



# **TUMORS OF THE PANCREAS**

Virginia Kneeland Frantz, M.D.

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ARMED FORCES INSTITUTE OF PATHOLOGY

# ATLAS OF TUMOR PATHOLOGY

Section VII—Fascicles 27 and 28

## TUMORS OF THE PANCREAS

by

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Published by the  
ARMED FORCES INSTITUTE OF PATHOLOGY  
Under the Auspices of the  
SUBCOMMITTEE ON ONCOLOGY  
of the  
COMMITTEE ON PATHOLOGY  
of the  
DIVISION OF MEDICAL SCIENCES  
of the  
NATIONAL ACADEMY OF SCIENCES—NATIONAL  
RESEARCH COUNCIL  
Washington, D. C.

1959

Accepted for Publication January 1959

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For sale by the American Registry of Pathology  
Armed Forces Institute of Pathology  
Washington 25, D. C. - Price — \$1.50

# ATLAS OF TUMOR PATHOLOGY

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UNITED STATES VETERANS ADMINISTRATION

## ACKNOWLEDGMENTS

Appreciative acknowledgment is made to the members of the Subcommittee on Oncology of the Committee on Pathology, Division of Medical Sciences, National Research Council for their helpful suggestions.

My many colleagues at the Presbyterian Hospital have also offered constructive criticism for which I would like to express my appreciation.

Drs. Mary Oldt, May Sherman, Helen M. Scoville, and Catherine W. Blumberg have been of great assistance during the somewhat prolonged preparation of this fascicle, and should be thanked not only for their editorial suggestions but for their patience.

Appreciative acknowledgment is also made for materials received from the following contributors:

Dr. D. H. Andersen, New York City.

Dr. W. F. Becker, New Orleans, La.

Department of Pathology, College of Physicians and Surgeons, New York City.

Department of Pathology, Presbyterian Hospital, New York City.

Dr. S. Dobkevitch, Paris, France.

Dr. A. A. Eggston, Bronxville, N. Y.

Dr. Graham Knox and Dr. L. C. Knox, New York City.

Dr. M. M. Melicow, New York City.

Dr. T. G. Morrione, Long Island, N. Y.

Dr. F. W. Stewart, New York City.

Dr. A. P. Stout, New York City.

Permission to use copyrighted illustrations has been granted by:

American Association of Pathologists and Bacteriologists:

Am. J. Path., 14:125-134, 1938. For fascicle figures 42, 49, 52

Department of Cancer Research of Columbia University:

Am. J. Cancer, 25:98-107, 1935. For fascicle figures 62-65

J. B. Lippincott Co.:

Ann. Surg., 101:1299-1335, 1935.

For fascicle figures  
41, 45, 48, 50, 51,  
and plate I-B

112:161-176, 1940.

For fascicle figures  
68-70, 73-75

119:824-844, 1944.

For fascicle figures  
47, 53-58

121:847-852, 1945.

For fascicle figures  
84-86

Franklin H. Martin Memorial Foundation:

Surg., Gynec. & Obst. (abst.), 90:417-455, 1950. For chart

The author wishes to express sincere thanks to Mrs. Jean McGuire Scherschel and Mrs. Margaret Dugo for their help in compilation of the figures and bibliography of the manuscript. Mrs. Scherschel also was of great assistance in correlating biopsy and autopsy diagnoses of pancreatic lesions.

Unless otherwise acknowledged, the illustrations are the author's. The A. F. I. P. accession numbers are used for identification of negatives at the Armed Forces Institute of Pathology.

### **DEDICATION**

The author wishes to express her great indebtedness to Dr. Allen O. Whipple and to Dr. Arthur Purdy Stout. Without the inspiration of the former and the patient guidance of the latter, this fascicle could not have been written. It is dedicated, therefore, to these two outstanding figures in surgery and surgical pathology with whom the author has been associated for 38 years as student, collaborator, and friend.

**Virginia Kneeland Frantz**

# TUMORS OF THE PANCREAS

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# TUMORS OF THE PANCREAS

## INTRODUCTION

It is not possible to interpret tumors of the pancreas without keeping constantly in mind the gross and microscopic anatomy of the organ with its possible variations, true anomalies, and heterotopias. When the pancreas, or a part, is surgically resected and the sought lesion not detected by gross or microscopic inspection, the surgical pathologist's value as a consultant in the solution of the clinical problem depends in part on his knowledge of anatomy and physiology.

### Anatomy

The size of the pancreas is subject to considerable variation, but in the adult it is somewhere between 12 and 15 cm. in length, between 1 and 3 cm. in thickness. The weight is variously quoted as between 60 and 125 gm.

The pancreas tapers from its head, the thickest portion of the organ lying in the curve of the duodenum, to its tail, which extends to the gastric surface of the spleen. A constriction, the neck, grooved by the gastroduodenal artery, separates the head from the body, but there is no such sharp demarcation between the body and tail. The posterior surface of the organ, except for the tail, is devoid of peritoneum; the head is in close approximation posteriorly to the vena cava and the renal veins; the body is in contact with the aorta, the splenic veins, the left kidney and its vessels, the left adrenal, and the origin of the superior mesenteric artery. These anatomic considerations concern the surgeon faced with removal of a part or the whole of the organ and the pathologist for routes of spread of disease. They should be borne in mind when a biopsy and frozen section diagnosis are requested as a guide to immediate surgical procedure.

There is also an uncinate process of the pancreas which extends downward from the lower left lateral border of the head; this may actually encircle the portal vein and make adequate cancer surgery impossible. The so-called "annular pancreas" is usually asymptomatic and found as an anomaly at autopsy, but can, when diseased, give symptoms such as those of duodenal or common duct obstruction requiring surgical intervention. It is sometimes wrongly considered neoplastic. Payne found 57 cases in the literature. To the 17 surgical cases, he added one more in which the duodenum was completely encircled. The anomaly becomes apparent clinically, not only because of obstructive symptoms, but in association with symptoms of acute or chronic pancreatitis, peptic ulcer, and gastrointestinal hemorrhage.

The gross anatomy of the lymphatic drainage of the human pancreas must likewise concern both surgeon and pathologist. Evans injected the lymphatics of the pancreas with India ink suspension in 30 human cadavers. This enabled him to observe the order in which the regional nodes were filled. As a result he has proposed the following classification based upon this order of filling: (1) suprapancreatic; (2) intrapancreatic; (3) superior mesenteric; (4) mesocolic; (5) splenic, hilar; (6) pancreaticoduodenal; (7) infrapyloric; (8) gastrohepatic; (9) juxta-aortic (left lateral aortic; interaorticocaval; preaortic—includes nodes about the celiac axis). These are the nodes which, if proven to be involved, are the basis for the surgeon's decision that a given case of primary carcinoma is or is not operable from the standpoint of possible removal of all disease.

The excretory duct system in general consists of the main pancreatic duct; this passes from the head of the pancreas into the duodenum with the common bile duct through a common orifice, i.e. in an ampulla in the papilla of Vater, which is on the inner side of the descending portion of the duodenum. The openings are sometimes separate. An accessory duct, the duct of Santorini, which springs from the duct of Wirsung, may open separately into the duodenum, 2 to 3 cm. above the papilla of Vater. These variations are important considerations in determining the possible sites of obstructive lesions.

Die Bauchspeicheldrüse, pancreas in German, actually means the salivary gland of the abdomen, but it is softer in texture than the salivary glands and is not enclosed in a distinct capsule. The areolar tissue surrounding it dips between the lobules which are determined by the arborizations of the main duct. In this areolar tissue, not only in the retroperitoneal aspect of the organ but also in the properitoneal tissue, there are a surprising number of large autonomic nerve trunks. These are so numerous that they almost characterize peripancreatic tissue. When only a small biopsy is taken of an obviously inoperable retroperitoneal neoplasm, pancreatic origin may be suspected by the surgical pathologist if he finds large nerves in the tissue, even though the microscopic sections show no pancreatic parenchyma.

The arborizations of the duct system extend from the main pancreatic duct as interlobular branches. These run in the interlobular connective tissue in which ganglion cells can also be found, as well as the nerve trunks already mentioned. Mucous glands are sometimes found in association with the large ducts. Mucin-secreting cells are also seen among the columnar cells lining the larger ducts, and occasionally ciliated cells are also found.

The smaller branches of the ducts enter the lobules as the intralobular ducts; the tall columnar epithelium becomes low columnar, then cuboidal, and finally, in the interacinar or centroacinar ducts, changes from low cuboidal to almost flat epithelium. The cells of the duct system contain no zymogen granules. The flat cells of the terminal ductules, called centroacinar cells,

are probably the origin of certain types of cystadenomas. These can be mistaken for lymphangioendotheliomas when the epithelial nature of the flat lining cells is not recognized.

The acini which manufacture the exocrine secretion of the pancreas are lined by cells, usually described as pyramidal, resting on a basement membrane. The acinar lumen is usually small. In the luminal pole of these acinar cells there are coarse granules, called zymogen granules. These vary in number with the phase of digestion and accumulate during fasting. The nucleus is basally placed, and the cytoplasm of the basal pole of the cell is basophilic, in contrast to the acidophilic granular staining at the apex. The basal pole often shows striations which are sometimes confused with mitochondria. Centroacinar cells are sometimes seen in the lumen of an acinus. The nature of the acinar cells has been studied by inducing changes with various agents. Selective pancreatic acinar destruction with ethionine has been reported (Elman and Wheat).

The islets, or islands of Langerhans, constituting the endocrine portion of the pancreas and known to secrete insulin, are also held responsible for an increasing number of hormones, some controversial. The islets are rounded masses of cells irregularly dispersed in the parenchyma, which vary in number in different portions of the gland, usually being most numerous in the tail. The islet size varies also. The structure is a cordlike or ribbon-like arrangement of the islet cells, sometimes difficult to make out, between which are capillaries with their endothelial lining cells in close apposition with the secreting cells. This "ribbon" pattern is more pronounced when there is hypertrophy and hyperplasia of islets and also, sometimes, in neoplasms. Islets may also lie in the connective tissue septa and occasionally in the peripancreatic areolar tissue, especially in the region of the tail.

By special technics it can be demonstrated that the normal islets are composed of at least two distinct types of granular cells in man. The Beta cells are more numerous and are somewhat centrally placed; they are thought to produce insulin, and can be selectively degranulated or destroyed in experimental animals by mesoxalyl urea (alloxan), thus rendering the animals diabetic. The Alpha cells are less numerous, more peripheral and therefore more closely applied to the capillaries; to these have been attributed variously the property of differentiating into Beta cells or of being responsible for other internal secretions such as glucagon, lipocaic, vagotonin, or a cicatrizing factor.

A third cell, designated as D, is usually described as clear, or at best very finely granular. It has been thought to be intermediate between Alpha and Beta cells or to be responsible for some of the other hormones. It is said to be absent in embryo and early infant tissues. As Verne and Théret point out, the increasing number of new pancreatic hormones is in excess of the cell types. In the guinea pig, clear cells designated as C have been

described. Other cells not found in man are also described, E in the opossum, X in the horse.

In general the Alpha cells contain numerous fine granules which stain brightly with red dye; the Beta cells have less numerous coarse basophilic granules and less clear cell membranes. The classical work of earlier investigators, particularly that of Lane and of Bensley, in the differentiation of Alpha and Beta cells still stands, although Laidlaw pointed out (p. 129) "...there is nothing characteristic about the nuclei which distinguishes one of these cells from the other." For special staining methods, the Gomori stain and its modifications are widely used. However, these stains have given much more consistent results in animal than in human pancreatic tissues (probably because of the better possibility of immediate fixation of fresh tissue not traumatized by operative handling) and are, in most hands, unreliable in islet neoplasms, whether or not these are clinically functional. Verne and Th  ret reviewed the whole subject of tinctorial and experimental methods for differentiating these cells, normal and neoplastic.

It has often been suggested that Alpha and Beta cells represent different phases of secretory activity, and according to Sergeyeva the numerical proportions can be altered by suitable stimuli. On the other hand, the specificity of the granulations in the Beta cells seems established by their hydropic degeneration in diabetes, presumably an exhaustion phenomenon which can be reversed by administration of insulin, and also by their reaction to alloxan.

The difficulty of differentiation of cell types is further complicated by the possibility that all types of islet cells and acinar cells can originate from fully-differentiated duct epithelium. This possibility is widely accepted as such, particularly by students of islet-cell neoplasms. Bensley thought that certain cells in the excretory ducts are totipotent. Proliferation of islets from duct epithelium has been observed—in infants born of diabetic mothers—by Bakay, who also reported regeneration of islets in a study of 30 adult pancreases in patients who had suffered from true diabetes, pancreatitis, and pancreatic sclerosis (figs. 37–39). He concluded that the "origin of these islands from ducts could be safely assumed." This makes the classification of neoplasms of the pancreas difficult, particularly in the cases of tumors not associated with hyperinsulinism.

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### Heterotopia

**SYNONYMS AND RELATED TERMS:** Aberrant pancreas; adenomyoma; Brunner's adenoma; choristoma; myo-epithelial hamartoma; supernumerary pancreas.

**NATURAL HISTORY.** The frequency of asymptomatic heterotopic pancreatic tissue in routine autopsies varies with the diligence of the search (Pearson). Barbosa and associates in 1946 reviewed the literature, from the year 1727 to March 1944, and found approximately 430 cases. To these they added 41 authentic cases from the Mayo Clinic, 25 of which were considered clinically significant.

Busard and Walters, in their 1950 statistical review, included the 43 unauthenticated cases excluded by Barbosa and associates, 28 additional cases reported by various authors from 1946 to 1948, and 1 case of their own, a total of 72 cases.

Benner in 1951 added 5 cases to the 149 involving the stomach; Pearson, also in that year, made a comprehensive review of the literature, and added 46 cases to the total. From the various autopsy series, he concluded that the incidence of heterotopic pancreatic tissue is approximately 1 to 2 percent.

Feldman and Weinberg stated that the subject had been neglected, and after diligent search in 1952, reported 33 cases of accessory pancreas in the duodenum (12.5 percent) from 265 consecutive adult necropsies and 22 cases (15 percent) from 145 infant necropsies.

Material from 70 surgical cases and 24 autopsies of Columbia-Presbyterian Medical Center has brought the total to 743 cases of accessory pancreatic tissue reported. Review of its records of 9,158 consecutive autopsies over a period of 45 years, to August 1, 1952, showed only 24 cases (0.26 percent) of accessory pancreatic tissue listed.

One form of heterotopia which has no clinical significance as far as the pancreatic elements are concerned (except for the possibility of extrapancreatic insulin-producing neoplasms, a great rarity to be discussed later) is pancreatic tissue occurring in teratomas. Schlumberger, reporting 16 mediastinal teratomas, found pancreas in 6 of the 10 benign and in 1 of the 6 malignant teratomas studied. In 30 cases of ovarian teratomas also studied by this author,

no pancreatic tissue was found; nor in 150 testicular teratomas reviewed by the staff of the Armed Forces Institute of Pathology. In 5 of the 6 instances of pancreatic tissue in the benign teratomas it was grossly recognizable, and the architecture of normal pancreas was present. In the one case of pancreatic tissue in a malignant teratoma, the pancreatic ducts, acini, and islets were all present. Schlumberger discusses the theories of genesis. It is conceivable that evidence of function of the heterotopic islet cells in such teratomas may one day be found, as it apparently has been in thyroid tissue in ovarian teratomas, i.e. "struma ovarii."

Clinical interest in the subject has been far greater in recent years, because of more frequent and meticulous study of the stomach and duodenum by x-ray, and also because of the search for other possible sites of functional islet cell neoplasms in cases of hyperinsulinism when no tumor is found in the pancreas itself. Barbosa and associates report that in clinical material, aberrant pancreas is found in 1 of every 500 upper abdominal operations.

X-ray studies are concerned chiefly with lesions of the stomach. In 1951 Benner stressed the moundlike elevation of the mucosa with the central depression, which he likened to a pseudodiverticulum. This depression, in my experience, only occurs when there is a considerable mass of tumor tissue in the submucosa, with fairly good-sized ducts opening into the stomach or duodenum. In suitable projections in gastrointestinal x-ray series, a fleck of barium may be seen in the projection. This almost clinches the diagnosis. However, as hemorrhage can occur from these lesions—Hudock and associates have reported a very dramatic case—and as no neoplasm of the stomach should be considered benign until so proven histologically, most surgeons feel obligated to operate to remove the tumor, however favorable the x-ray interpretation (see illustrations, pp. 28 and 29 in the fascicle "Tumors of the Stomach").

Common sites for pancreatic aberrant tissue reported in recent reviews of the literature and based on approximately 65 cases are: 24 to 27 percent in the stomach, 30 percent in the duodenum, 13 to 18 percent in the jejunum, 3 to 5 percent in the ileum, and 3 to 6 percent in Meckel's diverticulum. The Presbyterian Hospital series of 94 cases agrees with these figures, except for a 53 percent occurrence in the duodenum.

Other sites are: gallbladder; cystic and common bile ducts; mesentery, omentum, and transverse mesocolon; vicinity of pancreas and teratomas of the mediastinum. I have seen heterotopic pancreatic tissue in association with gastric mucosa in an enterogenous cyst in the mediastinum. The liver as a site of heterotopia appears once in every review since 1941. This is on the basis of a single case reported by Ballinger, about which I feel obligated to express doubt again (table III, Porter and Frantz). The case should have been listed as carcinoma of aberrant pancreas but not of "aberrant pancreas in liver." Dr. Allen O. Whipple originally explored this case, because of hyperinsu-

linism, at the Presbyterian Hospital (Frantz). At this time the malignant islet cell tumor was thought to originate just above and separate from the head of the pancreas—a not unusual site for aberrant pancreatic tissue. At the time of this operation there was already extension to the liver. At autopsy, this organ was found to be so extensively involved as to suggest primary hepatic origin of the carcinoma. No other instance of heterotopia of this kind in the liver has been reported, as far as can be ascertained; this adds to doubt that the anomaly exists.

In a series of heterotopias (Barbosa et al.), the sex ratio was 3:1 males to females. In 70 surgical and 24 autopsy cases at the Presbyterian Hospital, it was nearer 2:1. Of the 41 cases authenticated by histologic examination, which Barbosa and associates added to those already reported in the literature, 25 were of clinical significance. Of the 70 Presbyterian Hospital surgical cases, in only 11 was the exploratory operation done for the heterotopic mass. In appropriate sites, there may be various symptoms such as those of pyloric obstruction (some gastric tumors having even protruded as polypoid tumors into the duodenum), intestinal obstruction, common duct or pancreatic duct obstruction, pancreatitis, and hemorrhage, the last especially from aberrant tissue in Meckel's diverticula in association with heterotopic gastric mucosa.

When the heterotopic tissue is in the gastrointestinal tract, it is situated in the submucosa in about half of the cases (figs. 1, 2). However, the main mass can also be in the muscularis, and occasionally it is even subserosal. The tissue is not encapsulated and is sometimes patchily distributed in multicentric foci. Frequently in the stomach or duodenum it appears to be in a diverticulum or a pseudodiverticulum. Pearson points out that the tissue in the muscularis may weaken this coat and so give rise to a diverticulum.

**GROSS PATHOLOGY.** These tumors, when single, are characteristically fairly firm, circumscribed, sometimes lobulated and yellowish white, the color depending on the amount of acinar tissue present. The umbilication on the summit of those in the gastrointestinal tract—already described—can be mimicked by ulceration so frequently seen in leiomyomas, and occasionally seen in glomus tumors of the stomach and in carcinoids which present in the lumen of the stomach or intestine, although carcinoids are much more frequently found in the outer coats. The aberrant pancreatic masses vary in size from those which measure only a few millimeters (usually incidental findings) up to 4 to 5 cm. in greatest dimension.

In the stomach, the most frequent site is in the vicinity of the pylorus. In my experience, none has been found in the fundus. When the tissue is in very close proximity to the pylorus, the ducts may extend beyond it into the duodenum. However, if the tissue is composed only of ducts and Brunner's glands, with no recognizable acinar or islet tissue, i.e. "Brunner's adenoma," perhaps it should not be considered a pancreatic heterotopia but rather an adenoma of the duodenal glands. The most recent review of the stomach

## HETEROTOPIC PANCREATIC TISSUE IN DUODENUM

(Figures 1 and 2 are from the same case)

Figure 1. Low power photomicrograph of the wall of the duodenum showing irregular masses of pancreatic tissue in the submucosal and muscular coats. There is no ulceration of the duodenal mucosa, and ducts cannot be seen at this magnification.

The patient, a 20-year-old man, entered the hospital with atypical gastrointestinal symptoms. Under the fluoroscope a radiolucent defect was seen in the duodenal bulb which could not be dislodged on palpation. It was round and sharply demarcated. At operation a mass was found on the posterior aspect of the duodenum, which measured approximately 1 cm. in diameter. The mass was excised and immediate frozen section diagnosis was made. S.P.\* A-27793; A. F. I. P. Acc. No. 218895-1.

Figure 2. Higher power photomicrograph showing the islet tissue in the aberrant pancreas.

(This finding often depends on taking more than one section of the tumor.) A small duct can also be seen. Some heterotopias of aberrant pancreatic tissue show little if any islet tissue and consist chiefly of acini and ducts. There is often a central depression at the point where large ducts open into the stomach or the duodenum. S.P. A-27793; A. F. I. P. Acc. No. 218895-2.

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\*In this and in the following legends, S. P. stands for Surgical Pathology, Presbyterian Hospital, New York City.

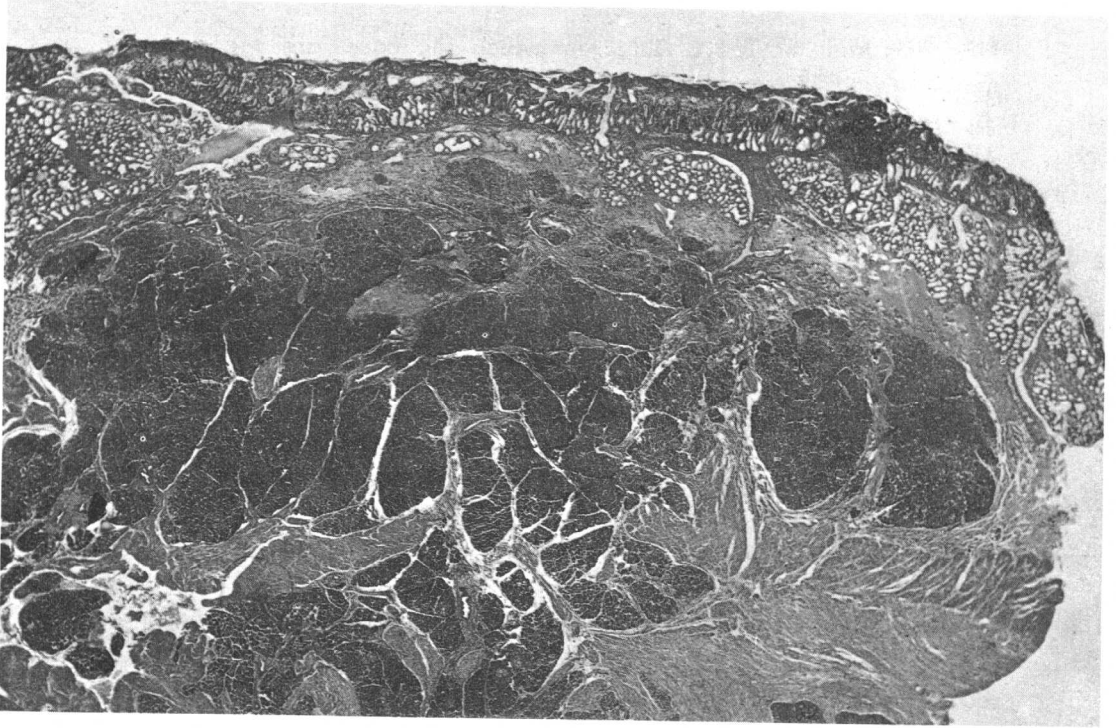


Fig. 1

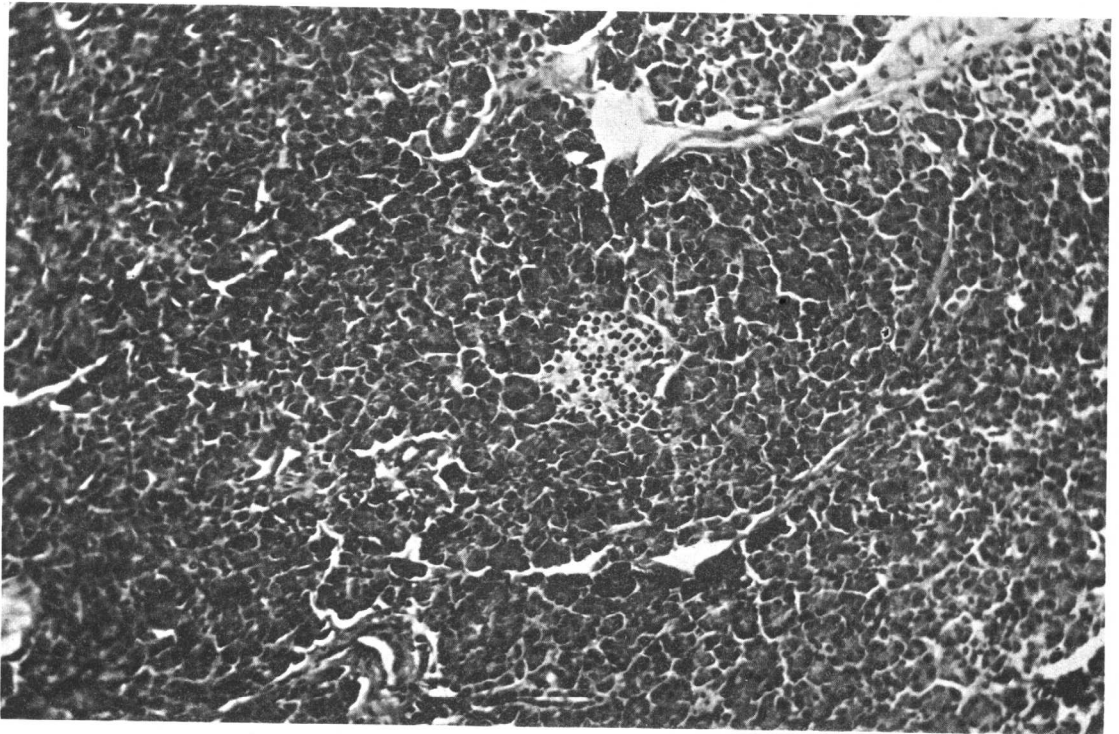


Fig. 2