Effect of Propylthiouracil on Adrenal-Regeneration Hypertension in the Rat. (23927)

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It is well established that important functional inter-relationships exist between thyroid gland and adrenal cortex. In animals rendered hyperthyroid the adrenal cortex enlarges, and it shrinks in size in animals made hypothyroid by thyroidectomy or antithyroid drugs. Studies in this field have been summarized by Deane and Greep(1). Recently Masson *et al.* showed that treatment of adrenal-regeneration hypertensive rats with thyroxine resulted in higher blood pressures and increased the severity of vascular lesions (2). Skelton reported that thyro-parathyroidectomy prevented development of hypertensive vascular disease in rats following adrenal enucleation(3). In this study we found that treatment of adrenal-regeneration hypertensive rats with propylthiouracil (PTU) caused a marked depressant effect on hypertension. These results are of interest in interpretation of the mechanism of action of Amphenone which has antithyroid properties and also causes a reversal of adrenal-regeneration hypertension in the rat(4,5).

Methods. The animals were male Wistar rats weighing 80-100 g. The operative technics we used have been described(5). In this study, groups of 10 animals were prepared as follows. Group 1 unilateral nephrectomy, Group 2 unilateral nephrectomy, right unilateral adrenal enucleation and contralateral adrenalectomy. Group 3 was operated upon as described for Group 2 and 5 weeks after operation treatment was begun with PTU and continued for duration of experiment. All animals were fed commercial rat food during experimental period and were given 1% saline to drink after operation. PTU was administered orally at dose of 40 mg/kg daily in water. Systolic blood pressures were measured before operation and 3 times weekly during experiment, by the method of Kersten and Brosene(6). At end of experiment the animals were killed with chloroform, tissues were weighed fresh on torsion balance and prepared for histological examination. Pituitary glands were stained by the method of Rona and Morvay(7) the remainder of the organs were stained by methods as described earlier(5).

Results. I. *Blood pressure.* Hypertension which develops following unilateral adrenal enucleation and contralateral adrenalectomy in unilaterally nephrectomized rats given 1% sodium chloride to drink is illustrated in Fig. 1. Systolic blood pressure during 5-week period rose from normal levels to a mean pressure of 180 mm of mercury. After this point the pressures reached a plateau and remained at hypertensive levels for duration of experiment. Rats which are unilaterally nephrectomized and receive saline show a moderate rise in blood pressure but fail to develop hypertension (Fig. 2). The effect of PTU on adrenal-regeneration hypertension is shown in Fig. 3. The PTU was administered to these animals when mean blood pressure was 160 mm of mercury and was continued for duration of experiment. During this time the usual hypertensive response failed to develop and blood pressure progressively declined to levels comparable to those of Group 1 controls.

II. Mean *tissue weights* of the groups are shown in Table I. Kidney and heart weights are greatest in the adrenal-regeneration hypertension group. Relationship between tissue weights of this group and that treated with PTU is obscured by failure of animals from the latter group to gain weight in a normal manner. Although absolute mean weights for heart, kidney, spleen, thymus and adrenal gland of PTU treated rats are significantly lower than those of adrenal-regeneration hypertension animals, these differences are, however, not significant when values are related to body weight. Thyroid and pituitary glands of PTU treated animals are significantly larger than those of other groups.

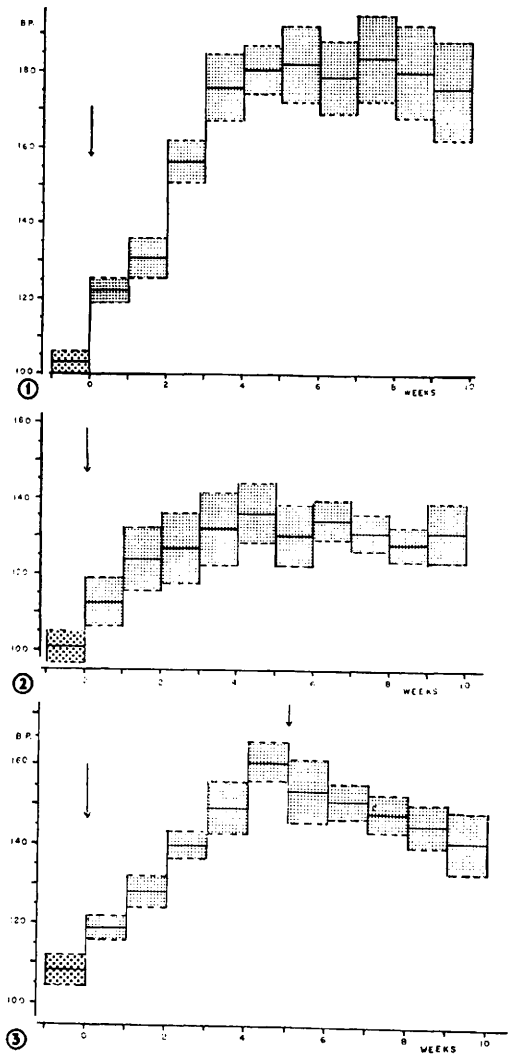

FIG. 1. Hypertensive response in rats of Group 2. Animals were surgically prepared at arrow. Solid horizontal lines represent mean weekly-blood pressure of group and shaded areas are 95% confidence limits.

FIG. 2. Moderate rise in blood pressure after unilateral nephrectomy and saline.

FIG. 3. Depressant effect of PTU treatment on blood pressure of adrenal-regeneration hypertensive rats. Animals were prepared at left arrow and PTU treatment was started as indicated by arrow on right.

III. *Histopathological lesions. Group 1.* Only one animal in this group showed any evidence of pathological lesions. This rat had a mild degree of chronic focal pyelonephritis without glomerular or vascular involvement. Terminal blood pressure of this animal was 159 mm of mercury.

Group 2. Renal and vascular lesions in this group correspond closely to those we have previously described in animals with adrenal-regeneration hypertension(5). One animal had a particularly severe nephrosclerosis and widespread vascular lesions of brain, thymus, mesentery, intestine, heart and adrenal capsule. Arteriolar necrosis and productive endarteritis in this animal was associated with encephalomalacia in the cortical area with lipoid and hemosiderin laden microglial cells surrounding the degenerated areas. Vascular lesions in the heart were found associated with areas of myocardial infarction. Four additional animals from this group had nephrosclerosis and vascular lesions which were less severe. The regenerated adrenal glands showed distinct zonal differentiation and a variable degree of nodularity. The zona glomerulosa was thin and composed of flattened, darkly stained cells with some traces of lipoid. The zona fasciculata was well developed and the cells contained a moderate amount of lipoid, occasional cell groups were swollen and vacuolated. The zona reticularis was distinct and normal in appearance. In pituitaries of these hypertensive animals a consistent change was noted in the basophils. These cells were increased in number and size compared to animals from Group 1. From 10 to 20% of these basophils contained clearly delineated single or less frequently multiple vacuoles which were approximately equal in size to the nuclei. In these vacuoles some evenly distributed purple granules were seen (Fig. 4). No changes were seen in eosinophil or chromophobe cells. The histological picture in thyroid, pancreas, liver and other organs was not remarkable.

Group 3. No evidence of either renal or vascular lesions was found in animals of this group. The regenerated adrenal gland was small and contained large masses of fibrous connective tissue and calcified areas. Zonation of the regenerated cortex was distinct, though marked differences were apparent compared to the animals of Group 2. The zona glomerulosa was normal in width and composed of darkly stained cells containing little lipoid. The zona fasciculata was quite narrow and this difference in size appeared to

TABLE I. Tissue Weights.

	Group 1 Unilateral nephrectomy	Group 2 Adrenal-regeneration hypertension	Group 3 Adrenal-regeneration hypertension + PTU	
Thymus (mg)	392 ± 38	333 ± 20	218 ± 15	*
Thyroid	23.7 ± 1.5	25.7 ± 2	61.6 ± 4	*
Adrenal, s	48.6 ± 2.4	34.1 ± 1.2	21.4 ± 1.3	*
Pituitary	11.0 ± .5	12.6 ± .9	16.4 ± .8	*
Spleen	629 ± 30	624 ± 22	444 ± 31	*
Heart (g)	.998 ± .045	1.16 ± .085	.792 ± .031	*
Liver	14.1 ± .8	12.7 ± 1.0	10.8 ± .6	
Brain	1.81 ± .04	1.82 ± .02	1.74 ± .03	
Kidney	2.18 ± .1	2.27 ± .1	1.64 ± .06	*
Body wt	331 ± 16	343 ± 10	266 ± 7	

* Significant at 99% confidence level compared to Group 2.

account for the overall decrease in size of gland. The cells of this zone were well outlined but cytoplasm and nucleus were reduced in size. The zona reticularis appeared relatively broad with deep penetrations of cells into the central connective tissue mass. The thyroid gland was composed of dilated acini surrounded by tall columnar cells. The colloid content of these acini was diminished with frequent resorption vacuoles at periphery. Papillary infolding was prominent. In the pituitary, the number of both eosinophil and chromophobe cells was reduced. Eosinophil cells were degranulated. Basophils appeared to make up about one-half of cells of the pituitary. These cells were swollen and stained only faintly with aniline blue. In more than half of these basophils (Fig. 5) the cytoplasm showed a honeycomb structure containing numerous vacuoles. Some basophils were ballooned out so that outlines were no longer visible. In a small percentage large distinct hyalin globules were found.

Discussion. It is clear from these results that PTU treatment exerts a depressant effect on development of adrenal-regeneration hypertension, thus indirectly confirming results previously reported by Skelton(3) after thyroparathyroidectomy. It would be of interest to know whether the effect shown on blood pressure is accompanied by a favourable influence on development of cardiovascular and renal lesions. However, as we have reported earlier(5), the incidence of these lesions in our studies is less than that reported by Skelton(8). In this experiment no cardio-

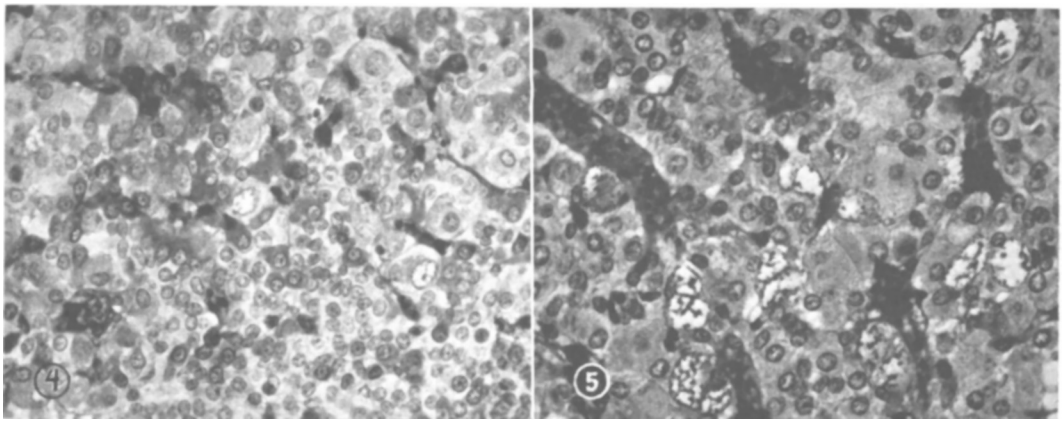

FIG. 4. Pituitary of adrenal hypertensive rat. Small cells with scanty pall cytoplasm are chromophobes. Darkly stained cells are eosinophils. Swollen large cells with occasional vacuoles are basophils. Rona-Morvay stain, × 310.

FIG. 5. Pituitary changes in animal from Group 3 treated with PTU: marked hyperemia, large, vacuolar basophils and degranulation of eosinophils. One basophil at left, below a capillary, contains rough hyaline granules. Rona-Morvay stain, × 310.

vascular or renal lesions were found in PTU treated animals, but since only 50% of adrenal-regeneration hypertensive controls developed such lesions no definite conclusions may be drawn from groups of animals of this size.

It is evident that with exception of weights of pituitary and thyroid glands, there is a general reduction in tissue weights in the PTU treated group. The generally lower weight of animals treated with antithyroid drugs is well known(9,10) and probably plays a large part in causing decrease in tissue weights. Although adrenal weights of PTU treated animals are not significantly lower than hypertensive controls when expressed in terms of body weight definite histological differences are seen when adrenals from these groups are compared. The shrinking of the fasciculata zone which we have observed has been reported by Deane and Greep following thiouracil therapy(1).

We reported earlier that Amphenone therapy, which lowers blood pressure of adrenal-regeneration hypertensive rats, affects primarily the fasciculata zone(5). Since Amphenone also possesses antithyroid properties (11), the possibility exists that the effects of this drug and PTU on blood pressure are mediated through a common mechanism. The histological picture of the pituitary gland, which we found after PTU treatment of rats with regenerated adrenals, is similar to that described by many workers after antithyroid drugs or thyroidectomy(12,13). However, the pituitary changes in control rats with adrenal-regeneration hypertension has not been reported. The basophilism in these animals may reflect a hyperactivity of the pituitary in response to hypofunction of the adrenal gland after unilateral adrenalectomy and contralateral adrenal enucleation. Available histochemical methods do not allow a differentiation between pituitary basophils responsible for thyroid-stimulating and adrenal corticotrophic hormones and it is not known whether these functions reside in the same cells(13,14). It is hoped that studies in progress may allow us to throw some light on the role of pituitary factors in adrenal-regeneration hypertension.

Summary. Treatment of rats having adrenal-regeneration hypertension with propylthiouracil, results in decrease in body and tissue weights and marked lowering of hypertensive blood levels. This treatment also results in shrinking of width of the fasciculata zone in regenerated adrenal gland and a marked change in pituitary basophils. An increase in basophils of the pituitary has also been found in control rats with adrenal-regeneration hypertension.

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