COMPARATIVE STUDY OF SOME ETIOPATHOGENETIC FACTORS IN THE DEVELOPMENT OF ACUTE PANCREATITIS

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The reflux of bile and intestinal contents and hypertension of the efferent ducts play a role in the development of acute pancreatitis. The course of the pancreatitis is particularly violent if all these factors are combined and superposed on increased pancreatic function.

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The most important factors causing acute pancreatitis are considered to be the reflux of bile and intestinal contents into the pancreatic ducts (the enzyme theory [5, 9, 11]), an increase of pressure in the pancreatic ducts (the obstruction theory [2, 6, 7-10]), and increased pancreatic function associated with a disturbance of the outflow of secretion, or of the innervation and blood supply to the pancreas [3, 10, 11]. These factors may act separately or in combination in the etiology and pathogenesis of acute pancreatitis. No adequate experimental evidence has yet been adduced to indicate the importance of each of these factors, alone or in combination, in the development of acute pancreatitis.

In an attempt to solve these problems, a series of chronic experiments was performed on dogs.

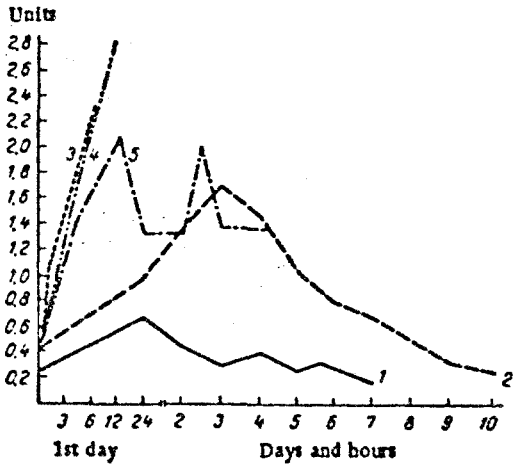

Fig. 1. Serum lipase activity of dogs developing pancreatitis under different conditions. 1) Ligation of main duct; 2) ligation of all pancreatic ducts; 3) injection of bile into main pancreatic duct; 4) combination of duodenostasis with stimulation; 5) duodenostasis with stimulation in the presence of cholecystojejunostomy. Abscissa: time after procedures; ordinate: serum lipase activity (in conventional units).

EXPERIMENTAL METHOD

Acute pancreatitis was caused by producing duodenal hypertension by K. D. Toskin's method and by ligating the pancreatic ducts, with or without other procedures on the gland. To stimulate pancreatic function, the animals were given a subcutaneous injection of 1 ml of 1% pilocarpine solution. To prevent hypertensive phenomena in the duodenum and pancreatic ducts, a cholecystojejunostomy was performed in a series of experiments. In the course of the experiments the lipolytic activity of the animals' blood serum was investigated by titration with olive oil emulsion [1]. The normal serum lipolytic activity of the dogs varied from 0.3±0.05 to 0.66±0.1 unit. At certain stages of the experiments the animals were sacrificed and the pancreas examined macro- and microscopically.

EXPERIMENTAL RESULTS

In the experiments of series I on 7 dogs the main and accessory pancreatic ducts were ligated. In 2 animals of this series only the main pancreatic duct was ligated.

Ligation of the main pancreatic duct led to a very slight and transient increase in serum lipase activity (Fig. 1). Under these experimental conditions the hypertension developing in the pancreatic tubules was of very short duration, because the secretion flowed out through the accessory ducts. At necropsy on these animals no visible changes were found in the pancreas.

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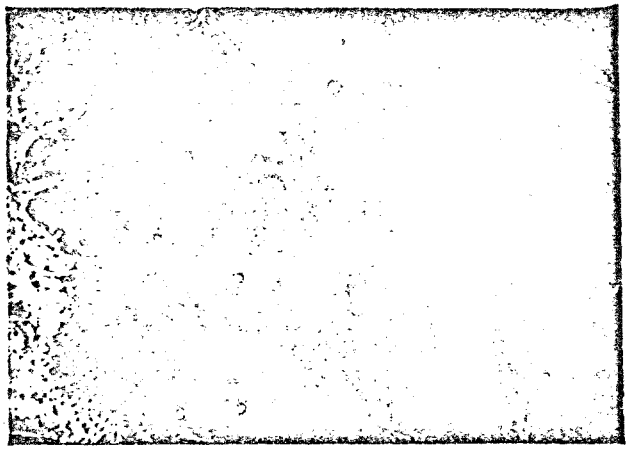

Fig. 2. Pancreas of a dog 19 days after ligation of ducts. Considerable infiltration of connective-tissue septs with leukocytes, most marked along the course of the ducts. Hematoxylin-eosin. Objective 8, ocular 10.

In the case of ligation of all pancreatic ducts in fasting dogs, an increase in serum lipase activity was found in the first 2 weeks after the operation. The highest level of activity was found on the 3rd-5th day after ligation of the ducts, returning to its initial level by the end of the 2nd week. The morphological changes in the pancreas were of the character of acute interstitial pancreatitis, progressing into sclerosis of the pancreas (Fig. 2).

Gravel was found in the dilated ducts of 2 animals sacrificed 167-200 days from the beginning of the experiment, in the region of the tail and head of the pancreas. Consequently, calculous pancreatitis had developed as a result of prolonged stasis of secretion in the pancreatic ducts combined with inflammation.

In the experiments of series II performed on 5 dogs, after ligation of the main pancreatic duct 0.5 ml bile was injected into its lumen. Acute edema of the pancreas developed 10-20 min from the beginning of the experiment, and after 1.5-2 h areas of stearin necrosis appeared. The serum lipase activity rose sharply in the first hour of the experiment (Fig. 1).

In the 15 dogs of the experiments of series III, after reaction of the pylorus the duodenal stump was exteriorized into a skin tube. Compression of the skin tube produced signs of duodenostasis, atony of the sphincter of Oddi, and reflux of intestinal contents into the pancreatic ducts followed by development of tubular hypertension. Under these experimental conditions, graded compression of the skin tube was accompanied by various morphological changes in the pancreas (ranging from edema to necrosis of its parenchyma) Pancreatic edema developed 3 h after compression of the tube, but an increase in serum lipase activity was not always observed. A considerable and persistent increase in the serum lipase activity of all the dogs was found after prolonged duodenostasis (6 h or longer), by which time marked destructive changes had developed as a rule in the pancreas. The dogs in this series of experiments survived from between 24 and 36 h.

In the experiments of series IV on 10 dogs, duodenostasis produced by compression of the skin tube was combined with stimulation of pancreatic function. In the animals of this group the pancreatitis followed a violent course and the dogs died 6-12 h after the beginning of the experiments. At necropsy severe hyperemia of the abdominal viscera and multiple foci of stearin necrosis were found. Massive foci of necrosis were observed in the parenchyma of the pancreas (Fig. 3). The serum lipase activity was sharply increased as in the series of experiments in which bile was injected into the main pancreatic duct, but higher values were attained.

In the experiments of series V on 10 dogs, in addition to exteriorization of the duodenal stump into a skin tube, cholecystojejunostomy was performed. In half the dogs of this group, compression of the tube was combined with stimulation of pancreatic function, while in the rest no stimulation was given. In the animals of this group, signs of duodenostasis appeared only in the first 2-3 h after compression of the tube. The escape of duodenal contents through the anastomosis relieved tension on the tube, vomiting ceased and the dogs took food. However, the decrease in pressure in the duodenum did not completely arrest the

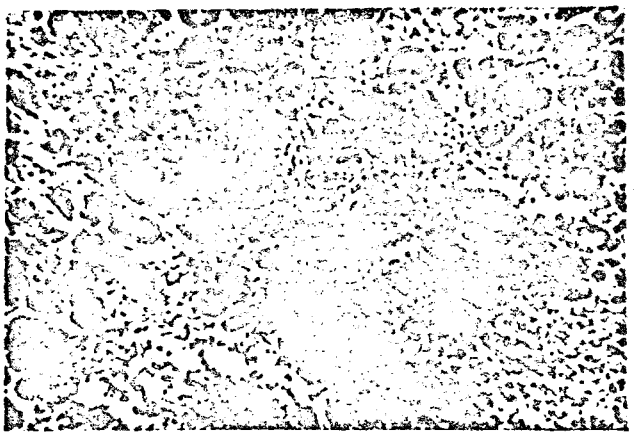

Fig. 3. Pancreatic necrosis arising in a dog after a combination of duodenostasis with stimulation of pancreatic function by 1% pilocarpine solution. Hematoxylin-eosin. Objective 20, ocular 10.

development of pancreatitis and the dogs died on the 3rd-5th day of the experiments. Infection of the pancreatic ducts by duodenal contents, leading in some animals to the development of suppurative pancreatitis with abscess formation, played a definite role in the development of pancreatitis under these conditions.

The serum enzyme activity was high throughout the experimental period, but was fluctuating in character.

The results of these experiments show that prolonged tubular hypertension leads to the development of pancreatitis without acute destructive changes, followed by sclerosis of the pancreas. We do not agree with Popper [12] that the changes taking place in the pancreas during stasis of the secretion in its ducts are not a sign of inflammation. In our observations considerable cellular infiltration always took place in the interstitial tissue, and was especially marked along the course of the ducts, undoubtedly indicating pancreatitis. Prolonged stasis of secretion after ligation of the ducts combined with inflammatory changes in the pancreas may lead to calculous formation in its ducts, which we observed in two experiments. However, the injurious action of tubular hypertension on the pancreatic tissue alone, without activation of the enzymes by enterokinase and bile, is not sufficient to cause the violent development of pancreatitis.

In all experiments the increase in pancreatic function was a factor accelerating the course of pancreatitis.

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