Atrophy of Adrenal Gland Following Thiouracil and Vit. B_{12}.* (22940)

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Although adrenal atrophy following thiouracil treatment has been demonstrated by numerous investigators(1-7), the evidence has not been unequivocal due to body weight loss that occurs concomitantly with administration of this drug. Thus, it has been also suggested that involution of the adrenal gland is merely the result of generalized inhibition of body growth(8-10). Recently, evidence has been presented to indicate that vit. B_{12} can prevent growth inhibiting action of thiouracil (11). Consequently, the present experiment was designed to determine whether adrenal involution could be obtained in the absence of marked depression in body growth through simultaneous administration of thiouracil and vit. B_{12}.

Material and methods. Male rats (Sprague Dawley strain) were used. All animals were placed on treatment when they reached approximately 100 g in body wt. The thiouracil was prepared as a 0.1% solution and administered in drinking water. Vit. B_{12}‡ was prepared in saline solution and injected intraperitoneally. The animals were divided into 7 groups and treated for 12 weeks to insure definite atrophy of the adrenal cortex(3). Groups A and B were kept as controls; group A receiving no treatment and group B receiving 0.1 ml of saline intraperitoneally daily. Groups C, F and G received 0.1% thiouracil in drinking water and in addition F and G received 10 and 20 μg of B_{12} respectively. Groups D and E received only 10 and 20 μg of B_{12} respectively. In all instances the vitamin was given daily via intraperitoneal route. Body weights were obtained weekly and the animals were killed after 12 weeks of treatments. Thyroid and adrenal weights were obtained at time of postmortem and weighed to nearest 0.1 mg.

Results. The data in Table I indicate that vit. B_{12} prevents growth inhibiting action of thiouracil. Normal, control rats injected with 0.1 ml saline showed final average body weight of 223 g; thiouracil treated rats a body weight of 147 g and rats given thiouracil and 10 or 20 μg of B_{12}, a body weight of 193 and 205 g respectively. The difference between body weights of thiouracil-treated rats and saline controls is significant whereas no significance is seen between the controls and groups receiving thiouracil and 20 μg of B_{12} simultaneously. Treatment with 10 μg of B_{12} partially prevented body weight depression due to thiouracil while 20 μg of B_{12} gave complete protection.

Thiouracil induced the expected hypertrophy and hyperplasia of the thyroid but no significant difference in weight of thyroid can be noted between groups receiving thiouracil alone and thiouracil plus B_{12}. Indication of a possible decrease in size of thyroid gland of rats treated with B_{12} may be seen, if comparison is made of weight of the thyroid expressed as per cent of body weight. However, a significant decrease in weight of the thyroid gland of the thiouracil-treated rat is seen only with the group receiving 10 μg of B_{12}.

Adrenal glands of untreated controls and saline controls weighed 64.7 and 53.9 mg respectively. This is a difference of approximately 20% and is significant although we can suggest no reason, since one might have expected the increase in saline controls, if at all. Adrenal glands of rats treated with thiouracil weighed 19.3 mg or 12.9 mg% body weight. Treatment with 10 and 20 μg of B_{12} alone resulted in adrenal glands of 24.8 and 25.4 mg% respectively, indicating no effect as compared with saline controls. The combined treatment with thiouracil and vit. B_{12} at 10 and 20 μg gave adrenal weights of 28 $\pm$ 7 and 33 $\pm$ 8.5 mg (Table I). Statistical

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TABLE I. Effect of Thiouracil and Vit. B_{12} on Body Weight, Thyroid and Adrenal Cortex of the Rat.

Treatment	Group	No. of rats	Body wt, g	Thyroid		Adrenal cortex	
				mg	mg % body wt	mg	mg % body wt
Controls	A	8	229.4 ± 21.2*	14.8 ± 1.87	6.5 ± .58	64.7 ±10.04	28.2 ± 2.38
Saline	B	8	223.1 ± 11.1	13.6 ± 1.04	6.1 ± .58	53.9 ± 4.96	24.1 ± 1.59
Thiouracil	C	11	147.1 ± 32.3	51.5 ± 4.06	35.1 ±7.34	19.3 ± 7.85	12.9 ± 2.48
10 μg B_{12}	D	10	226.4 ± 18.2	12.7 ± 2.49	5.6 ± .98	56.0 ± 4.49	24.8 ± 2.69
20 " "	E	7	253.8 ± 18.2	12.2 ± 2.49	4.8 ± .99	64.4 ± 4.20	25.4 ± 1.36
Thiouracil + 10 μg B_{12}	F	10	193.2 ± 17.5	49.4 ± 7.54	25.6 ±3.32	28.0 ± 7.17	14.4 ± 2.75
Thiouracil + 20 μg B_{12}	G	10	205.4 ± 26.7	59.3 ± 8.80	29.8 ±8.40	33.0 ± 8.45	15.8 ± 2.55

* Stand. dev.

analysis revealed no significant difference between absolute weight of adrenal gland of rats treated with thiouracil or thiouracil and 10 μg B_{12}. A significant difference was noted at 20 μg B_{12} dosage but it should be noted that the adrenals still showed marked atrophy (approximately 40%) when compared with controls. A further comparison of adrenal gland weight when expressed as a function of body weight, revealed a lack of any statistically significant difference between the adrenal gland of rats treated with thiouracil or a combination of thiouracil and vit. B_{12}.

These data confirm the report by Meites(8) in that vit. B_{12} prevents body growth inhibiting action of thiouracil. In spite of this action, however, the vitamin was unable to prevent adrenal atrophy induced by thiouracil. Since this experiment was able to separate the action of thiouracil on body growth and adrenal gland, it can now be stated conclusively that thiouracil specifically inhibits the adrenal gland. The mechanism whereby this is done can not be stated at this time. Money (12) stated that the mechanism of adrenal involution following thyroidectomy or thiouracil treatment remains obscure. While we can now eliminate the possibility of a nonspecific, generalized effect due to failure of body growth, the following possibilities await further clarification: 1) a possible shift in pituitary production from ACTH to TSH (13,14); 2) an independent decrease in ACTH elaboration; 3) a critical need for thyroxine in the normal growth of the adrenal gland(8); 4) a decreased utilization of the adrenocortical hormone(15); or 5) a direct action of thiouracil on the adrenal gland. Thus far, the validity of the pituitary shift as a possible explanation has been questioned by several investigators(15,16).

Conclusions. Vit. B_{12} prevented the growth inhibiting action of thiouracil but failed to prevent adrenal atrophy. Atrophy of the adrenal cortex was due to a specific action of the goitrogen and not a reflection of generalized inhibition of body growth.

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