to changes in the hormonal pattern of the organism.

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Epinephrine and Insulin Effect on Potassium Mobilization: Relationship of Lipid and Carbohydrate Metabolism. (20229)

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The comparative effects of epinephrine and insulin on the potassium content of plasma, skeletal muscle, and liver in adrenalectomized-alloxanized rats given a glucose infusion were reported in a recent paper by Dury(1). The use of that type of animal and the design of the experiments were discussed in that report. The results indicated that the effects of epinephrine and of insulin upon tissue potassium content were of such divergent pattern that it reflected differences in the action of these two hormones on intermediary metabolism. Experiments were designed to obtain more detailed information concerning the constituents of the tissues of adrenalectomized-alloxanized rats given an infusion of a

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TABLE I. Effect of Epinephrine and Insulin Pretreatment of Adrenalectomized-Alloxan Groups of Rats Given Glucose Infusion upon Liver and Plasma Water and Electrolytes, Liver Glycogen, and Plasma Glucose Content.

	Liver constituents (per kg wet tissue)				Plasma constituents			
Groups	Water, g	K, m.eq.	Na, m.eq.	Glycogen, mg %	Water, %	K (m.eq./kg plasma water)	Na (m.eq./kg plasma water)	Glucose, mg %
Adrenx-alloxan: glucose, i.v.* (6)	723±3	93.3±1.9	28.7±1.1	113±21	93.7±.1	5.52±.16	151.5±1.1	500—
Glucose, i.v.+ epinephrine preRx (7)	717±3	*102.5±2.6*	30.0± .7	*257±15*	*92.8±.2*	4.96±.26	*163.3±3.0*	500—
Glucose, i.v.+ insulin preRx (5)	732±4	*102.1±1.9*	28.9±1.2	*585±161*	*92.9±.1*	*4.66±.15*	*160.6±1.4*	*270±20*

Figures in parentheses are No. of animals in each group. All values are mean ± S.E.
Italicized values in table are significantly different from controls; "P" = <0.05.
* Glucose (208 mg) inj. intrav. 60 min. before tissues taken for analyses.
Epinephrine (0.04 mg/100 g rat) inj. subcut. 30 min. after the glucose administered.
Insulin (regular, 0.5 unit/rat) inj. subcut. 30 min. after the glucose administered.

standard amount of glucose and pretreated with epinephrine or insulin. It is the purpose of this paper to report the comparative effects of these procedures upon liver lipid partition and glycogen content, plasma glucose, and the water and electrolytes content of liver and plasma.

Materials and methods. The materials and methods employed in the experiments reported here were identical with those described in the preceding paper(2). In order to have rats with combined adrenal and insulin insufficiencies available for these studies, rats 2-3 days after adrenalectomy were injected with a 5% solution of Alloxan monohydrate (Eastman No. 1722) directly into an exposed saphenous vein at the dose level of 40 mg/kg body weight. The rats were maintained on a 1% NaCl solution for drinking purposes and a chow biscuit *ad libitum* during the entire period after adrenal ablation. Tissues for analyses of liver and plasma constituents were taken approximately 65 hours after the alloxan injection (viz, 5-6 days after adrenalectomy). The following groups were used: (A) 60 minutes after intravenous administration of 208 mg of glucose as an 8% solution freshly prepared in Sorenson's sodium phosphate buffer M/15, pH 7.4. (B) 30 minutes after the infusion of the glucose solution, epinephrine (Adrenalin tablets; Parke, Davis & Co.) freshly prepared in isotonic saline was injected subcutaneously at the dose level of 0.04 mg/100 g body weight. Tissues for analyses were taken 60 minutes after the glucose administration (or 30 minutes after the hormone was injected). (C) 30 minutes after the glucose infusion, insulin (ILETIN, regular; Lilly) freshly prepared in isotonic saline was injected subcutaneously at the dose level of 0.5 Units/rat. Tissues for analyses were taken 60 minutes after glucose administration (or 30 minutes after the insulin injection). In all groups, cardiac blood was obtained by direct puncture, immediately centrifuged, and aliquots of plasma taken for determinations of water, electrolytes, and glucose content. Specimens of liver were taken for determinations of liver lipid partition, glycogen, water, and electrolytes content. All surgical procedures, and the injections of the various agents were done with the animals anesthetized with n-methylcyclo-hexenyl-methyl barbituric acid (Evipal).

Results. The means (±S. E.) of the plasma and liver constituents (other than the lipids partition) are presented in Table I. A statistically significant difference between the means of the respective values in each of the pretreated groups and those of the non-pretreated group were found for the following: In the epinephrine pretreated group the liver potassium and glycogen content, and the plasma sodium content were significantly greater than those of the controls; and the plasma water content was significantly lower than the con-

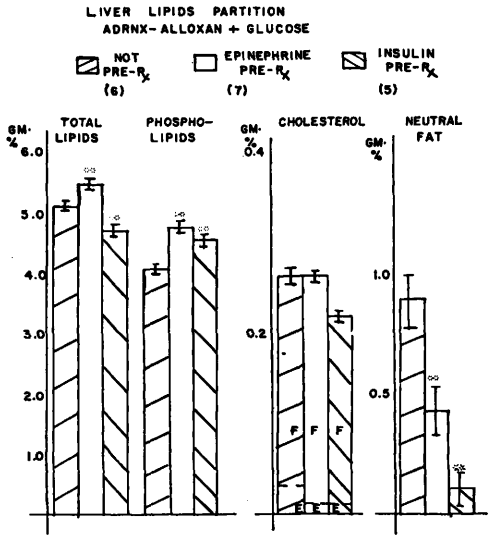

FIG. 1. Starred lipid values are significantly different from controls: * "P" = <0.05; ** "P" = <0.01.

trol value. The high glycemic level is noteworthy in conjunction with the evidence of glucose utilization indicated by the increased liver glycogen content. The plasma potassium level although considerably lower than that of the control was found to be just beyond the 5% limit of significance. In the insulin pretreated group the liver potassium and glycogen content, and the plasma sodium content were significantly greater than those of the respective control values; and plasma water, potassium, and glucose content were significantly lower than the respective values of the controls. The change in glycemic level and the increased glycogen content of the liver are in accord with the known pattern of the influence of insulin action on carbohydrate metabolism. The lowered plasma potassium level consequent to insulin administration has been reported in man and animals several times [see references quoted by Dury(3)].

The partition of the liver lipids in these same three groups are illustrated in Fig. 1. In both pretreated groups the phospholipid fractions were significantly increased and the neutral fat fractions were significantly lower than those of the controls. Although the pattern of changes in the phospholipid and neutral fat fractions were similar in the two pretreated groups compared with the controls, it is evident that the extent of the drop in neutral fat in conjunction with the lowered total cholesterol fraction in the insulin pretreated group accounted for the significantly lower total lipid content in this group compared with the controls. The total lipid level in the insulin pretreated group was also significantly lower than the corresponding value in the epinephrine pretreated group.

Discussion. In the preceding paper(2) it was shown that there were distinct differences in the concentration of liver glycogen, plasma glucose and plasma potassium, and the partition of liver lipids in intact and adrenalectomized-alloxanized groups of rats given an infusion of glucose compared with their respective untreated controls. In the former group the results were generally consonant with the interpretation that the changes in the levels of the constituents reflected the predominant effects of insulin action in response to an imposed glucose load in the organism, viz, upon carbohydrate metabolism and (direct or indirect) effects upon lipid metabolism. However, in the rats with imposed dual-glandular deficiencies similarly treated with glucose there was no evidence of increased carbohydrate utilization; and the liver lipid partition was suggestive of decreased lipogenesis or decreased lipid mobilization. As was pointed out in the preceding paper(2) these divergent results after similar treatment in the two types of animal preparations did not warrant the deduction that these differences were due to the influence of insulin, per se, in the intact animals, or insulin lack in the adrenalectomized-alloxanized groups. The intimate interrelationships extant in the intact animal between insulin, epinephrine, adrenocortical steroids and carbohydrate utilization (particularly the elicitation of secretion of these hormones by any one of the others) were recently reported from this laboratory(3-5), by Somogyi(6), and by Euler and Luft(7). That the partition of liver lipids may likewise reflect the resultant of these hormonal interrelationships in the intact animal, especially after insulin or epinephrine injection, was indicated in the results and the discussion of Experiment II of the preceding paper(2).

The data of these experiments indicate that

a lowered plasma potassium level in the insulin pretreated group occured in conjunction with mobilization of potassium and glycogen into the liver. This, and the fall in glycemic level suggest that the alterations in plasma and liver potassium levels were induced in these animals consequent to insulin action promoting carbohydrate utilization. In accord with this, the fall in the level of liver neutral fat and the increase in the phospholipid fraction would follow due to a shift in the metabolic pathways of predominantly fat catabolism to a more normal pattern consequent to glucose and insulin availability. It is perhaps significant that the levels of the liver lipid fractions in these adrenalectomized-alloxanized rats pretreated with insulin closely resembled the values found (see previous paper) in the intact post-absorptive rats. It is evident that there were several changes in tissue constituents induced with insulin pretreatment all of which are in agreement with the generally accepted manifestations of insulin action upon metabolism.

The association of increased potassium and glycogen levels in the liver after epinephrine pretreatment suggests that the effect of the hormone on potassium mobilization was comparable to that of insulin: Likewise, the changes in the liver lipid partition in the epinephrine pretreated group indicate comparable effects upon fat metabolism as with insulin pretreatment, except for the extent of change in the neutral fat fraction. However, the high glycemic level and the considerably less liver glycogen content in the epinephrine pretreated group (in contrast to those found after insulin) indicate that the changes in liver and plasma potassium content cannot be attributed to an increased level of carbohydrate utilization in the epinephrine pretreated group. These findings are sufficiently notable to suggest that mobilization of potassium to the liver and the fall in plasma potassium level although the common resultant of epinephrine and of insulin pretreatment in these animals probably were not produced by the same mechanism of action with both these hormones.

Summary. The effects of epinephrine and of insulin pretreatment on liver lipid partition, glycogen, water and electrolytes content, and certain plasma constituents were compared in adrenalectomized-alloxanized groups of rats given a glucose infusion. A similar pattern of changes in liver lipid partition was found in both pretreated groups compared to the non-pretreated controls. An increased liver potassium and lowered plasma potassium content was found in both pretreated groups. However, differences in liver glycogen content and glycemic level in the pretreated groups were sufficiently notable to suggest that common resultant effects on potassium mobilization probably were not produced by the same mechanism of action of both hormones.

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