THE PATHOGENESIS OF POLYCYSTIC PANCREAS
RECONSTRUCTION OF CYSTIC ELEMENTS IN ONE CASE *

ROBERT F. NORRIS, M.D.,† and RALPH M. TYSON, M.D.

(From the Ayer Clinical Laboratory and the Pediatric Service, Pennsylvania Hospital, Philadelphia, Pa.)

Polycystic disease of the pancreas has not been recognized at autopsy so frequently nor studied so widely as polycystic disease of the kidney. Although variation in the character and distribution of the lesions is great, "fibrocystic disease" of the pancreas, as it is often called in the pediatric literature, is a well recognized entity in infancy. Essentially the pancreatic ducts are characteristically distorted and segmented. Some of the segments are atrophic, others are dilated and cystic. Many of these cysts may be isolated. The main pancreatic duct may or may not be atretic. Much of the glandular tissue is atrophic or is replaced by proliferating fibrous tissue and scar tissue accompanied by varying amounts of acute and chronic inflammatory exudate. The amount of fibrous stroma is often greater than is the case in polycystic disease of other organs. Squamous metaplasia of the ducts of varying degrees is often observed. Although some of the ducts are dilated and cystic, the disease is rarely characterized by diffusely distributed and large cysts. For this reason, it has not always been clear to authors reporting such cases that the disease is similar to polycystic disease of other organs. Yet the frequent association of cystic fibrosis of the pancreas with polycystic disease of the kidney, liver, and lung indicates that the lesions are essentially identical in etiology if not in morphology.

When the lesions are manifest in infancy, steatorrhea and malnutrition are often conspicuous symptoms, and are evidently the result of deficiency or absence of the external secretion of the pancreas. Since the disturbances of metabolism are usually profound and fatal, the early death of most of these children probably accounts for the rarity of extensive polycystic lesions of the pancreas in adults.

The clinical importance of polycystic disease of the pancreas was reviewed by Andersen,[1,2] and additional reports more recently have been made by Rauch, Litvak, and Steiner,[3] Oppenheimer,[4] Robbin and Bernhard,[5] Wolman,[6] Daniel,[7] Snelling and Erb,[8] Kennedy and Baggenstoss,[9] and Menten and Middleton.[10] Although the etiology of the

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† Now at the William Pepper Laboratory of Clinical Medicine of the University of Pennsylvania, Thirty-sixth and Spruce Streets, Philadelphia 4, Pa.

lesions is discussed, these papers are concerned more with the clinical aspects of the disease and the frequently associated cystic lesions of the lung than with pathogenesis. In the past, however, careful microscopic studies to determine the cause of the lesions have been made, but agreement on the pathogenesis is lacking. Reviews of the earlier literature may be found in the papers of Sears,[11] Teuscher,[12] Bartoli,[13] Rümler,[14] and Pazzagli.[15]

In general, like polycystic liver, the polycystic lesions of the pancreas have not been so thoroughly studied by means of models as have those in the kidney. The various theories of causation suggested for polycystic kidney have also been proposed for the congenital lesions of the pancreas. By some, therefore, it is held that chronic inflammation and proliferation of fibrous tissue is the fundamental lesion and causes obstruction, segmentation, and cystic dilatation of the pancreatic ducts. Although inflammation is almost always present in the polycystic pancreas, there are many cases of polycystic liver and kidney in which it is absent. By others it is assumed that failure of the two anlagen of the pancreas properly to unite may cause obstruction of the proliferating ducts and cystic dilatation of the segments. Functionally and anatomically, however, these anlagen are not analogous with those of the kidney. In addition, the theory fails to explain the occurrence of polycystic lesions of the liver and lung which are not formed by the fusion of separate anlagen. Finally, the most commonly held theory among the older German writers is the concept of Albrecht [16] that an abnormal tumorlike proliferation of epithelial and fibroblastic tissue results in faulty development of the organ. Although in many instances of polycystic disease the epithelium and fibrous stroma may have the appearance of excessive proliferation, there is nothing characteristically neoplastic about the tissue.

A different approach to the problem of polycystic disease was that of Kampmeier [17-20] and McKenna and Kampmeier [21,22] who demonstrated that the first generations of nephrons in the normal kidney are provisional and who suggested that persistence of these provisional elements would explain the occurrence of polycystic kidneys. Recently, cystic disease of the kidney and liver were studied by Norris and Herman [23,24] and Norris and Tyson,[25] respectively. By means of serial sections and reconstructions it was demonstrated that the general development of organs in the presence of polycystic disease is remarkably normal and continued normal differentiation of many epithelial elements occurs simultaneously with distortion, segmentation, and cystic dilatation of others which are fully formed. This observation suggests that a "hamartoma" is not the fundamental cause and that defects occur only after the structural units of an organ are differentiated. In the kidney

it was not determined whether the segmentation was confined to the collecting ducts or included the uriniferous tubules as well. In the liver, however, only the small intrahepatic bile ducts were segmented and cystic. It was concluded that, since early generations of nephrons and intrahepatic bile ducts normally become segmented and then are resorbed, polycystic disease is an extension of this normal process of degeneration which includes a greater number of elements than normally. Instead of complete resorption, however, many of the epithelial segments persist to form the isolated cysts of polycystic disease. The cause of this abnormality is still problematical.

In continuance of the study of polycystic disease, we have reconstructed elements of a cystic pancreas in order to determine whether this theory is also applicable to other organs. This pancreas is from case 2 previously reported by Norris and Herman [24] and Norris and Tyson [25] in which case the kidneys and liver were also cystic. Although there were no dilated cysts in the kidney, liver, or pancreas, this case has been selected as previously indicated because it is believed that the lesions represent an early stage of polycystic disease and that a proper evaluation of the essential defect can be obtained only by a study of the disease in its incipiency.

Materials and Methods

Briefly, the patient was a full-term infant who died 24 days after birth following the onset of a hemorrhagic diathesis, jaundice, and evidence of renal failure. Sixth digits of both hands were amputated after delivery. In the preceding papers [24,25] the clinical history, anatomic diagnosis, and pathologic findings in the kidneys and liver were described and will not be repeated. Only the gross and microscopic lesions of the pancreas will be presented at this time.

The tissues were fixed in Kaiserling's and Regaud's solutions. Blocks were embedded in paraffin and sections were stained with Delafield's hematoxylin and eosin. Sections for ordinary study were cut at 5 μ. In addition, several hundred serial sections, 15 μ in thickness, were cut at right angles to the long axis of the pancreas from three blocks about 2 cm. on a side. These were taken from the head, body, and tail, respectively. The cystic pancreatic ducts were traced and studied microscopically in the serial sections and some of them were reconstructed by the method previously described.[23]

GROSS EXAMINATION

At autopsy the pancreas was not weighed or measured but was described as uniformly enlarged. The contours were entirely normal and the position of the organ in the body was normal. On section, the main

pancreatic duct and its orifice were not identified. Only scattered, small, irregular, tubular and cystic ducts were present in the stroma. The parenchyma was fibrous, pale, and slightly mottled. There were no large cysts.

Microscopic Examination

In blocks from the head, body, and tail, the microscopic findings were similar. There were scattered lobules of acini, which were normally formed and were frequently located at the periphery of the pancreas. Individually the epithelial cells were smaller than is normal and appeared atrophic. Nearly all of the small pancreatic ducts in these areas were irregular and slightly dilated. Many of them contained inspissated débris resembling coagulated protein. The ducts were lined by single layers of flattened or cuboidal epithelium (Fig. 1). The epithelium of some of the ducts was duplicated and some showed varying degrees of squamous metaplasia. In other areas, the ducts were not associated with acini and were completely surrounded by dense fibrous stroma (Fig. 2). Invariably these ducts were distorted and irregularly dilated. The main pancreatic duct was not identified. The extent of these areas may be more readily appreciated in a low-power photomicrograph (Fig. 3). Few islets of Langerhans were seen. Those which were present were normally formed, but also appeared shrunken and atrophic. Like some of the ducts, many of them were isolated from any glandular tissue and were embedded in fibrous stroma. All of them, however, were in the vicinity of pancreatic ducts (Fig. 4). The fibrous stroma was compact and rarely was associated with fatty tissue except about the periphery of the pancreas. Blood vessels were numerous but were arranged in no definite pattern. Inflammatory exudate was scanty. Only a few lymphocytes, plasma cells, and mononuclear phagocytes were seen and these were usually scattered (Fig. 2).

In serial sections, the larger ducts varied greatly in contour and diameter. Although there were numerous zones of constriction between areas of dilatation, most of the ducts extended for considerable distances before ending blindly. There were, however, numerous blindly-ending outpocketings approximately at right angles to the main axes of the larger ducts. Some of these were pointed, others were blunt and bulbous. Many had multiple blindly-ending branches. These resembled branches of the larger ducts, but were atypical in arrangement and were irregularly distributed. Near the larger ducts were many completely isolated but undilated cysts which appeared to be pinched-off segments of the smaller branches of the ducts (Fig. 2). A segment of one of the larger ducts showing the characteristics described has been reconstructed and is illustrated in the model (Fig. 5).

Discussion

According to Lewis,[26] the human pancreas is normally formed from two separate anlagen, the ventral and dorsal pancreases, which arise from the duodenum and which are present in embryos of 3 to 4 mm. They are still separated at 10 mm. by the portal vein, but at 16 mm. are united and partly surround the vein. With the elongation of the common bile duct, the ventral pancreas becomes completely separated from the duodenum and forms part of the head and much of the uncinate process. The dorsal pancreas forms the rest of these structures and the entire body and tail. The main ducts of the dorsal and ventral pancreases unite by a single anastomosis and only rarely are there any anastomoses between their branches. The main duct of the mature pancreas, formed by this anastomosis, empties into the common bile duct and is called the duct of Wirsung. The proximal portion of the duct of the dorsal pancreas, which arises from the duodenum, may persist as an accessory duct and is called the duct of Santorini. At first the newly formed main duct is a simple wide and hollow tube having numerous radial, pear-shaped buds and branches. These become canalized and continue to subdivide. The glandular epithelium is later differentiated into mature acini. The islets of Langerhans appear in the body and tail at 54 mm. but are not present in the head until a later period. At first they are connected with the ducts by epithelial stalks. In later stages they become detached from the epithelial tubes and remain isolated thereafter.

It is not clear whether early generations of pancreatic ducts are normally provisional as are early generations of nephrons and intrahepatic bile ducts. Since isolation of epithelial ducts by segmentation is a normal process of embryologic degeneration in other organs, it is quite possible that this process may at times occur in the normal fetal pancreas.

In the present case, although slightly and diffusely enlarged, the pancreas was remarkably normal in contour and in position. A main duct was not distinguished either grossly or microscopically. The small ducts illustrated in Figures 2 and 3 were not parallel with the long axis of the pancreas but formed angles of at least 45° with it. This angle is evident in the reconstruction, in which the vertical axis of the illustration corresponds with the long axis of the pancreas (Fig. 5). Because of their number, size, and position it is thought that these ducts were large branches of the main duct which was no longer present. Although glandular tissue was lacking in much of the pancreas, when present the acini were normally formed and differentiated and were often situated at the periphery of the organ (Fig. 1). The

number of the islets of Langerhans was definitely less than is normal, but even when completely isolated in fibrous stroma the configuration was normal although the cells individually were often shrunken and atrophic (Fig. 4).

As in the kidneys and livers previously reported,[23-25] the normal gross structure of the pancreas implies that the early development of the organ was normal and that differentiation of the components continued normally for a considerable time. It is very likely that the main duct was originally present, but disappeared, probably as the result of segmentation and resorption, following the proliferation of many of its branches. These branches persisted as the numerous, small, irregular ducts, in turn with the distorted outpocketings or branches which are illustrated. It may also be assumed that normal proliferation and differentiation of the glandular tissue occurred simultaneously with segmentation and resorption of the main duct. The process of segmentation and resorption did not stop with the main duct but also involved the smaller ducts and their branches. As a result the glandular tissue became isolated and much of it atrophied and disappeared. Although isolated, some of the islets of Langerhans also persisted. Simultaneously, the degenerating epithelial elements were replaced by proliferating fibrous tissue so gradually that the gross structure of the pancreas remained normal.

If this recapitulation is correct, then the sequence of anatomic changes in the epithelial structures of the pancreas is identical with that which has been postulated for polycystic disease of the kidney and liver. Persistence of many of these isolated segments as gradually enlarging cysts can explain the lesions of polycystic disease in later life. It may be concluded, therefore, that the changes described in the pancreas of the present case are consistent with the theory that in polycystic disease the fundamental defect is segmentation of epithelial tubules and ducts after their formation in accordance with the normal architecture of the organ.

Although the process of segmentation and resorption of the ducts appears to be similar to that which occurs in the polycystic kidney and liver, the greater reduction in the glandular tissue and the much greater amount of fibrous stroma in the pancreas require further comment. It may be argued that the amount of epithelium in the anlagen was deficient from the beginning and that the extensive zones of fibrosis merely represent a condensation of fetal mesenchyma in those areas normally occupied by glandular tissue. This hypothesis seems unlikely, however, since, in contrast to the kidney, in the pancreas both the

glandular tissue and ducts are derived from the same anlage and there appears to be no deficiency of the smaller ducts in the present case. Furthermore, if the epithelial anlagen were actually deficient, the grossly normal development which was found in the pancreas of the present case hardly could have occurred. It may be argued that chronic inflammation of the pancreas, associated with contraction of fibrous tissue, may have constricted many of the pancreatic ducts and led to segmentation and resorption. This hypothesis is supported by the fact that chronic inflammatory exudate has often been reported as extensive. Such a process, however, if actually significant, would almost certainly lead to distortion of the gross structure of the pancreas. The signs of inflammation in the present case were minimal, and it has been previously emphasized by us that inflammation is frequently inconspicuous in polycystic disease of other organs. Consequently, although inflammation may contribute to the segmentation and resorption of epithelial elements in certain cases, it does not appear to be a primary factor in the pathogenesis of polycystic disease.

Summary and Conclusions

1. The polycystic lesions of the pancreas in an infant were studied by the usual methods and by a three-dimensional model which is illustrated.

2. The characteristic progressive distortion, cystic dilatation, and segmentation of the ducts are thought to have occurred simultaneously with replacement fibrosis and did not prevent the normal gross development of the pancreas.

3. It is believed that the changes described correspond with those postulated for the polycystic lesions of the kidney and liver, and indicate that in polycystic disease epithelial tubules and ducts are formed in accordance with the normal architectural pattern of the organ but then become distorted and segmented. Instead of complete resorption of these segments, as occurs in the normal degeneration of the mesonephros and in early generations of tubules of the metanephros and liver, many of them persist to form isolated cysts.

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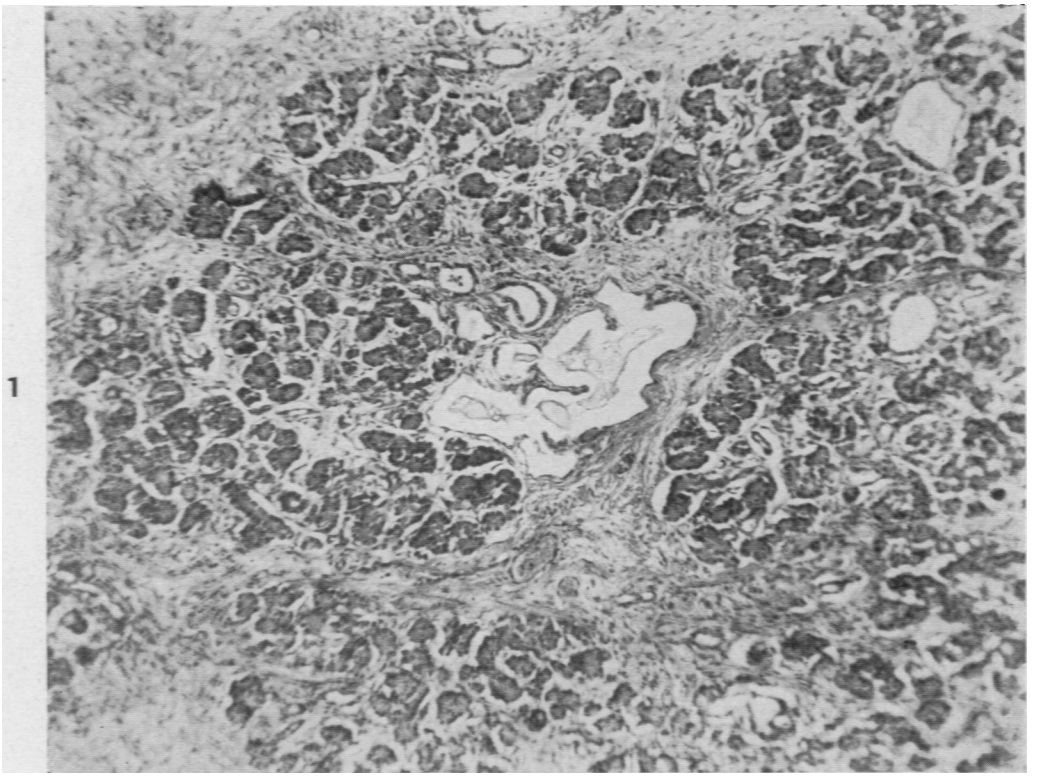
[*Illustrations follow*]

DESCRIPTION OF PLATES

PLATE 81

FIG. 1. The pancreatic acini are normally formed, but the small ducts are distorted and cystic. Hematoxylin and eosin stain. × 105.

FIG. 2. A medium-sized duct is distorted and is completely surrounded by dense fibrous stroma. At the left, the duct-like structures are in reality small cysts which may be pinched-off branches of the larger duct. Hematoxylin and eosin stain. × 180.



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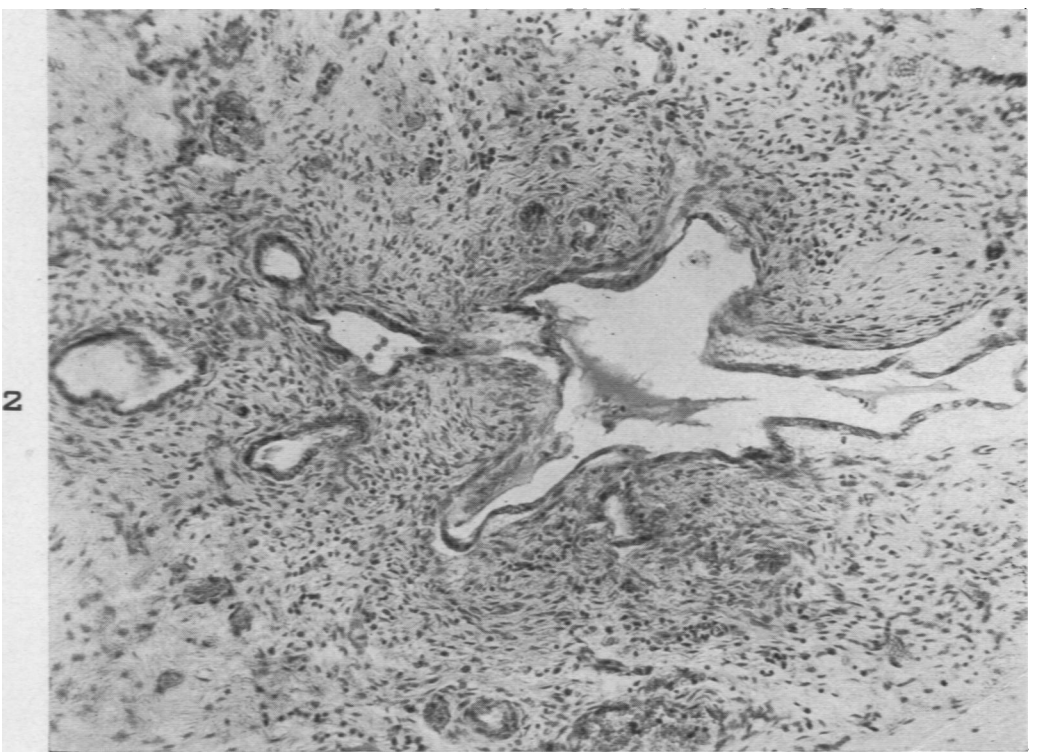

2

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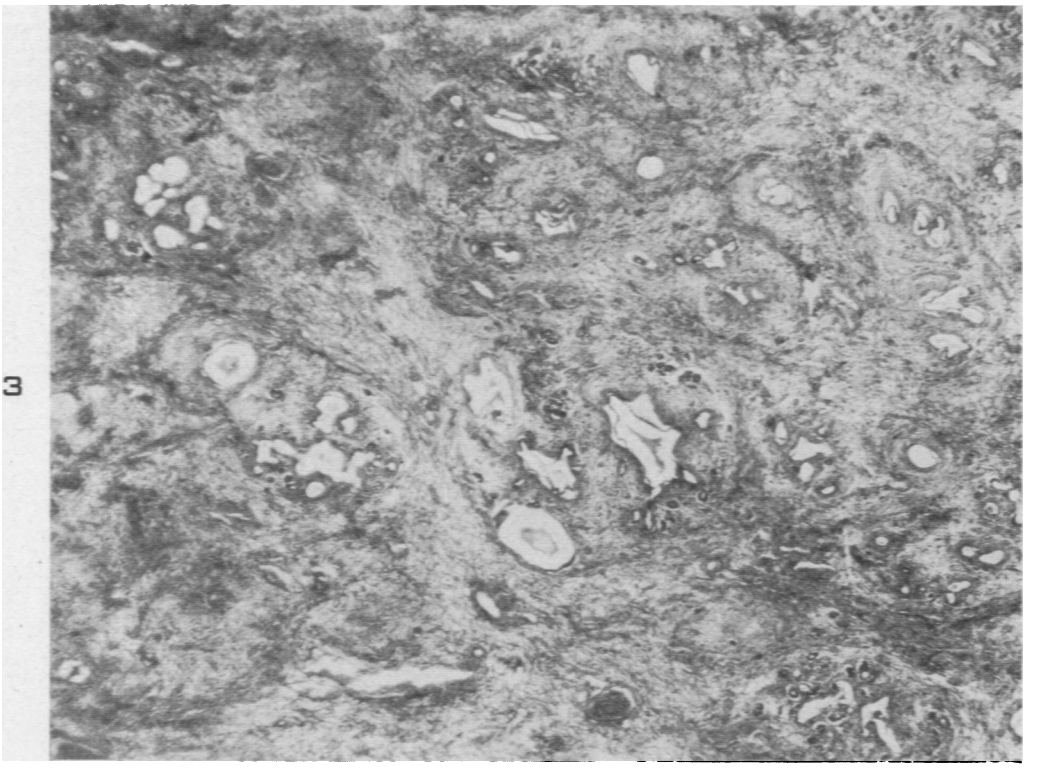
PLATE 82

FIG. 3. In large areas, the pancreatic ducts and their branches are surrounded only by fibrous stroma. Hematoxylin and eosin stain. × 50.

FIG. 4. In the center of the field, three islets of Langerhans embedded in fibrous stroma are normally formed, but the epithelial cells are individually shrunken and atrophic. Hematoxylin and eosin stain. × 105.



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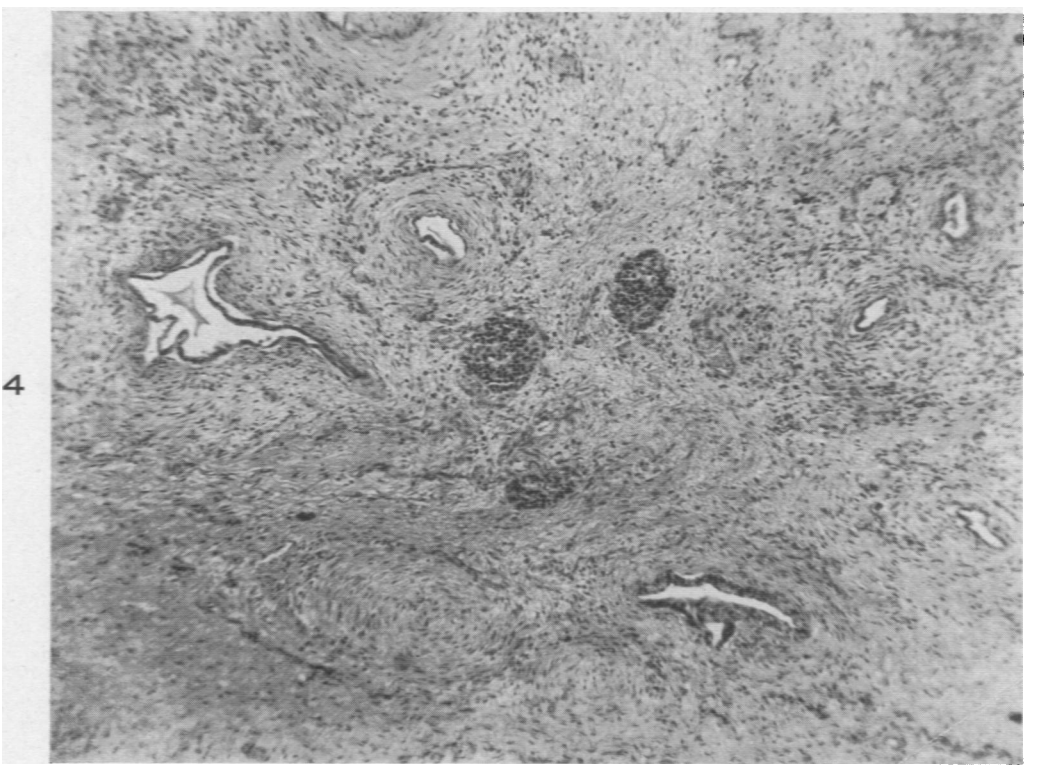

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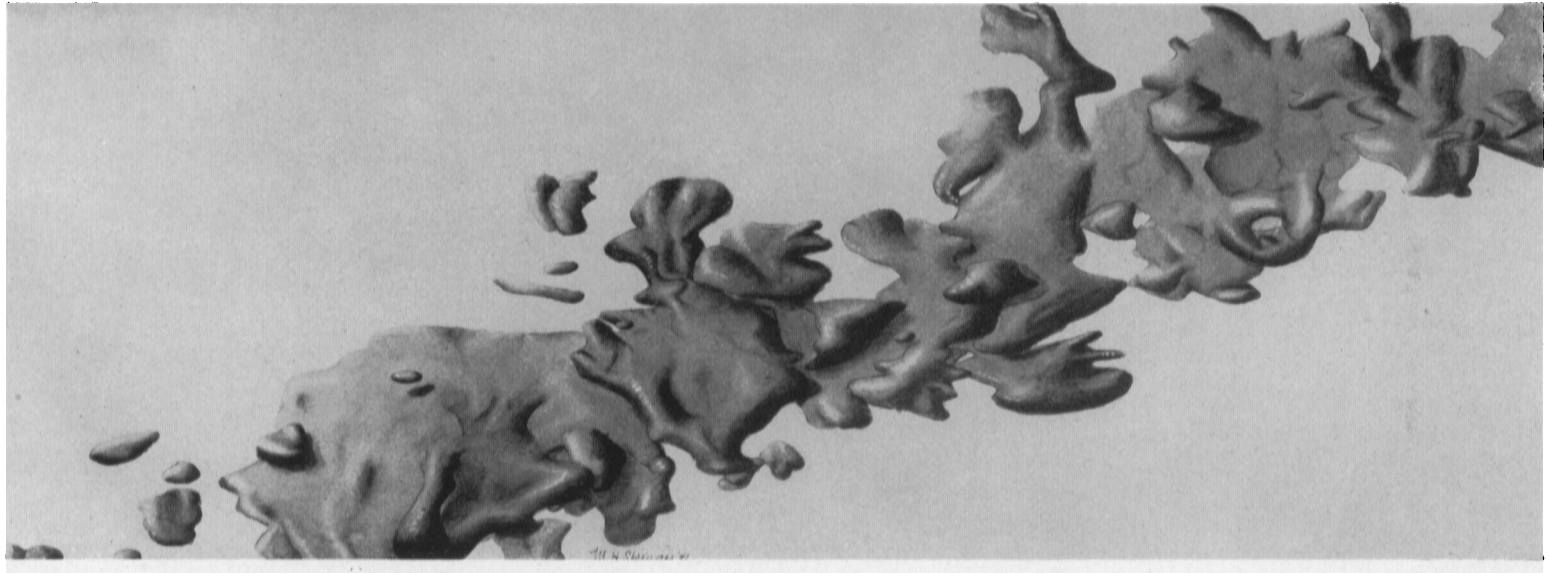
PLATE 83

FIG. 5. The model of one of the larger pancreatic ducts shows the marked irregularity and focal dilatation. There are numerous branches, some pointed and others bulbous. To the left and above the main duct are several isolated, undilated cysts which may be pinched-off segments of some of the branches. The vertical extent of the reconstruction in the pancreas was 0.68 cm.



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