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14 December 1955

Effect of Cortisone on 17-Ketosteroid Excretion in Patients with Diabetes Mellitus

It has been fairly well established by several investigators (*1–6*) that the administration of cortisone to normal healthy adults as well as to patients with various nonmalignant diseases is associated with little if any rise in the excretion of urinary 17-ketosteroids. Hence our unexpected finding of a substantial rise in urinary 17-ketosteroids following the oral administration of cortisone to patients with diabetes mellitus was regarded with considerable interest, especially in view of the current interest in the possible role of the pituitary-adrenal axis in the development of vascular complications in diabetes mellitus (*7, 8*). The studies being reported were performed as part of a systematic exploration of the metabolic interrelationships between the adrenal cortex and diabetes mellitus (*9*). The effects of cortisone on the urinary excretion of 17-ketosteroids and also of reducing corticosteroids forms the basis of this preliminary report.

Each of six patients (four with unstable and two with stable diabetes, *10*), was studied on the metabolism ward for a prolonged period. Each patient received a chemically constant diet of identical foods and food values throughout the period of hospitalization. An initial stabilization period of at least 2 to 3 weeks, during which insulin type and dose were adjusted to achieve optimal regulation, was allowed before each cortisone experiment was begun. Patients received cortisone daily in equally divided doses around the clock (Table 1). Total urinary 17-ketosteroids were determined in duplicate by the modification of the method of Talbot *et al.* (*11*), including a correction for nonketonic chromogens. The reducing corticosteroids in urine were extracted with chloroform at *p*H 1.0 after hydrolysis for 48 hours with beta-glucuronidase at 47°C. The corticosteroids in the neutral extract were determined by a modification of a colorimetric method using blue tetrazolium (*12*).

The results are listed in Table 1. As a whole, the base-line excretion of 17-ketosteroids tended to be in the low-normal or slightly below-normal range. In the four patients who received both the low and moderately high doses of cortisone, a significant rise in the excretion of 17-ketosteroids was observed when small daily doses of cortisone were administered. An example is shown in Fig. 1. When the dose of cortisone was increased to 150 mg daily, a prompt sharp additional rise occurred in all four patients. The highest 24-hour increment above the average base-line value for these four patients was 40.1, 30.8, 34.3, and 23.9 mg, respectively. In the two patients who received the 150-mg doses only, the increments were less pronounced, being 7.1 and 9.1 mg, respectively.

In contrast to the control values for 17-ketosteroids, the control values (average) for total reducing corticosteroids were in the normal range. However, individual values both above and below the normal range were noted. The rise in reducing corticosteroids in response to

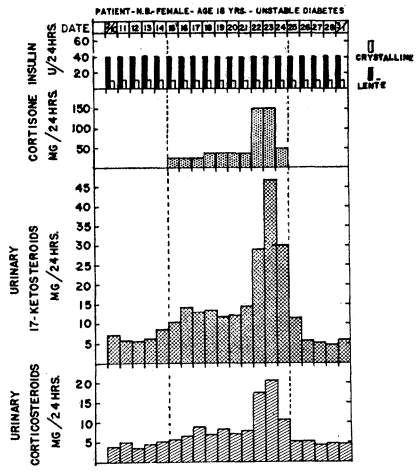

Fig. 1. An example of the marked response in the excretion of 17-ketosteroids and reducing corticosteroids to low and moderately high doses of cortisone.

low and moderately high doses of cortisone paralleled the rise in 17-ketosteroids, although in most cases it was not as great. When the cortisone was discontinued, both the urinary 17-ketosteroid and reducing-corticosteroid levels reverted promptly to the control values or below.

Marked rises in the urinary excretion of 17-ketosteroids following cortisone administration have also been reported in patients with prostatic carcinoma and other malignancies (*4, 13, 14*). These patients received larger doses of cortisone (300 mg daily) than those used in the present study. Although cortisone has induced sharp rises in the excretion of 17-ketosteroids in both diseases, it remains for future studies to determine whether or not the mechanisms are similar.

It is noteworthy that a diabetic may

Table 1. Excretion of 17-ketosteroids and reducing corticosteroids in response to oral administration of cortisone. The range of values of the amounts excreted is given in milligrams per 24 hours.

Patient	Control		Cortisone				Recovery	
	Days	Amount	Dose of 25–37.5 mg/24 hr		Dose of 150 mg/24 hr		Days	Amount
			Days	Amount	Days	Amount		
17-Ketosteroids								
N.B.	5	5.7– 8.7	7	10.3 –14.6	2	29.0–46.8	5	4.9– 5.8
S.S.	5	4.1– 7.5	6	4.9 –12.1	2	17.0–37.1	4	5.9–10.3
R.E.	5	1.7– 4.8	7	0.66– 9.3	2	10.8–37.1		4.89
J.P.	5	4.8– 8.7	7	8.7 –20.0	2	27.1–31.0	5	3.5– 8.3
G.W.	5	10.1–10.2			3	9.0–17.2	4	3.3–10.3
L.V.	5	2.3– 4.3			3	4.0–12.4	5	2.5– 5.3
Reducing corticosteroids								
N.B.	5	3.5– 5.1	7	5.7 – 8.9	2	17.6–20.5	5	4.2– 5.2
S.S.	5	2.3– 6.4	6	6.5 – 8.6	2	8.0–14.0	5	3.2– 7.9
R.E.	5	4.8– 5.8	7	6.5 – 9.5	2	10.6–21.7	4	4.3– 6.3
J.P.	5	6.9–15.5	7	3.7 –16.8	2	22.2–33.6	5	5.5–10.4
G.W.	5	5.5– 7.9			3	22.0–28.0	4	4.4– 5.5
L.V.	5	1.3– 7.7			3	6.2– 9.0	5	2.4– 5.9

show a transformation of cortisone to 17-ketosteroids that is much greater than normal, while the base-line excretion tends to be in the low-normal or below-normal range. The latter finding is in accord with the observations of Miller and Mason (*15*) and Lundbaeck (*16*). At the same time, base-line levels of corticosteroid excretion, although variable, tend to lie within the normal range (*17*).

The present findings suggest a possible altered steroid metabolism in diabetes mellitus. Their significance may be clarified by studies now in progress. A more detailed report of this study will be submitted for publication elsewhere.

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Effect of Reserpine on Adrenocortical Function in Unanesthetized Dogs

Reserpine produces tranquility in agitated patients (*1*), and depressed hypothalamic function has been suggested as the mechanism of this action. Because the hypothalamus is involved in the regulation of ACTH secretion from the adenohypophysis (*2*), an assessment of adrenocortical function following reserpine administration is indicated. Gaunt and coworkers (*3*) have demonstrated adrenocortical hypertrophy in rats following reserpine administration—a finding suggesting stimulation of ACTH secretion rather than suppression. The present study (*4*) was undertaken to determine the effect of reserpine on adrenocortical function in dogs; we employed a direct and specific method for evaluating the secretory activity of the adrenal cortex.

Table 1. Effect of intravenous reserpine on adrenal 17-hydroxycorticosteroid secretion in unanesthetized dogs. Output values for right adrenal gland only. When zero output is indicated, steroid concentration was below the sensitivity of the analytic method (0.1 to 0.2 μg).

Dog No.	Dose of reserpine		Minutes prior to injection			Adrenal 17-hydroxycorticosteroid output (μg/min) Minutes after injection								
	mg	mg/kg	10–20	5–10	0–5	0–5	5–10	10–20	20–30	30–45	45–60	60–90	90–120	120–180
1	5	0.12	1.3	0.4	0.5	1.0	0.0	0.0	1.3	17.5				
2	5	0.18		0.0	0.0	0.0	0.0	0.0	0.0	0.4	15.5			27.4
3	5	0.21	0.0		0.0	0.0	0.0	0.0	0.0	5.2	20.0	2.6	18.1	29.4
4	5	0.31	0.0	0.2	0.1	0.1		1.6	19.0	17.8	6.4	13.0		15.4
5	5	0.33	1.1	0.5	0.8	0.4	7.8	12.2	8.5		15.1	24.7	12.0	

In each of five male mongrel dogs, the right lumboadrenal vein was cannulated according to a technique described by Hume and Nelson (*5*). After a recovery period of 48 hours, samples of adrenal venous blood were collected from the resting, unanesthetized animals. Each dog was then given 5 mg of reserpine (Serpasil, Ciba) intravenously, and samples of adrenal venous blood were collected at intervals thereafter. All blood samples were analyzed for 17-hydroxycorticosteroid content (*6*). The animals became drowsy soon after the reserpine injection and remained so during the 3-hour period of blood sampling.

The results are presented in Table 1. Following reserpine administration, a marked increase in adrenal corticoid secretion was observed in all cases. In four dogs, the response was delayed, with highest values occurring between ½ and 3 hours after drug injection. The maximal corticoid values following reserpine administration are similar in magnitude to those obtained following the intravenous injection of large doses of ACTH, though comparatively much delayed. While it may be assumed that the increase in adrenal steroid secretion following reserpine injection is mediated by ACTH secreted from the adenohypophysis, the mechanism underlying the delay in response remains obscure. This study indicates that reserpine, in the doses used, is a potent stimulus to adrenal cortical secretion in unanesthetized dogs. It should be emphasized that these results represent an acute response to a large dose of reserpine. They do not necessarily imply that any comparable adrenal response occurs to smaller oral doses used in clinical practice.

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9 September 1955

Note on Murphy's and Rhine's Comments

In recent issues of *Science* there have appeared comments by Murphy (*1*) and by Rhine (*2*), criticizing our report of "A methodological refinement in the study of 'ESP,' and negative findings" (*3*). We feel that these comments call for a brief rejoinder.

Both Murphy and Rhine seem inclined to dismiss our findings on the basis of the fact that our study "did not even pretend to replicate any previous research" (*2*) in the field of extrasensory perception. We can but point out that methodological improvement is generally considered a scientific desideratum and that the comparison of results obtained by one methodology with those obtained by another is a common scientific procedure.

Both critics object, also, to the nature of the targets employed in our study. In an effort to forestall such objections, we communicated in some detail with Rhine, as he has stated (*2*), before we actually undertook our experiment. We were particularly concerned with the question of the form of the targets and called it especially to Rhine's attention. Rhine's only misgivings on this point had to do with the issue of the "stacking error" (*2*; compare with Rhine, *4*), an issue that happens to have no relevance for our experimental design. Although he now makes an assertion to the contrary (*2*), Rhine did not at that time object to "the curious device of making