Cushing's Syndrome. IV. Urinary 17-Ketosteroids in Patients with Adrenal Cortical Tumors.* (24405)

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This report presents a study of urinary 17-ketosteroid excretion in patients with Cushing's syndrome due to adrenal cortical neoplasms. A similar study of urinary 17-ketosteroids in Cushing's syndrome associated with bilateral adrenal cortical hyperplasia has been carried out(1). Comparison of the ketosteroid pattern in the 2 groups of patients indicates that there are a number of similarities between them, and that the pattern of 17-ketosteroid excretion is not always sufficiently characteristic to permit a distinction between adrenal carcinoma and adrenal hyperplasia.

Materials and methods. In each of 5 patients, the diagnosis of adrenal cortical tumor was proved surgically. Four patients with typical clinical features of Cushing's syndrome and having varying degrees of virilism had unilateral malignant adrenal cortical neoplasms. In 3 cases there were gross metastases and in one patient there was histologic evidence of blood vessel invasion. One patient (Lev., a 6-month-old boy) showed hypertrophy of the opposite adrenal rather than the atrophy usually observed. One additional patient, a 41-year-old white woman, had classical Cushing's syndrome without virilization. The tumor found at operation was a benign adenoma by microscopic criteria. Atrophy of the adrenal not involved by tumor was suggested by signs and symptoms of adrenal insufficiency following surgical removal of the adenoma. Pertinent clinical and laboratory data are presented in Table I. Urinary and plasma steroids were determined by established methods(2-4). The abnormally high values found supported the diagnosis of Cushing's syndrome(4). Twenty-four hour urine specimens were subjected to acid and beta-glucuronidase hydrolysis(5). After extraction, 17-ketosteroids were fractionated on alumina(6), and quantitated by the methods of Holtorff and Koch(2) and Bitman, *et al.* (7). Steroids in the individual chromatographic peaks were identified by infrared spectroscopy. Appropriate corrections were made for differences in chromogenicity of the various steroids(8).

Results. 1. *Adrenal cortical carcinoma.* Values for total identified 17-ketosteroids were elevated in all 4 patients (Table I). Two of these 4 patients showed abnormally large proportions of 11-oxygenated 17-ketosteroids (Sca., Lev., Table I). All 4 exhibited increase in absolute quantity of 11-oxy-17-ketosteroids. In 3 of the 4 subjects, 11-beta-OH-androsterone was increased to the greatest degree (Lev., Sca., Low.).

Three of the 4 patients showed increase in absolute amount of 11-deoxy-17-ketosteroids (all but Sca., Table I). In the alpha fraction, all patients had a marked predominance of etiocholanolone over androsterone. No androsterone could be detected in patient Gra., and only trace amounts were found in Lev. and Sca. In normal subjects, these 2 steroids are generally excreted in about equal proportions (1,9). A high ratio of urinary etiocholanolone to androsterone was also reported by Gallagher in 3 patients with adrenal cortical carcinoma(10).

Only 2 of the 4 patients showed increased excretion of beta-ketosteroids (Gra. and Low., Table I). The increase in dehydroisoandrosterone was striking in only one of these two (Low.).

2. *Adrenal cortical adenoma.* Patient Cor. (Table I) excreted 3.0 mg/day of identified 17-ketosteroids, a quantity slightly below the lower limit of normal for females of this age (1). Forbes and Albright reported low urinary 17-ketosteroid values in patients with

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TABLE I. Clinical and Laboratory Data of Patients with Cushing's Syndrome Due to Adrenal Cortical Tumor. Urinary 17-ks values given in mg/24 hr unless otherwise indicated.

Name	Age	Sex	Pathologic diagnosis	"Crude" urine 17-ks, mg/24 hr(2)	Urine 17-OH-CS, mg/24 hr*	Plasma 17-OH-CS, μg/100 ml(4)	Total identified urine 17-ks†	Iso.	Dehydro-iso.	3-beta	% 3-beta	Andro.	Etio.	Etio./Andro.
Lev.	½	♂	Carcinoma	8.5, 12.6	.4, .5	36	13.6	1.1	.3	1.4	10	tr	2.4	> 2.4
Sca.	36	♀	"	35–83	5–16	45, 57	36.6					"	11.5	>11.5
Gra.	37	♀	"	26, 65	16, 27	68	26.7	5.0	5.1	10.1	38		10.3	>10.3
Low.	20	♀	"	51–110	12.2–19.8		129.9	24.5	45.5	70.0	54	8.7	23.0	2.6
Cor.	41	♀	Adenoma	8, 12	11, 17	40	3.0							
Normal range				8–15	3–9*	4–23	5–20†	0.3–3.0	0.1–8.8	0.4–10.0	5–57	1.8–5.7	0.8–6.5	0.43–1.5

Name	Age	Sex	Pathologic diagnosis	3-alpha	% 3-alpha	Total 11-deoxy-17-ks Amt	Total 11-deoxy-17-ks %	11-beta-OH-andro.	11-beta-OH-etio.	11-keto-etio.	Total 11-oxy-17-ks Amt	Total 11-oxy-17-ks %
Lev.	½	♂	Carcinoma	2.4	18	3.8	28	6.8	1.4	1.6	9.8	72
Sca.	36	♀	"	11.5	31	11.5	31	13.6	7.3	4.2	25.1	69
Gra.	37	♀	"	10.3	38	20.4	76		4.1	2.2	6.3	24
Low.	20	♀	"	31.7	24	101.7	78	15.5	5.8	6.9	28.2	22
Cor.	41	♀	Adenoma					.2	1.8	1.0	3.0	100
Normal range				2.7–10.9	—	3.7–14.9	67–91	0.6–3.5	0.2–0.9	0.2–1.2	1.4–5.6	9–33

* Porter-Silber chromogen following beta-glucuronidase hydrolysis.
† Normal 17-ks values derived from Ref. (1). Methods same as in present study.

Cushing's syndrome due to benign adrenal cortical adenoma(11). The 11-oxygenated 17-ketosteroids, 11 beta-OH-androsterone, 11 beta-OH-etiocholanolone, and 11-ketoetiocholanolone were the only compounds identified, and the sum of the values for these 3 made up the total.

Discussion. Adrenal cortical adenoma. It is not possible to explain why the major C19 metabolites of hydrocortisone(12) were not greatly elevated in a patient with overt Cushing's syndrome and high urinary and plasma 17-OH-corticosteroid levels (Table I). The 17-ketosteroid pattern found in patient Cor. differs from that observed in 7 patients with Cushing's syndrome and bilateral adrenal hyperplasia(1), and is similar to what would be expected if the adrenal adenoma were secreting only hydrocortisone(12). The validity of such an assumption and the question of whether or not this excretory pattern is typical of adenomata in general must await study of more patients with this rare lesion.

Adrenal cortical carcinoma. The absolute amount of 11-oxygenated 17-ketosteroids was increased in all 4 patients, as was the case in all of 7 patients with Cushing's syndrome and adrenal hyperplasia(1), and as would be expected in consequence of excessive adrenal secretion of hydrocortisone(12). The absolute quantity of 11-deoxy-17-ketosteroids was elevated in 3 of the 4 patients (all but Sca., Table I) with adrenal carcinoma; this group of 17-ketosteroids was increased in only one of 7 patients with adrenal hyperplasia(1).

The finding in each of the 4 patients with adrenal carcinoma of more etiocholanolone than androsterone was also a constant observation in the patients with adrenal hyperplasia(1). The possible role of Reichstein's Substance S (11-deoxy-17-hydroxy-corticosterone) as an adrenal secretory precursor of etiocholanolone is suggested by the following 2 observations: 1) administration of this steroid gives rise to greater urinary excretion of etiocholanolone than of androsterone(13, 14); and 2) tetrahydro S, a metabolic product

of Substance S has been identified in patients with Cushing's syndrome due to adrenal carcinoma(15,16). In fact, tetrahydro S was found in urine of one patient under study (Sca.)(15). It should be emphasized that a relationship between Substance S and the abnormal etiocholanolone:androsterone ratios observed in these patients remains to be proved.

One surprising observation was failure to find consistent, marked increases in excretion of dehydroisoandrosterone, a steroid which has often been found in very large amounts in urine of patients with adrenal carcinoma (17). Only patient Low. excreted dehydroisoandrosterone in large quantity. One of 7 patients with Cushing's syndrome and adrenal hyperplasia excreted 14 mg of dehydroisoandrosterone/day, a value 8 times as great as the average daily quantity of this steroid excreted by normal subjects(1).

Summary. In 5 patients with Cushing's syndrome due to adrenal cortical tumors, urinary 17-ketosteroids were fractionated by column chromatography and identified by infrared spectroscopy. The findings were: 1. One patient with benign adrenal cortical adenoma had a low value of total urinary 17-ketosteroids. The only steroids identified were 11-oxygenated 17-ketosteroids. 2. Four patients with adrenal cortical carcinoma showed elevated urine 17-ketosteroid levels. All 4 had absolute increases in the quantity of 11-oxy-17-ketosteroids. All showed increases in ratio of etiocholanolone to androsterone. Only one showed a marked increase in amount of dehydroisoandrosterone. 3. Certain similarities to and differences from the 17-ketosteroid pattern of patients with Cushing's syndrome due to bilateral adrenal hyperplasia are pointed out. It is suggested that the urinary 17-ketosteroid excretion pattern in patients with Cushing's syndrome due to adrenal carcinoma may not always be sufficiently characteristic to point to a diagnosis of tumor as opposed to hyperplasia of the adrenal cortex.

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