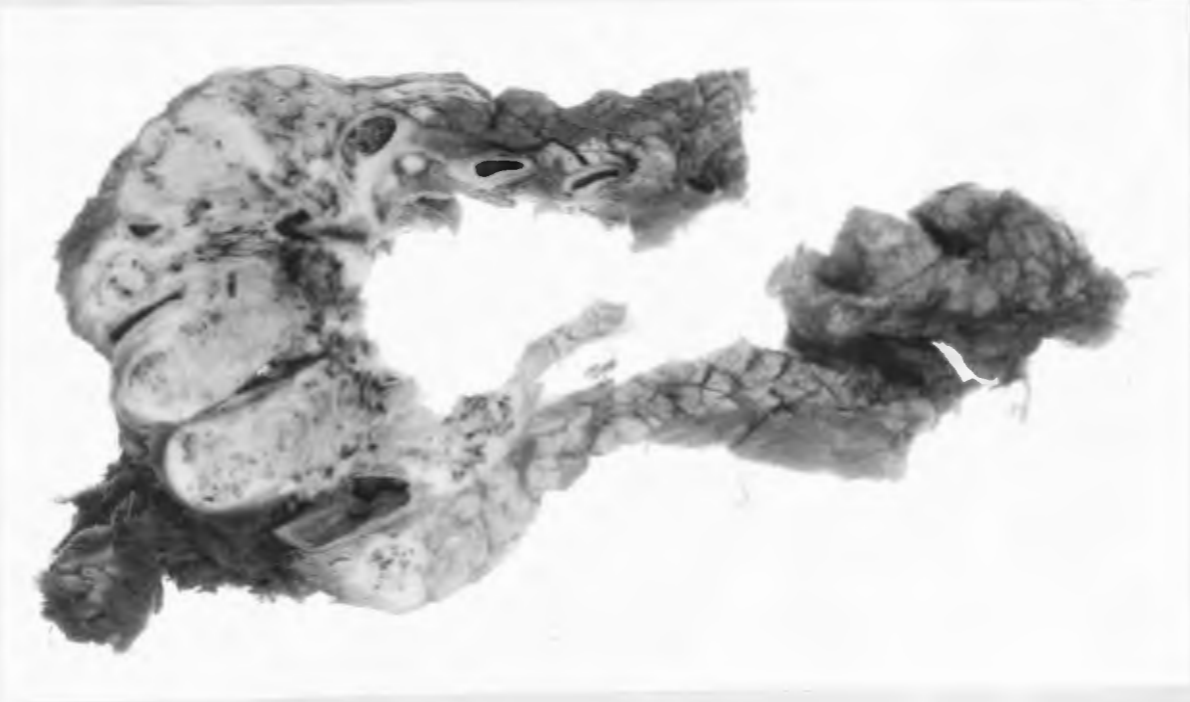

Fig. 47. (A142013, AuT 269-1915). Advanced carcinoma of pancreas.

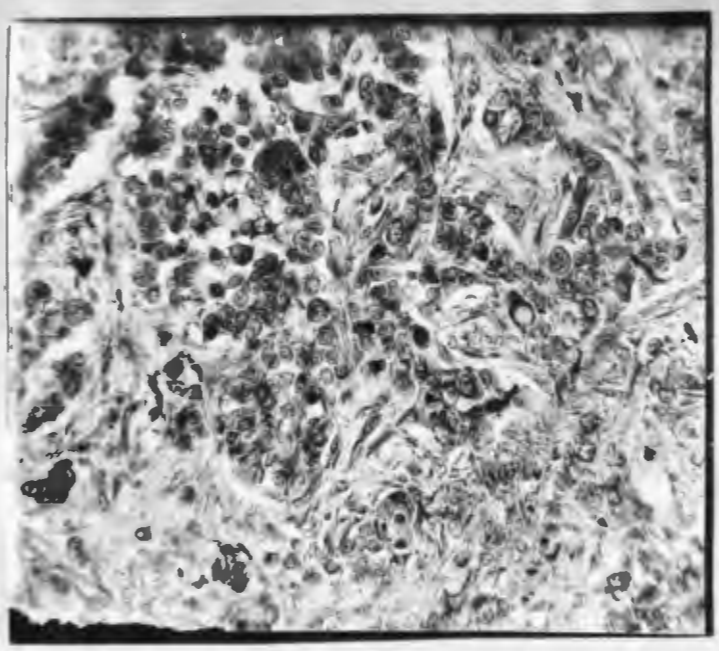

Fig. 48. (A142013, AUT 269-1915). Microphotograph of section from advanced carcinoma of pancreas showing degenerating epithelial cells in dense fibrous tissue (X250).

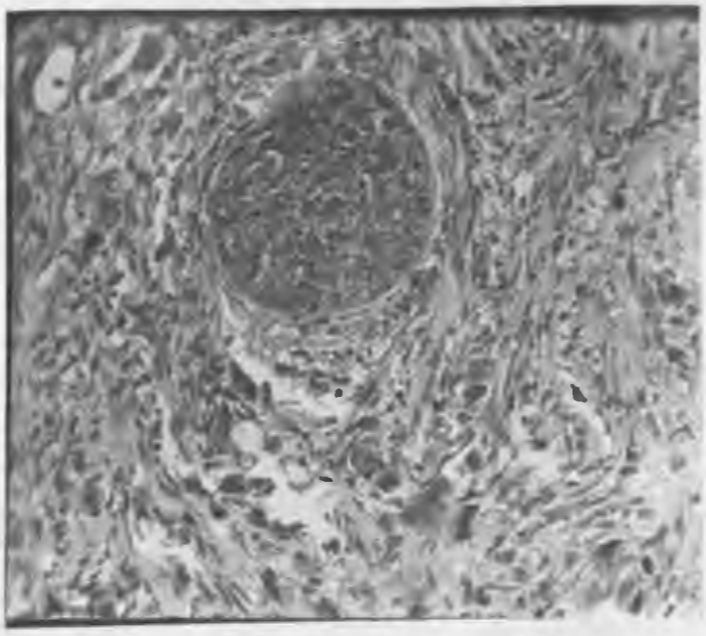

Fig. 49. (A142013 AUT 269-1915). Microphotograph of section from advanced carcinoma of pancreas showing fibrosis of islet (X250).

In the hypertrophic islets I found hypertrophic differentiated cells. Accompanying this cellular hypertrophy the connective tissue within and surrounding the islets had increased to protect the adjacent cells from encroachment.

In similar islets I sometimes found also hyperplasia of undifferentiated epithelial cells. These undifferentiated cells, however, are distinctly confined within the dense capsule of the islet.

In some of the hypertrophic islets I found hyperplastic undifferentiated cells migrating through the capsule, a condition which is undoubtedly carcinoma.

These three graphic descriptions apparently represent the stages of neoplasia as described by MacCarty in other epithelial tissues.

Simple fibrosis and sometimes hyalinized fibrosis were the only purely inflammatory reactions found in this series (Figs. 50 and 51).

The biologic reactions in the epithelial cells of the islets in the pancreas conform to those that have been observed in epithelial cells in other tissues. MacCarty has pointed out that each organ should be studied from the standpoint of each tissue; that each tissue must be considered alone from the standpoint of regeneration in all its phases; and that each phase should be named with a descriptive term applicable to that tissue; these biopathologic reactions of the epithelium of the islets in the pancreas might then be described as follows:

Pancreatico (Primary, Secondary, Tertiary) Adeno-cytoplasia

These descriptive terms are expressive of the successive biopathologic reactions in the regeneration of cells in neoplasia.

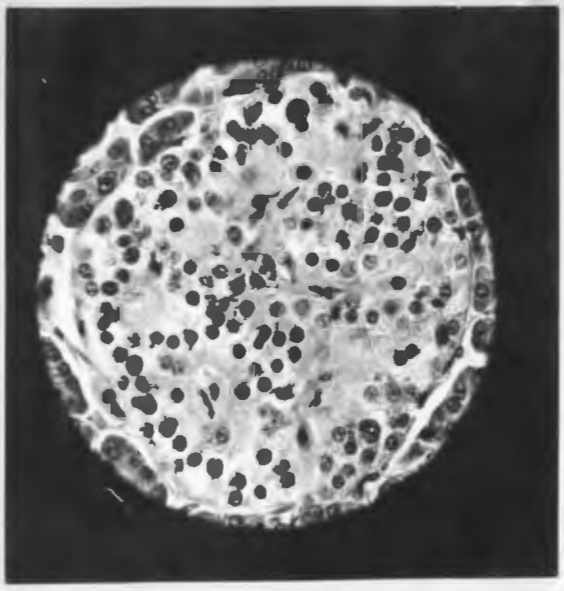

Fig. 50. (A122622). Microphotograph showing hyalinized fibrosis of islet. (X250).

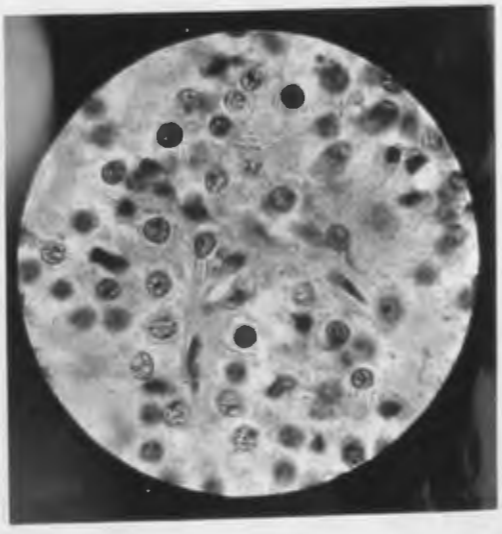

Fig. 51. (A122622) Oil immersion microphotograph of epithelial cells in hyalinized fibrosis of islet (X500).

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