

MORPHOLOGICAL CHANGES DURING TREATMENT OF ACUTE EXPERIMENTAL PANCREATITIS WITH 5-FLUOROURACIL AND INTRALIPID

R. I. Kaem and Kh. T. Nishanov

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The treatment of acute pancreatitis still remains an important problem in abdominal surgery. Even the use of proteinase inhibitors has not proved sufficiently effective. The mortality in destructive forms of pancreatitis reaches 51% [1, 2].

In the treatment of acute pancreatitis some workers have suggested the use of 5-fluorouracil, an inhibitor of RNA synthesis and which, in the opinion of Martin et al. [7], depresses protein synthesis by the exocrine cells of the pancreas. Fukatani et al. and Tanimura et al. [8] showed that a deficiency of the principal fatty acids reduces the stability of cell membranes of pancreatic exocrine cells and used lipid emulsions with success in the treatment of acute pancreatitis.

The object of the present investigation was a morphological study of the dynamics of acute experimental pancreatitis during combined treatment with 5-fluorouracil and intralipid.

EXPERIMENTAL METHOD

Experiments were carried out on 44 male rats weighing 180-230 g. Altogether four series of experiments were carried out (8-10 rats in each series). Pancreatitis was produced in all series by Arai's method [3]. Series I was the control. In series II at the end of the operation 5-fluorouracil was injected intraperitoneally in a dose of 4.5 mg/100 g body weight. In series III intralipid was injected, and in series IV a combination of 5-fluorouracil and intralipid.

The animals were killed 3, 6, 12, and 24 h after the operation. Pancreatic tissue was fixed in 10% neutral formalin and embedded in celloidin. Sections were stained with hematoxylin and eosin.

EXPERIMENTAL RESULTS

In series I (control) 3-6 h after the operation marked congestion of the blood vessels and capillaries of the pancreas, edema, focal hemorrhages, and infiltration of the interlobular and interacinar spaces with leukocytes, dilatation of the lumen of the efferent ducts, and many glands filled with secretion were observed. Destruction and necrosis of exocrine cells were seen in some lobules of the gland. After 12 h edema and leukocytic infiltration of the interstitial tissue of the gland were increased and necrotic glands in the acinar tissue were more numerous. Foci of necrosis and suppuration were found in the surrounding adipose tissue. After 24 h signs of stasis and microthrombosis were seen in the vessels. Diffuse inflammatory edema and leukocytic infiltration of the interlobular and interacinar spaces, multiple foci of degeneration and necrosis of the tubular glands were observed. The remaining glands were sharply dilated and the cytoplasm of their cells contained much eosinophilic secretion. Signs of suppurative infiltration were observed in the surrounding cellular tissue (Fig. 1).

In the experiments of series II 3-6 h after the operation and injection of 5-fluorouracil moderate edema of the interlobular tissues and congestion of the blood vessels of the gland were observed. The efferent ducts

Department of Pathological Anatomy and Department of Abdominal Surgery, A. V. Vishnevskii Institute of Surgery, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Smol'yannikov.) Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 90, No. 12, pp. 742-745, December, 1980. Original article submitted May 16, 1980.

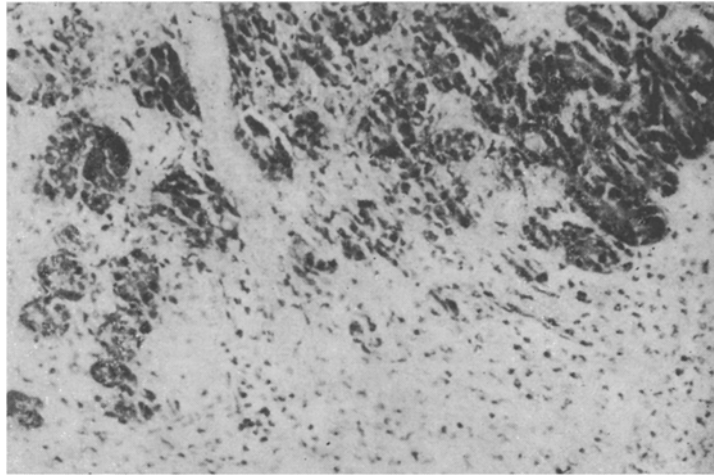


Fig. 1. Experiments of series I (control), 6 h after operation: edema and leukocytic infiltration of interlobular tissues; degeneration and necrosis of glandular cells of parts of pancreatic acini. Here and in Figs. 2 and 3: hematoxylin-eosin, 260 \times .

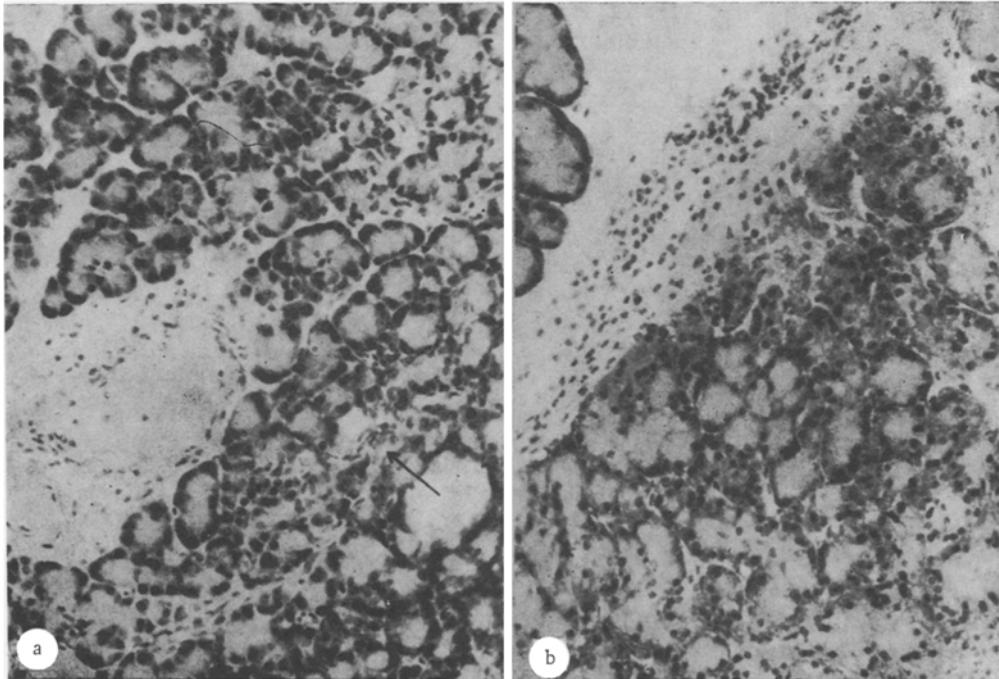


Fig. 2. Changes in pancreas after separate injection of 5-fluorouracil (a) and of intralipid (b). a) Experiments of series II, 6 h after operation and injection of 5-fluorouracil: moderate degree of perivascular edema; glandular structures well preserved; destruction visible only in single acini (arrow). b) Experiments of series III, 6 h after operation and injection of intralipid: variation in diameter of acini as a result of dilatation of some of them; degenerative changes and necrosis of glandular cells in individual groups of acini.

contained little secretion. Many cells — polymorphs, macrophages, mononuclear cells — could be seen in the exudate filling the interlobular spaces. After 12-24 h, signs of moderate vascular and capillary congestion were still present in the gland, but the intensity of the interstitial inflammatory edema was reduced. The architectonics of the acini was normal; the cytoplasm of the exocrine cells was weakly eosinophilic and it contained distinctly fewer zymogen granules. No foci of destruction were present in the gland tissue. Many round cells could be seen in the interlobular spaces (Fig. 2a).

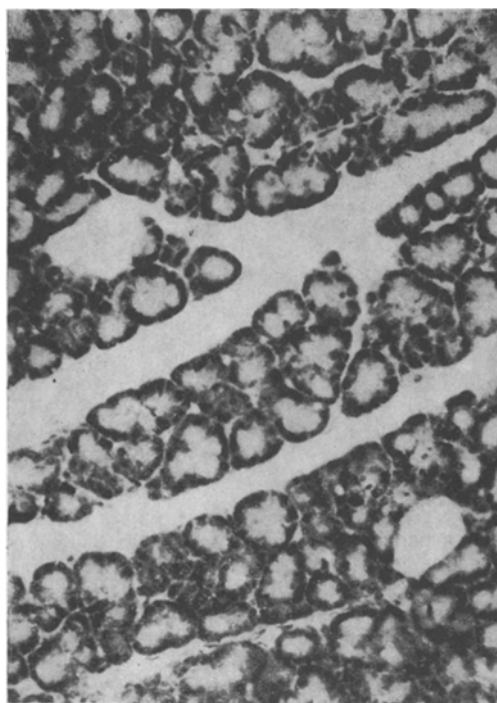


Fig. 3. Experiment of series IV, 6 h after operation and injection of 5-fluorouracil and intralipid: absence of edema, leukocytic infiltration of interlobular and interacinar tissues; absence of degenerative and necrobiotic changes in exocrine cells of pancreas.

In the experiments of series III, 3-6 h after the operation and injection of intralipid, moderate vascular congestion and inflammatory edema with a focal, and predominantly perivascular, accumulation of polymorphs and lymphocytes, was observed in the interlobular tissues. The cytoplasm of most exocrine cells was eosinophilic and contained large quantities of zymogen. Individual cells were deeply eosinophilic and their nuclei were pycnomorphic. After 12-24 h, moderately severe interstitial edema and focal infiltration of the interlobular spaces with polymorphs and lymphocytes were observed. Circulatory disturbances and infiltration of the adipose tissue surrounding the gland with polymorphs were more marked. The tubular glands were somewhat dilated, mainly at the periphery of the lobules. The cytoplasm of the exocrine cells was strongly eosinophilic and contained a large quantity of zymogen, vacuolated in places. Only a few cells were in a state of necrobiosis, with pycnotic nuclei (Fig. 2b).

In the experiments of series IV 3-6 h after the operation and injection of 5-fluorouracil together with intralipid, moderate interstitial inflammatory edema was observed, with weak focal infiltration of interlobular and perivascular tissue, predominantly by lymphocytes. The acini were uniform in diameter and the cytoplasm of the exocrine cells was weakly eosinophilic, evidence of a considerable reduction in their zymogen content. After 12-24 h, interstitial inflammatory edema was absent. Moderate congestion of the veins in the adipose tissue surrounding the gland was still present. The acini of the gland were closely packed together. They were mainly equal in diameter. The cytoplasm of the exocrine cells was weakly eosinophilic and the number of zymogen granules in them was sharply reduced. The efferent ducts were collapsed and contained no secretion. No foci of necrosis were present in the tissue of the gland (Fig. 3).

The results of this investigation show that combined administration of 5-fluorouracil and intralipid in the experimental model used prevented the development of acute pyonecrotic pancreatitis. The compound 5-fluorouracil, a powerful inhibitor of RNA and DNA synthesis which, at the same time, blocks the liberation of secretion, inhibited autolysis of the gland. Intralipid, which itself has no such action, acted largely as a stabilizer of the lipid component of the cell membranes of the exocrine cells, so preventing enzyme diffusion and cell destruction. With their complementary action, 5-fluorouracil and intralipid together give a well-marked therapeutic effect.

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