

A RESEARCH ON BLOOD SUGAR IN DEPANCREATIZED DOGS *

B. J. DELATOUR, M.D.
NEW YORK

Recent experiments on the intravenous injection of epinephrin in normal dogs give rise to a question of considerable interest. If the injection of epinephrin causes a temporary hyperglycemia in normal animals, the blood sugar increasing shortly after injection, what would be the result in animals from which the pancreas has been removed? On this idea of investigation, these series of experiments were commenced. The intravenous injection of epinephrin in man has shown, in addition to a temporary hyperglycemia, in some cases a decrease in the output of carbon dioxide from the lungs, which supports the theory that epinephrin inhibits the combustion of sugar in the body, in opposition to the school that believes epinephrin increases the blood sugar by increasing the output of glycogen from the liver. At least, it seemed probable in undertaking this work that a relationship or antagonism might be determined between the pancreas and epinephrin toward the metabolism of the sugar in the body.

My procedure in carrying out a number of experiments to this end was to depancreatize completely a dog and inject a given amount of epinephrin several days after operation; after injection withdrawing the blood at regular intervals, from four minutes to one hour, for the purpose of the blood sugar determination.

The method of removing the pancreas was one of dissecting it away from the mesentery in which it is enveloped. It is not difficult to ligate the minute vessels leading to the gland from the duodenal artery and vein, which can be dissected out carefully without destroying the circulation to the duodenum, and at the same time all the surrounding pancreatic tissue separated from them intact with the pancreas. At least one layer of mesentery can be preserved, except a small area about 3 cm. in diameter, where the pancreatic duct enters the duodenum. However, the preservation of a large portion of the duodenal mesentery seems to be of little importance, as adhesions will form about the duodenum. In a satisfactory number of dogs, the adhesions did not interfere with the function of the intestine, or cause obstruction, waiting a sufficiently long time after operating before following out the experiments.

* This work was done in the laboratory of Prof. C. Achard with Mm. A. Ribot and Leon Binet, whom I thank for their council in the work.

The greatest difficulty encountered in removing the pancreas was in the region of the splenic artery and vein, where, in order to avoid hemorrhage, there is danger of leaving a small portion of the gland.

Six dogs were operated on for removal of the pancreas by the method described above. Two died from postoperative hemorrhage, one twenty-four hours, the other forty-eight hours after operation. One animal died three days after operation, owing to obstruction from adhesions formed about the duodenum.

If any pancreatic tissue is left behind, the blood sugar is certain to give indication of the error. One dog (B) forty-eight hours after operation showed a blood sugar of 2 gm. per thousand c.c., and two days later when the blood was withdrawn for examination it showed approximately a normal sugar content (1 gm. per thousand c.c.). This animal was killed twenty-one days after operation. Dense adhesions were found in the region of the pylorus and duodenum. In spite of the adhesions, the duodenum had functioned well. For fifteen days the dog had been eating the usual diet of meat, stew and rice. At necropsy a search was made for pancreatic tissue, and after a prolonged examination a small piece of tissue, not exceeding in size half that of a hazel nut, was found in the region of the postmesenteric glands. Two other dogs that were operated on continued to show a hyperglycemia. One of these animals (Dog A) died the tenth day after operation, and the other (Dog C) was killed twenty-four days after pancreatectomy. No pancreatic tissue could be found in either of these animals at autopsy.

Those animals from which nearly all of the pancreas is removed, usually showed a hyperglycemia the first two or three days after operation. They may be useful in that time to observe the effect of intravenous injection of adrenalin upon the blood, but not after the blood sugar has returned to normal, as we then have quite the same condition as in normal dogs. In Dog B (Table 1) we have an example of this, as four days after operation the blood sugar was normal, and incomplete removal of the pancreas was found at necropsy. Two days after operation the blood sugar was double the normal amount. It does not concern this particular work whether the small amount of pancreas left in the body was insufficient, together with the shock of the operation, for the first couple of days, to take over the glycogenetic function of the pancreatic tissue removed, or whether in a few days the remaining pancreatic tissue hypertrophied sufficiently to take up the glycogenetic function of the pancreas. But it is quite certain that the hyperglycemia existing in dogs up to the time of their death, from ten to twenty-four days after operation, was not due to the operation

per se, but to an absolute removal of the pancreas, as sufficient time had elapsed for any remaining tissue of the gland to reestablish its function.

As will be seen in Table 1, in the normal dog (Dog A) there was a marked rise of sugar in the blood, after the intravenous injection of epinephrin. Whether epinephrin inhibits the metabolism of sugar in the body or tissues, or whether it augments the output of glycogen from some organ is of great interest, but difficult to determine absolutely. The decrease in the output of carbon dioxide after the administration of epinephrin is injected in man speaks strongly for the increase in blood sugar being due to an inhibition on the part of epinephrin to the burning of the sugars in the tissues.

TABLE 1.—RESULT OF INJECTION OF EPINEPHRIN IN NORMAL AND DEPANCREATIZED DOGS

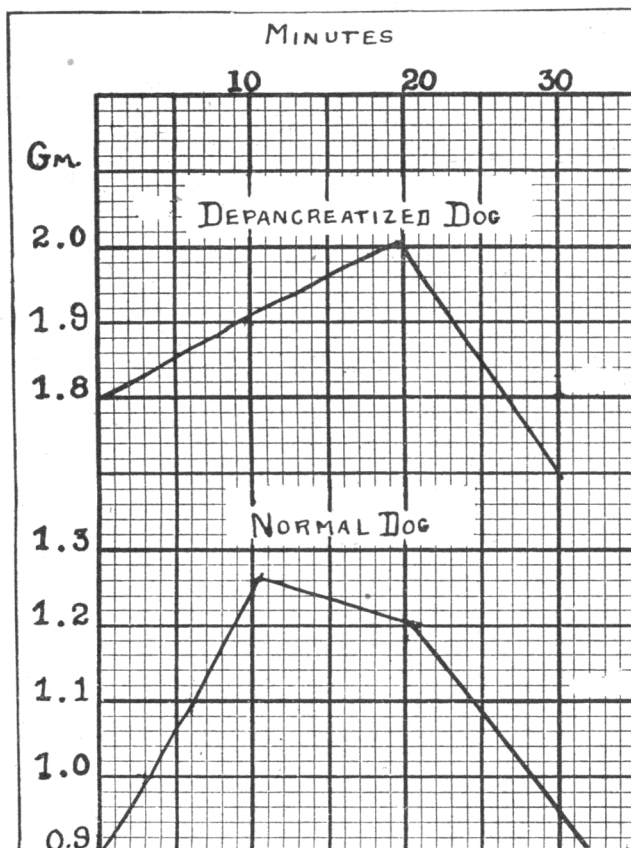
Dog		Amount of Epinephrin Injected	Blood Sugar, Gm. per 1,000 C.e.				
			Before Injection of Epinephrin	Minutes After Injection of Epinephrin			
				10	20	30	40
A	Before depancreatization	1 mg.	0.95	1.25	1.20	0.95	
A	After depancreatization	1 mg. 1 day after operation	1.80	1.90	2.00	1.65	1.55
B	After depancreatization	2 mg. 4 days after operation	1.00	1.30	1.50		
C	After depancreatization	2 mg. 11 days after operation	3.00	3.00	3.00	3.10	

In Dog A the rise of blood sugar after epinephrin injection proportionately was not as great after depancreatization as before, and the fall to the previous sugar level was more abrupt than in normal dogs. This can plainly be seen by a comparison of the two curves. We also see the rise in blood sugar of the dog when depancreatized was much slower after injection than in a normal dog.

In Dog B, where a very small portion of the pancreas had been left in the animal, the rise in blood sugar after injection was quite similar to that of a normal dog.

In Dog C the injection of epinephrin after operation had practically no effect on the blood sugar. There was not any rise in the blood sugar observed in this depancreatized dog, as in the normal animal. One would suppose that if epinephrin inhibits the metabolism of sugar in the tissues in normal dogs it would do likewise in depancreatized dogs, and thus produce a higher blood sugar, by allowing sugar to pass into the circulation unburned. But in depancreatized dogs there

is a constant hyperglycemia, showing by our experiments very little or no rise by the injection of epinephrin. By removal of the pancreas, it seems quite possible that something has been removed favorable to the combustion of sugar in the body, and in depancreatized dogs the blood sugar is increased permanently in the way that it is increased temporarily after injection of epinephrin in normal dogs. The sugar



Blood sugar in grams per thousand cubic centimeters after injection of 1 mg of epinephrin.

is passing into the circulation unburnt, as the influence favorable to the combustion of the sugar has been removed. If in depancreatized dogs, sugar passes into the circulation and is not broken down by the tissues, then epinephrin by injection can have no further action in inhibiting the metabolism of the sugars and be capable of producing much of a rise in blood sugar. It would seem that the pancreas has

exactly the opposite effect of epinephrin on the metabolism of the sugars in the tissues, the pancreas augmenting, the epinephrin inhibiting.¹

Dogs injected with sugar intravenously show some difference before and after depancreatization in the rapidity of reducing additional sugar added to the blood.

TABLE 2.—FIVE GM. OF GLUCOSE IN SOLUTION INJECTED INTRAVENOUSLY

	Blood Sugar, Gm. per 1,000 C.c.					
	Before Injection	Minutes After Injection				
		10	20	30	40	50
Normal dog.....	1.15	1.35	1.15	1.15	1.15	
Depancreatized dog 48 hours after operation.	2.00	3.00	2.6	2.7	2.45	2.35

In each case, that of the normal and depancreatized dog, the tables show the result in blood sugar expressed in gm. per thousand c.c. after equal amounts of glucose have been injected. The dog without pancreas had a slower fall in blood sugar than the normal animal. In other words, the normal dog showed a greater ability to handle the added amount of sugar than the dog without the pancreas. If the pancreas did not play a part in the metabolism of sugar in the body we would expect the blood sugars after the injection of glucose to fall to their former respective levels with about the same rapidity. If the glycogenetic function of the pancreas was merely to control the output of glycogen from the liver, the removal of the pancreas ought not to interfere with the handling of an added amount of sugar to the blood. But Table 2 shows that the fall in blood sugar to the level before injection is not as rapid as in the depancreatized dog.

SUMMARY

1. Complete removal of the pancreas produced a permanent hyperglycemia, and any part of the pancreas left in the animal after operation later manifested itself by a fall in blood sugar.

2. Epinephrin by intravenous injection in normal dogs increased the blood sugar. With the pancreas removed, epinephrin produced

1. It may be possible in life that the pancreas acts as a check on the output of epinephrin from the suprarenal glands, and that with the pancreas removed there is an excessive production of suprarenal secretion put out into the circulation, thus inhibiting the metabolism of the sugars and allowing them to pass unburnt into the circulation. Examination of the suprarenals of one person dying with diabetes and two depancreatized dogs showed a very low epinephrin content by the Folin colorimetric method for quantitative examination of epinephrin. *J. Exper. Med.* **19**:536, 1914.

very little, if any, change in the blood sugar. Under this condition, as a possible explanation, sugar is passing freely into the circulation unburnt, and therefore the epinephrin can have very little further effect in increasing the blood sugar by inhibiting sugar metabolism.

3. It is reasonable to believe that the pancreas produces some substance which favors the metabolism of the sugars in the tissues, as sugar injected intravenously is not handled as readily in the depancreatized animal as in the normal dog.