reprint from
ACTA DIABETOLOGICA LATINA Vol. XV - September-December 1978 - n° 5-6

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FUNCTIONAL MODIFICATIONS OF ENDOCRINE PANCREAS AFTER INTERNAL BILIARY FISTULA (EXPERIMENTAL RESEARCH)

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In a previous research [2] we observed that the total internal biliary fistula (IBF), obtained by performing a cholecysto-jejunostomy after closure of the common bile duct, can remarkably affect the endocrine pancreas of the dog. After this operation, in fact, the number and total volume of the pancreatic islets show a 3-fold increase in 60 days and the percentage of B-cells in the islets is also increased.

In order to gain a better understanding of the adaptive mechanism operating in this experimental model, we decided to explore the endocrine function of the pancreas of the operated dogs, so as to verify if the increase of islet tissue resulting from IBF is accompanied by an increased ability of the islet to release insulin when required.

MATERIALS AND METHODS

In order to compare the results of the morphologic and endocrine investigations, in these experiments we followed the previously reported surgical procedure [2].

Twenty mongrel dogs, from 2 to 4 years old and about 10 kg body weight, were divided into two groups of 10 animals each, and were either submitted to IBF or used as controls. Surgery was well tolerated by the animals: there was neither change in food intake nor weight loss. Operated and control dogs were maintained in the same conditions and fed the same standard diet (500 g meal, containing 35% protein, 20% lipid and 45% carbohydrate on a dry weight basis, supplemented with salt and vitamins). Experiments were always preceded by a 24-h fast.

The endocrine function of the pancreas was explored 45-60 days after surgery, i.e. when the morphologic changes of the islet tissue had reached their maximum.

Key-words: Biliary fistula; Endocrine pancreas; Experimental biliary fistula; Internal biliary fistula.

Received: May 31, 1978.

Acta diabet. lat. *15*, 303, 1978.

The following tests were performed: basal levels of blood glucose and serum insulin; IVGTT (0.50 g/kg body weight as a 50% solution); tolbutamide test (1 g of pure substance – Rastinon®, Hoechst – administered i.v. at time 0).

Blood glucose and serum insulin were always assayed in the same serum specimen. Blood glucose was determined by the photometric reading (Ames Reflectance Meter) of reactive paper strips (Destrostix, Ames). Serum insulin was determined by double antibody radioimmunoassay technique [3] using commercially available kits (The Radiochemical Center, Amersham). Human insulin was used as standard.

Results were submitted to statistical evaluation by analysis of variance (F-test)*, individual differences being checked by the Tukey test.

RESULTS

When the results obtained in operated and control dogs are compared, it becomes apparent that most indices of endocrine pancreatic function were changed after IBF.

Basal blood glucose was significantly decreased after IBF ($p<0.01$); simultaneously, serum insulin was lower than normal, but this decrease was not significant (fig. 1).

In operated dogs, the response to IVGTT was remarkably different from that of control dogs. As for blood glucose curves (fig. 2), the 5-min values were always significantly lower than normal ($p<0.01$); also, the subsequent decrease of blood glucose concentration was much faster ($p<0.01$). Serum insulin (fig. 3) was higher than normal after 5 and 15 min ($p<0.05$), but subsequently decreased at a faster rate than in the controls.

The tolbutamide test, too, yielded different results after IBF (fig. 4) even though changes were less marked and more difficult to interpret than those of the IVGTT. In the operated dogs, blood glucose concentrations reached their lowest values much earlier (i.e. 20 min after tolbutamide injection) than in controls so that the decrease at 40 min was less marked than normal ($p<0.01$). As regards serum insulin, changes after tolbutamide did not significantly differ in operated and in control animals (fig. 5). However, a different insulin pattern became apparent when results were expressed as per cent changes with respect to hormone concentrations at time 0.

DISCUSSION

Our results indicate that IBF remarkably affects B-cell function. According to the results of the function tests, the ability to release insulin is increased after surgery and this causes an increased carbohydrate tolerance.

This shows the enlargement of islet tissue resulting from IBF to be a true hypertrophic process, i.e. the endocrine function of the islet tissue increases with islet number and total volume, at least as far as the B-cells are concerned.

This artificially induced hyperfunction manifests itself as increased ability to release insulin under stimulation rather than as a constant increase of insulin secretion. In fact, the decrease of basal blood glucose was significant (fig. 1) although not considered

* F-test includes the following parameters: effect of operation (OF), effect of time (TF) and effect of interaction (IF).

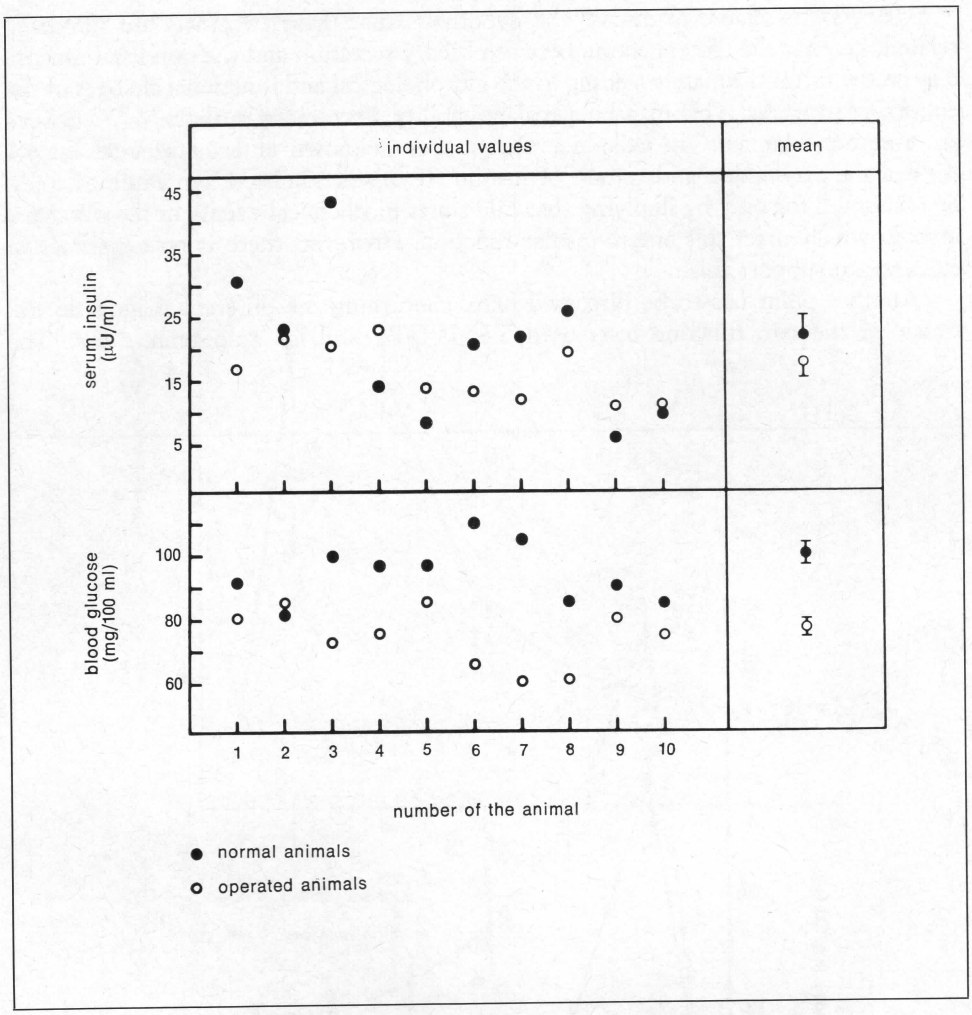

Fig. 1 - Basal blood glucose and serum insulin levels in normal and operated animals. A 24-h fast preceded each experiment.

a true hypoglycemic state but cannot be accounted for by insulin changes (whose serum levels were simultaneously decreased). We have no explanation for this finding; we may only add that we could observe a case of fatal hypoglycemia in an operated dog after a 2-day fast. On the other hand, blood glucose and insulin changes after glucose load or tolbutamide administration showed higher B-cell reactivity, these results being in accordance with the expectation that the control of hormone release would be preserved in the hypertrophic gland.

In order to unterstand the adaptive mechanisms which are at the basis of our findings, we should consider two essential aspects of this experimental model. First, in animals with IBF duodenal bile flux is completely and permanently suppressed and, second, increased B-cell function is the consequence of a hypertrophic process which has been previously reported.

It seems justifiable to discuss the hypothesis that these two facts are somehow related, i.e. that the disconnection between biliary secretion and the duodenal mucosa may be the factor ultimately leading to the morphological and functional changes of the endocrine pancreas. This may be a real possibility since many authors [4,5,7,8,9] believe an 'entero-insular axis' to exist, i.e. that as yet unknown entero-hormonal factors control the production and release of insulin. If this is admitted, our findings could be accounted for only by implying that bile starts biochemical events in the duodenal mucosa which affect this entero-insular function. However, there is no experimental evidence to support this.

Another point has to be discussed here, concerning the different diagnostic efficiency of the two function tests used, i.e. IVGTT and i.v. tolbutamide test. The

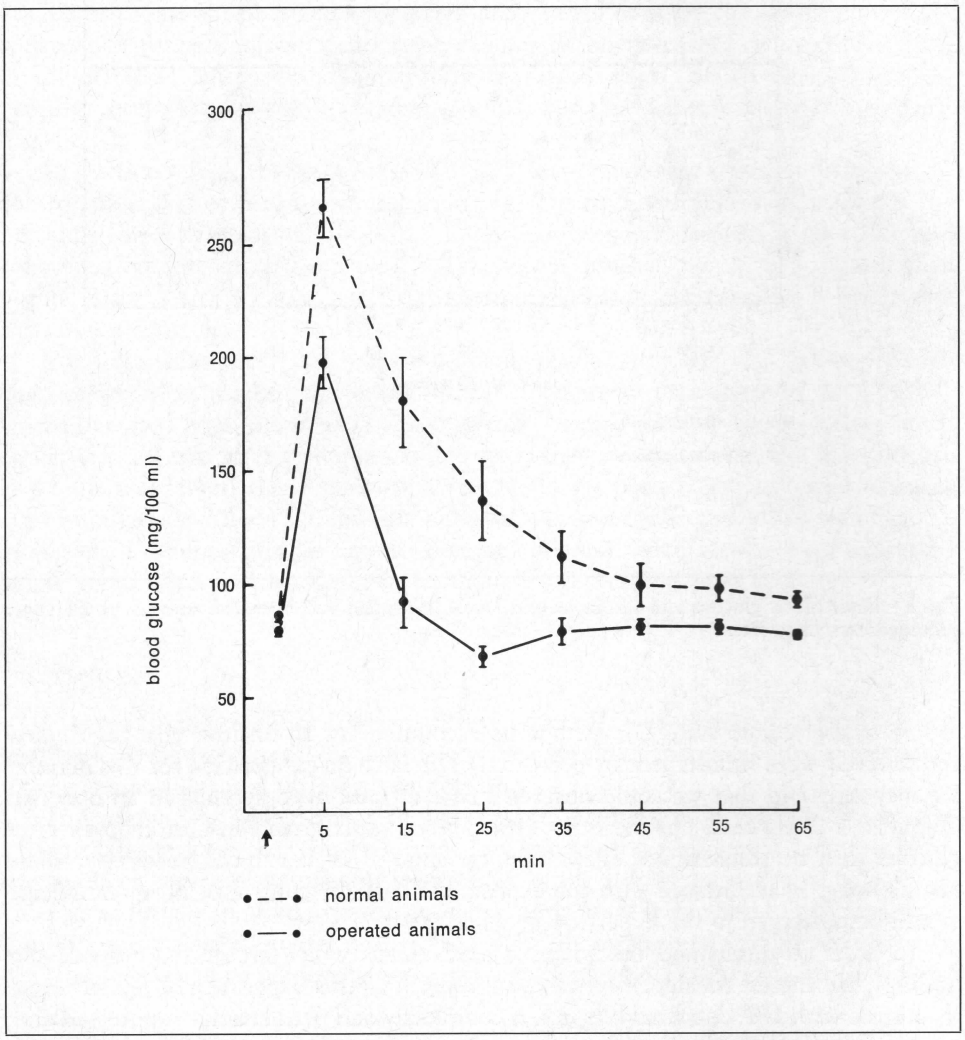

Fig. 2 - Changes of blood glucose in normal and operated animals during IVGTT (0.5 g/kg body weight). OF = 66.08 ($p \ll 0.01$); TF = 54.00 ($p \ll 0.01$); IF = 5.05 ($p < 0.01$).

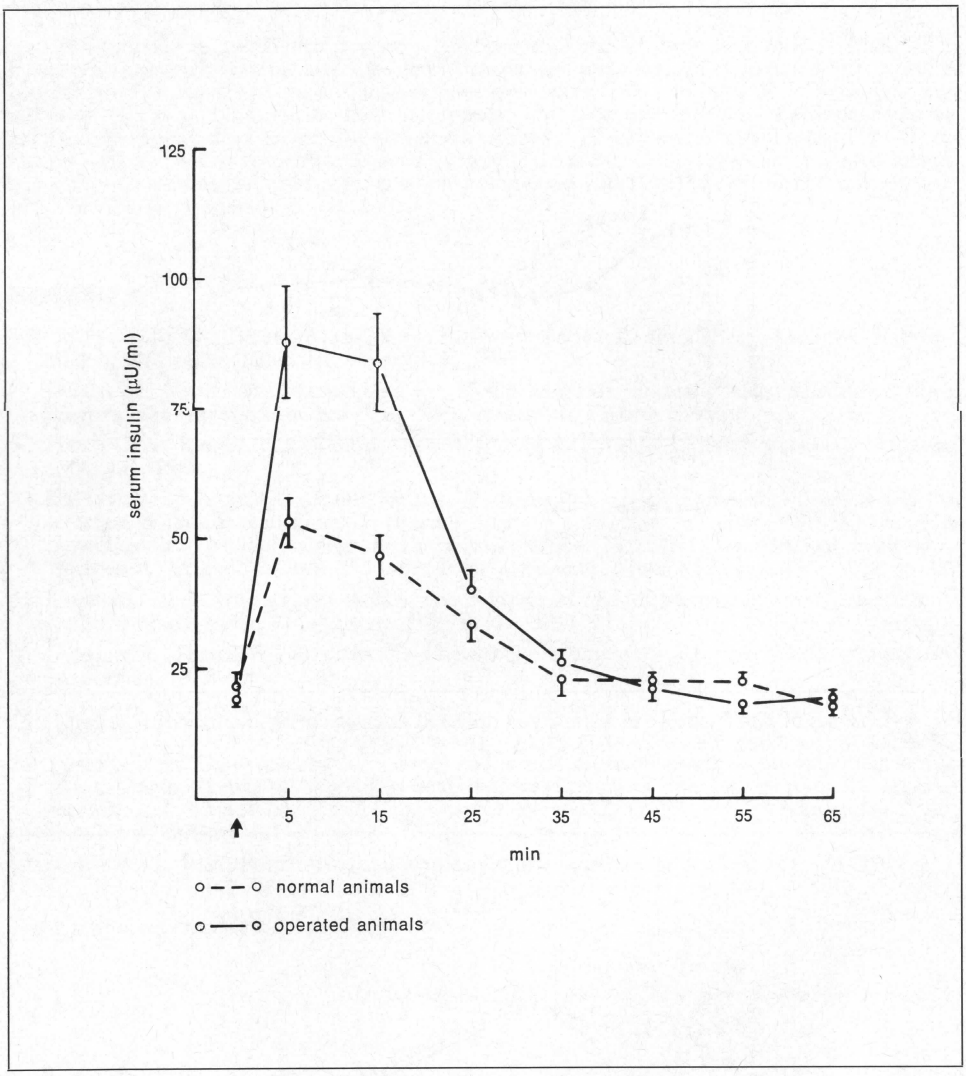

Fig. 3 - Changes of serum insulin in normal and operated animals during IVGTT (0.5 g/kg body weight). OF = 4.18 ($p<0.01$); TF = 10.90 ($p<0.01$); IF = 1.58 (n.s.).

former proved to be a more sensitive index of the changes occurring in the endocrine capacity of the gland. These differences at least partly reflect the different meaning of the two tests: IVGTT, based on a purely homeostatic reaction, expresses the real capacity of the B-insular system; the effects of the i.v. tolbutamide test, on the contrary, not only depend on dosage and on the functional capacity of the islet tissue but also on extrapancreatic factors. Furthermore, we should emphasize that the mild hyperreactivity to tolbutamide observed contrasts with the dramatic effect of drug administration in human hyperinsulinism of neoplastic origin [1,6]. This is in line with the fact that islet tissue changes caused in the dog by IFB had no pathological consequences.

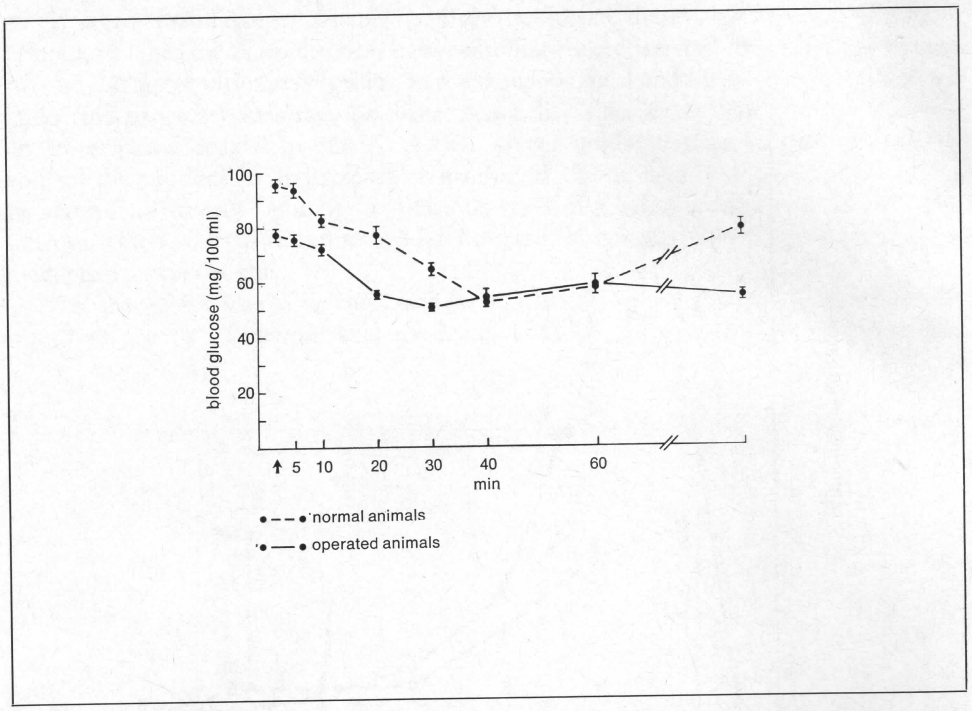

Fig. 4 - Changes of blood glucose in normal and operated animals during i.v. tolbutamide test (1 g). OF = 48.78 ($p \ll 0.01$); TF = 23.17 ($p \ll 0.01$); IF = 3.40 ($p < 0.01$).

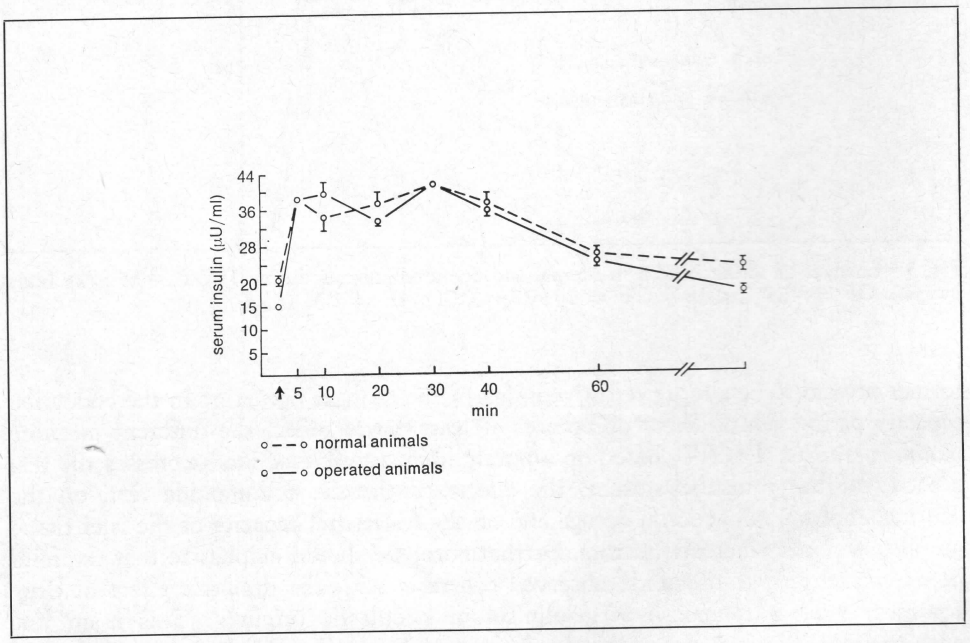

Fig. 5 - Changes of serum insulin in normal and operated animals during i.v. tolbutamide test (1 g). OF = 0.36 (n.s.); TF = 6.24 ($p < 0.01$); IF = 0.29 (n.s.).

SUMMARY

The function of the B-insular system has been explored in dogs with total internal biliary fistula (cholecysto-jejunostomy after closure of the common bile duct), an operation which causes an increase in the number and total volume of pancreatic islets. Two groups of 10 animals each were either submitted to operation or used as controls. The endocrine function of the pancreas was explored 45-60 days after surgery by assessing basal blood glucose and serum insulin. IVGTT and i.v. tolbutamide test were performed subsequently. The results indicate that in operated animals the ability to release insulin after stimulation is increased and that the control of basal hormone secretion is fully preserved.

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