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# REINNERVATION OF A SEGMENT OF THE PANCREAS

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The pancreas is an integral organ which stands at the crossroads of local and general endocrine influences arising from the gland itself and from other organs [3]. However, the mechanisms of the central nervous regulation of this complex internal hormonal and external secretory complex have been inadequately studied. Yet there are grounds for considering that the by no means brilliant late results of pancreatic transplantation in clinical and experimental practice [12], even in cases when the effect of immune conflict is minimal or absent altogether, are not only the result of biological incompatibility, but are also connected with disturbance of regulation of the function of the transplanted organ [16]. The adverse consequences of division of the nervous connections of intestinal and renal transplants, expressed as disturbance of their function at various times after the operation, have been demonstrated by several investigations [4, 6, 7, 10, 11]. It has been shown that the method of transplantation of the kidney and intestine can be used as a model of complete nervous reflex isolation of these organs in order to study the role of nervous reflex influences in the regulation of their functions. In relation to the pancreas, however, this problem has not been studied at all.

The aim of this investigation was to create an experimental model of nervous reflex isolation of the pancreas, without permitting temporary ischemia of the organ. It was necessary to develop an anatomically and physiologically based model of restoration of the innervation of the pancreas after its nervous reflex isolation or transplantation.

## EXPERIMENTAL METHOD

Experiments were carried out on 22 dogs, 32 cats, and nine rabbits. To obtain anatomically sound methods of reinnervation, the splenic and hypogastric plexuses of 12 dogs, 10 cats, and five rabbits were studied by dissection and morphometry. The following operations were performed: nervous reflex isolation of the "body—tail" segment of the pancreas of the different animals without disturbance of its blood supply, by dividing all connections between it and the rest of the body, division of the gland

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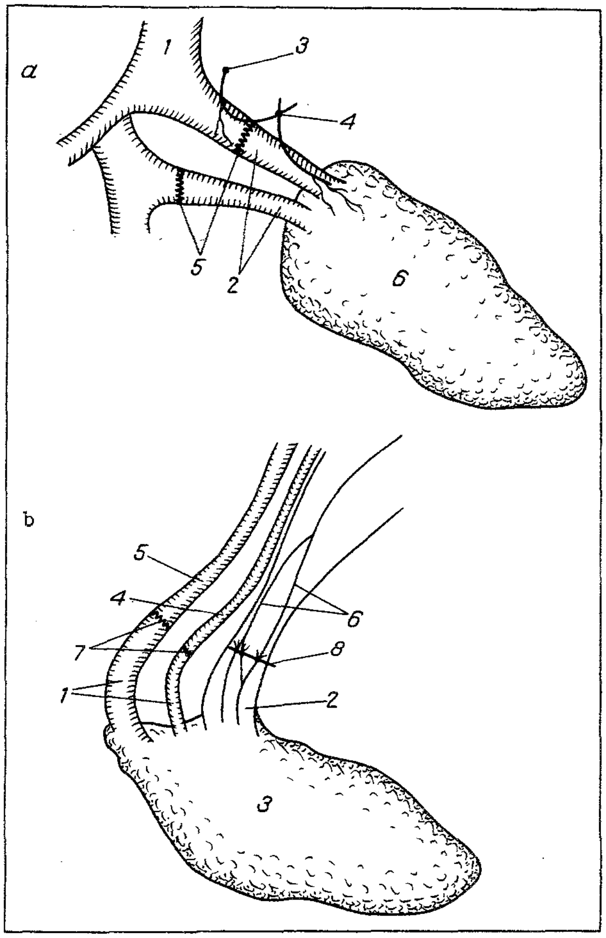


Fig. 1. Diagram of orthotropic (a) and heterotopic (b) reinnervation of the "body—tail" segment of the cat pancreas. a) Splanchnic trunk (1), splenic vessels (2), splenic nerve plexus (3), suture of nerve trunks of splenic plexus (4), vascular anastomosis (5), graft (6); b) splenic vessels (1), splenic plexus (2), graft (3), iliac artery (4), and vein (5), hypogastric nerve plexus (6), anastomosis of blood vessels (7), suture of nerve plexuses (8).

itself at the appropriate level, and division of the fascia and nerve trunks of the splenic plexus around the splenic vessels proximally and distally to the sites of branching of the pancreatic vessels; orthotopic reinnervation of the nervous reflex-isolatedsegment of the pancreas by suturing the previously divided trunks of the splenic plexus by epi- and paraneural interrupted sutures (Fig. 1a), heterotopic reinnervation of the pancreas after its transplantation by methods described previously [5, 8], by suturing the nerve trunks of the divided splenic plexus to nerve trunks of the hypogastric plexus, which also includes in its composition both sympathetic and parasympathetic fibers (Fig. 1b). The state of pancreatic function was studied by biochemical tests, the blood sugar was determined by the glucose oxidase method and the rapid method using "Dextrostix" strips, the blood amylase level by Caraway's method in the modification of Yu. I. Naumov and N. V. Zaretskaya, the concentrations of P-peptide and motilin in the blood by radioimmunoassay, and blood levels of nucleotides, RNA and DNA. The neuronally isolated and transplanted pancreas, after staining with hematoxylin and eosin and impregnation with silver by the Bielschowsky—Gros method, also was subjected to histological investigation. Numerical results were analyzed statistically by Student's test.

## EXPERIMENTAL RESULTS

After nervous reflex isolation of the pancreatic segment changes similar to those described after autographing of a segment of the pancreas with or without restoration of the flow of pancreatic juice were observed in all species of experimental animals with reflex isolation of the pancreatic segment [5, 8]. The glucose loading test also revealed a shift of the curves upward

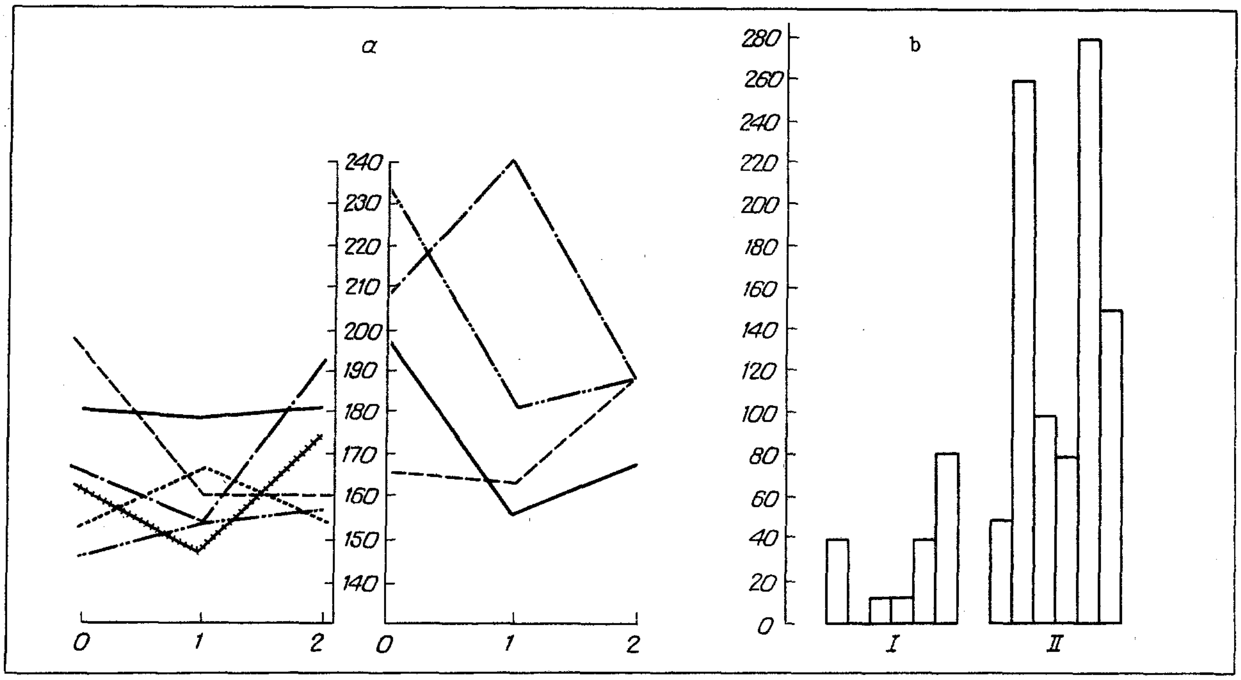


Fig. 2. Effect of nervous reflex isolation of pancreatic segment on its secretory function. a) Blood amylase level (in units) in dogs; b) concentration of P-peptide (in rabbits). Abscissa, time after injection of glucose (in h); O) before injection of glucose; ordinate, P-peptide (pg/ml). I) Control, II) after nervous reflex isolation.

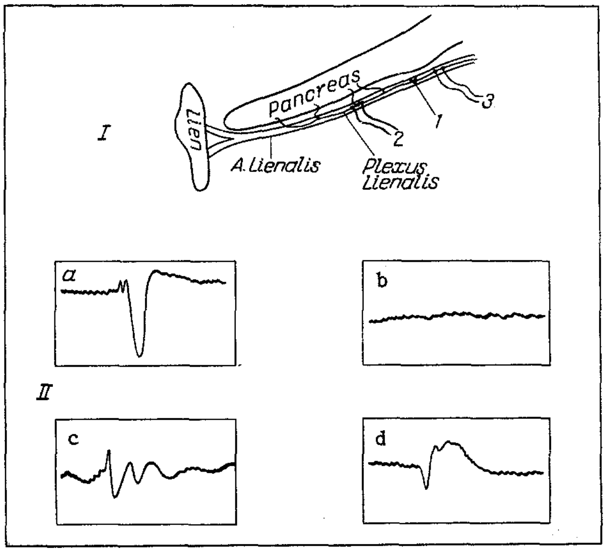


Fig. 3. Results of investigation of evoked potentials. I) Diagram showing arrangement of electrodes: 1) nerve suture; 2, 3) electrodes. II: a) Normal response of reticular formation to stimulation of pancreas; b) 1 h after nervous reflex isolation: stimulation of isolated segment of gland did not evoke a response in the brain; c, d) 3 months after reinnervation (orthotopic). Simulation of "body—tail" segment of pancreas evokes a response in the cortex (c) and reticular formation (d).

and to the left, i.e., intensification of the hyperglycemic reaction, but shortening of its duration. A tendency also was observed for the blood P-peptide and amylase levels to rise (Fig. 2). Parameters such as the blood levels of motilin, nucleotides, and RNA and DNA showed no significant change after nervous reflex isolation of the pancreatic segment but remained within the limits of 150-180 pg/ml for motilin, 70-100, 44-100, and 500-800 μg/ml for nucleotides, RNA and DNA, respectively. Only after allografting of a segment of the pancreas, i.e., in the case of biological conflict with the recipient, was an increase in the blood levels of nucleotides, RNA, and DNA to 235, 143, and 1300 μg/ml observed, compared with 73 ± 5.90 ± 15, and 870 ± 100 μg in the control, which evidently reflects necrosis of the graft tissues at the time of the rejection crisis. In the late stages after reflex isolation of the pancreas sclerosis of this segment was observed and was particularly marked in the case when drainage of the pancreatic juice was absent.

The beginning of passage of impulses from the pancreas to the brainstem reticular formation and cerebral cortex was observed 3 weeks after surgically guided orthotopic reinnervation. Normal evoked potentials to each stimulus of the pancreas by a series of pulses (50 mV) in the course of 0.3 msec were not recorded until 3-4 months after the operation (Fig. 3). Reinnervation was confirmed morphologically. The effect of reinnervation on restoration of pancreatic function and preservation of its structure was studied and first impressions were positive, but the information obtained is still insufficient to allow conclusions to be drawn.

Analysis of the data showed that after nervous reflex isolation of the pancreatic segment, even if the remainder of the gland was preserved, there was a tendency for pancreatic secretion of enzymes and hormones to increase. The increase in insulin secretion explains the shortening of the hyperglycemic reaction of the dogs to a standard glucose load. This means a tendency toward hyperfunction of the exocrine and endocrine tissue of part of the organ deprived of its nervous connections with the CNS. These observations agree with data on function of the reflex-isolated intestine [4, 7] and they can be explained in terms of the concept [3] of the hypersensitivity of denervated structures to humoral stimuli. They also indicate a predominantly inhibitory influence of the CNS on pancreatic secretory activity, just as on function of the intestine, kidney, and heart. In this situation one concept does not exclude the other.

A convenient experimental model has thus been created to allow the isolated study of the action of long-term abolition of central nervous reflex influences on pancreatic structure and function and to monitor their recovery. Considering the importance of abolition of central nervous influences as protection or adaptation of the organ to a pathological situation, the creation of a model of long-term deafferentation provides new opportunities for theoretical research. An analogy is found between certain disturbances of structure and function after pancreatic autografting and its nervous reflex isolation, evidence that the nervous factor plays a role in the pathogenesis of these disorders. Accordingly, if it becomes possible to restore connections of the graft with the CNS surgically, this will be of great applied importance in clinical transplantology.

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