Studies of Glucose Metabolism Immediately Following Total Pancreatectomy

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SUMMARY

Blood sugar changes were studied in anesthetized dogs before and after pancreatectomy, which was carried out in two stages, the latter being relatively atraumatic. The blood sugar remained normal for 1.5 to 4 hrs. after total pancreatectomy, then increased to the diabetic level.

Comparison of glucose tolerance before and immediately after acute pancreatectomy revealed no significant change by either intravenous or intraduodenal route.

Thus, a sudden cessation of insulin supply does not necessarily result in immediate hyperglycemia. A normal glucose tolerance appears possible temporarily in the absence of any increase in insulin secretion. DIABETES *15*:179-82, **March, 1966.**

It is generally assumed that insulin release from the pancreas is primarily regulated by the glucose concentration in circulating blood,[1-13] and that a transitory increase in insulin secretion in response to hyperglycemia is essential for a normal glucose tolerance curve.[1,4,9-12] In our previous reports,[14-17] however, it has been pointed out that the proponents of this hypothesis have not necessarily proved that an increased rate of insulin secretion in response to a glucose load is an indispensable requirement for a normal glucose tolerance.

In the present study, blood sugar changes and glucose tolerance were measured following quick removal of the pancreas, and the persistence of normoglycemia and normal glucose tolerance were demonstrated during a few hours after pancreatectomy.

METHODS

Blood is supplied to the canine pancreas by three important artery systems. The head of the pancreas receives blood from the superior and inferior pancreaticoduodenal arteries, and the tail of the pancreas is perfused by the pancreatic branches of the splenic artery. However, since the head of the pancreas is attached closely to the duodenum and the pancreatico-duodenal vessels also give many branches to the duodenum, rapid removal of the pancreas without sacrificing the blood supply of the duodenum is technically very difficult. For this reason, a two stage pancreatectomy was employed.

Adult mongrel dogs weighing approximately 10 kg. were anesthetized with injection of sodium pentobarbital. The first stage of the pancreatectomy was a preliminary separation of the pancreas from the duodenum, in which most of the small pancreatic branches of the pancreatico-duodenal vessels were ligated, leaving the blood supply to the duodenum intact. Upon separating the pancreas from the duodenum, a change in color was occasionally seen in small parts of the pancreas. At the end of this procedure, the pancreas was perfused only by ten to fifteen main branches of the vessel systems mentioned above. This separating procedure usually took about one hour.

The second procedure of the pancreatectomy was carried out about one to four hours after the end of the preliminary procedure, when the elevation of blood sugar due to the first operation had subsided in most cases. In this procedure, the remaining major arterial and venous branches were ligated and cut within five minutes, thus completing a total pancreatectomy.

Two types of experiments were performed using these operative procedures. In experiment 1, to observe the pattern of development of hyperglycemia in dogs that were not challenged with glucose, blood sugar was determined at frequent intervals before and after the pancreatectomy for about six hours.

In experiment 2, two successive glucose tolerance tests were performed in each dog, before and immediately after the second stage of the pancreatectomy. The first test was begun approximately two hours after the end of the preliminary separation of the pancreas from the duodenum. At two and one-half hours after the beginning of the first glucose tolerance test, the second operative procedure, i.e., the quick removal of the pancreas, was carried out and immediately followed by the second glucose tolerance test within three minutes. The

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glucose was administered either into the duodenal lumen by injection of one gram per kilogram, dissolved in 100 ml. of water, or intravenously in ten minutes in a dose of one gram per kilogram in 50 per cent solution. Blood samples were obtained every ten minutes for ninety minutes. Two tests were performed with the same amount of glucose by the same route. Blood sugar was determined by Hagedorn-Jensen's method[18] with 0.05 or 0.1 ml. of whole blood from a cut on the ear.

RESULTS

As shown in figure 1, a slight temporary increase in blood sugar, which returned to normal in one hour, was noted after the preliminary separating procedure. Following the second procedure of complete pancreatectomy, no significant rise or fall in blood sugar was observed for 1.5 to 4 hrs. Then, the blood sugar tended to rise steadily to diabetic levels at a rate of approximately 40 mg./dl. per hour. After twenty hours, all animals had hyperglycemia above 300 mg./dl.

As shown in figures 2 and 3, and tables 1 and 2, a close similarity was noted between two glucose tolerance curves obtained in the same animal before and after pancreatectomy. This was true of both types of glucose tolerance test. No significant differences between the blood sugar levels before and immediately after pancreatectomy were observed at any time during ninety minutes following glucose loading.

DISCUSSION

The indispensability of a continuous secretion of a small amount of insulin for maintenance of homeostasis of blood sugar was demonstrated by Hedon[19] and Houssay et al.[20] by transplantation of the excised pancreas, and by Houssay et al.[21] and Holm[22] with insulin infusions. Soskin et al.,[23,24] who maintained pancreatectomized dogs with constant infusions of insulin, also

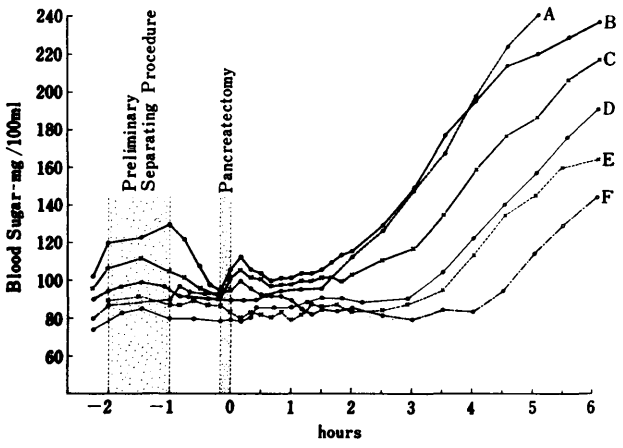

FIG. 1. Blood sugar changes following pancreatectomy.

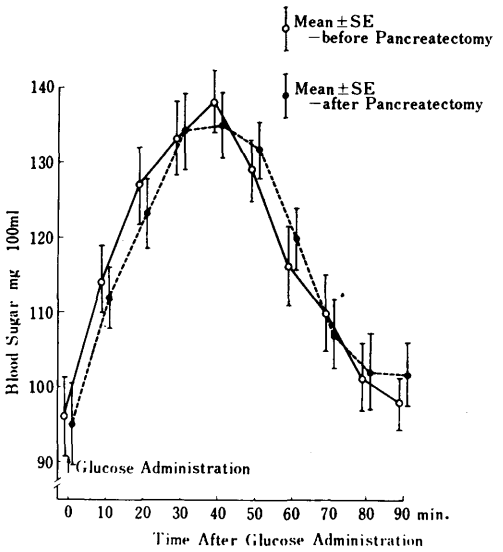

FIG. 2. Glucose tolerance curves by glucose loading (1 gm. glucose per kilogram body weight) into the duodenum before and immediately after total pancreatectomy.

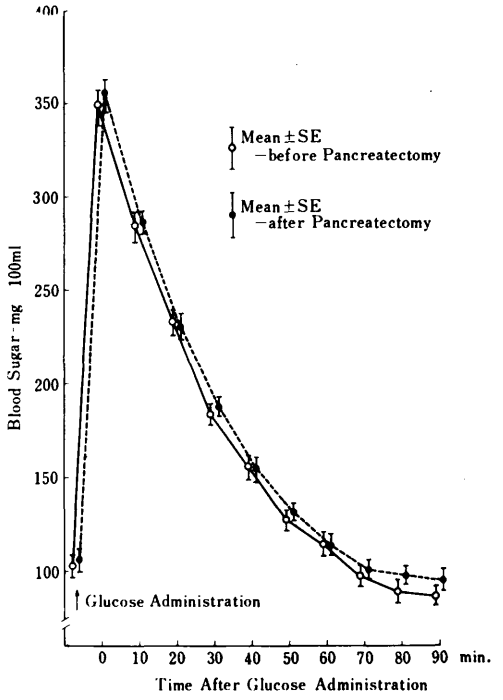

FIG. 3. Intravenous glucose tolerance curves before and immediately after total pancreatectomy.

regarded a basal supply of insulin as an essential prerequisite for a normal glucose tolerance curve.

Although Chambers and Coryllos[25] observed in five dogs that the blood sugar may remain normal for two hours after pancreatectomy, the normoglycemic period was not clearly demonstrated and the paper was not

TABLE 1
Time course of the blood sugar values (in mg./dl.) following glucose loading into the duodenal lumen before and immediately after total pancreatectomy

Number of Experiment		Time after glucose loading (min.) 0	10	20	30	40	50	60	70	80	90
1	Before	113	130	140	143	148	145	141	130	119	108
	After	117	128	135	149	145	140	135	126	120	115
2	Before	82	102	112	119	123	120	113	110	104	100
	After	88	102	108	118	122	118	113	105	108	104
3	Before	95	110	123	136	144	128	120	112	93	92
	After	90	107	120	130	135	135	125	110	100	102
4	Before	90	112	125	127	140	132	110	102	98	90
	After	94	111	128	138	137	128	115	98	90	98
5	Before	102	118	136	142	135	119	106	95	91	99
	After	37	110	126	135	138	137	114	95	91	89
Mean ± SEM	Before	96 ±5.3	114 ±4.7	127 ±4.9	133 ±4.7	138 ±4.3	129 ±4.7	116 ±6.3	110 ±4.9	101 ±5.0	98 ±3.2
	After	95 ±5.6	112 ±4.4	123 ±4.5	134 ±5.1	135 ±3.8	132 ±3.9	120 ±4.3	107 ±5.5	102 ±5.6	102 ±4.2

TABLE 2
Intravenous glucose tolerance tests (blood sugar values in mg./dl.) immediately after total pancreatectomy

Number of Experiments		Before	Time after glucose loading (min.) 0	10	20	30	40	50	60	70	80	90
1	Before	105	356	296	232	188	164	132	120	110	112	107
	After	109	338	283	217	167	154	137	120	108	100	101
2	Before	98	372	310	248	190	170	138	124	108	100	99
	After	114	348	380	238	200	166	140	126	112	105	101
3	Before	112	356	284	225	186	149	127	119	87	80	82
	After	100	360	300	245	199	163	130	118	92	90	90
4	Before	89	340	260	219	161	138	115	105	82	70	72
	After	87	362	280	222	180	152	127	108	80	82	83
5	Before	102	330	280	236	190	155	122	102	100	88	86
	After	100	378	290	228	189	135	116	100	106	98	100
Mean ± SEM	Before	101 ±3.1	350 ±7.2	286 ±8.4	232 ±4.9	183 ±5.5	155 ±5.6	127 ±3.6	114 ±4.4	97 ±4.6	90 ±7	89 ±6.2
	After	102 ±4.6	357 ±7.1	287 ±3.8	230 ±5.1	187 ±4.8	154 ±5.2	130 ±4.2	114 ±4.7	100 ±5.5	97 ±4	95 ±3.8

much noticed recently. It is probable that this normoglycemic period was obscured in the work of others by blood sugar changes accompanying the pancreatectomy in which extensive operations such as gastrojejunostomy or choledochojejunostomy often were involved. In our method of operation the manipulations accompanying the actual pancreatectomy, i.e., the second procedure, have been minimized by completing the time-requiring separation procedure first.

Recently, Wrenshall et al.[29] reported that clamping of the subcutaneously transplanted pancreatic graft in dogs induced an acute rise of blood sugar within four to ten minutes. Apparent contradiction between their result and ours might be attributed to differences in experimental procedure. In their experiment, partial pancreatectomy carried out one week before clamping, might have induced a marginal deficiency in circulating insulin which rapidly became complete after the supply from the graft was cut off.

Recent establishment of acute hyperglycemia following single injection of anti-insulin serum by several authors,[26-28] which is in contrast to several hours of normoglycemia in our experiment, may be attributable to the difference between neutralization of all the insulin from the circulation when anti-insulin serum is administered and simple cessation of insulin secretion following pancreatectomy.

The demonstration of normal glucose tolerance after total pancreatectomy apparently rules out the indispensability of increased insulin secretion from the

pancreas in response to hyperglycemia for the maintenance of normal glucose tolerance, although additional supply of active insulin either by its dissociation from a state of "bound" form[30] or from an adsorbed state to some tissues outside of the pancreas cannot be ruled out. This conclusion is in accordance with the studies of Soskin et al.[23,24] who were able to maintain normoglycemia, normal glucose tolerance, alimentary hypoglycemia and even the Staub effect in pancreatectomized dogs given a constant infusion of insulin. In our experiments, exogenous insulin was not necessary for normal glucose tolerance, suggesting that endogenous insulin may persist for a short period after pancreatectomy, in an amount sufficient to preserve normoglycemia and normal glucose tolerance.

Although it appears true that the secretion of insulin is augmented by glucose loading, as has been reported by many authors, the present study suggests that this extra secretion is not always a necessary prerequisite for normal glucose tolerance.

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