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PRELIMINARY COMMUNICATIONS

The Effect of Splenectomy on Carbohydrate Metabolism

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Summary. The authors have studied the role of the spleen in carbohydrate metabolism in animal experiments as well as in humans in connection with splenectomy. — Splenectomy was found to exert on carbohydrate metabolism an acute influence which is not identical with glycogenolysis induced by surgical stress.

Effet de la splénectomie sur le métabolisme des hydrates de carbone

Résumé. Les auteurs ont étudié le rôle de la rate dans le métabolisme des hydrates de carbone, dans des expériences effectuées sur l'animal aussi bien que chez l'homme, en relation avec la splénectomie. — Ils ont trouvé que la splénectomie exerce sur le métabolisme des hydrates de carbone une influence aiguë qui n'est pas identique à la glycogénolyse produite par le stress opératoire.

Auswirkungen der Milzexstirpation auf den Kohlenhydratstoffwechsel

Zusammenfassung. Die Verfasser untersuchten die Rolle der Milz im Kohlenhydratstoffwechsel durch Tierexperimente und am Menschen nach Splenektomie. Der Eingriff beeinflußte den Kohlenhydratstoffwechsel unabhängig von der durch den Operations-Stress induzierten Glykogenolyse.

Key-words: Splenectomy, diabetes mellitus after splenectomy, diabetes mellitus, abdominal vessels, carbohydrate metabolism, insulin antagonism.

In recent years research workers concerned with diabetes mellitus have been devoting steadily increasing attention to the role of insulin-binding and neutralizing substances in the pathology of the disease [2, 14, 15, 11, 1, 3, 12].

An outstanding part is attributed — among others — to the lymphoid system in the production of antibodies. Starting from this assumption, attempts have been made to apply immuno-suppressive substances in cases of diabetes resistant to insulin [8, 4, 13]. CONSTANZI et al. [5] immunized guinea-pigs with insulin. It was shown that upon the effect of insulin marked local and distal lymphoid reaction developed, the spleen being the most actively involved in this respect. At histological examination lymphoid hyperplasia, eosinphilia and a slight increase of plasma cells could be observed. Histo-immunological findings obtained by various techniques indicated that reaction to insulin was the specific cause responsible for hyperplasia of the lymphatic system. It was demonstrated that antigens could be found in the cytoplasm of mature lymphocytes as well as in a few histiocyte elements of the spleen, whereas they were absent from other mesenchymal cells deriving from the RES. Although plasma cells and lymphocytes were known to be closely connected with antigen production, STEIGERWALD et al. [17] were the first to point out the fact that these cells produced insulin antibodies too in immunized animals.

Besides the general immunological role of the spleen, the significance of local circulatory conditions is also an issue to be considered. It is known that insulin is liable to be bound by its antigens intravasally. The anatomical conditions of the vascular system of the spleen raise the possibility that in certain cases the inactivation of insulin may take place partly or entirely in the area before the liver.

The aim of the present study was to gain insight into the role of the spleen in carbohydrate metabolism.

Methods and results

1. Animals experiments have been performed on rabbits and cats. The animals were operated under pentothal anaesthesia, while arterial blood pressure values were registered in the femoral artery. The animals were starved for twelve hours before surgery. The blood sugar level was read before the operation: after laparotomy and exposure of the portal vein and the vena cava inferior we performed splenectomy. Blood samples were collected from the two above mentioned vessels before and after splenectomy at several points in time (Table 1). The sugar level was determined in every sample after the method of SOMOGYI-NELSON, and so too were fatty acids, triglyceride and non-esterified fatty acid values [16, 10, 6]; the insulin-like activity (ILA) of serum was determined by our own method [9]. The summary of our method is as follows. We used an isolated frog heart preparation sec. STRAUB. We decided that, using certain glucose solutions, the added insulin and insulin-like material produced according to its (ILA) concentration proportional a diminution of glucose.

For these studies we used fourteen one-year-old male rabbits of 6 kg average weight, and ten cats of both sexes of 5 kg average weight. As controls, five rabbits and five cats were subjected to the same procedure, without splenectomy.

Table 1. *Blood sugar levels of experimental animals before and after having splenectomy in the marked periods, compared with non-splenectomised animals*

Blood Sugar Levels of Splenectomized Animals

	Initial values	5′	15′	Splenectomy 30′	60′	90
Femoral artery	94 mg% (78—124 mg%)	98 mg% (83—118 mg%)	97 mg% (81—128 mg%)	156 mg% (130—171 mg%)	117 mg% (109—139 mg%)	105 mg% (92—119 mg%)
Vena cava inferior		96 mg% (81—120 mg%)	102 mg% (90—119 mg%)	162 mg% (143—182 mg%)	125 mg% (118—149 mg%)	98 mg% (92—124 mg%)
Portal vein		95 mg% (84—117 mg%)	100 mg% (87—115 mg%)	178 mg% (141—196 mg%)	147 mg% (130—152 mg%)	119 mg% (105—136 mg%)

Blood Sugar Values of Controls

		5′	15′	30′	60′	90′
Femoral artery	96 mg% (75—121 mg%)	101 mg% (81—117 mg%)	108 mg% (82—119 mg%)	121 mg% (114—130 mg%)	131 mg% (118—140 mg%)	142 mg% (128—161 mg%)
Vena cava inferior		95 mg% (84—117 mg%)	103 mg% (91—119 mg%)	124 mg% (108—133 mg%)	137 mg% (122—150 mg%)	154 mg% (140—169 mg%)
Portal vein		94 mg% (81—109 mg%)	104 mg% (91—116 mg%)	127 mg% (112—137 mg%)	139 mg% (118—147 mg%)	155 mg% (142—173 mg%)

Fasting blood sugar values of the involved animals (rabbits, cats) are within similar limits.
Extreme values are indicated in brackets.

Table 2. *The statistical analysis according to changes of blood sugar levels in experimental animals and operated patients*

Statistical evaluation of the data was performed according to Student's "*t*" test.

Animals

	Femoral artery				Vena cava inferior				Portal vein			
	30′		90′		30′		90′		30′		90′	
	Control	Splen.	C	S	C	C	S	C	C	S	C	S
n	10	24	10	24	10	24	10	24	10	24	10	24
x	121.00	156.00	142.0	105.0	124.0	162.0	155.0	98.46	126.50	178.0	155.0	119.0
p	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
siqnificance	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high

Patients

	Finger pad								Aorta				Superior mesenteric vein			
	30′		60′		90′		180′		30′		60′		30′		60′	
	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S
n	9	7	9	7	9	7	9	7	9	7	9	7	9	7	9	7
x	123.0	154.0	142.0	118.0	142.0	106.0	130.0	101.0	137.0	164.0	149.0	132.0	133.0	176.43	146.0	149.0
p	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%	< 0.1%
siqnifi-cance	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	very high	none

The results obtained are illustrated in the tables, which demonstrate that after splenectomy blood sugar levels increased in the vena cava system as well as in

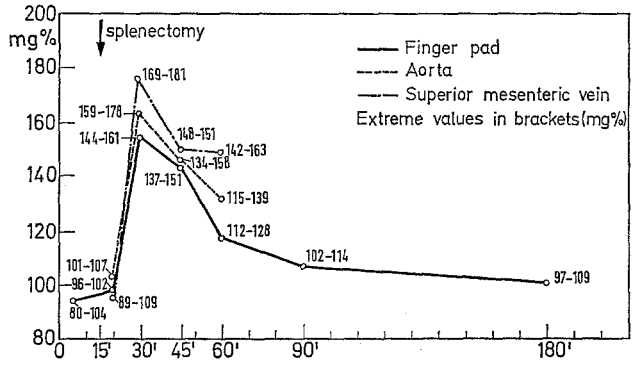

Fig. 1. The curves represent in different vessels the blood sugar level changes, in the marked moments after and before splenectomy in patients

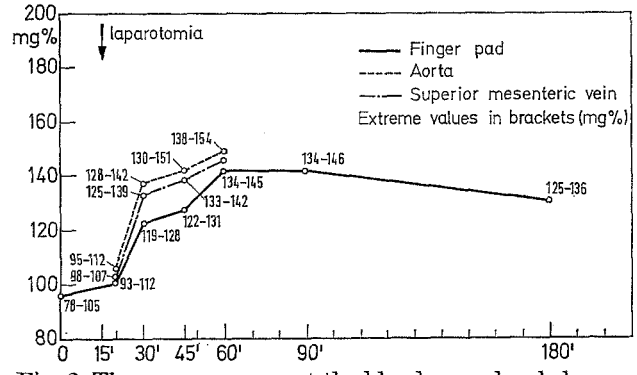

Fig. 2. The curves represent the blood sugar level changes in those patients, where a splenectomy had not been carried out

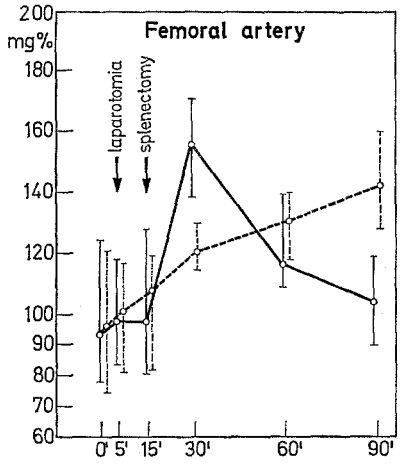

Fig. 3. A comparative blood sugar curve, taken from the femoral artery in splenectomised and control animals
——— splenectomised animals
-------- control animals

the portal vein, hyperglycaemic values being higher in the latter. When blood sugar values were read at later points of time, they were found to have returned to the initial level in the vena cava system, while in the portal system values were slightly increased up to the end of the experiment. After splenectomy, ILA displayed a moderate increase, but no appreciable change was observed in lipid values compared with those registered for the controls.

In the controls, gradually increasing hyperglycaemia was noted in both venous systems, observable up to the end of the investigation Figs. 3, 4, 5. ILA activity did not change.

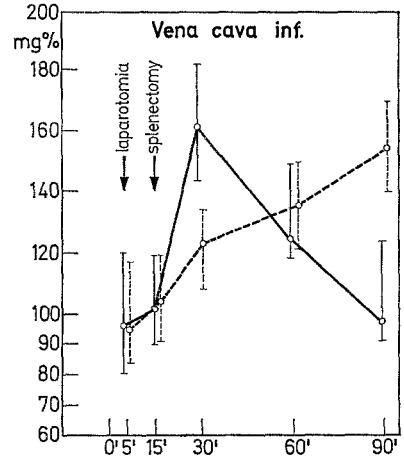

Fig. 4. A comparative blood sugar curve taken from the vena cava inferior in splenectomised and control animals
——— splenectomised animals
-------- control animals

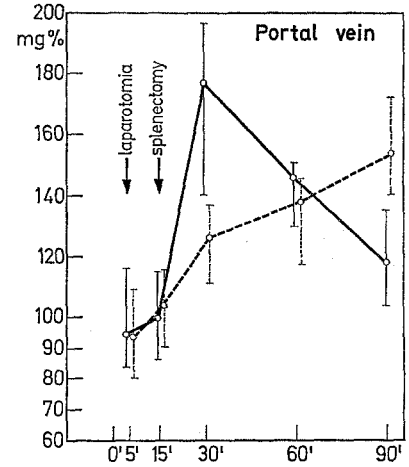

Fig. 5. A comparative blood sugar curve, taken from the portal vein in splenectomised and control animals
——— splenectomised animals
-------- control animals

2. Clinical Studies. Studies on clinical patients fall into two parts: a) observations related to splenectomy: b) other operations. All of our patients received their last meal 12 h before the operation. Significant differences between the two groups due to their body-weight, and general condition could not be found. The average time for splenectomy was 45 min, but it required another 15 min to close the abdominal wound. The opera-

tion time of the control group was generally longer, but we ended our examinations of the abdominal vessels after 60 min, the period used for the former group.

The operations were carried out under intratracheal N_2O+O_2+Halothane narcosis.

Splenectomy was performed in ten cases: for WERLhof's disease, for haemolytic anaemia, and for splenomegaly-hypersplenia. Special mention should be made of the tenth case, where splenectomy had to be performed in a diabetic on account of haemolytic anaemia. Oral dextrose load test with 100 g sugar, as well as a tolbutamide test with 1 g sodium tolbutamide was performed in every case except for the diabetic patient. The results did not reveal any pathological sign. Blood samples were collected from a finger pad directly before surgery, from the aorta and the superior mesentec vein before splenectomy. After splenectomy fresh samples were taken from these vessels. As a control, blood samples were collected for sugar tests from the same vascular area in nine other cases of laparotomy in gastrectomy for gastric carcinoma, gastrectomy for duodenal ulcer, cholecystectomy, or explorative laparatomy. The results are presented in Figs. 1 and 2.

As shown by these investigations, in seven out of nine splenectomized patients the sugar level of aortic and of peripheral blood quickly increased after splenectomy but soon began to sink gradually. Hyperglycaemia was more marked in the superior mesenteric vein than in the aorta. ILA was moderately enhanced in six cases, in the other three cases it was unchanged. No difference was observed in lipid values.

In the series where splenectomy had been omitted, hyperglycaemia was found in blood samples drawn from the aorta as well as in those from the superior mesenteric vein.

The fate of our splenectomized diabetic patient deserves special attention. The 42 years old woman had suffered for 12 years from severe diabetes mellitus. During the last 5 years she had needed 60—80 units of mixed insulin per day. Her first haemolytic signs had been observed 6 months before her operation. She had been treated unsuccessfully with large doses of corticosteroids etc. Her general state got worse, and a large splenomegaly developed. Surgical treatment, splenectomy, was decided upon. As a consequence of the steroid medication, her carbohydrate metabolism showed marked signs of abnormal lability. Just before the operation she was receiving over 140 units of insulin per day, in three injections.

On the 8th day after the operation we carried out an oral glucose tolerance test with 100 gram glucose.

Result: Fasting blood sugar level:		104 mg%
15 min after loading:		118 mg%
30	,,	134 ,,
45	,,	178 ,,
60	,,	186 ,,
90	,,	143 ,,
120	,,	109 ,,

Eleven days after the operation the patient died of pulmonary embolism.

Discussion

Our intention was to study the role of the spleen in certain acute changes of carbohydrate metabolism. It may be stated that splenectomy exerted a definite influence on sugar metabolism both in animal experiments and in the majority of the patients involved.

This effect is not identical with increased glycogenolysis induced by surgical stress, on the one hand because significant hyperglycaemia found in the posthepatic vascular area of splenectomized patients shortly returned to the initial level, on the other because the measure of hyperglycaemia was reduced less markedly in the prehepatic vascular region than in the posthepatic vascular system. Finally, the difference between arterial and venous sugar levels displayed a trend which was contrary to that observed in shock. The fact that, similar to conditions prevailing in control animals, persistently increased blood sugar levels were found in both vascular areas in non-splenectomized patients, also argues against enhanced glycogenolysis caused by surgical stress.

Our animal experiments, and studies concerned with non-diabetic splenectomized patients clearly show that splenectomy induced acute hyperglycaemia, which was later rapidly reduced in the manner described elsewhere in the present paper. In non-splenectomized operated patients, hyperglycaemia was more uniform and more sustained, and no reduction was noticeable in either vascular area up to the end of the operation.

Owing to technical reasons no changes of such a nature could be registered during surgery on our splenectomized diabetic patient. However, disorders of sugar metabolism were normalized in a noteworthy manner in the postoperative stage. For several years metabolic balance had been maintained by the administration of approximately 80 U insulin daily; from the fourth day after surgery carbohydrate metabolism was nevertheless normalized on an adequate diet, without any insulin.

According to our hypothesis, "products" of the spleen (insulin antibodies, inhibitors, norepinephrine, etc. [7] may play an acute, in certain cases, a prolonged role in the control of carbohydrate metabolism. This is suggested by our animal experiments and clinical observations. We think that after splenectomy the promoting effect of insulin on glycogen storage may assert itself more forcibly in the liver. The remarkable improvement of tolerance seen in our diabetic patient may have resulted from such a development. The initially increased posthepatic hyperglycaemia associated with splenectomy — not encountered in conjunction with the control operation — was most probably precipitated by the effect of factors deriving from the spleen. We are unable to offer any explanation for the increased hyperglycaemic values found after

splenectomy in the prehepatic vascular area, values which were moreover higher than posthepatic readings.

In non-diabetic, splenectomized patients endocrine balance was subsequently restored. This is confirmed by the results of carbohydrate load tests performed after splenectomy.

Further studies on the question are in progress, pursued in animal experiments and by clinical methods.

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