Prevention of Loss of Body Fat by Cortisone. (17811)

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Fragmentary evidence for an unclarified action of the adrenal cortex upon fat metabolism has appeared in the literature. The subject has been reviewed by several authors (1,2,3). Recently, Schiffer and Wertheimer (4) reported that total body fat was much lower in adrenalectomized rats than in "paired fed" controls. In their experiments the excessive loss of fat was prevented by the administration of desoxycorticosterone acetate (DCA) but not by whole adrenal cortical extract.

In the present experiments, it was observed that in the fully fed animal, adrenal insufficiency had no influence upon the amount of body fat. In contrast, partially starved, adrenalectomized rats lost fat more rapidly than intact animals on the same caloric intake. The excessive loss of fat in adrenalectomized rats on a restricted food intake was prevented by the administration of cortisone acetate (17-hydroxy-11-dehydrocorticosterone acetate) but not by DCA.

Experiments. Male rats of the Sprague-Dawley strain weighing from 165-230 g were grouped as indicated in the tables. Until the start of the experiments the animals had access to a complete stock diet and to water. During the 5-day period after operation the rats (Group I-VII in Table I) were fed 3 g of diet in the morning and 3 g in the evening. This quantity, representing about one-third of the rats' food intake when fed *ad libitum,* was consumed completely by the animals of all groups. Groups VIII to XI (Table II) were maintained on the restricted food intake for 8 days. The animals were then operated upon and thereafter permitted food *ad libitum.* Adrenalectomies were performed under ether anesthesia by the lumbar approach. Intact rats had continuous access to tap water, adrenalectomized animals were given 1% NaCl. The cortisone acetate employed was Cortone Merck which is a saline suspension of the micronized material. Desoxycorticosterone acetate was similarly suspended before administration. One mg of cortisone acetate was administered subcutaneously twice daily to the animals in groups VII and XI, while the rats in group VI received two doses of 1 mg of DCA per day. After 5 days of treatment, the animals were killed with ether and each liver and testicular fat body was dissected and weighed. In groups III, IV, VI and VII, the fat tissue was returned to the decapitated carcass which was minced in a meat grinder after removal of the intestines. Total lipids were extracted with alcohol from the ground carcasses and livers(5). For these extractions the pooled carcasses and livers from 4 animals of each of the groups examined were used. Cholesterol, free and total, was determined according to Sheffel(6). Total phosphorus was determined by the method of Fiske and SubbaRow(7) and the factor 25 was used for the conversion to phospholipid values(5).

Results. Previous experience of others(8) confirmed by our own has demonstrated that the testicular fat body is a structure with as highly a reproducible weight and relative growth(9) as that of any other organ. The average weight of the testicular fat body in Groups I and II was used as a base line for the calculated loss of fat in the animals in Groups III-VII. A comparison of the loss of adipose tissue in the various groups showed

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5. Bloor, W. R., Reinhold Publishing Corp., New York, 1943.

6. Sheffel, A. G., *J. Lab. Clin. Med.,* 1944, v29, 875.

7. Fiske, C. H., and SubbaRow, Y., *J. Biol. Chem.,* 1925, v66, 375.

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9. Unpublished observations.

TABLE I.

Effect of Adrenal Activity on Loss of Weight of Testicular Fat Body. All operated rats on restricted food intake for 5 days.

		G			G % of final body wt		
Experiment	Group	Initial body wt	Final body wt	Body wt loss	Wt of fat body	Loss of fat	No. of rats
Intact controls	I	—	200	—	.480	—	12
" "	II	—	175	—	.436	—	10
Sham op. contr.	III	200	181	19	.395	.085	16
Adrx.	IV	195	182	13	.287	.193	8
"	V	176	157	19	.243	.192	8
" + DCA	VI	175	162	13	.266	.169	8
" + KE	VII	200	167	33	.436	.054	8

TABLE II.

Effect of Adrenal Activity on Weight Gain of Testicular Fat Body. All rats on restricted food intake for 8 days, then operated and fed *ad libitum* for 7 days.

		G			G % of final body wt		
Experiment	Group	Initial body wt	Final body wt	Body wt gain	Wt of fat body	Gain of fat	No. of rats
Intact controls	VIII	—	148	0	.149	0	5
Sham op. contr.	IX	146	203	57	.318	.169	6
Adrx.	X	144	189	45	.287	.138	6
" + KE	XI	142	154	12	.360	.211	6

that sham operated rats (Group III) lost less than one-half of the amount of adipose tissue lost by adrenalectomized animals (Groups IV and V) on an isocaloric food intake. The loss of fat in underfed, adrenalectomized rats (Groups IV and V) was about 4 times greater than that in similar animals receiving 2 mg of cortisone acetate daily (Group VII), in spite of the fact that in these rats, body weight loss was much greater than in any of the other groups. The administration of 2 mg of DCA (Group VI) had no significant retarding effect upon the rate of disappearance of the adipose tissue.

The neutral-fat, phospholipid, and cholesterol contents of carcass and of liver are compared in Fig. 1. These values were determined in Groups III, IV, VI and VII. The changes in the amount of neutral-fat in the carcasses as well as in the livers, closely paralleled the changes in the weights of the testicular fat bodies. Phospholipid and total cholesterol concentrations were identical in the carcasses of all 4 groups. However, liver phospholipid concentrations appeared to be altered in the same direction as the neutral-fat. Perhaps worthy of further mention is the apparently marked increase in the ratio of cholesterol ester: total cholesterol in the carcasses, but not in the livers, of animals injected with cortisone acetate (Group VII) and the relative decrease of phospholipids in the livers of the same animals.

The recovery of the fat body in animals first starved, then adrenalectomized, and then fed *ad libitum* (Group X) was essentially the same as in the sham operated controls (Group IX). Adrenalectomized animals injected with 2 mg of cortisone acetate daily regained much less body weight but gained somewhat more adipose tissue than any of the other groups.

Discussion. The apparent discrepancy between our findings and those of Schiffer and Wertheimer appears readily explained from the following: for reasons not given by the authors, in Schiffer and Wertheimer's experiments adrenalectomized rats were exposed to the stress of a relatively high K^+ intake. In addition to a diet apparently quite high in this element, 0.035% of KCl was given with 0.7% NaCl and other salts in the drinking water. It is clear that their adrenalectomized rats, although they had access to food *ad libitum,* failed to eat and gain weight when not given DCA, but ate and grew normally when injected with DCA, which counteracts the increased toxicity of K^+ in

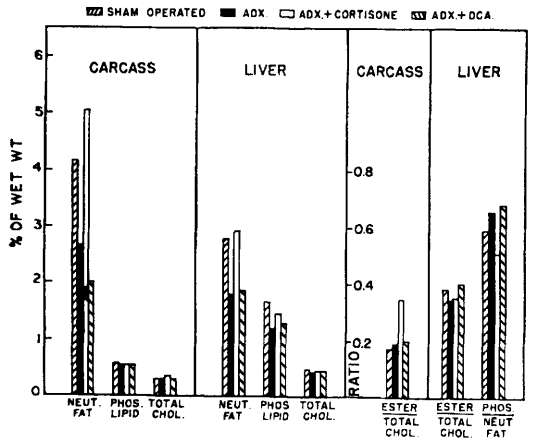

FIG. 1.

Comparison of neutral-fat, phospholipid, and cholesterol contents of carcass and of livers in sham operated (Group III), adrenalectomized (Group IV), adrenalectomized + cortisone (Group VII), and adrenalectomized + DCA (Group VI) rats.

adrenalectomized animals(10). The action of DCA in these experiments appears to be primarily upon the restoration of appetite in adrenalectomized rats exposed to the stress of a relatively high K^+ intake. "Paired fed" intact animals were used by Schiffer and Wertheimer to control the effect of adrenal insufficiency (complicated by high K^+ feeding) but not paired fed adrenalectomized controls injected with DCA. In the present experiments, caloric intake was controlled and was the same for all partially starved groups. Under these conditions it was seen that cortisone acetate prevented the excessive loss of fat in partially starved, adrenalectomized rats while DCA had no such effect. Furthermore, in adrenalectomized rats fed *ad libitum,* no appreciable abnormality could be detected with respect to the amount of body fat. Animals starved prior to adrenalectomy and then permitted free access to food regained adipose tissue at essentially the same rate as sham operated controls. However, in adrenalectomized rats receiving cortisone acetate the gain of fat tissue, in spite of a markedly retarded recovery of the body weight, was even somewhat greater than in the other groups. Although from the above it appears justified to question the validity of some of Schiffer and Wertheimer's conclusions, it is obvious that their experiments have yielded important information. It was seen from their work that the deposition of labelled fat was unimpaired in the underfed adrenalectomized rat and that the excessive loss of fat in such animals occurs irrespective of whether the rats were consuming a diet high in protein, carbohydrate or fat. Also, no differences in the amounts of fecal fat were demonstrable.

From these findings and from the present observations, it is evident that adrenal cortical activity influences both fat and carbohydrate in a parallel fashion. Since partially starved, adrenalectomized rats utilize more fat than cortisone injected controls, it is logical to assume that the deficit in carbohydrate is likewise due to excessive utilization. The metabolic changes in adrenal insufficiency, rather than being primarily due to reduced protein catabolism and decreased gluconeogenesis, may then perhaps be better explained as a result of decreased utilization of amino acids which causes a compensatory excessive utilization of carbohydrate and of fat. Conversely, overdosage of cortisone would lead to increased utilization of amino acids followed by sparing of carbohydrate and of fat.

Summary and conclusions. Adrenalectomized rats, partially starved for 5 days, lost approximately 4 times as much adipose tissue as similar animals injected with 2 mg of compound E daily and twice as much as sham operated controls. The daily injection of 2 mg of DCA did not prevent the excessive loss of fat in adrenalectomized animals. The weight changes of the adipose tissue were paralleled by changes in the content of neutral-fat in the carcasses and livers of the same animals. No appreciable lag in recovery of adipose tissue was observed when starved rats were adrenalectomized and then fed *ad libitum.*

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