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Influence of Epinephrine on Blood Sugar Utilization of Functionally Hepatectomized Rats.

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Previous experiments[1] have led to the conclusion that one of the principal causes for the epinephrine hyperglycemia consists in a decreased utilization of blood sugar in the tissues. It was pointed out that mobilization of liver glycogen alone is an inadequate explanation for the hyperglycemia, because there is not enough liver glycogen present to provide the tissues for hours with sugar at a rate which is greater than their normal ability to utilize sugar. Mobilization of liver glycogen can only lead to a protracted hyperglycemia of the type observed after epinephrine injections, (1) if a new formation of liver glycogen occurs which keeps pace with the conversion of liver glycogen into blood sugar and (2) if utilization of blood sugar itself is diminished. A new formation of liver glycogen exceeding its mobilization was demonstrated during epinephrine action and the source for the newly formed liver glycogen was found to be lactic acid derived from muscle glycogen.[1] That blood sugar utilization is low during epinephrine hyperglycemia was suggested by a comparison of the arterial and venous blood sugar concentration in men. Whereas the arteriovenous difference rises during alimentary hyperglycemia, it fails to do so during the much more pronounced epinephrine hyperglycemia, showing that the tissues are unable to withdraw sugar from the blood at a higher rate. A carbohydrate balance on sugar fed rats showed that the disposal of absorbed sugar after epinephrine injections is markedly diminished in the peripheral tissues.[1]

Since epinephrine inhibits blood sugar utilization in the peripheral tissues of the intact animal, this should also be demonstrable on hepatectomized animals. Mann[2] found that epinephrine did not cause an increase in the blood sugar following hepatectomy or delay the development of the characteristic symptoms associated with hypoglycemia. This is not surprising, because muscle glycogen cannot contribute glucose directly to the blood; it can only do so indirectly through the intervention of the liver. In the absence of the liver, lactic acid derived from muscle glycogen can no longer be con-

[1] Cori, C. F., and Cori, G. T., *J. Biol. Chem.*, 1928, lxxix, 309, 321, 343.

[2] Mann, F. C., *Medicine*, 1927, vi, 419.

verted into glucose and consequently epinephrine is unable to produce hyperglycemia in hepatectomized animals. Since it takes several hours until the blood sugar falls to 50 mg. % in the hepatectomized dog and since the time at which hypoglycemic symptoms appear is variable, an inhibitory action of epinephrine on the fall in blood sugar might easily escape attention, or it might even be absent, owing to the extremely low utilization of blood sugar. In order to demonstrate the inhibiting action of epinephrine in hepatectomized animals it is necessary to provide for a larger utilization of blood sugar by means of a glucose injection.

The experiments were made on rats fasted previously for 24 hours. Such animals contain 5.8±1.4 mg. liver glycogen per 100 gm. rat (average of 24 determinations). The tolerance limit for intravenously injected glucose is at a rate of 250 mg. per 100 gm. rat per hour.[3] When 0.03 mg. of epinephrine is injected subcutaneously and glucose supplied at a rate of only 100 mg. per 100 gm. rat per hour, an average of 75% of the amount of glucose injected remains unutilized in the blood and body fluids. This result on intact animals cannot be explained either by a failure of the liver to form glycogen or by mobilization of liver glycogen, because without epinephrine injection, only 10 to 15% of the 250 mg. of glucose utilized per hour is disposed of in the liver. The hyperglycemia must therefore be due to an inhibition of blood sugar utilization in the peripheral tissues. Since there was the possibility that the presence of the liver was essential in some other way for the action of epinephrine on blood sugar utilization, the above experiments were repeated on functionally hepatectomized rats. For this purpose the portal vein was subtotally ligated in a preliminary operation. Ten to 21 days later the hepatic pedicle was completely ligated under amytal anesthesia and glucose was infused at a constant rate into a femoral vein. In all cases the sugar and lactic acid content of the blood was higher after glucose plus epinephrine than after glucose alone (10 experiments each). The average values were as follows. *No epinephrine:* glucose infused per 100 gm. rat per hour 109 mg.; blood sugar 134 mg. %; blood lactic acid 55 mg. %. *Epinephrine:* glucose infused per 100 gm. rat per hour 110 mg.; blood sugar 246 mg. %; blood lactic acid 135 mg. %. The rather high blood lactic acid of the rats receiving glucose alone is due to the absence of the liver, since this organ normally removes lactic acid from the blood and the further increase in blood lactic acid after epinephrine is due to mobilization of muscle glycogen. When the hepatic pedicle was

[3] Cori, C. F., and Cori, G. T., *J. Biol. Chem.*, 1927, lxxii, 597.

tied but no glucose injected, the rats developed the typical symptoms associated with hypoglycemia which could be relieved by the injection of glucose. The above experiments will be repeated on completely hepatectomized animals.

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Absorption of Glucose From Alimentary Tract of Rats Deprived of Vitamin B Complex.

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(Introduced by J. R. Murlin.)

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Rats from 3 different colonies were placed upon adequate diets and diets deficient in the vitamin B complex. The absorption of glucose from the alimentary tract of these rats was determined by means of the method devised by Cori.[1]

The rate of absorption of glucose was not constant for the 1, 2, and 3-hour periods, there being a marked falling off during the last hour of a 3-hour period. This does not agree with Cori's findings.

The percentage of glucose absorbed during 1, 2, and 3-hour periods appeared to be dependent upon the amount of glucose remaining unabsorbed in the alimentary tract.

Two groups of animals which had been on a diet containing no vitamin B absorbed a smaller percentage of the glucose fed than did normal animals. A third group of animals, which had come from a colony whose members were able to resist the effects of vitamin B-deprivation, did not show a decreased absorption of glucose following a period during which they had received a diet containing no vitamin B.

[1] Cori, C. F., *J. Biol. Chem.*, 1925, lxvi, 691.