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New Conception of the Mechanism of Epinephrine Glycosuria.

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It has been shown previously¹ that liver glycogen is mobilized in fasting adrenalectomized animals when they receive insulin, or, is formed less rapidly, when they receive glucose plus insulin. This result led to an investigation of the influence of small doses of epinephrine on the carbohydrate metabolism of normal rats. During glucose absorption, epinephrine in doses of 0.02 mg. per 100 gm. rat, produced the following effects, with great regularity. It increased heat production, decreased the rate of intestinal absorption, and caused glycosuria. On an average, 6% of the glucose absorbed during 4 hours was excreted in the urine. An equally constant result was increased glycogen formation in the liver, demonstrable not only after 4 hours, but also after 1, 2 and 3 hours of glucose absorption. For the 4 hour period a complete balance of the absorbed glucose has been made. A comparison with the balance sheet of control rats shows:

Per 100 parts of absorbed glucose, x parts are:

	oxidized	deposited as liver glycogen	deposited as body glycogen	excreted in urine
Glucose alone	44	18	25	0
Glucose plus epinephrine	39	23	15	6
Difference	-5	+5	-10	+6

It will be noted that glycogen formation in the muscles and glucose oxidation are diminished, while glycogen deposition in the liver is increased. This indicates that the muscles are unable to dispose of part of the absorbed glucose. According to our present conception, the sugar which the muscles fail to utilize, which is

therefore excreted in the urine, is derived from liver glycogen. A part of the glycogen deposited in the liver during glucose absorption is mobilized by epinephrine. This sugar cannot be utilized by the muscles, for an unknown reason, while the glucose which reaches the muscle directly from the intestine is utilized in a normal way.

Experiments with the same dose of epinephrine have also been made on rats in the post-absorptive state. As much glucose was fed by stomach tube as is absorbed in 4 hours, and the metabolism was determined during the 4 hours. Since the amount of glucose absorbed and oxidized is known, the amount of glycogen formed in liver and muscles during the 4 hours can be calculated. After the 4 hours of glucose absorption, epinephrine or insulin was injected, while control animals were given an equivalent amount of saline. The metabolism was determined for 3 hours after the injection. Then the animals were killed, and glycogen in the liver, and in the rest of the body was determined.

The following table indicates how much glycogen disappears from liver and muscles during 3 hours of fasting, and how much glucose is oxidized during that time. If the calculated loss of glycogen is correct, it should check with the observed oxidation of glucose. It will be noted that the agreement between these two values is satisfactory. This justifies the use of the method outlined above.

TABLE I.

Disappearance of liver and muscle glycogen (in mg. of glucose) after epinephrine and insulin injections. The values are per 100 gm. of body weight per 3 hours. Each figure is an average of 4 experiments.

	Liver glycogen	Muscle glycogen	Glucose in body fluids	Glucose disappeared	Glucose oxidized	Blood sugar
Control	-53	-171	-23	247	221	113
Epinephrine	+14	-312	+5	293	271	174
Insulin	-143	-191	-44	378	434	69

The same dose of epinephrine which produced glycosuria during active glucose absorption, caused only hyperglycemia when the animals were in a post-absorptive state. There was an increase in heat production, which was met in part by an increase in carbohydrate oxidation. It will be noted that normal animals oxidized 221 mg. of glucose, while those receiving epinephrine oxidized 271 mg. Where did the glucose which was oxidized come from? In the normal animal about $\frac{1}{4}$ came from the liver and about $\frac{3}{4}$ from the muscle glycogen. In the animals with epinephrine none came from the liver, indicating that the sugar mobilized in the liver is not utilized by the tissues, and is therefore reconverted in part into liver glycogen. All the carbohydrates that the epinephrine animals oxi-

dized came from muscle glycogen. In the insulinized animals there was a strong increase in carbohydrate oxidation, with approximately an equal disappearance of liver and muscle glycogen. Contrary to expectation, it is not epinephrine but insulin which causes a disappearance of liver glycogen in fasting rats.

The generally accepted assumption is that epinephrine causes glycosuria because it mobilizes liver glycogen. Recent experiments on fasting rabbits make it certain that mobilization of liver glycogen alone cannot account for the epinephrine glycosuria. It was argued that if mobilization of liver glycogen is the only factor, the problem is obviously one of glucose tolerance. It should make no difference whether glucose is injected into a peripheral vein, or whether the sugar is given off by the liver into the *vena cava*. The tolerance limit of rabbits for intravenously injected glucose is at a rate of 0.9 gm. per kilo per hour.

If epinephrine glycosuria is caused by mobilization of liver glycogen only, the rate at which sugar is given off by the liver must be greater than 0.9 gm. per kilo per hour. Such rates of glycogen mobilization have not been found during epinephrine glycosuria. With rates as low as 0.2 gm. per kilo per hour, more than 50% of the glucose given off by the liver were recovered in the urine, while about 35% were retained in the blood and body fluids. This indicates that only a negligible quantity of the sugar given off by the liver following epinephrine injections is utilized by the tissues. However, it must not be supposed that this lack of utilization is of the nature of a diabetic disturbance, because, as the experiments on rats have shown, glucose reaching the muscles directly from the intestine, or glycogen already present in the muscles, is utilized in a normal way. It is the sugar circulating in the blood, originally derived from liver glycogen, which the tissues are unable to attack for a reason as yet unknown. Consequently, a part of this sugar is excreted in the urine, while another part may be reconverted into liver glycogen. Reconversion into liver glycogen is also suggested by the experiments of Pollak² and Kuriyama,³ who found storage of liver glycogen after daily injections of epinephrine into fasting rabbits. The full implication of our results will be given in more detail in later papers.

¹ Cori, C. F., and Cori, G. T., *J. Biol. Chem.*, 1927, lxxiv, 473.

² Pollak, L., *Arch. exp. Path. u. Pharm.*, 1909, lxi, 166.

³ Kuriyama, S., *J. Biol. Chem.*, 1918, xxxiv, 269.