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# THE INFLUENCE OF ACTH, CORTISONE, AND HYDROCORTISONE ON THE DISTRIBUTION AND PERIPHERAL METABOLISM OF THYROXINE<sup>1</sup>

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Renewed interest in thyroid-adrenal interrelations has followed recent demonstrations that alterations in the availability of certain adrenocortical steroids may induce pronounced changes in the metabolism of iodine (1-9). These changes have been variously ascribed to effects of cortical steroids on the pituitary gland (1), the thyroid (10, 11) and the kidney (12, 13). Resolution of the precise modes of action of adrenocortical steroids is not yet complete. Nevertheless, it remains of clinical interest that prolonged administration of ACTH or cortisone may produce in man both laboratory findings and a clinical state suggestive of hypothyroidism (3).

It is generally agreed that alterations in the requirements of peripheral tissues for thyroid hormone induce sequential changes in the plasma's concentration of thyroxine and in the thyroidal metabolism of iodine. The present studies were therefore designed to ascertain whether changes in the peripheral degradation of thyroxine participate in the disruption of thyroidal economy induced by cortisone and related steroids. The data obtained indicate that cortisone, hydrocortisone and ACTH, when administered in replacement or in therapeutic doses do not influence the rate of degradation of circulating thyroid hormone.

## MATERIALS AND METHODS

Ten patients were studied on a metabolic ward, prior to and during the administration of ACTH or cortical

steroids, while receiving constant weighed diets. Eight patients with primary myxedema, maintained in the euthyroid state by means of exogenous thyroid hormone, received average "pharmacologic" doses of cortisone or hydrocortisone (75 to 200 mg. per day). Two moderately hypothyroid patients with panhypopituitarism, receiving no supplemental thyroid hormone, were given 25 mg. of cortisone daily. The control rate of degradation of thyroxine was determined by means of a method employing radioactive thyroxine<sup>4</sup> and described in detail in an earlier communication (14). In accord with their euthyroid clinical status and BMR's, patients with treated myxedema displayed values for the daily degradation of thyroxine within the range of normal for the method employed (14) (Table I). Sufficient time was allowed to elapse following the control test to permit the concentration of radiothyroxine in the serum to decline to negligible values. Administration of ACTH, cortisone or hydrocortisone was then begun according to the dosage schedule listed in Table I. Following a 4 to 5-day period of equilibration, a second determination of the rate of degradation of thyroxine was begun. Administration of hormone was continued throughout the second period of study. Thus, each patient was subjected to a treatment period of at least 14 days. A profound and persistent reduction in circulating eosinophiles was uniformly demonstrated in the myxedematous patients, and was considered an index of the efficacy of ACTH or steroid therapy. In patients with panhypopituitarism, cortisone in daily doses of 25 mg. resulted in moderate reduction of the number of circulating eosinophiles. Serial measurements of serum precipitable iodine (SPI) were made during both test periods, according to the method of Barker, Humphrey, and Soley (15).<sup>5</sup>

## RESULTS

Statistical significance of results obtained in individual patients was analyzed according to the "paired-t" test, as described by Snedecor (16).

In only one patient (G. S.) did the administration of ACTH or cortical steroid induce an alteration (decrease) as great as 1  $\mu$ g. per cent in serially determined values of SPI (Table I). In

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<sup>3</sup> Fellow of the American Cancer Society, Inc., recommended by the Committee on Growth of the National Research Council.

<sup>4</sup> Obtained from Abbott Laboratories, Chicago, Ill.

<sup>5</sup> Performed by Bioscience Laboratories, 2231 Carmelina Ave., Los Angeles 64, Calif.

TABLE I  
The effect of cortisone, hydrocortisone, and ACTH on the peripheral metabolism of thyroxine\*

Pt.	Diagnosis	Treatment (daily dose)	TDS (Liters)		k (%/day)		V (ml./day)		SPI ( $\mu$ g./l. %)		D ( $\mu$ g./day)		ETT ( $\mu$ g./l.)		Body weight (Kg.)	
			1†	2†	1	2	1	2	1	2	1	2	1	2	1	2
Cortisone																
M. B.	Panhypopituitarism	25 mg. p.o.	11.6	9.0	7.14	8.45	828	761	3.0	3.5	24.7	26.6	348	315	73.0	71.8
R. R.	Panhypopituitarism	25 mg. p.o.	8.6	8.4	7.53	6.55	648	550	1.9	2.2	12.3	12.1	163	185	65.9	65.9
V. M.	Myxedema	75 mg. p.o.; thyroid gr. 1	7.0	6.5	10.83	11.55	758	751	4.7	4.8	35.6	36.0	329	312	46.8	46.8
M. F.	Myxedema	100 mg. p.o.; thyroid gr. 3	9.8	8.7	9.76	10.04	956	873	6.3	6.8	60.2	59.4	617	592	56.4	55.5
P. C.	Myxedema	200 mg. p.o.; thyroid gr. 2	7.9	6.3	10.19	13.10	805	825	4.8	5.3	38.6	43.7	379	334	58.2	57.7
Hydrocortisone																
E. G.	Myxedema	75 mg. p.o.; thyroid gr. 2	11.7	11.9	10.66	9.90	1,247	1,178	3.2	3.4	39.9	40.1	375	404	44.5	44.5
M. McC.	Myxedema	75 mg. p.o.; sodium-L-thyroxine 0.3 mg.	8.1	6.7	10.83	12.16	878	815	9.0	9.8	79.0	79.9	729	657	66.4	66.8
L. McK.	Myxedema	75 mg. p.o.; thyroid gr. 2	7.0	7.2	9.76	10.83	683	780	6.0	5.3	41.0	41.3	420	382	60.5	61.4
ACTH																
G. S.	Myxedema	80 mg. i.m.; thyroid gr. 1.5	9.5	7.7	9.00	11.95	855	920	4.4	3.4	37.6	31.3	418	262	52.7	56.8
A. W.	Myxedema	80 mg. i.m.; thyroid gr. 3.5	9.2	8.3	11.74	13.33	1,080	1,107	6.4	6.5	69.2	72.0	589	540	60.5	60.9
Mean			9.0	8.1	9.74	10.79	874	856	5.0	5.1	43.8	44.2	437	398	58.5	58.8
P Value			<.01		<.05		>0.5		>0.5		>0.5		.05		>0.2	

\* TDS—Thyroxine distribution space. Mean normal value, 9.4 (14).

k—Fractional rate of turnover of radiothyroxine. Mean normal value, 10.56.

V—Daily volume turnover (TDS  $\times$  k). Mean normal value, 1000.

D—Daily degradation of thyroxine (SPI  $\times$  V/100). Mean normal value, 53.6.

ETT—Extrathyroidal thyroxine (SPI  $\times$  TDS  $\times$  10). Mean normal value, 508.

† 1—Control test.

2—Test during administration of ACTH or cortical steroid.

eight of ten patients, SPI increased during the experimental period. These changes, however, did not prove to be statistically significant.

The administration of ACTH or cortical steroid was accompanied by a statistically significant reduction in the volume of distribution of thyroxine ( $p < .01$ ), and a significant increase in its fractional rate of turnover ( $p < .05$ ). The volume of the "thyroxine space" diminished in eight of ten patients, in seven of whom the fractional rate of turnover of radiothyroxine was augmented. As a result of the generally reciprocal changes in these functions, the daily volume turnover, *i.e.*, the volume of the thyroxine space whose hormone was replenished daily, remained essentially unchanged. The only changes in volume turnover which exceeded 10 per cent were an increase of 14 per cent in patient L. McK. and a decrease of 15 per cent in patient R. R.

A reduction in the total quantity of hormonal iodine in extrathyroidal tissues (thyroxine space  $\times$  SPI) <sup>6</sup> was observed in eight of ten patients. Changes in this function were at the borderline of assumed limits of statistical significance ( $p = .05$ ).

Values for the absolute rate of degradation of thyroxine, calculated as the product of the daily volume turnover and the SPI, were not significantly altered by the administration of ACTH or cortical steroid ( $p > 0.5$ ).

#### DISCUSSION

In normal animals and man, administration of ACTH or cortisone may result in a diminution of the thyroidal accumulation of  $I^{131}$  (1-9), a reduction in thyroidal clearance of radioiodide (17), and a decline in the concentration of circulating thyroid hormone (1, 3, 18-20). These effects alone might produce secondary alterations in the peripheral degradation of thyroxine. For this reason, studies were performed in patients with primary myxedema, in whom a thyroidal effect of cortical steroids could not contribute to changes in the rate of degradation of thyroid hormone. In such patients, constant doses of exogenous thyroid hormone were the sole source of circulating thyroxine. Changes in the SPI, during the administration of

ACTH or cortical steroids, would then reflect either an alteration in peripheral degradation or in the volume of distribution of thyroxine. These alternatives could in turn be distinguished by studies of the distribution and rate of turnover of radioactive thyroxine. Thus, effects of cortical steroids could be evaluated by two criteria. The two patients with panhypopituitarism afforded an opportunity to study the effects of restorative or replacement doses of cortisone, under circumstances in which it might be anticipated that central (hypophyseal or thyroidal) effects of the steroid would be minimal.

The results of these studies indicate that under conditions of constant dietary intake, ACTH, cortisone and hydrocortisone may alter the volume of distribution of thyroid hormone, but do not regularly influence its rate of degradation. Thus, reduction in thyroxine space was accompanied by an increase in the fractional rate of turnover of thyroxine. As a result, the daily volume turnover, *i.e.*, the volume of thyroxine space whose hormone was degraded daily, remained unchanged.

Although the daily degradation of thyroxine was not altered, the total quantity of hormone contained in extrathyroidal tissues appeared to decrease. A possible explanation for these findings may be offered. In all patients, hypophyseal or adrenal hormone was administered for several days prior to determination of the rate of degradation of thyroxine. This was done in order to allow equilibration of the patient under the new hormonal regimen. If, as the present data indicate, these hormones induce a reduction in thyroxine space, an increase in SPI would be anticipated. Since within the normal range of SPI, utilization is proportional to the plasma's concentration of hormone (14), an increase in the total quantity of thyroxine degraded would result. This would tend to reduce the SPI toward its initial value. Excessive utilization of thyroxine during the period of contraction of the thyroxine space, would, in the face of a constant supply of exogenous hormone, diminish the total quantity of hormone contained within the extrathyroidal pool.

In only one patient in ten were the findings not consistent with this hypothesis. Patient G. S. demonstrated a diminution in both the thyroxine space and SPI. Despite the diminution in SPI,

<sup>6</sup> In calculating values of the daily degradation and the extrathyroidal thyroxine, serum precipitable iodine was considered to consist solely of thyroxine iodine.

the rate of degradation of thyroxine during the administration of ACTH was as great as it had been during the control period. Others have reported profound diminutions in the SPI of euthyroid patients receiving cortisone for no longer than the period of treatment employed in the present study (2, 18). Furthermore, no abnormality in the peripheral degradation of thyroxine could be demonstrated in a patient with long-standing active Cushing's syndrome.<sup>7</sup> These observations indicate that failure of the SPI to decline during the present study did not result from therapy of insufficient duration.

The present findings are in accord with the observations of O'Neal and Heinbecker, who noted that cortisone induced no alterations in the rate of decline of SPI in the serum of hypophysectomized dogs following the administration of TSH (21). Similarly, Hill, Reiss, Forsham, and Thorn (1), as well as Engstrom and Markardt, have reported that cortisone did not influence the SPI of myxedematous patients given exogenous thyroid hormone (22). No explanation is apparent for the discrepancy between these observations and those of Bondy and Hagewood, who reported that in thyroidectomized rats given thyroxine, the administration of cortisone was accompanied by a marked augmentation of SPI (20).

If, as the present data indicate, cortisone does not alter the peripheral degradation of thyroxine, then reduction in the concentration of circulating thyroid hormone, which frequently follows the administration of this steroid, must be ascribed to other mechanisms. Whether this decline in SPI results from a diminution in the glandular production of hormone, the rate of turnover of the glandular hormonal pool, or both, and whether it is mediated by an action of cortisone on the pituitary gland or directly on the thyroid remains to be elucidated.

#### SUMMARY

1. The distribution and rate of turnover of radioactive l-thyroxine have been examined in ten patients with primary myxedema or panhy-

<sup>7</sup> Values observed: thyroxine distribution space, 9.7 liters; fractional turnover rate, 9.63 per cent per day; daily volume turnover, 934 ml.; SPI, 3.4  $\mu$ g. per cent; thyroxine degradation, 31.7  $\mu$ g. iodine per day; extra-thyroidal thyroxine, 330  $\mu$ g. iodine.

popituitarism prior to and during the administration of ACTH, cortisone or hydrocortisone.

2. As judged by the metabolism of radioactive thyroxine and by measurements of serum precipitable iodine, ACTH and cortical steroids did not alter the rate of degradation of thyroxine.

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