Microcirculation of the Normal and Inflamed Canine Pancreas

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Pancreas of normal dogs and the inflamed gland of experimental pancreatitis were studied by intra-arterial injection of Microfil, a silicone-rubber compound especially suited for study of the microcirculation. Duodenal vasculature and lobular vessels of the pancreas were studied as were those supplying the duct. Interlobular vessels were well visualized in the normal pancreas and intralobular vessels formed a fine reticular pattern throughout the cleared lobules. A complex network of vessels in the pancreatic duct was observed using this technique, apparently derived from the interlobular vessels. The blood supply of each layer of the duodenum was evaluated.

Intraductal trypsin injection produced focal areas of pancreatitis associated with edema, poor vascular filling and spastic changes of the lobular vessels. Extravasation of Microfil, although not apparent on normal specimens, was prominent in inflamed specimens and suggested vascular weakness and disruption. Pancreatic lobules adjacent to inflammatory areas showed definite evidence of dilatation. The inflamed pancreatic ducts were markedly edematous, thickened, and showed incomplete vascular filling. When the duodenum adjacent to pancreatitis was injected with Microfil, edema and vasoconstriction were especially prominent in the duodenal muscular layer.

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MICROSCOPIC VASCULAR CHANGES in the inflamed pancreas were observed in 1936 by Rich and Duff[15] to consist of adventitial condensation, swelling of muscle fibers in the media and fraying of the internal elastic lamina. These observations were reported both in human autopsy specimens following hemorrhagic pancreatitis and in experimentally produced pancreatitis in dogs and subsequently, other investigators[5,8] have published similar reports.

Additional information was published by Thal in 1954,[17] concerning the pancreatic microcirculation following retrograde ductal injection of bile into the rabbit pancreas. Using a transillumination device, he demonstrated segmental spasm of the lobular arteries and veins, with sluggish capillary flow followed within 20 minutes by capillary rupture and erythrocyte extravasation. Alterations in the pancreatic vasculature following experimental pancreatitis were further quantitated in 1966 by Papp and associates[10] who used radioactive[86] rubidium to measure decreased pancreatic blood flow rates in bile and trypsin-induced pancreatitis. Redistribution of capillary flow from inflamed to more normal areas in canine trypsin-induced pancreatitis was reported in 1968 by Anderson and Schiller.[1]

The following year, Goodhead used radioactive rubidum to demonstrate decreased pancreatic blood flow during bile-trypsin or bile induced pancreatitis.[6] Studies with mild edematous pancreatitis revealed an increase in pancreatic blood flow apparently secondary to vasodilatation associated with inflammation. A decreased blood flow to the gastrointestinal tract, including the duodenum was also seen with hemorrhagic pancreatitis.

In 1969, Papp and co-workers visualized the microcirculation using intra-arterial injection of either polyvinyl chloride or an india ink-gelatin mixture.[11] They found uniform capillary filling in control animals, while poor filling was observed with pancreatitis. There was occlusion of some small arteries with stump-like or pointed terminations and arterial constriction bands were described. In addition, arteriovenous shunting was observed in animals with pancreatitis.

Although these studies contributed valuable data concerning the pancreatic lobular microcirculation, they provided little information concerning changes in the pancreatic ducts and adjacent duodenum. Pathologic changes in these structures are of importance because ductal stricture is reported to be a factor in recurrent pancreatitis and alteration of duodenal motility is commonly observed radiographically.[18]

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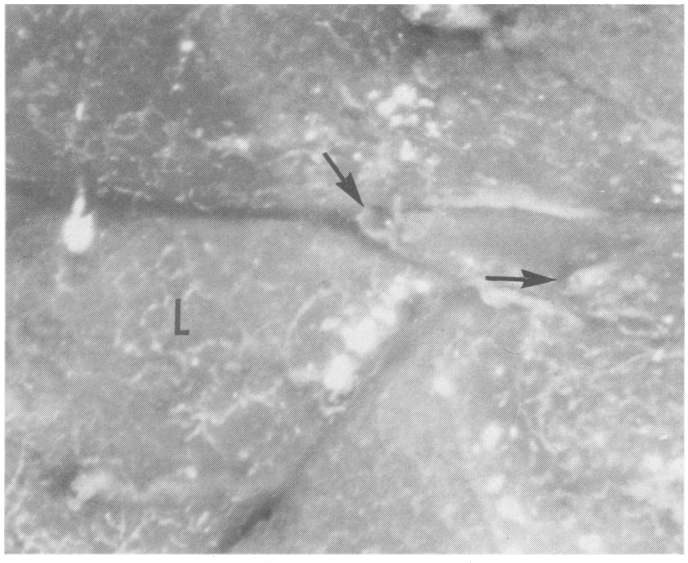

FIG. 1. Dissection microscope view of the cleared, injected pancreas shows several lobules (L) with the typical intralobular vascular pattern. Within the interstitial spaces, larger interlobular vessels are evident (arrows). (×18)

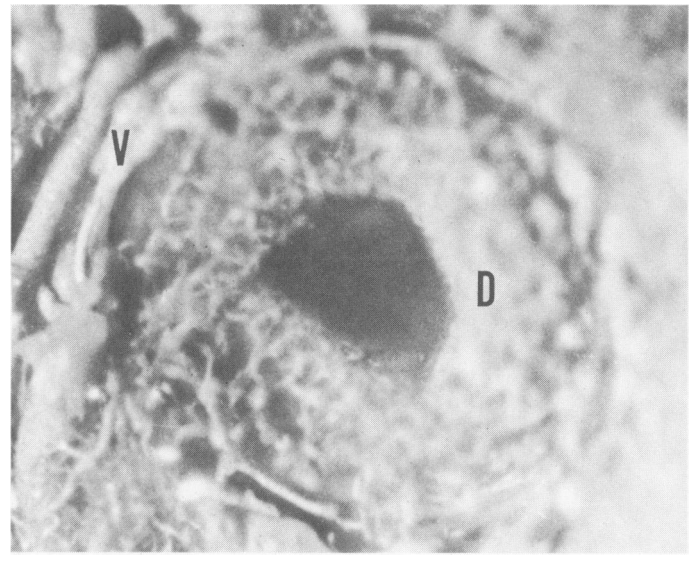

FIG. 3. Proportion of pancreatic duct demonstrates the complex vasculature in the ductal wall (D). The ductal vessels appear to be derived from adjacent interlobular vessels (V). (×18)

Material and Methods

Using sterile technique, laparotomy was performed through a midline incision upon 10 anesthetized adult mongrel dogs. In 5 control animals, Microfil, a silicone-rubber compound with a particle size of 1 to 3 microns, was injected under a pressure of 150 mm Hg or less into the cranial pancreaticoduodenal artery according to a technique described by Sobin.[16] The pancreas and adjacent duodenum were immediately excised between clamps and stored in a refrigerator overnight to allow polymerization of the Microfil. Specimens were cut into 10 mm slices, cleared in glycerin solutions graduated from 75 to 100%, examined with a dissecting microscope and photographed.

In 5 animals, pancreatitis was induced by a transduodenal retrograde injection of 150,000 units of trypsin in 15 ml of saline into the major pancreatic duct, using a controlled pressure of 150 mm Hg. The lesser pancreatic duct was ligated prior to injection and the major pancreatic duct was ligated following injection and the duodenotomy closed in two layers. Twenty-four hours later, the animals were re-operated, Microfil was injected according to the procedure described above, and specimens were obtained and processed.

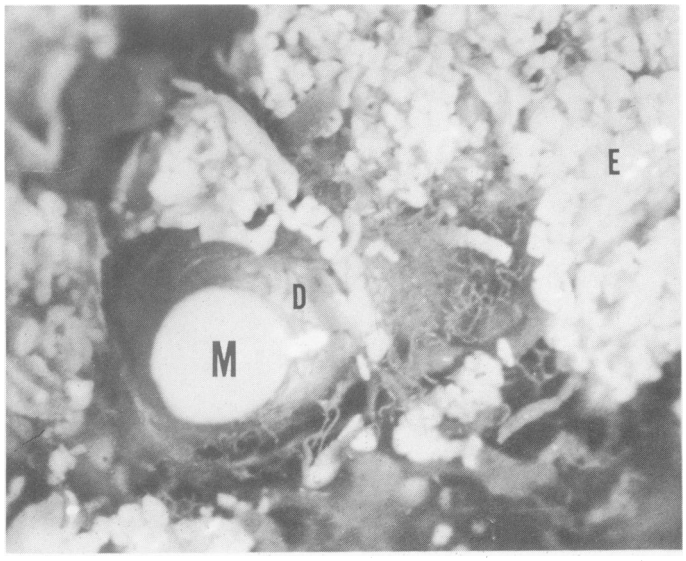

FIG. 2. Preparation was injected sequentially through the pancreatic duct and artery to demonstrate Microfil within the duct lumen (M) and in the surrounding ductal vasculature (D). Intralobular Microfil from the ductal injection is seen in the upper right of the photograph (E). (×18)

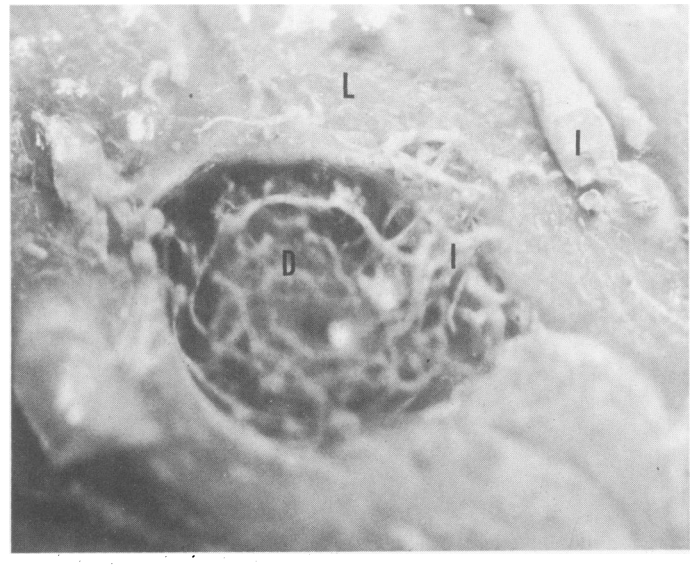

FIG. 4. Small calibre pancreatic duct which shows the ductal vasculature (D) derived from the interlobular vessels (I). The adjacent normal pancreatic lobules (L) are apparent in this preparation. (×18)

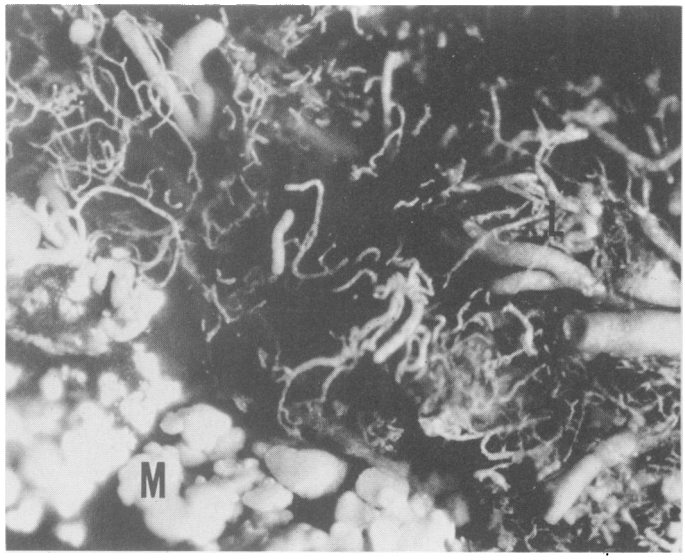

FIG. 5. Following experimental production of acute pancreatitis, injection of this specimen revealed extravasated Microfil (M) suggestive of vascular weakness and disruption. Areas not containing vessels represent edema and there is incomplete filling of vasculature suggesting vasoconstriction. Adjacent areas of pancreas appear to respond by vasodilatation (L). (×18)

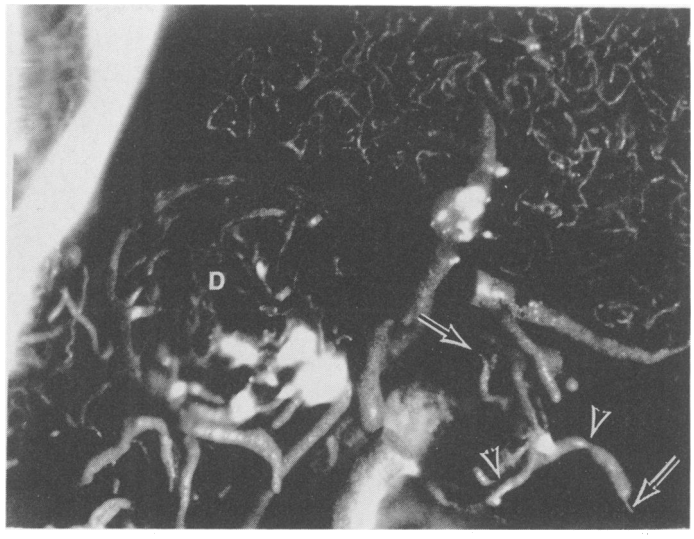

FIG. 7. Vessels in inflamed portions of pancreas often develop beading (short arrows) and pointed terminations (long arrows). Edema is evident and appears to involve the small duct included in this section (D). (×19)

Results

Normal pancreatic lobules were well visualized at low power magnification using the dissecting microscope. The intralobular vessels formed a fine reticular pattern with no evidence of extravasation of contrast material. Larger interlobular vessels were also evident (Fig. 1). When the pancreas was injected with red Microfil in the arteries, after yellow Microfil was injected retrograde into the pancreatic duct, a vascular network was observed surrounding the duct lumen (Fig. 2). Further study revealed that medium sized ducts were endowed with a highly developed vascular supply, apparently derived from interlobular vessels (Fig. 3). The entire wall of the duct was generously supplied by this vascular plexus. Smaller ducts were similarly supplied, although the lumens were more difficult to discern (Fig. 4).

Intraductal trypsin injection produced focal areas of pancreatitis associated with edema and a pronounced tendency for extravasation of contrast material, suggesting vascular damage. Pathologic changes in intralobular vessels were present, with poor vascular filling and apparent fragmentation of vessels (Fig. 5). Normal lobules adjacent to the focal pancreatitis showed evidence of

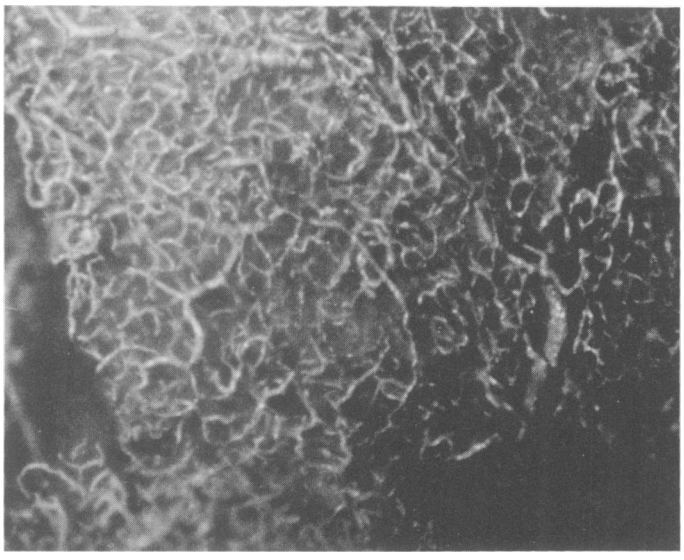

FIG. 6. Areas of pancreas not directly involved by inflammation demonstrate vasodilatation of intralobular vessels as compared to the normal pancreas in Fig. 1. (×18)

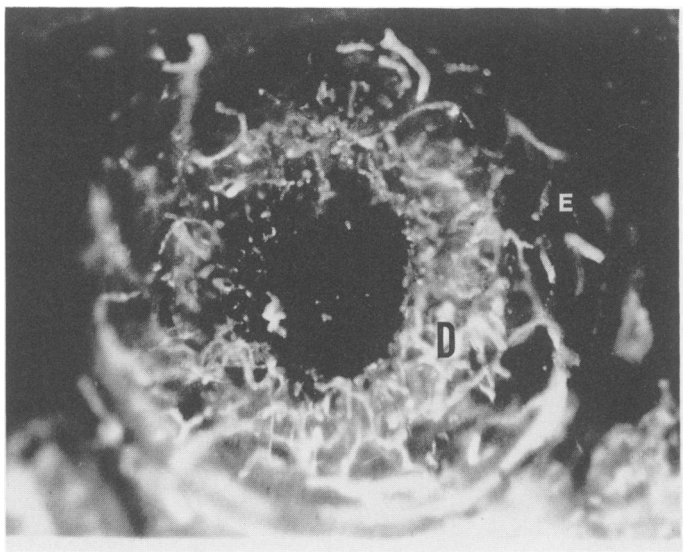

FIG. 8. The duct wall (D) in this section of inflamed pancreas exhibits a striking degree of edema and incomplete vascular filling (E), illustrating the severity of damage to the duct. (×18)

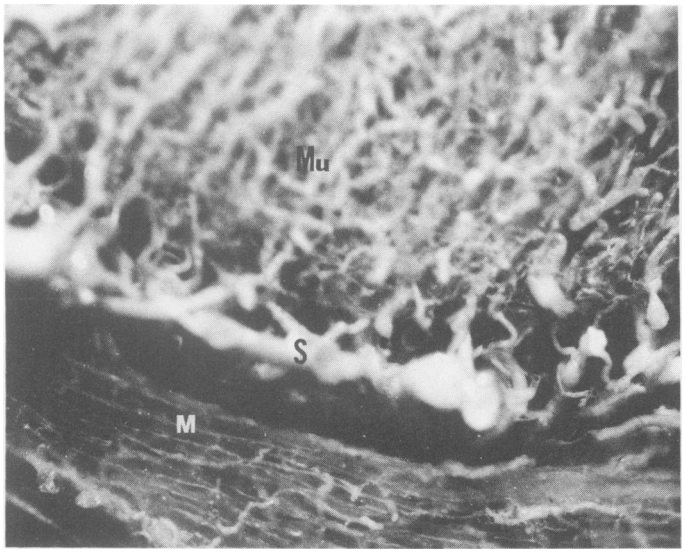

FIG. 9. Microfil injected portion of normal duodenum shows the vascularity of submucosa (S), muscularis (M) and mucosa (Mu). (×18)

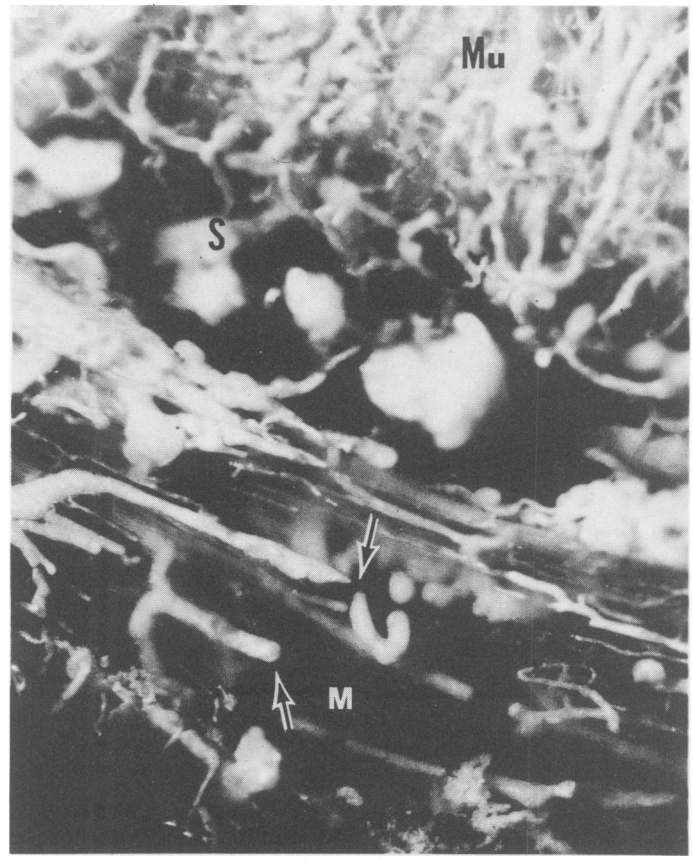

FIG. 10. A portion of duodenum adjacent to uninflamed pancreas shows edema in the muscular layer (M) and vessels in the muscularis exhibit abrupt terminations characteristic of vasoconstriction (arrows). The submucosa (S) and mucosa (Mu) are seen in the upper portion of the photograph. (×22)

vasodilatation manifested by all vessels which also appeared to be of larger than normal calibre. (Fig. 6).

Pancreatic ducts involved in the inflammatory process showed edema and poor vascular filling of ductal vessels. Some interlobular vessels had pointed terminations while others showed evidence of beading, suggesting vasoconstriction (Fig. 7). Larger ducts involved by the pancreatitis had severe edema in the ductal wall and a definite decrease in vascularity (Fig. 8).

The vascular supply of the normal duodenal muscularis was found to consist of small, closely approximated vessels (Fig. 9). The duodenum adjacent to pancreatic inflammation showed edema of the seromuscular layer along with dilatation and incomplete filling of vessels in the muscularis (Fig. 10).

Discussion

This study demonstrates the focal pattern of edema and vasoconstriction in areas of severe pancreatic inflammation. These observations are especially well seen in the pancreatic lobules and correlate well with those of Goodhead[6] and Papp and co-workers[10] who studied pancreatic blood flow using radioactive rubidium. As suggested by Popper and associates,[14] this compromise of parenchymal circulation in combination with enzyme extravasation into the gland parenchyma may contribute to increased severity of the pancreatic inflammation. Equally pertinent is the observation that less affected areas seem to develop vasodilatation. These findings suggest that a re-distribution of pancreatic blood flow occurred with hyperperfusion of minimally involved areas and stasis in the inflamed pancreas. These pathologic events were previously observed in 1968 using an india ink injection technique.[1] Most authors agree that while replacement of fluid losses are of paramount importance in reversing these changes, other adjunctive measures are worthy of consideration.

Further information concerning canine pancreatic blood flow has been published by Delaney and Grim[3] who used K^{42} and Rb^{86} clearance techniques. They studied the effects of intravenously administered drugs and found that blood flow was increased by secretin, norepinephrine, and cortisone and decreased by epinephrine and Pitressin. No significant effect was produced by pancreozymin, histamine, dibenzyline or hypercarbia. These results suggest possible pharmacologic methods of improving pancreatic blood flow. One interesting study by Pissiotis, Condon and Nyhus[12] showed that pancreatitis produced by retrograde ductal injection of an incubated mixture of blood and trypsin resulted in a 40 to 60% decrease in local blood flow. They were able to prevent the blood flow reduction secondary to pancreatitis by an intravenous infusion of vasopressin, although there was no significant effect on normal pancreatic microcirculation. The mechanism of this protective effect of vasopressin observed during pancreatitis was

not well defined. Additional efforts to improve the microcirculation of the inflamed pancreas have been reported[6] and include administration of heparin and low molecular weight dextran as a means of maintaining patency and flow in small vessels.

Another method of treatment, both experimentally and clinically has been postganglionic sympathetic denervation of the pancreas with the goal of relieving vasospasm and improving pancreatic perfusion. Goodhead and Wright[7] studied this problem in dogs and found that pancreatic blood flow and perfusion were increased by sympathetic denervation in normal dogs. Furthermore, they concluded that the postganglionic sympathectomy significantly lowered the mortality rate of experimental pancreatitis and prevented the occurrence of severe hemorrhagic pancreatitis as determined by histologic examination. Most of the treated animals developed a milder form of edematous pancreatitis instead of hemorrhagic pancreatitis.

Clinical application of postganglionic sympathectomy as a form of therapy has been published by several authors.[2,4,9,13] In this small series of patients, the authors reported relief of pain in most and there were some subjective signs of improvement in the course of the disease.

The well developed ductal vasculature seen in this study has not been observed previously in such clear detail. While the present study was not concerned with investigating the precise function of this ductal plexus of vessels, it is interesting to speculate that it is intimately related to the secretory processes of the pancreas. The abnormal vascular filling and edematous changes in the ductal wall secondary to pancreatic inflammation may be responsible for the development of fibrotic ductal strictures in patients with recurrent pancreatitis. Another potentially helpful experimental model might be produced by allowing animals to recover from induced pancreatitis for 30 to 60 days prior to Microfil injection so that the effects of chronicity could be studied. Use of Microfil to inject surgical specimens from humans with chronic pancreatitis also may help to elucidate the relationship of fibrosis to ductal ischemia.

The changes observed in the duodenal microcirculation suggest that the abnormal gastrointestinal motility associated with pancreatitis may result in part from an altered circulation in the duodenal muscularis. This apparent ischemia should be kept in mind when contemplating duodenotomy in the presence of acute pancreatitis. Poor healing with resultant fistula formation may occur. Although these changes have not been directly visualized previously they are not surprising, since the duodenum and pancreas share a common blood supply. The changes, which may be responsible for long term abnormality, such as ampullary obstruction or chronic abnormalities in duodenal function, deserve further study.

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