Adrenal Cortex and Lipid Metabolism: Effects of Cortisone and Adrenocorticotropin (ACTH) on Serum Lipids in Man.* (18075)

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It has now been established that cortisone and ACTH affect the metabolism of protein and carbohydrate in man. These effects are manifested by an increased urinary excretion of nitrogen, as well as hyperglycemia and glycosuria(1). It is the purpose of this report to present evidence that lipid metabolism is also affected.

From clinical observation it has been known that patients with hyperfunction of the adrenal cortex (Cushing's syndrome) have hypercholesterolemia and an abnormal distribution of body fat, whereas individuals suffering from adrenal insufficiency (Addison's disease) tend to a low serum cholesterol and a loss of body fat(2). In the animal experiment fatty infiltration of the liver produced by pancreatectomy has been prevented by adrenalectomy(3); marked hypercholesterolemia was observed in rabbits after adrenal homotransplantation or injection of adrenal cortical extracts(4); and loss of body fat in the adrenalectomized rat was prevented by the administration of cortisone(5).

The availability of ACTH and cortisone has now made it possible to study further the physiologic effects of these hormones. The following results were obtained in 15 persons with various diseases who were given cortisone in doses varying from 25 to 200 mg a day. In Table I the basic disease, the duration of hormone administration, the dosage, and the changes of total cholesterol, phospholipids, and neutral fat levels of the serum are presented. The determination of total and esterified cholesterol was done by the method of Schoenheimer and Sperry, lipid phosphorus by the Sperry modification of the Fiske-Subbarow method (phospholipid equals lipid P times 25), total lipids were determined by the Bloor method, and neutral fat was calculated by subtracting the figures for total cholesterol and phospholipids from the figure for total fat.

It is evident from Table I that there was an average increase of 15% in the total serum cholesterol of the 15 patients who received cortisone. The phospholipids increased an average 26% with 14 of the 15 showing this change. The neutral fat was calculated in 12 instances, and in each case there was a decrease in this fraction; the average drop was 51%. By using the t-distribution for statistical evaluation, a probability of .032 was obtained for the change in phospholipids, and of .005 for the change in neutral fat.

The fluctuations of serum lipids under cortisone occurred regardless of the clinical course of the patient or the underlying disease. They occurred in patients 4, 6, and 12 although no symptomatic improvement was observed. In patient 11, who died, and in patient 14, who failed to improve, the serum phospholipids rose, but the level of serum cholesterol fell. The described changes occurred in patients 2 and 6 even while they were maintained on a fat-free, cholesterol-free, salt-free diet (Kempner regimen). In 4 patients (1, 2, 3, and 6) studies of the serum lipids were continued after cortisone was stopped, and in each instance there was a reversal of the previous trend, *i.e.*, the cholesterol and phospholipids fell, and the neutral fat rose, so that the values eventually approached those of the control periods.

In contrast to the effects of cortisone,

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TABLE I. Effects of Cortisone.

Pt.	Disease	Dose, mg	Days	Cholesterol*			Phospholipids*			Neutral fat*		
				Before	After	% change	Before	After	% change	Before	After	% change
1	Disseminated lupus	150	10	192	293	+53	240	398	+66	712	169	—77
2	" "	150	10	208	284	+35	240	322	+34	404	216	—47
3	Polyarteritis nodosa	100–150	12	167	218	+23	157	279	+78	356	149	—58
4	Scleroderma	100–150	19	177	210	+19	185	248	+34	273	58	—79
5	Disseminated lupus	75–150	26	167	215	+22	166	260	+57	277	109	—61
6	Chronic nephritis	38–150	9	271	300	+11	339	432	+27	680	506	—26
7	Acute leukemia	100–200	8	163	173	+ 6	179	176	— 2	208	144	—31
8	Hodgkin's disease	60	21	183	167	— 8	227	230	+ 1	—	—	—
9	Disseminated lupus	100–150	12	211	248	+17	271	322	+19	241	120	—50
10	Rheumatoid arthritis	25–200	23	155	200	+29	217	268	+22	301	287	— 5
11	Disseminated lupus	150–200	19	212	205	— 3	232	256	+11	191	139	—27
12	Chronic leukemia	150	6	153	186	+22	188	238	+27	—	—	—
13	Dermatitis	100–200	6	500	510	+ 2	421	485	+15	—	—	—
14	Chronic leukemia	100–150	9	131	100	—22	205	252	+23	421	81	—81
15	Dermatomyositis	25–150	9	239	286	+20	331	365	+10	270	154	—43
			Avg	209	240	+15	240	302	+26	361	178	—51

* In mg per 100 ml of serum.

TABLE II.
Effects of ACTH.

Pt.	Disease	Dose, mg	Days	Cholesterol*			Phospholipids*			Neutral fat*		
				Before	After	% change	Before	After	% change	Before	After	% change
101	Polyarteritis nodosa	5–100	28	194	270	+39	280	304	+ 9	154	202	+31
102	Scleroderma	10– 75	17	210	198	— 4	232	244	+ 5	—	—	—
103	Disseminated lupus	25– 75	28	215	198	— 8	260	222	—15	—	—	—
104	Pemphigus	25– 80	13	161	184	+14	220	223	+ 1	169	73	—55
105	Disseminated lupus	10– 75	34	248	219	—12	322	295	— 8	120	106	—12
106	" "	75–100	25	188	199	+ 6	260	205	—21	139	46	—67
107	" "	100	5	289	278	— 4	349	352	+ 1	352	493	+40
108	" "	50–100	15	132	111	—16	174	285	+63	177	21	—68
109	Hypoproteinemia	100	11	175	156	—11	205	268	+30	—	—	—
110	Disseminated lupus	50–100	11	264	295	+11	285	311	+ 9	341	301	—12
111	Polyarteritis nodosa	50–100	11	174	212	+10	222	310	+40	167	118	—29
112	Disseminated lupus	25– 75	15	246	271	+10	299	350	+17	—	—	—
			Avg	208	216	+ 4	259	281	+ 9	202	170	—16

* In mg per 100 ml of serum.

ACTH produced less pronounced changes in the serum lipids (Table II). A small drop in total serum cholesterol was noted in 6 of 9 patients during the first few days of treatment as originally observed by Conn(6), but this was usually followed by a subsequent moderate rise, and the overall average for the group showed an increase of 4%. There was an average increase of 9% in the phospholipids with 9 of the 12 exhibiting a rise, and an average decrease of 16% in the neutral fat, with 6 of 8 showing this effect. None of the changes which occurred during ACTH therapy were statistically significant.

Of special interest was the fact that the fasting sera of 7 of the 15 cortisone-treated patients and 3 of the 12 ACTH patients became turbid ("lipemic") despite the fact that the level of neutral fat had decreased. This may indicate that the rise in phospholipids and cholesterol was due to the production of a lipid which was less soluble than normal, or that there was a change in the conjugated lipids (possibly lipoproteins).

It is evident, then, that there was a difference between the effects of cortisone and ACTH on the serum lipids. This difference of effects may be explained by the different nature and points of attack of these substances. Cortisone is a cortical hormone of a well-defined structure, while ACTH is an organ extract of the anterior lobe of the pituitary which stimulates the production of several cortical hormones. Evidence is available(1) that the adrenal cortex of man when stimulated by ACTH secretes Compound F rather than cortisone (Compound E). It is also possible that serum cholesterol represents the material for the synthesis of cortical hormones under ACTH stimulation(6), and that prolonged stimulation results in functional exhaustion and atrophy of the adrenal cortex, as well as in the production of antihormones(7).

Summary. This investigation indicates that cortisone produced well-characterized changes of serum lipids in man. The effects of ACTH on the serum lipids were less pronounced.

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Positive Inotropic Action of Ouabain on Rat Ventricle Strips.* (18076)

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Previous work in this laboratory on the metabolism and functional activity of the rat heart(1,2) led us to an investigation of the effect of cardiac glycosides on the force of contraction of rat ventricle muscle. The present paper reports a positive inotropic action of ouabain on the isolated rat ventricle strip, and the effects of various factors upon this response. A literature survey reveals that this is the first conclusive demonstration of a cardiotonic effect of ouabain on rat myocardium.

Method. Adult male rats (225-275 g) were killed by decapitation and a strip prepared from the right ventricle, attached to a semi-isometric optical lever, and mounted according to the method developed in this

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