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THE EFFECT OF ECK AND REVERSE ECK FISTULA IN DOGS WITH EXPERIMENTAL DIABETES MELLITUS

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SINCE the time of Eck, investigators have been intrigued by the physiologic changes induced by portacaval shunt, in which the liver is partially devascularized by diversion of the splanchnic drainage directly into the systemic venous system. It is now clear that portal-systemic venous shunts are attended by changes in protein metabolism which are of considerable clinical importance.⁸ Knowledge of the changes in carbohydrate and fat metabolism is less well developed.

The present study was undertaken to determine if experimental diabetes in dogs was altered by the formation of a portacaval shunt. Conversely, to determine if augmentation of hepatic blood flow resulted in any change in the diabetic state, a companion study of the influence of reverse portacaval shunt on experimental diabetes has been included.

METHODS

Healthy mongrel dogs weighing from 10 to 18 kilograms were kept in metabolism cages and quantitative 24-hour urine specimens were collected at 8 A.M. The animals were fed daily at 4 P.M. The quantity of meal was constant and contained 24 per cent protein, 7 per cent fat, and 67 per cent carbohydrate, and fiber with vitamin B, C, and D supplement. Dogs with diabetes received commercial protamine zinc insulin at 9 A.M. daily. The dose was regulated by the previous day's quantitative glucose excretion.

Alloxan diabetes was produced by the method of Goldner and Gomori.³ Eck fistula was formed by the technique of Freeman.¹ Reverse Eck fistula was produced by side-to-side portacaval anastomosis with ligation of the vena cava above the entrance of the adrenal veins.⁹

Reducing substance in the urine was measured with Benedict's quantitative solution. Blood samples were treated with sodium fluoride and glucose measured, using a Somogyi filtrate, by colorimetric determination on the auto-analyzer. The method of colorimetry was based on the reduction of potassium ferricyanide in the presence of potassium cyanide.

THE EFFECT OF ECK FISTULA ON 5 DOGS WITH ALLOXAN DIABETES

Insulin Requirement.—After the injection of alloxan and the appearance of glycosuria, 4 to 8 weeks elapsed during which the daily insulin requirement

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was determined. When the animals appeared to be in a stable metabolic state, portacaval shunt was performed.

A typical experimental animal is shown in Fig. 1. Immediately after operation, the necessary insulin dose was not appreciably altered. One week after surgery, a marked increase in insulin requirement became manifest. This occurred in all dogs from 1 to 5 weeks postoperatively. After this phenomenon was first observed in a given dog, the insulin requirement progressively rose (Fig. 1) until the dog was either sacrificed or died. The ultimate daily insulin dosages were 3.3, 3.0, 2.8, 2.0, and 1.5 times higher than had been required prior to operation. The average daily insulin injection preoperatively was 16.4 units and postoperatively the ultimate requirement averaged 44 units.

The Effect of Fasting on Blood Sugar and Glycosuria.—Two diabetic dogs with Eck fistula were subjected to periods of starvation. Food deprivation resulted in an abrupt diminution or cessation of glycosuria (Fig. 2). During a period of fasting (as long as 3 days) blood sugar fell toward normal values (Fig. 2). As soon as the diet was resumed the diabetic state quickly reverted to the pre-existing condition with glycosuria and elevated blood sugar.

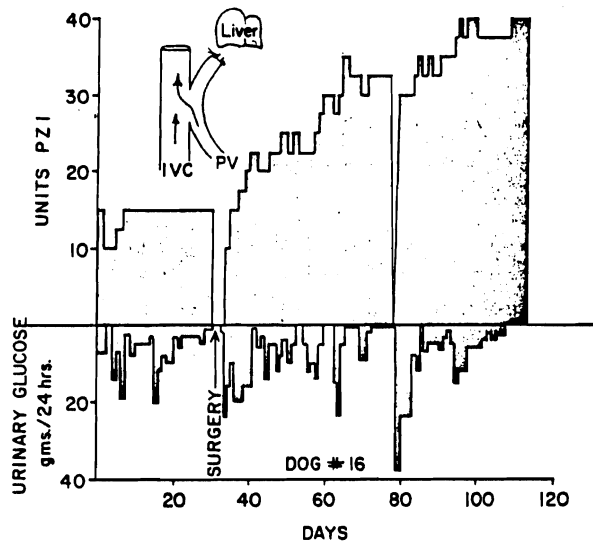


Fig. 1.—Daily insulin requirement in a dog with alloxan diabetes before and after Eck fistula. Included is data on 24-hour urine sugar excretion. Note the sharp rise in insulin requirement after surgery.

THE EFFECT OF REVERSE ECK FISTULA ON 2 DOGS WITH ALLOXAN DIABETES

Insulin Requirement.—Two dogs with stable alloxan diabetes were subjected to simple reverse Eck fistula. Insulin requirement in these animals was slightly increased but the excessive alteration noted in diabetic Eck fistula dogs was not seen. The course of the diabetes in this preparation is shown in Fig. 3. The ultimate daily insulin dosages were 1.3 and 1.1 times higher than had been present prior to operation. The average daily preoperative insulin

requirement was 21 units and the ultimate postoperative requirement averaged 25 units. No difference was noted in effect during test periods during which all injections were given either in the foreleg or hindleg.

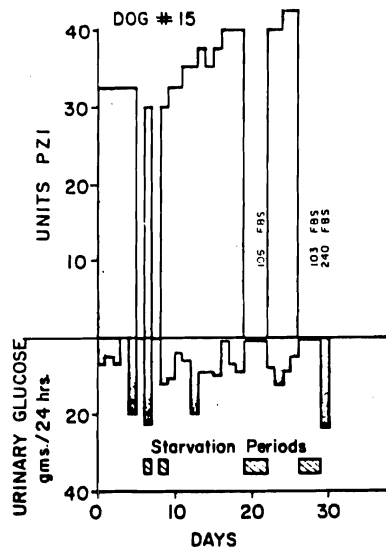


Fig. 2.—Influence of starvation on glycosuria and blood sugar in a dog with alloxan diabetes and Eck fistula. With food deprivation, glycosuria ceases and blood sugar elevation is minimal or absent.

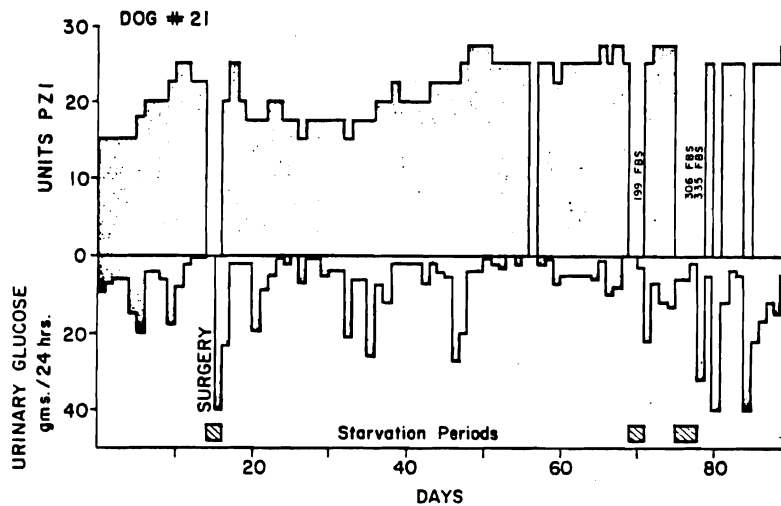


Fig. 3.—Daily insulin requirement in a dog with alloxan diabetes before and after reverse Eck fistula. Also shown is the effect of starvation on glycosuria and fasting blood sugar.

The Effect of Fasting on Blood Sugar and Glycosuria.—Food deprivation in these animals caused a distinctly different effect than in the diabetic dogs with Eck fistula. Despite starvation, glycosuria continued in both animals and blood sugars remained elevated (Fig. 3).

Clinical Behavior.—The animals were healthy and presented no maintenance problems except for the care of the diabetes.

COMPARISON OF CLINICAL BEHAVIOR OF DOGS WITH ECK FISTULA ALONE, AND DOGS WITH DIABETES PLUS ECK FISTULA

Eck Fistula Alone.—A control group of 4 normal dogs were subjected to Eck fistula. After operation, these animals were all unhealthy. They all had weight loss, episodic stupor, and convulsions characteristic of meat intoxication. These animals all died within the first 5 postoperative weeks.

Eck Fistula Plus Diabetes.—The clinical behavior of the 5 dogs with Eck fistula plus diabetes provides an interesting contrast to the nondiabetic dogs with Eck fistula. Their health was much better. Only one animal had weight loss, and 2 gained weight postoperatively. Two animals died in the night during the third postoperative month (probably from insulin reaction) and the remaining 3 were sacrificed in good health during the second, third, and fourth months after surgery. None of the animals manifested the episodic stupor, staggers, or blindness which were noted in the dogs with Eck fistula alone.

AUTOPSY FINDINGS

Gross examination of all dogs operated upon was conducted. In each case, the anastomosis was patent. The dogs with Eck fistula had livers which were smaller than normal. There were no consistent gross abnormalities of the pancreas.

DISCUSSION

The influence of Eck fistula on experimental diabetes has been the subject of previous investigation with apparently contradictory results. After pancreatectomy, Hendrix and Sweet⁴ described alleviation of the diabetes following Eck fistula, under conditions of prolonged fasting. Similarly, Mann and Magath⁷ found that fasting hyperglycemia did not develop with the combination of pancreatectomy, Eck fistula, and partial hepatectomy. In contrast, Koide and Freeman⁵ found alloxan diabetes to be chronically aggravated in 4 of 5 dogs receiving regular feedings. The present data suggest that these seemingly discrepant observations are due to the fact that, in some of the previous investigations, the dogs were being fed, and that, in others, the animals were being starved. In the present study it was shown that dogs with diabetes plus Eck fistula are unusually sensitive to alterations in carbohydrate intake. When on a standard laboratory diet the amount of insulin necessary to control glycosuria is considerably increased. When food is withheld, glycosuria rapidly disappears, blood sugars fall toward normal, and insulin is no longer required.

That the liver has an important role in the hemostatic control of blood sugar level has been known for some time.^{6, 11, 12} It seems reasonable to believe that the progression in alloxan diabetes observed after the construction of an Eck fistula is related in some way to the deviation of portal blood flow away from the hepatic bed, but the mechanism of this effect is not clear. Presumably, it could result from the suppression of liver function known to follow Eck fistula,^{2, 10} as suggested by Koide and Freeman.⁵ A second aggravating factor could be the absence of primary passage of alimentary glucose through the hepatic bed, a circumstance which would remove oral glucose intake from im-

mediate regulatory control by the liver. An additional unexplored possibility is that there is an alteration in insulin metabolism following Eck fistula.

The protection apparently afforded Eck fistula dogs by the addition of diabetes will require further study. Conceivably it is related to the hyperglycemia present with diabetes. Any explanation of this effect would be conjectural but it seems likely that some abnormality of protein metabolism associated with the meat intoxication of Eck fistula is alleviated by changes in the metabolic pattern present with diabetes.

SUMMARY

1. Dogs with alloxan diabetes were subjected to Eck fistula. This procedure produced a marked increase in the amount of insulin necessary to control glycosuria. When the dogs were fasted, glycosuria disappeared, blood sugars fell toward normal, and the need for insulin was eliminated.

2. Reverse Eck fistula was created in dogs with alloxan diabetes, and resulted in minor increases of doubtful significance in daily insulin requirement. When fasted, the blood sugar of these animals remained elevated and glycosuria continued.

3. Nondiabetic dogs with Eck fistula all died of meat intoxication. Dogs with Eck fistula plus diabetes had no evidence of meat intoxication and in general were in better health than dogs with Eck fistula alone.

4. Possible mechanisms of the role of Eck fistula in the alteration of the diabetic state are discussed.

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