COMPENSATION OF EXPERIMENTAL INSULAR INSUFFICIENCY BY MODIFICATION OF THE PORTAL BLOOD FLOW

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The search for ways of correcting insular insufficiency is a matter of urgency at the present time because the problem of diabetes has not been solved. In view of data indicating that insulin is metabolized in the liver [3, 6, 7, 8], it is interesting to study possible ways of preserving and utilizing most fully the endogenous insulin. It has been shown [2] that selective drainage of venous blood from the pancreas (by-passing the liver) into the systemic circulation by splenicocaval anastomosis (SCA) in dogs can reduce experimental hyperglycemia.

In the investigation described below the compensatory powers of the endocrine tissue of the pancreas after resection and the effect of SCA accompanying this procedure on carbohydrate and lipid metabolism and on the state of the liver were investigated.

EXPERIMENTAL METHOD

Altogether 26 experiments were carried out on mongrel dogs weighing from 10 to 25 kg. Animals of group 1 (13 dogs) underwent subtotal resection of the pancreas. A piece of pancreas equivalent to 20% of its total weight, receiving its blood supply from the splenic vessels, was left in situ. Venous blood drained from it along the splenic vein and in the usual way into the liver. The pancreatic duct was ligated. Subtotal resection of the pancreas was performed on 13 dogs in group 2 and this was accompanied by the formation of an SCA by the method described below. The splenic vein was divided where it empties into the portal vein, its distal end was ligated, and its proximal end, carrying blood from the pancreas, was anastomosed with the inferior vena cava. Under these circumstances insulin from the pancreas passed into the systemic circulation, whereas glucose and gastrointestinal hormones were carried to the liver in the usual way. Blood was taken from the femoral vein of all the animals before and 2, 7, 14, 30, 60, 90, and 120 days after the operation; the blood sugar was determined in the fasting state and during the glucose tolerance test (GTT; 1 g glucose/kg body weight per os) by the neocuproin method, and the following determinations also were carried out: insulin, C-peptide, and glucagon, by radio-immunoassay using standard test kits. Regularly once a month triglycerides and total cholesterol were investigated. Dogs of group 1 were withdrawn from the experiments after 1, 2, and 4 months, and dogs of group 2 were withdrawn 2 and 4 months after the operation. Patency of the SCA was verified visually in all animals of group 2. Material for histochemical study consisted of the pancreas, liver, and gastrocnemius muscle. Sections were stained with hematoxylin and eosin and by Van Gieson's method. Natural fat was demonstrated by Sudan III and glycogen by Shabadash's method with amylase control.

EXPERIMENTAL RESULTS

Of the 26 dogs seven died: four from the anesthetic, three from intestinal obstruction and peritonitis 1-7 days after the operation. Parameters of carbohydrate metabolism, given in Table 1 and Fig. 1, show the temporary character of the hyperglycemia after subtotal resection of the pancreas. By the end of the first month after the operation the normal fasting blood sugar level was restored, and by the end of the 3rd or 4th months, the GTT was normal.

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TABLE 1. Parameters of GTT (in mg %) at Different Times after Operation (in min)

Type of operation (n=7)	1 month after operation				3 months after operation			
	0	30	60	120	0	30	60	120
Resection (control) (n=7)	111±6	239±44	171±22	120±3	122±4	212±30	152±23	122±7
Resection + SCA	105±8	161±22*	144±15	101±7	101±4	169±15	154±21	122±11

Legend. *P < 0.05.

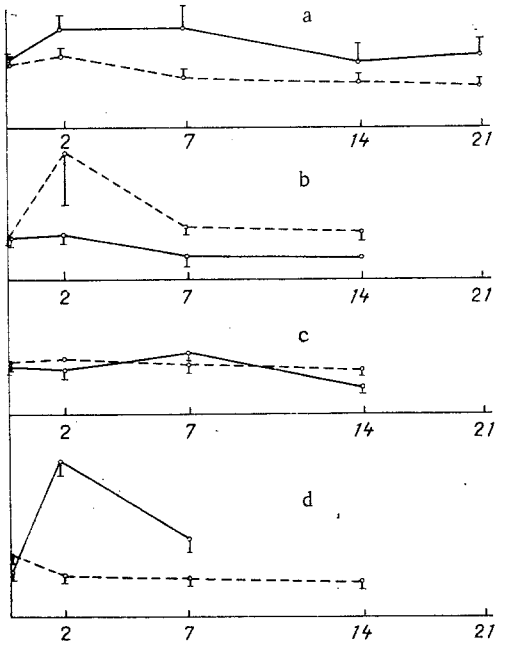

Fig. 1. Time course of parameters of fasting carbohydrate metabolism after subtotal resection of pancreas (continuous line) and after SCA (broken line). Abscissa, days after operation. a) Glucose (in mg %), b) insulin (in IU/liter), c) C-peptide (in ng/ml), d) glucagon (in ng/ml).

No significant changes were found in concentrations of insulin and C-peptide, but the glucagon level showed a marked rise during the first week after the operation.

Shunting the blood by SCA led to an increase in the insulin concentration in the peripheral blood for 1 week after the operation. This was not due to increased insulin production by the pancreas, for the C-peptide level was unchanged. The blood sugar, despite resection of 80% of the pancreas, became normal by the end of the first week. By the end of the first month the GTT values were back to normal in the dogs of group 2. The glucagon concentration was very slightly reduced. As regards lipid metabolism, no changes in its parameters could be observed in the animals of group 1. In dogs of group 2 the operation of SCA led to a fall in the triglyceride level: 78 ± 9.5 mg % before the operation, 51 ± 5 mg % 4 months after it (P = 0.05). The fall in the cholesterol level was not significant.

The results of the biochemical tests thus demonstrate that selective drainage of blood carrying insulin from the pancreas, by-passing the liver at the first passage, into the systemic circulation causes more rapid compensation of the hyperglycemia produced by subtotal resection of the pancreas. This can be explained by preservation of the endogenous insulin

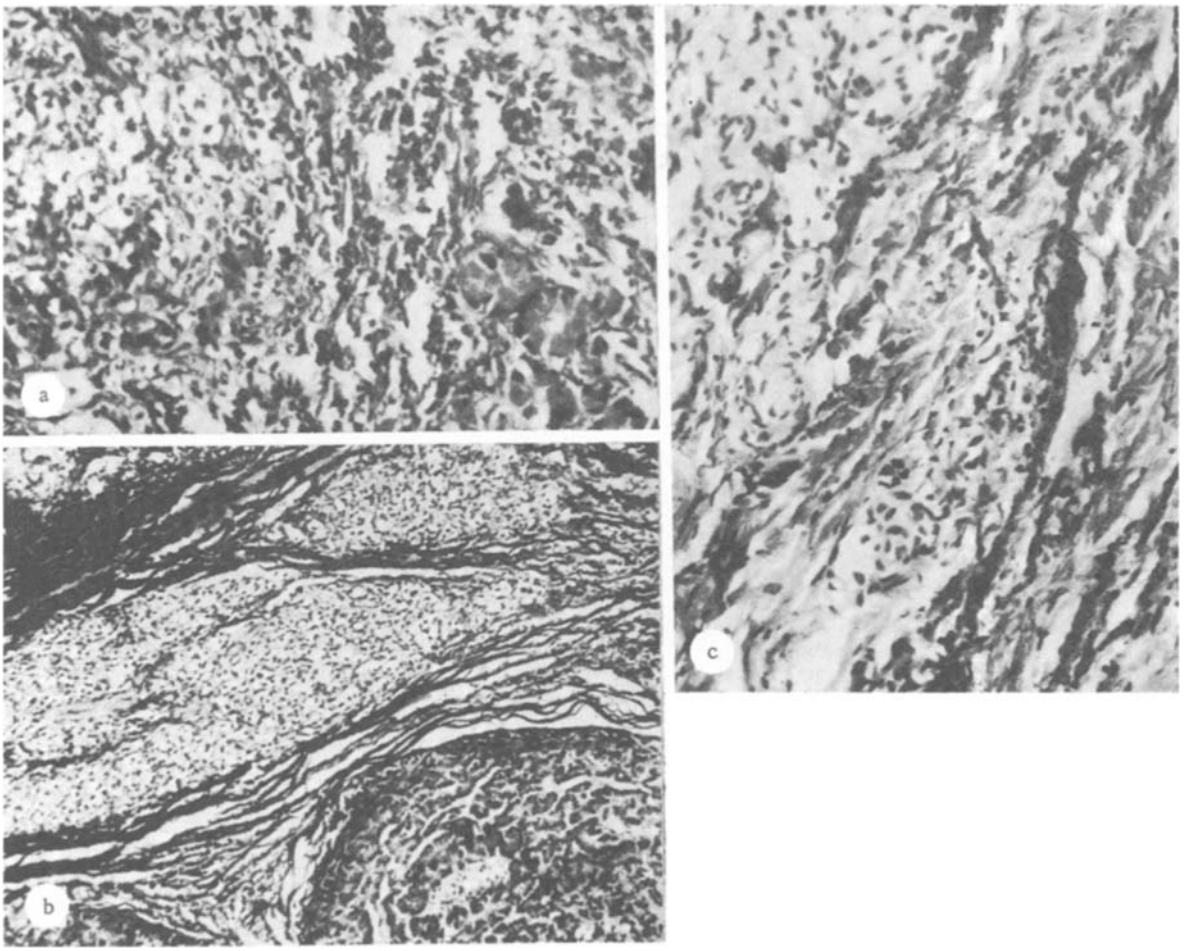

Fig. 2. Time course of morphological changes in pancreas after subtotal resection and SCA. a) Degeneration and necrobiosis of parenchyma against a background of proliferation of a connective-tissue cells, 1 month after operation. Hematoxylin-eosin 250 ×; b) pancreatic fibrosis with pseudolobule formation and formation of areas of endocrine tissue in place of the necrotic acini, 2 months after operation. Van Gieson. 100 ×; c) coarse scar replacing pancreas 4 months after operation; groups of endocrine cells visible between collagen fibers. Van Gieson. 250 ×.

which, since it is not metabolized in the liver, promotes glucose utilization by peripheral tissues.

Visual inspection of the anastomosis when the animals were withdrawn from the experiment showed that in two dogs the SCA was constricted to 1.5 mm but in the rest it was well patent. Histological investigation 1 month after resection showed inflammatory changes in the pancreas (infiltration by neutrophils, lymphocytes, and plasma cells), and atrophy and necrosis of the acinar cells and of whole lobules (Fig. 2a), with their gradual replacement by fibrous tissue. Connective-tissue cells, penetrating inside the pancreas, formed "pseudolobules." Intensified atrophy of the acini was observed in them: vacuolation of the cytoplasm and balloon degeneration. The lumen of the interlobular and intralobular ducts was dilated and devoid of contents. The epithelium of the ducts also showed various degrees of dystrophy and atrophy: Basophilia of the cytoplasm, shrinking and reduction in size of the nuclei were observed. In areas of inflammation no ducts could be identified. Changes in the endocrine tissue were mosaic in character. The number of islets of Langerhans (IL) in the preserved lobules was one or two per square millimeter; in the fibrosed lobules, besides atrophy of the acini, endocrine cells no longer connected with one another and scattered throughout the lobule could be seen.

Against the background of progressive fibrosis of the pancreas 2 months after resection a combination of atrophy in the acini and duct system with hypertrophy in the insular tissue

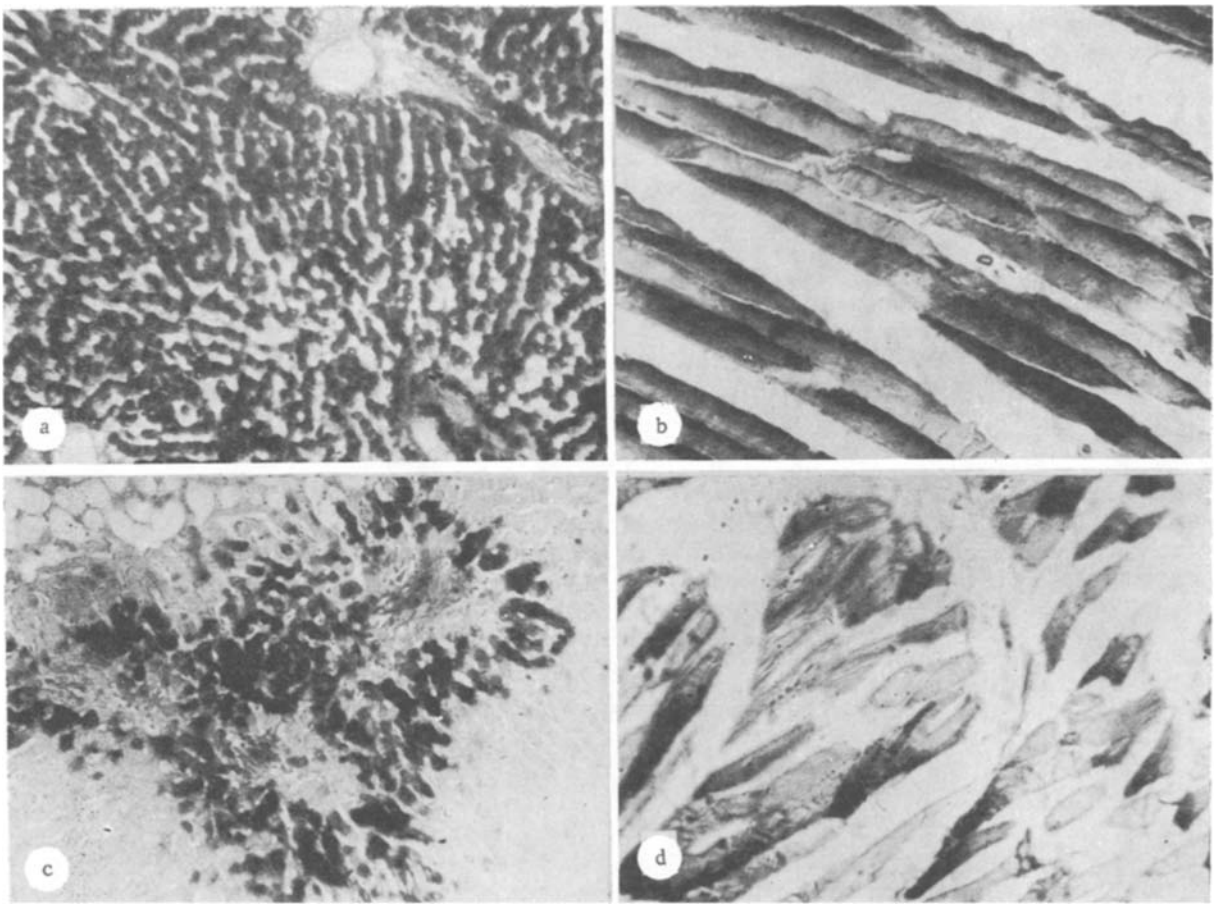

Fig. 3. High glycogen content in liver (a) and gastrocnemius muscles (b) in dogs of group 1 after subtotal resection, and marked decrease in glycogen content in the same organs (c and d respectively) in dogs of group 2 after SCA. Shabadash's reaction . · 100 ×.

was observed in dogs of both groups against the background of progressive fibrosis of the pancreas in the "pseudolobules" (Fig. 2b). In cases of complete absence of acinar cells in the remnants of the lobules no epithelial duct could be found, but the predominant cells (50%) were undifferentiated cells with basophilic nuclei and indistinct cytoplasm. There were 30% of cells with elongated nuclei, surrounded by thin collagen fibers (fibroblasts), and 20% of typical endocrine cells, scattered among the other kinds of cells.

Four months after the operation (Fig. 2c) the stumps of the pancreas were found with difficulty, for they consisted of a scar measuring 1.0 × 0.5 × 0.5 cm^3. On histological examination the structure of the gland was completely destroyed. Ducts were not differentiated and acini were absent. Among the coarse, thickened collagen fibers, loose bands of well vascularized and innervated scar tissue could be seen, with concentrations of endocrine cells among them. In the peripheral parts involution of the scar was observed: It was replaced by adipose tissue in which concentrations of endocrine cells also were visible.

The character of the morphological changes in the pancreas, incidentally, was the same in dogs of both groups. Resection of the organ and ligation of the duct led to atrophy, necrobiosis, and focal necrosis of the acinar cells. The organ was gradually replaced by fibrous tissue. Endocrine cells appeared less vulnerable to the damaging action of ligation of the duct and development of fibrosis. Initially they remained intact, but later they lost their close connections with each other, and during progression of the fibrosis they underwent hypertrophy, to form well vascularized and innervated groups scattered among the connective-tissue fibers, and in the course of involution of the scar, between cells of the fatty areolar tissue.

The endocrine tissue of the pancreas, unlike its acinar tissue, thus possesses great powers of compensation, in agreement with results obtained by other workers [1].

Histological investigation of the liver of dogs of group 1 at all times of the experiment revealed signs of cloudy-swelling degeneration and focal fatty degeneration, and the glycogen content was increased (Fig. 3a). Cloudy-swelling degeneration and focal fatty degeneration also were observed in animals of group 2, but the glycogen content of the liver was sharply reduced, and it could be detected only at the periphery of the lobules (Fig. 3c). The character of glycogen distribution in the peripheral muscles of the dogs corresponded to its content in the liver (Fig. 3b, d). These results show that SCA does not lead to any gross changes in the structure of the liver. Cases of focal fatty degeneration observed equally in the two experimental groups may be the result of subtotal resection of the pancreas and ligation of its duct [4, 5], whereas the fall of the glycogen level in the groups with SCA is perhaps connected with its more intensive metabolism as a result of rapid utilization of glucose.

Data showing a raised peripheral blood insulin level and more rapid compensation of hyperglycemia after SCA, and also the identical morphological changes in the pancreatic endocrine apparatus of dogs of both groups suggest that the effects of SCA combined with subtotal resection of the pancreas are associated with a reduction in metabolization of endogenous insulin in the liver during its first passage through that organ and with increased utilization of the hormone by the peripheral tissues.

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