Influence of Cortisone on Thyroid-Pituitary Interaction in Normal and Goitrous Rats.* (20302)

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It is difficult to reconcile the conflicting reports regarding the effect of cortisone on the pituitary-thyroid system. In man, prolonged administration of cortisone appears to inhibit thyroid function as measured by thyroidal I^{131} uptake and serum protein-bound iodine (1-3) but other indices of thyroid function (BMR, serum cholesterol) respond less consistently(1,3,4). It has been postulated that this thyroid inhibition—and its sequel, "corticogenic hypothyroidism"—is a consequence of pituitary TSH suppression(1,4). Results of animal experimentation do not fully support this. In the intact rat, cortisone administration may(5,6) or may not(7) reduce thyroidal I^{131} uptake, and is without effect on the rate of release of labeled thyroid hormone(6,8). The histologic response of the thyroid to cortisone is variable; diminished activity(9), no change(10), and activation (11,12) have been reported. In the hypophysectomized rat, simultaneously administered cortisone and TSH inhibits TSH-induced thyroidal radioiodine uptake(13-15), but fails to prevent the expected increase in thyroid cell height(16). In no instance have the levels of TSH in blood and pituitary in cortisone-treated animals been measured and correlated with other parameters of thyroid-hypophyseal interplay. The present study supplies this information for both normal and hypothyroid rats.

Materials and methods. Cortisone¶ was administered (dosage and duration in Table I) to adult female rats (Albino Farms, Red Bank, N. J.) by subcutaneous injection. All rats receiving cortisone were fed unrestricted amounts of the normal ration (Purina chow and tap water). For control groups, food was limited to amounts consumed by experimental groups for the previous 24-hour period (pair-fed) or was given *ad libitum*. In the first goitrogen experiment, cortisone and propylthiouracil‖ (PTU; 0.05% in the ration) were given concurrently throughout (18 days); in the second experiment, the goitrogen was given for 130 days, cortisone being administered for the last 24 days only. The thyroid, hypophysis, adrenals, and thymus were quickly removed at sacrifice (20-24 hours after last injection), were trimmed, weighed on a microtorsion balance, and prepared for histologic study. In the radioiodine studies, 4 μc of I^{131} (carrier free)** were injected intraperitoneally 24 hours prior to sacrifice. Radioactivity in single thyroid lobes was determined by a method described previously(17). Extracts of adenohypophyses for TSH assay were made by a standardized procedure(18). The pituitary extracts, and also the serum obtained from pooled blood of animals in respective groups were bioassayed for TSH in the stasis tadpole(19).

Results. The results are summarized in Table I. Cortisone invariably caused body weight loss. Cortisone treatment alone produced no significant change in thyroid- or adenohypophyseal-body weight ratios and was without significant effect on the TSH content of the pituitary. Blood TSH titers in cortisone-treated animals and in pair-fed controls were diminished as compared with those in normally fed rats. Adrenal atrophy and thymic involution were found consistently in all cortisone-treated animals. The smallest ad-

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‖ Propylthiouracil was supplied by the American Cyanamid Co. through the courtesy of Dr. S. M. Hardy.

** I^{131} was obtained from the Atomic Energy Com., Oak Ridge.

TABLE I. Effect of Cortisone on TSH Content of Blood and Adenohypophysis.

Group	No. of animals	Mean body wt (g) Initial	Mean body wt (g) Final	Mean gland wt (mg) 100 g final body wt Adenohyp.	Mean gland wt (mg) 100 g final body wt Thyroid	% I^{131} uptake Per mg thyroid	% I^{131} uptake Total gland	TSH assay in Stasis tadpole — Serum† Thyr. cell ht.	TSH assay in Stasis tadpole — Serum† TSH/μg/ml‡	TSH assay in Stasis tadpole — Adenohypophysis† Thyr. cell ht.	TSH assay in Stasis tadpole — Adenohypophysis† TSH/μg/mg‡
Normal, fed *ad lib.*	10		204±15*	4.5±.3	7.0± .4	—	—	5.9±.15	.36(.32– .44)	9.3±.24	21.7(15.0–26.7)
Cortisone, 2.5 mg daily for 15 days	10	196±12	180±17	5.3±.4	7.7± .3	—	—	5.4±.14	<.20	8.9±.35	13.3(10.0–20.0)
Normal, pair-fed	10	187±13	190±13	4.7±.4	8.4± .4	—	—	5.2±.05	<.20	9.2±.21	20.0(15.0–23.3)
PTU and cortisone, 2.5 mg daily, 18 days	12	226±23	195±22	5.3±.3	26.6±1.4	.026±.005	1.4± .9	6.7±.07	1.00(.88–1.08)	8.0±.10	4.3(4.0– 5.3)
PTU, pair-fed	12	225±15	213±15	4.6±.3	19.8±1.4	.030±.004	1.4± .2	6.2±.14	.60(.44– .64)	7.9±.33	4.0(2.7– 6.0)
PTU, 130 days, and cortisone, 2.5 mg daily, 24 days	9	163±14	125±12	9.3±.8	112.0±8.2	.032±.004	4.5± .6	6.9±.15	1.18(.90–1.33)	6.7±.20	.8(.7– 1.1)
PTU, 130 days	8	170±15	151±13	6.4±.5	54.0±4.1	.040±.005	3.2± .4	6.8±.17	1.08(.88–1.26)	7.3±.20	1.6(1.3– 2.3)
Normal, fed *ad lib.*	9		202±15	3.2±.3	6.6± .3	.575±.080	7.6±1.1	5.8±.07	.30(.26– .36)	8.8±.27	12.3(9.0–16.7)

* Mean body wt ± avg deviation; in all other columns ± values refer to stand. error of mean.
† Test animals received 0.05 ml of serum daily, 5 successive days; total amt of pit. extract given (over 4 inj.) represented .30 mg adenohypophysis.
‡ TSH concentration given in mean μg equivalents (range) of a standardized TSH preparation (D'Angelo, *Endocrinology*, 1951, v48, 249).

renals occurred in rats receiving both cortisone and PTU.

The simultaneous administration of cortisone and PTU induced marked changes in thyroid and pituitary. In rats receiving both cortisone and goitrogen for 18 days, thyroid hyperplasia was greater (34%) than with the goitrogen alone. Thyroid size in the latter group was approximately 3 times that of normal controls. Thyroid hyperplasia was accompanied by increased concentration of serum TSH. Hormone titers were higher in animals receiving cortisone and PTU than in those treated with PTU alone. TSH concentrations in the pituitary were substantially and equally reduced after 18 days of goitrogen treatment with or without cortisone.

The effect of cortisone on the thyroid and adenohypophysis of goitrous rats was found to be more marked if goitrogen treatment was prolonged prior to administration of the steroid. Under these circumstances, thyroid-body weight ratios in cortisone-treated rats were twice greater than with goitrogen alone and were increased to approximately 1700% of normal. In contradistinction to the findings in the short term experiment, pituitary enlargement occurred after 130 days of ingestion of PTU. This was significantly greater in the cortisone-PTU-treated animals. Pituitary TSH concentrations in goitrous animals were reduced still further, with lowest values found in the cortisone-PTU group. Diminished TSH stores were only partially offset by the increase in pituitary size. Blood TSH concentrations, however, were elevated equally in both groups.

As expected, there was marked diminution in the thyroidal I^{131} uptake of PTU-treated rats. The decreased avidity of thyroid tissue for radioiodine was not significantly modified by cortisone administration. Total radioiodine accumulations were below normal although the increased thyroid mass in cortisone-treated animals (2nd experiment) resulted in significantly greater I^{131} collections than with goitrogen alone.

Discussion. It is evident that the level of thyroid function may itself condition the response of the pituitary-thyroid system to high

levels of circulating adrenocortical steroids. Cortisone increases the size of the thyroid and adenohypophysis under conditions of inhibited thyroid hormone formation. Expected changes in blood and pituitary TSH levels are also induced in goitrous rats with cortisone. However, our data on TSH levels do not establish a strict parallelism as regards time sequence. The absence of such responses in the normal animal indicates that this steroid is not itself a goitrogenic agent. The decrease in blood TSH levels found in both cortisone-treated and pair-fed rats may well result from the reduced food intake. It is known that in acute starvation blood TSH levels fall(20). Lowering of the blood TSH titers due to malnutrition could conceivably account for some of the reduction in thyroidal radioiodine uptake occasionally reported in the rat.

The claim by Lederer(21) that cortisone depresses thyroid function through inhibition of TSH secretion from the pituitary was not confirmed. The decrease in TSH content found by Lederer in the hypophyses of thyroidectomized rats given cortisone may have resulted from augmented release; blood TSH levels were not measured. The present study reveals that enhancement of pituitary TSH secretion with cortisone occurs in the hypothyroid but not in the euthyroid animal. Halmi and Barker(12) have described morphologic changes in thyroid and hypophysis which suggest that cortisone promotes TSH function of the pituitary in non-goitrous rats. Differences in diet, or in dosage and duration of hormone treatment may possibly account for the dissimilar findings. The potentiating action of cortisone on PTU-induced goitrogenesis may be mediated through a direct action of the steroid on TSH release from the adenohypophysis, or the latter may result secondarily from further decrease in thyroid hormone production and/or alteration in the extra-thyroidal metabolism of iodide. The failure of cortisone to influence the I^{131} uptake of the thyroid depressed by PTU, does not preclude a direct effect of the steroid on the thyroid; uptakes are so diminished by PTU that further lowering may not be possible. The iodide-concentrating mechanism of the thyroid, however, does not appear to be involved(22).

Summary and conclusions. 1. Cortisone potentiates the effect of PTU on goitrogenesis in rats; a) thyroid and pituitary enlargement is greater than with goitrogen alone, and b) the respective changes in TSH levels of blood and pituitary are augmented. 2. The depressed avidity of thyroid tissue for I^{131} (with PTU) is not influenced by cortisone. 3. The results suggest that the potentiating action of cortisone on goitrogenesis involves augmentation of TSH secretion from the adenohypophysis. The implications are briefly discussed.

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Suppression of Normal Bactericidal Action of Rabbit Serum Following Whole Body X-Irradiation.* (20303)

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The observations that x-irradiation injury results in the development of bacteremia(1), that the x-irradiated animal is more susceptible to infection(2), and that antibiotic therapy affords partial protection following mid-lethal to lethal exposure to x-irradiation(3) emphasize the significance of infection among the pathological processes which follow irradiation. Increase in susceptibility to infection and increased incidence of bacteremia are primarily due to the deleterious action of x-irradiation on the host defense mechanisms. Among the suppressed host defense mechanisms which have been implicated are: depressed antibody formation(4), depressed phagocytosis, and destruction of the normal mechanical fascial barriers against infection(5). Even with depression of the previously mentioned host defenses however one would expect neither the large incidence nor the degree of bacteremia encountered if the sera of x-irradiated animals maintained normal bactericidal activity. This latter function has been studied in rabbits; the present report is concerned with the suppression of the normal bactericidal action of rabbit serum following acute whole body x-irradiation.

Materials and methods. Albino rabbits weighing approximately 3 kg were irradiated in air by means of a Westinghouse Quadrocondex x-ray machine. Radiation factors were: 250 KV; 15 ma; 1.0 mm Al and 0.5 mm Cu filters in addition to an inherent filtration of 2.5 mm Al and 0.25 mm Cu; distance from focal point to surface on which rabbits were standing was 105 cms; the dose rate was approximately 25r per minute as measured by a Victoreen r meter. The whole body x-irradiation doses in these experiments varied from 500 to 725r with a 30-day mortality of 675 $\pm$ 11.3r as calculated by the method of Miller and Tainter(6). Group III (Table I) received 2 doses of 650r whole body x-irradiation with a 28-day interval between exposures. Blood was withdrawn by cardiac puncture or via the marginal ear vein from an equal number of x-irradiated and normal control rabbits at various intervals. The serum was separated, stored at 4°C and the serum bactericidal test performed within 30 hours. Bactericidal activity was tested in the following manner: 0.2 ml of blood serum was added to 1.8 ml of 0.9% NaCl solution (saline) and 0.25 ml of 1:100 dilution of an 18-hour nutrient broth culture of *Bacillus subtilis* (PCI 220) was added to the 1:10 dilution of serum. The serum, saline, culture suspension was placed in a 37°C water bath for 2 hours before the nutrient agar pour plates were prepared from various dilutions of the suspension. The plates were then incubated at 37°C for 48 hours and colony counts were made. Because of variation in the number of viable bacteria in the original inoculum it was neces-

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