mained below the control level. Parallel with activation of NAD-diaphorase a sharp increase was observed in G6PDH activity in all three zones, which was not found in animals with acute pancreatitis. This comparison showed that restriction of the active participation of the adrenal cortex in the response to acute stress reduces the degree of divergence between the principal metabolic processes in the adrenal cortex during the period of formation of secondary changes in the pancreas.

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# MORPHOLOGICAL CHANGES IN HEMATOPOIETIC ORGANS AND PANCREAS PRODUCED EXPERIMENTALLY BY 5-FLUOROURACIL


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KEY WORDS: 5-fluorouracil; pancreas; hematopoietic organs.


The treatment of acute pancreatitis still remains a difficult problem in emergency surgery. The mortality from destructive forms is extremely high [3, 4, 6]. Several workers [2, 8, 9] have suggested using antimetabolities (5-fluorouracil — 5FU, Ftorafur) which inhibit RNA synthesis, prevent protein synthesis in pancreatic exocrine cells, depress enzyme secretion, and block autolysis of the treatment of acute pancreatitis.

In the present investigation the effect of 5FU was studied experimentally on the parenchyma of the pancreas, liver, bone marrow, and spleen during absorption of the compound introduced into the peritoneal cavity. The need for such an investigation is evident because of the extensive use of 5FU in clinical practice for producing a block of Kappis-Roman type in patients with acute pancreatitis. Confirmation that the compound has no adverse effect on pancreatic tissue and on the hematopoietic organs would be objective evidence of the safety of the method under clinical conditions.

## EXPERIMENTAL METHOD

Experiments were carried out on 30 mongrel dogs weighing 6-19 kg. The control group consisted of five dogs. Laparotomy was performed under thiopental anesthesia. A polyvinyl chloride tube was led to the pancreas and fixed with a suture to the parietal peritoneum, whereas its proximal end was brought out through an incision in the neck. Through this catheter the peritoneal cavity was irrigated with 5FU in a dose of 5 mg/kg body weight at times chosen beforehand. The animals were killed by artifical pneumothorax under anesthesia 3, 5, 10, and 60 days later, after irrigation with the compound for 2, 3, and 5 days. Biopsy of the internal organs was carried out at relaparotomy before sacrifice of the animals. The material was fixed in 12% neutral formalin and embedded in a paraffin wax. Sections were stained with hematoxylin and eosin and with picrofuchsin by van Gieson's method.

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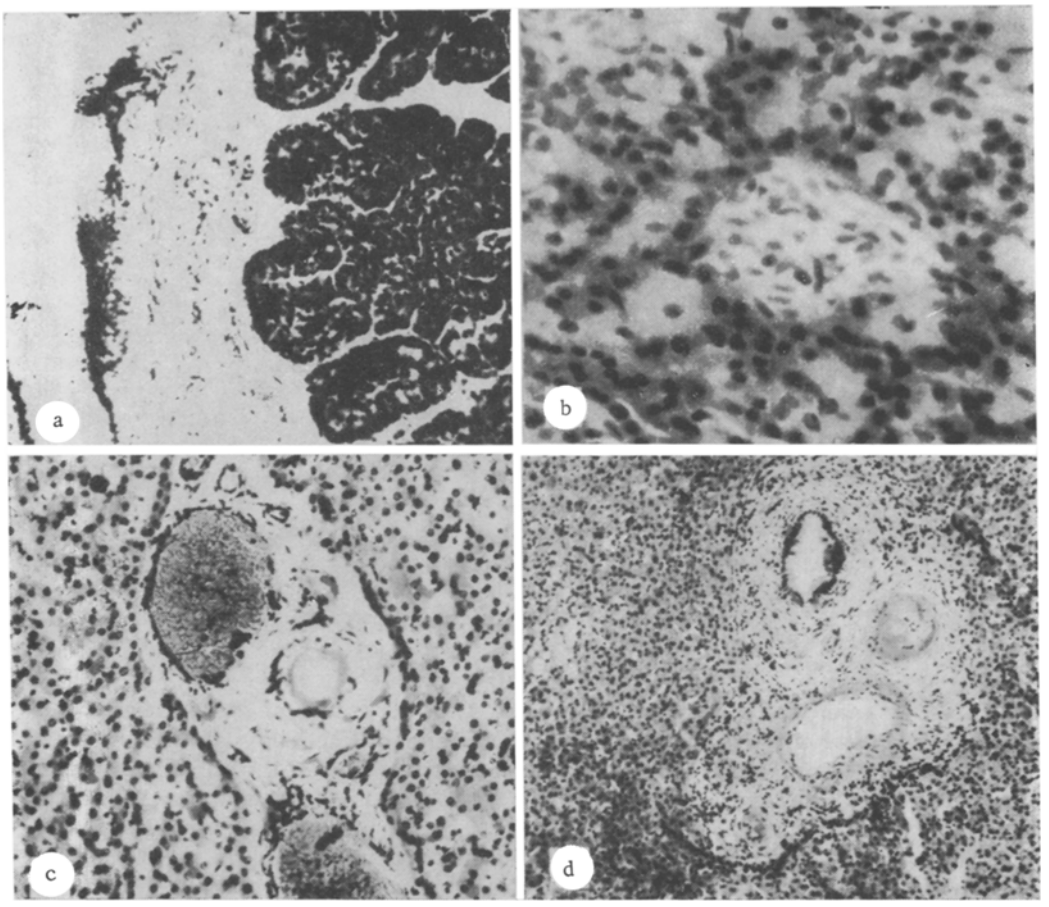


Fig. 1. Pancreas and liver of experimental animals after intraperitoneal irrigation with 5FU. a) Pancreas after administration of 5FU for 2 days. Widening of interlobular and interacinar spaces. Hematoxylin–eosin, 160 ×; b) pancreas on 10th day after irrigation with 5FU for 5 days. Structure of islet of Langerhans intact, basophilia of exocrine cells of terminal and intermediate portions. Hematoxylin–eosin, 260 ×; c) liver after irrigation with 5FU for 3 days. Marked congestion of veins in region of triad and of interlobular capillaries. Hematoxylin–eosin, 260 ×; d) liver on 60th day after administration of 5FU for 5 days. Structure of parenchyma intact. Hematoxylin–eosin, 70 ×.

## EXPERIMENTAL RESULTS

Morphological study of the pancreatic preparations on the 3rd-5th days after irrigation with 5FU revealed acute venous congestion and paralytic dilatation of the veins and capillaries of the interlobular connective tissue and surrounding fatty areolar tissue (Fig. 1a, b). In some case the lumen of the bile ducts and efferent ducts were dilated and the interlobular and interacinar spaces widened. Some activation of the secretory function of the glands was observed, i.e., accumulation of eosinophilic zymogen material in the lumen of the acini. On the 10th-60th days the signs of congestion subsided and the cytoplasm of the exocrine cells of the terminal and intermediate portions of the zymogen part became basophilic in character. The quantity of secretion in the glandular cells was within normal limits. The architectonics of the gland was well preserved.

On the first days after irrigation with 5FU marked and acute congestion of the central veins, intralobular capillaries, and veins in the region of the triads were observed, although these changes disappeared by the 10th-60th days. The architectonics of the pancreas was completely preserved (Fig. 1c, d).

In the early stages (until the 10th day) marked congestion of the splenic pulp with dilatation and congestion of the sinuses were noted (Fig. 2a). By the 60th day the signs of congestion had disappeared and the organ had regained its normal structure.

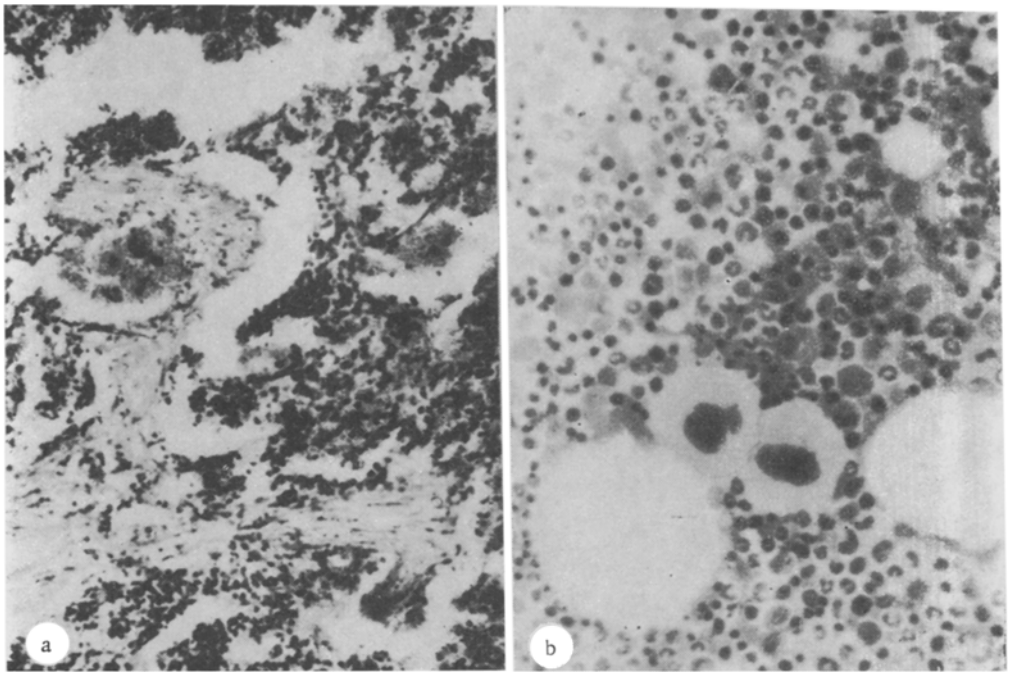

Fig. 2. Spleen and sternal marrow of experimental animals after intraperitoneal infusion of 5FU. a) Spleen on 3rd day after irrigation with 5FU for 2 days. Marked congestion of pulp with dilatation of sinuses. Hematoxylin–eosin, 260 ×; b) sternal marrow on 3rd day after irrigation with 5FU for 2 days. Among numerous erythrocytes, normoblasts, and erythroblasts two megakaryocytes can be seen. Hematoxylin–eosin, 260 ×.

On the first days after irrigation with 5FU the sternal marrow responded by some intensification of erythropoiesis. Single megakaryocytes, normoblasts, and basophilic erythroblasts were observed in the bone marrow (Fig. 2b). By the 5th-10th days, however, normal erythropoiesis was restored.

The results of these experiments thus indicate that intraperitoneal infusion and absorption of 5FU in the dose studied did not induce dystrophic changes in the pancreas or hematopoietic organs. The response of the body to irrigation with 5FU on the first days consisted of acute congestion with some signs of activation of secretory activity of the pancreas; the congestion in the pancreas and hematopoietic organs disappeared completely by the 10th-60th days of observation. The bone marrow responded by some intensification of erythropoiesis during the first days after irrigation, after which erythropoiesis returned to normal, in agreement with results of other experimental studies [5].

The absence of dystrophic changes in the pancreas and hematopoietic organs as a result of local administration of 5FU in a dose of 5 mg/kg confirms its safety when used in clinical practice for the treatment of acute pancreatitis.

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