

# THYROID-ADRENOCORTICAL INTERRELATIONS: FAILURE TO DEMONSTRATE ANTAGONISM BETWEEN TRIODO-THYRONINE AND HYDROCORTISONE IN MAN<sup>1</sup>

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It is generally accepted that acute injury results in an outpouring of adrenocortical hormones<sup>5</sup> (1, 2), and that these hormones play an important role in the response of the total organism to such injury. The marked increase in urinary nitrogen excretion which characteristically occurs immediately following acute injury is usually considered to result from the catabolic action of the adrenocortical hormones on protein metabolism (3). Supporting this concept are recent studies correlating the negative nitrogen balance following surgical trauma in man with the rise in 17-hydroxysteroid excretion (4).

The participation of the thyroid gland in the response to acute injury in man is less well delineated. Certain observations have suggested that there may be an increase in circulating thyroid hormone in man following trauma (5, 6); other investigators have been unable to confirm this finding (7, 8). The role of the thyroid is particularly difficult to evaluate following injury because the increased output of adrenocortical hormones may affect some of the methods used to assay thyroid function (9-11), and may also tend to inhibit thyroid activity (9, 11-14).

Goldenberg, Lutwak, Rosenbaum, and Hayes (15) have recently proposed that the catabolic response to injury is due primarily to excess thyroid hormone rather than adrenocortical hormones.

They further postulate that the adrenocortical hormones are antagonistic to the effects of excess thyroid activity on protein metabolism. According to this thesis, the increased output of adrenocortical hormones following acute injury tends to decrease the catabolism and nitrogen-wasting caused by excess thyroid activity, and thus acts to restore nitrogen balance and homeostasis. The clinical observations and experimental evidence marshalled by Goldenberg *et al.* (15, 16) in support of this hypothesis, however, have appeared inconclusive to us as well as to others (17). We decided to determine directly whether large amounts of adrenocortical and thyroid hormones are antagonistic in their metabolic effects in normal man.

1-Triiodothyronine<sup>6</sup> and hydrocortisone were selected as representative hormones of the thyroid and the adrenal cortex, respectively (18, 19). Each hormone was administered separately in large dosage, 1 mg. and 200 mg. daily by mouth, respectively, for three or four days to two normal human males (subjects Nos. 1 and 2); subsequently, both hormones were administered simultaneously at the same dosage as before. Evidence for mutual antagonism between the two hormones was sought in the nitrogen, potassium and sodium balances; urinary steroid excretion was also followed. A further study was carried out on a patient who had undergone adrenalectomy for Cushing's syndrome five months before and who repeatedly failed to respond to adrenocorticotrophic hormone postoperatively (subject No. 3).<sup>7</sup>

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<sup>5</sup> Throughout this paper the term "adrenocortical hormones" is used to refer exclusively to the glucocorticoids.

<sup>6</sup> Kindly provided by Dr. Frederick K. Heath, Merck & Co., Inc., Rahway, New Jersey.

<sup>7</sup> This patient will be reported in detail elsewhere. A solitary left adrenal adenoma was removed at operation together with the atrophic left adrenal gland; no adrenal gland could be found on the right. Postoperatively he received maximal stimulation with ACTH on five separate occasions (four and three months before, and one, two and four months after the studies reported in this

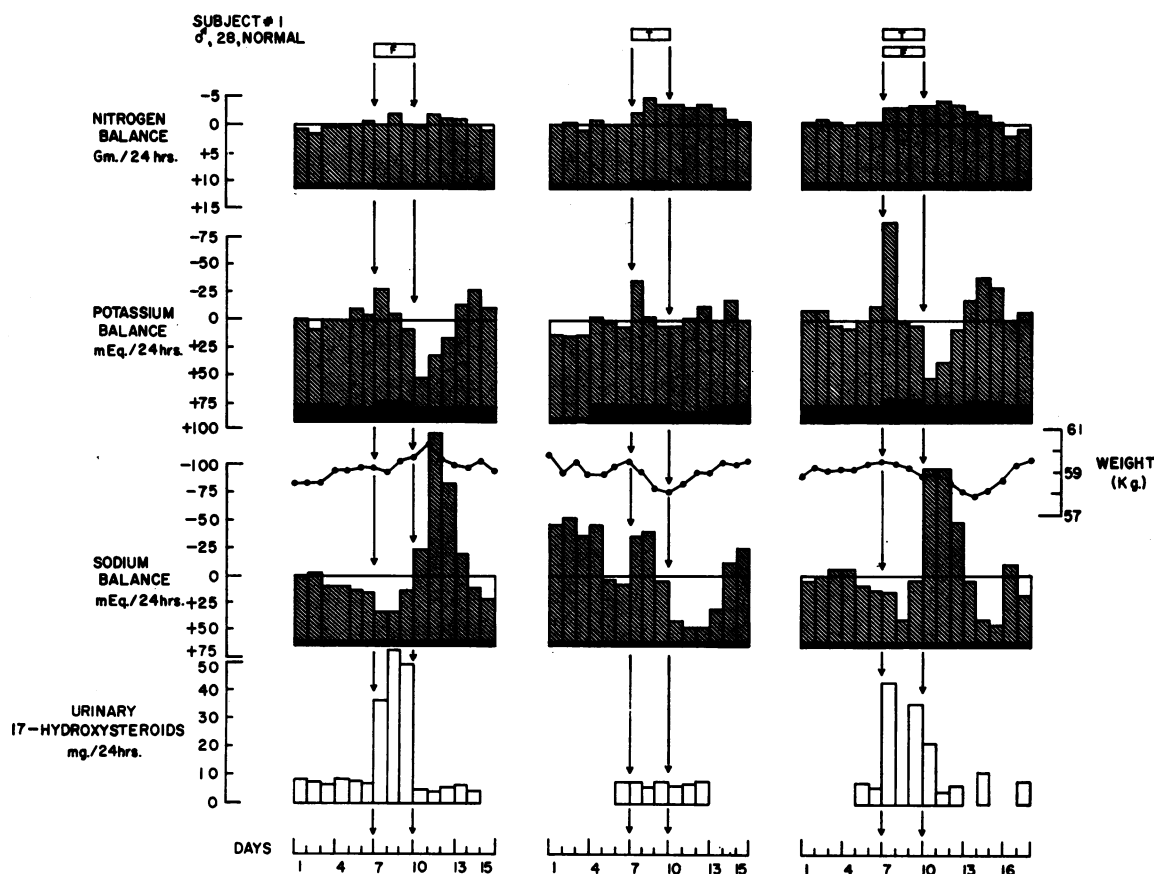


FIG. 1. BALANCE STUDIES IN SUBJECT NO. 1 (NORMAL), CHARTERED AFTER REIFENSTEIN *ET AL.* (21)

Equilibration periods not shown; no equilibration period obtained before the l-triiodothyronine study. F = Hydrocortisone Acetate (Compound F), 50 mg. orally every 6 hours; T = l-Triiodothyronine, 0.5 mg. orally every 12 hours.

#### METHODS

Prolonged metabolic balance studies were conducted on the Metabolic Ward of Walter Reed Army Hospital. Balance procedures employed in this department have been described previously (20). Liquid diets, identical from day to day, were used throughout except for a two-day period during the study of subject No. 3 (see Results). Diets for the two normal subjects were adequate in calories (50 Cal. per Kg.) and protein (1.3 and 1.5 Gm. per Kg.); subject No. 3 was maintained on a diet adequate in protein (0.9 Gm. per Kg.) but inadequate in calories (10 Cal. per Kg.) because of residual obesity. Urine collection periods were 24 hours in duration with the exception of several 48-hour periods in the study of subject No. 3; completeness of urinary collections was checked by daily urinary creatinine determinations. Stool

paper) for periods ranging from three to ten days. At no time did the urinary steroid excretion reveal any response whatsoever. We have been forced to conclude that the patient has no remaining adrenocortical tissue.

collection periods were 72 or 96 hours in duration. The balance data are charted according to Reifenshtein, Albright, and Wells (21); the zero line is constructed as the average of the control balance periods. Equilibration periods of two to seven days' duration (not shown in the figures) were obtained before each study of subjects Nos. 1 and 2 with one exception.<sup>8</sup> Subject No. 3 had been on the identical reducing diet for over a month at the time of the start of his study.

Standard methods were employed for the chemical analyses (22). The urinary 17-ketosteroid determinations were made by a modification of the Zimmerman reaction (23) and the 17-hydroxysteroids by a modification (24) of the Porter-Silber method (25).

#### RESULTS

The results of the balance studies in the two normal subjects are shown in Figures 1 and 2. In

<sup>8</sup> There was no equilibration period prior to the triiodothyronine study in subject No. 1.

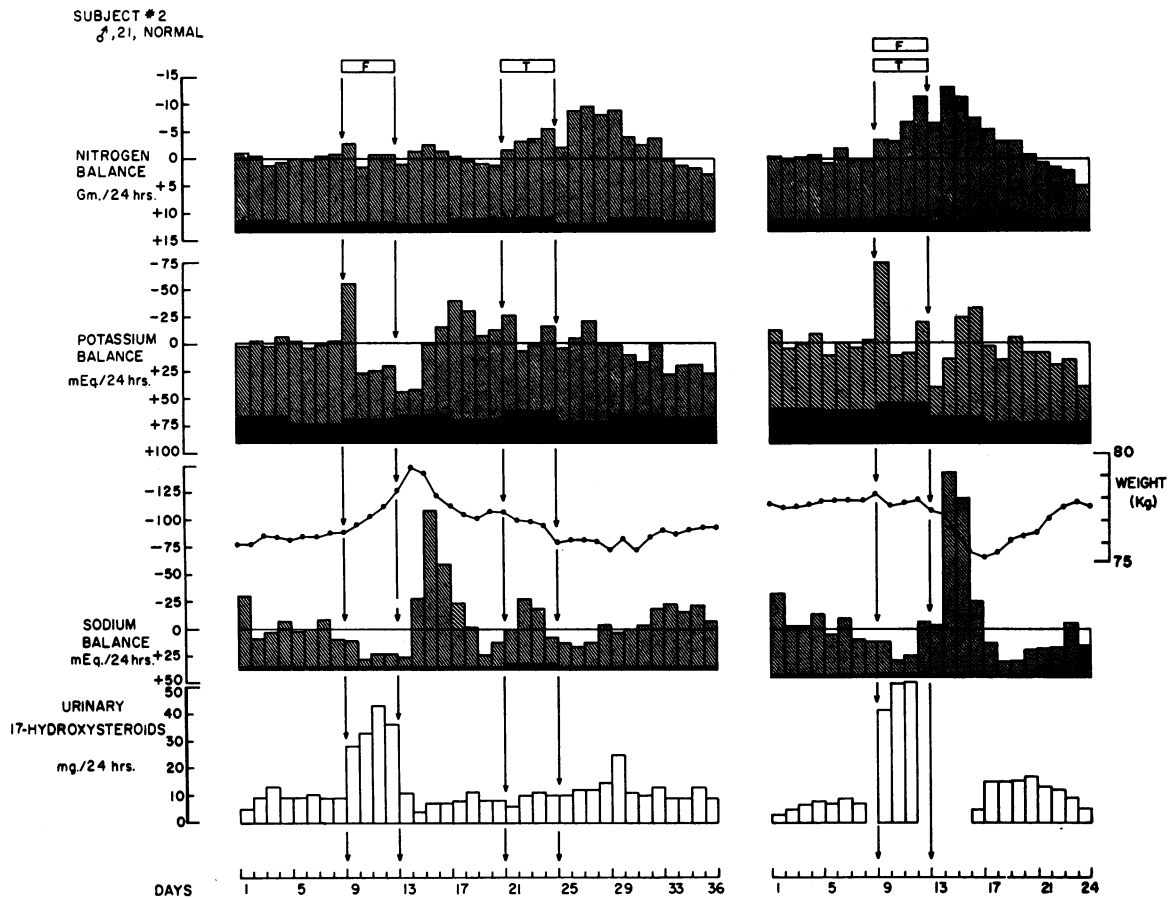


FIG. 2. BALANCE STUDIES IN SUBJECT NO. 2 (NORMAL)

Equilibration periods not shown. F = Hydrocortisone Acetate (Compound F), 50 mg. orally every 6 hours; T = l-Triiodothyronine, 0.5 mg. orally every 12 hours.

each study, hydrocortisone had little effect on the nitrogen balance, whereas triiodothyronine resulted in a prolonged period of nitrogen loss in the urine. When both hormones were administered together, the resulting negative nitrogen balance was at least as great as that produced by the triiodothyronine alone (Table I).

The balances of potassium and sodium showed the expected changes during hydrocortisone administration, but were not consistently affected by triiodothyronine. When both hormones were given simultaneously, the results were essentially the same as those observed with hydrocortisone alone.

The excretion of urinary 17-hydroxysteroids increased as expected with each administration of hydrocortisone in both normal subjects. In subject No. 1 there was no apparent change with

triiodothyronine administration, although observations were not extended throughout the recovery period (Figure 1). Subject No. 2, however, showed a small but definite rise in 17-hydroxysteroid excretion during the five days immediately following triiodothyronine administration, approx-

TABLE I  
Cumulative negative nitrogen balance (Gm.) resulting from hormone administration

	Hydrocortisone*	l-Triiodothyronine†	Hydrocortisone* and l-Triiodothyronine†
Subject No. 1	10.0	23.9	23.0
Subject No. 2	5.4	59.0	73.4

\* 200 mg. daily.

† 1.0 mg. daily.

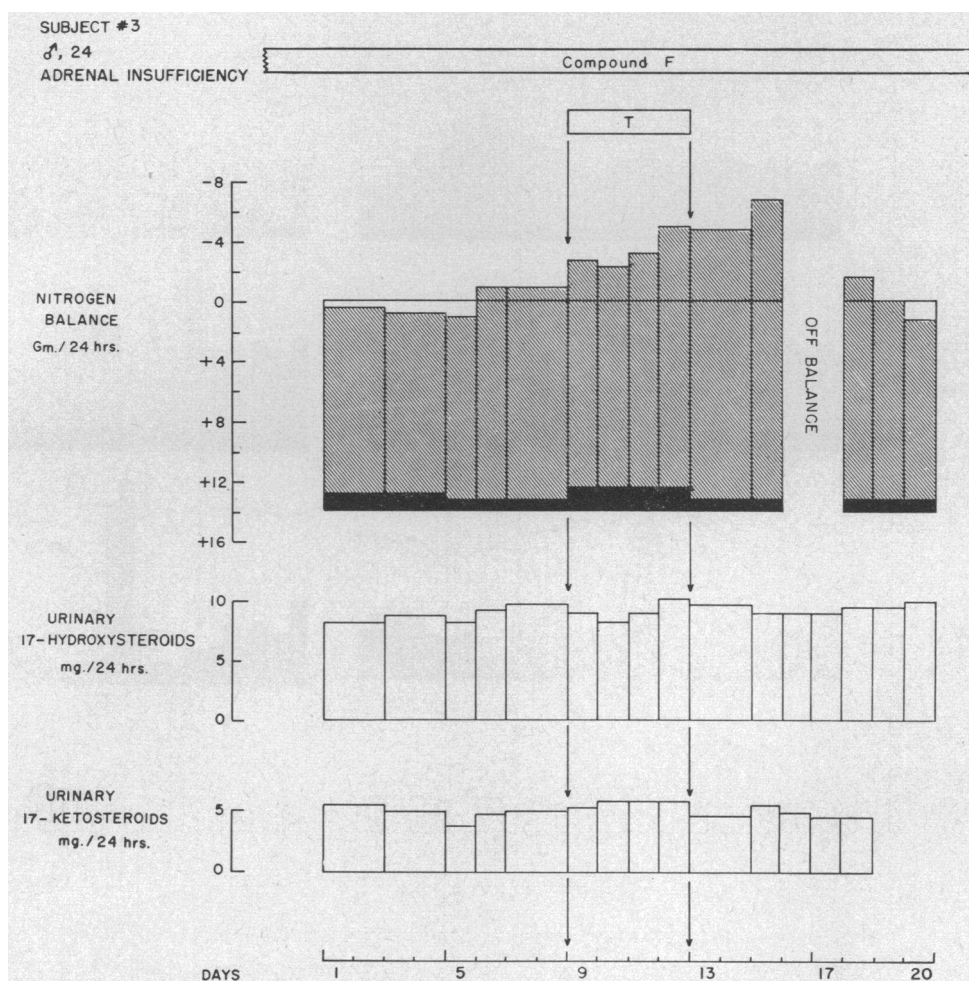


FIG. 3. BALANCE STUDY IN SUBJECT NO. 3 (TOTAL ADRENOCORTICAL INSUFFICIENCY)

Equilibration period not shown. Compound F = Hydrocortisone Acetate, 10 mg. orally every 6 hours; T = l-Triiodothyronine, 0.5 mg. orally every 12 hours. See foot-note number 10 for explanation of period off balance.

imately coinciding with the period of maximal nitrogen excretion (Figure 2). This slight increase was also seen in this subject during the recovery period following the simultaneous administration of both hormones. It appeared possible that triiodothyronine administration had resulted in an increased output of adrenocortical hormones in this subject; had this been the case, the negative nitrogen balance following triiodothyronine might have been due in part to adrenocortical stimulation. An alteration in peripheral utilization, degradation or renal excretion of adrenal hormones presented alternative possibilities.

Subject No. 3 was studied with these questions

in mind. This patient was maintained throughout the study (and for one month previously) on hydrocortisone<sup>9</sup> alone, his only source, exogenous or endogenous, of glucocorticoids. When triiodothyronine was administered in the same dosage as to the normal subjects, a period of negative nitrogen balance resulted entirely similar to that seen in the normal subjects (Figure 3)<sup>10</sup> and was

<sup>9</sup> 10 mg. every six hours by mouth.

<sup>10</sup> At the peak of the period of negative nitrogen balance (72 hours after stopping triiodothyronine), there was such a marked increase in this patient's sense of lassitude and fatigue that the balance study had to be discontinued for 48 hours for morale purposes. Complete urinary collections for steroid determinations were con-

not accompanied by any significant change in steroid excretion.

#### DISCUSSION

The thesis proposed by Goldenberg *et al.*, that adrenocortical hormones may have anabolic activity in the presence of increased thyroid hormone, deserves careful scrutiny. Both adrenocortical hormones and thyroid hormone are usually considered to have catabolic effects on protein metabolism when present in excess (27). If the concept under consideration were correct, it would prove that the effects of these two hormones at a cellular or enzyme level, hitherto thought to be independent, are instead closely interrelated.

Goldenberg and co-workers (15) have submitted metabolic balance data following operative procedures and during the administration of desiccated thyroid, propylthiouracil, ACTH, and adrenocortical extract in various combinations (16) in support of their theory of thyroid-adrenocortical antagonism in man. Certain changes in urinary excretion of nitrogen and other metabolites have been interpreted as representing major and significant alterations in metabolism in accord with their concept. Scrutiny of the balance charts suggests to the present authors that these changes are often consistent with minor fluctuations in baseline of the type which plague all balance studies. In our opinion, their data as presented do not strongly support their thesis.

The metabolic studies in the two normal subjects reported in this paper failed to show antagonistic action between large doses of adrenocortical hormone (hydrocortisone) and of thyroid hormone (triiodothyronine) by the criteria of nitrogen, potassium and sodium balance. Simultaneous administration of both hormones produced responses as great as those produced by either

tinued, however. Physical examination provided no clue as to the cause of the patient's symptoms. Serum electrolytes were within normal limits. Recovery was complete within 12 hours on a free, solid diet without caloric restriction; no medications were administered. It is interesting that both normal subjects experienced similar symptoms, although not nearly so severe, at the height of the negative nitrogen balance. Conceivably hypomagnesemia may have been responsible for these symptoms (26); unfortunately serum magnesium determinations were not made.

alone. The study done on the patient with complete adrenocortical insufficiency (subject No. 3) revealed that the protein catabolism caused by excess triiodothyronine does not depend upon an increased output of adrenocortical hormones, and that the urinary excretion of exogenous hydrocortisone is not grossly altered by triiodothyronine.

#### SUMMARY AND CONCLUSIONS

1. Studies designed to demonstrate antagonistic metabolic effects between large doses of hydrocortisone and l-triiodothyronine in two normal human subjects have been negative with regard to nitrogen, potassium and sodium balance. Simultaneous administration of both hormones produced responses as great as those produced by either alone.

2. Studies on a patient without endogenous adrenocortical hormones revealed that:

a. An increased output of adrenocortical hormones is not necessary for the protein catabolic response to large doses of l-triiodothyronine.

b. The rate of urinary excretion of exogenous hydrocortisone is uninfluenced by large doses of l-triiodothyronine.

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#### ADDENDUM

Since this paper was submitted for publication, subject No. 3 received a sixth course of ACTH stimulation, ten months after completion of the studies reported in this paper. As with several of the previous courses of ACTH, he was maintained throughout the period of maximal stimulation on 2 mg. of 9- $\alpha$ -fluorohydrocortisone daily. For the first time there was a slight but definite response in the urinary excretion of 17-hydroxysteroids, from an average control value of 0.9 mg. per 24 hours to 3.7 mg. per 24 hours after five days of intravenous ACTH administration. Thus, contrary to our prior belief, this patient does have remaining viable adrenocortical tissue; however, it was demonstrably impossible to elicit a response from this small adrenal remnant at the time of the studies herein reported. The premise that he was unable to elaborate endogenous glucocorticoids at the time of the studies here reported would still appear valid.

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