DISTURBANCES OF THE VENOUS CIRCULATION OF THE PANCREAS IN THE PATHOGENESIS OF ACUTE HEMORRHAGIC PANCREATITIS

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There are reports in the literature that, in acute hemorrhagic pancreatitis, thrombosis of the large veins of the pancreas lying outside the organ, and especially of their small ramifications within the organ, is often observed [8, 15, and others]. Thrombus formation in the veins under these circumstances is connected with the action on the vascular wall of trypsin, liberated by death of the glandular tissue, and subsequent clotting of the blood [13, 17]. In addition to this secondary thrombosis, in accordance with Ricker's views [14], a primary thrombosis of the veins may also be postulated, as the result of neurovascular disturbances. The significance of primary venous thrombosis in the development of acute pancreatic necrosis is confirmed by individual observations from post-mortem examinations, and by the results of experimental work [4, 5, and others].

The existence of divergent views on this subject, and the inadequacy of its study, provided a motive for the present investigation. Since it is impossible to reproduce acute pancreatitis by an experimental model, with all its various causative factors and complicated reflex neurovascular mechanisms, we made it our aim to ascertain the importance of disturbances of the venous circulation of the pancreas in the development of acute hemorrhagic pancreatitis.

EXPERIMENTAL METHOD

The experiments, which were carried out on cats, consisted of ligation of the splenic vein, which was followed by thrombosis proximally to the site of the ligature. Thrombosis of the vein was produced by injection of substances into it which caused coagulation of the blood proteins (alcohol, tannin, acetic acid, vikasol – a vitamin K analog) or agglutination of erythrocytes. The latter was brought about by infusion of heterogenic blood (from a rabbit or white mouse) into the vein. In individual cases only the splenic vein was ligated. In all the experiments the spleen was removed as a preliminary measure. The operation was performed under ether anesthesia. Some animals died in the first few hours or days after the operation; others were sacrificed at different times: during the first few hours or after many days (see table).

Mortality among Animals after Ligation and Thrombosis of the Splenic Vein

Character of experiment	Number of animals		
	total in experiment	sacrificed	dying
Ligation of vein	4	4	–
Ligation of vein and thrombosis by means of:			
alcohol	23	17	6
tannin	43	19	24
acetic acid	6	4	2
vikasol	2	2	–
heterogenic blood	12	7	5
Total number of experiments	90	—	—

EXPERIMENTAL RESULTS

In those cases in which only the splenic vein was ligated, both at operation and at post-mortem (the animals were sacrificed after 1-3 days) the pancreas macroscopically appeared unchanged. Microscopically only a slight or moderate edema was observed, mainly in the interlobular stroma. When ligation of the splenic vein was followed by thrombosis, changes in the color of the organ were observed very soon after injection of the thrombosing substances, in the majority of cases at the operation itself. In particular, the "splenic part" of the pancreas to a considerable extent acquired a pinkish-red color with a slightly bluish tinge.

In the subsequent hours (especially during the first day) the pancreas, over a large extent, appeared greatly increased in volume, swollen, very firm, and dark red in color. The adjacent fatty cellular tissue was also swollen, with greatly congested vessels and focal hemorrhages (Fig. 1). The lumen of the splenic vein throughout its whole extent was filled with red thrombus. A blood-stained effusion was found in the peritoneal cavity. In individual cases, on the surface of the gland and in the surrounding fatty cellular tissue could be seen a few dull, whitish patches of fat necrosis. All these changes, but to a greater degree, were observed on the following days (on the 2nd-5th day after the experiment). Destruction and sequestration of the dead tissue in the gland were

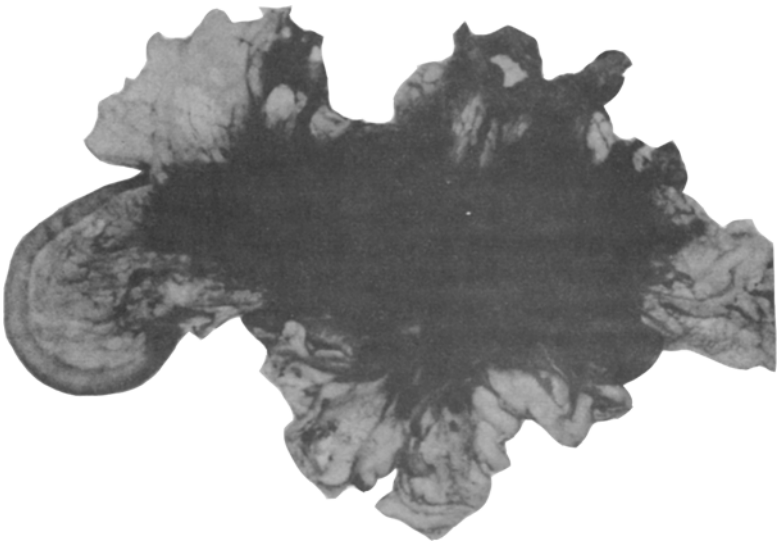

Fig. 1. General appearance of the pancreas in the first 24 hours after the experiment (ligation of the splenic vein and injection of 0.2 ml of tannin solution into its lumen). Side by side with the unchanged area of the gland, its "splenic part" is swollen, congested with blood, and dark red in color.

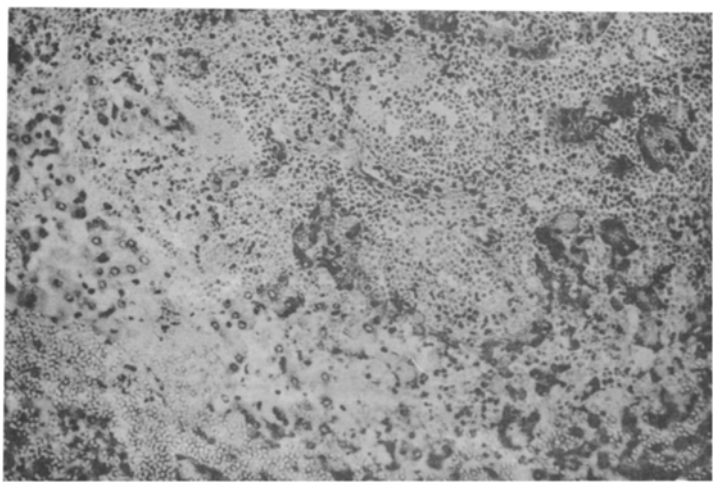

Fig. 2. Hemorrhages in the intralobular stroma. Disorganization and necrobiosis of the glandular cells. First 24 hours of the experiment. Moderate magnification. Stained by Van Gieson's method.

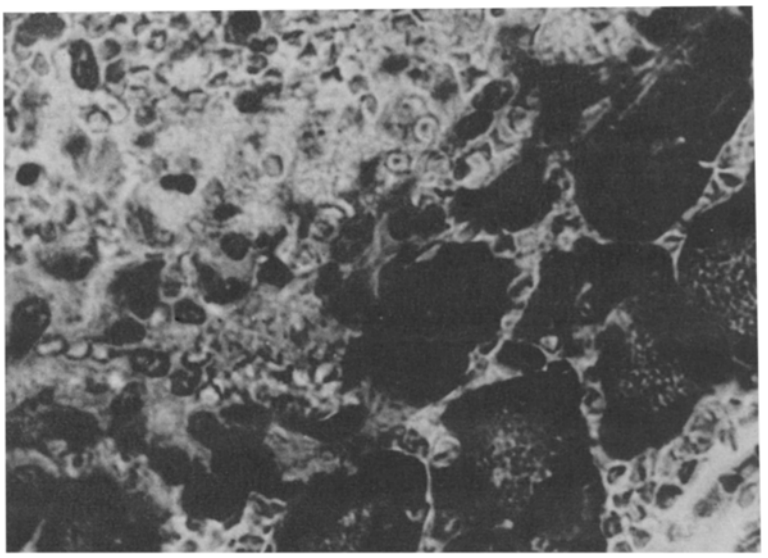

Fig. 3. Death of glandular tissue by means of gradual dissolution of the acinose cells (lysis of the nuclei and protoplasm of the cells). High power. Stained by Van Gieson's method.

later observed. At later periods (from 10 to 30 days) adhesions between the organ and the surrounding tissues were found in the region of the "splenic part."

The microscopic changes, like the macroscopic, were dependent on the degree of spread of the thrombosis into the branches of the splenic vein within the organ, and on the duration of the experiment. If the thrombosis was confined purely to the main trunk of the splenic vein, then, as in the case when the vein was ligated without injection of thrombosing substances, the changes consisted only of edema, mainly affecting the interlobular stroma. With spread of the thrombosis into the veins within the organ, considerable changes were observed in the stroma and parenchyma in the form of edema and hemorrhages in the interlobular and intralobular stroma, and of subsequent tissue and fat necrosis (Fig. 2). Studies of the trend of the changes at different periods of the experiment showed that the necrosis of the glandular tissue was secondary, i.e., it arose against the background of progressive hemorrhages by means of diapedesis. The gradual death of the glandular cells took place as a result of the lysis of their nuclei and protoplasm (Fig. 3). By the second or third day, considerable accumulations of leukocytes were observed in the foci of necrosis, and at later stages (6th-10th day), a fibroblastic reaction and gradual organization of the foci of necrosis were observed.

At about the end of the third week, an obvious fibrosis of the organ developed.

In discussion of the experimental results it must be remembered that the question of the localization of the primary changes in acute pancreatitis has found different answers in the literature. Some authors [6, 7, 12] considered that necrosis of the glandular tissue arises first, and then, in succession, changes develop in the stroma and vascular system in the form of edema, congestion, and hemorrhages. Experimental research in recent years [10, 11, 16], however, has clearly shown the primary character and the important role of circulatory disturbances in the development of changes in the parenchyma of the organ. The results of our experiments are in agreement with those obtained by Longo et al. [9], and show that glandular cell death set in secondarily, under the influence of "compressing" edema, hemorrhages, and anoxia. In our view, in acutely developing stasis of the blood, and subsequent hemorrhages, both the acinose cells and the capillary walls suffer damage. As a result of the disturbance of the "blood-tissue" barrier and of anoxia, a severe disturbance of the metabolic processes in the glandular cells takes place, which ultimately leads to progressive autodigestion of the organ. It must be emphasized that conditions such as these, which can lead to death of the glandular tissue and its autodigestion, are present only after spread of the thrombosis to the small branches of the splenic vein within the organ, whereas ligation or thrombosis of the main trunk alone does not lead to significant changes, on account of the numerous anastomoses in the portal vein system [1, 2, 3].

This pathogenesis of acute hemorrhagic pancreatitis which we have described is not common to all cases of acute involvement of the pancreas. Besides the hemorrhagic form of acute pancreatitis, for instance, are met edematous, necrotic, and suppurative forms, as well as pancreatic necrosis, with predominance of fat necrosis. In the development of these forms, other pathogenetic factors are of importance.

SUMMARY

Experimental induction of acute hemorrhagic pancreatitis in cats with the aid of venous thrombosis has demonstrated the importance of the pathogenetic role of acute venous circulatory disturbances within the organ in the development of this disease.

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