

Effect of Desoxycorticosterone on the Development of Rats Treated with Thiouracil.

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It has been shown that either adrenal cortical extracts or desoxycorticosterone acetate (DOCA) hastened the development of newborn rats.¹ Under the effects of these substances, the rats' teeth erupted earlier and their eyes opened sooner than littermate controls. The mechanism whereby this precocious development takes place is under investigation. It has been reported that thyroxine produced a qualitatively similar hastening of tooth development² and experiments were undertaken to determine whether the adrenal cortical action was mediated through the thyroid gland.

Thyroidectomy in the newborn is an extremely hazardous and frequently fatal operation.³ Depression of the normal thyroid activity can be accomplished in baby rats by means of thiouracil.^{4,5} The effects of DOCA on thiouracil treated rats are reported.

Method. Sixty-two one-day-old rats from 6 litters of the Sprague-Dawley strain were divided into 4 groups. Wherever there were sufficient rats the individual litters were divided so that there were at least 3 rats for each of the following experimental conditions. A total of 15 rats received daily (including Sunday) subcutaneous injections of 0.25 mg of DOCA in 0.05 ml of peanut oil. Eleven rats received similar injections of one to 4 mg of thiouracil, suspended in 0.1 ml of peanut oil. Twenty-one rats received daily injections of both drugs, and 15 rats

remained as the untreated control group. Injections were usually given for about 2 weeks. Each litter of rats remained with its respective mother throughout the experiment. Daily body weights were recorded for each rat and observations of tooth development, eyelid opening, and general physical condition were made each morning and night. At the completion of the experiments, the animals were sacrificed and their thyroids were sectioned and stained with hematoxylin and eosin.

Results. All the rats tolerated the injections and handling fairly well in the newborn period. Hair growth at the site of the DOCA injections was sparse in both groups of rats receiving the drug.

Table I reveals the effects of the drugs on the eruption of the incisor teeth and opening of the eyelids. Although figures given are means of results from 6 litters, the results in individual litters were similar. DOCA invariably hastened the eruption of the teeth, stimulated the differentiation and separation of the lips from the gingiva, and hastened the opening of the eyelids. Thiouracil, in doses of one to 4 mg per day, on the other hand markedly depressed all these developmental changes. In those rats receiving injections of both DOCA and thiouracil, a mutually antagonistic effect was observed. The tooth eruption and eyelid opening in these rats was within normal limits. This was confirmed statistically in that the means of the DOCA and thiouracil groups were significantly different from that of the controls, but the mean of the group receiving the combination of both drugs was not significantly different from that of the controls.

The effects on the body weight and growth curve of one representative litter of 12 rats are shown in Fig. 1. DOCA in the dose em-

¹ Mulinos, M. G., and Parmer, L. G., *Science*, 1942, **95**, 484.

² Karnofsky, D., and Cronkite, E. P., *Proc. Soc. Exp. Biol. and Med.*, 1939, **40**, 568.

³ Salmon, T. N., *Endocrin.*, 1938, **23**, 446.

⁴ Hughes, A. M., *Endocrin.*, 1944, **34**, 69.

⁵ Goldsmith, E. D., Gordon, A. S., and Charipper, H. A., *Am. J. Obst. Gyn.*, 1945, **49**, 197.

TABLE I.

Effect of Injections of Desoxycorticosterone Acetate, Thiouracil, and Combination of Both Drugs on Teeth and Eyes of Baby Rats.

	Control 15 rats		DOCA 15 rats		Thiouracil 11 rats		Thiouracil + DOCA 21 rats	
	Mean	σ	Mean	σ	Mean	σ	Mean	σ
Age at eruption of incisors (days)	9.5	0.63	8.4	0.29	11.3	0.61	9.2	0.84
Age at opening of eyelids (days)	15.1	0.43	14.1	0.61	16.9	0.45	15.5	0.73

ployed had no effect on the body weight of rats even though the injections were continued for 23 days. Thiouracil also had little or no effect on the growth curve for the first 10 to 15 days. However, there then occurred a plateauing of body weight so that in the next week, the thiouracil treated rats showed marked stunting of growth and evidence of immaturity in activity and physical appearance. This has been described by Hughes⁴ as cretinism. DOCA, despite its antagonistic effect on the thiouracil depression of tooth, mouth and eyelid development, had no effect whatsoever on antagonizing this stunting effect of thiouracil. Their sickly state was not affected by DOCA and occasionally they seemed more depressed than the rats receiving thiouracil alone. One group of rats which received both drugs for a period of 2 weeks was observed further and the weight curve was compared to that of the littermate controls. At the end of 3 weeks without injections the average weight of the rats was about 15% below that of their controls. In another litter, 2 of the 4 rats in a similar group became weak, stopped feeding

and died, despite the cessation of treatment.

The thyroid glands of the thiouracil treated rats were grossly much larger than those of the controls. Histologically they showed enlargement and increased height of the follicle cells. The glands of the animals receiving the combination of DOCA and thiouracil were indistinguishable from those treated with thiouracil alone, whereas those injected with DOCA alone resembled the normal controls.

Comment. There is little evidence from these experiments to indicate that the precocious development produced by DOCA is mediated through the thyroid gland. Although thiouracil depresses the normal thyroid gland function, there is no certainty that it does so completely in the first few injections. If DOCA could produce its usual changes in a surgically thyroidectomized rat, a definite conclusion could be arrived at.

It is of interest, that despite the fact that thiouracil produces marked changes in the development and growth of the rats, DOCA was able to antagonize its effects on tooth eruption and eyelid opening. Whether the same phenomena can be produced by large doses of other steroid hormones and whether other effects of the thiouracil-thyroid deficiency can be corrected by these hormones remains to be studied.

Summary. Thiouracil injections into baby rats resulted in retardation of tooth eruption and opening of the eyelids. Desoxycorticosterone, when injected into thiouracil treated rats, was able to antagonize these developmental effects so that the time of tooth eruption and eyelid opening returned to normal. It had no antagonizing effect, however, on the stunting of body growth or on the histological picture of the thyroid gland produced by thiouracil.

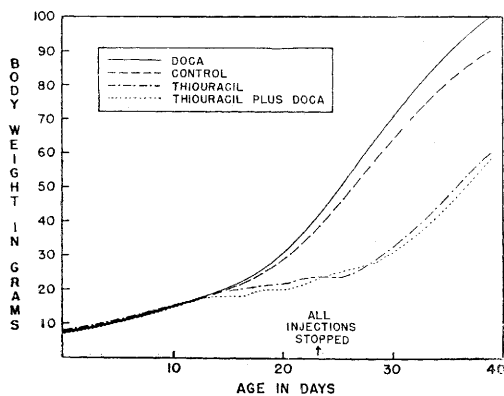


FIG. 1.

Growth curves of baby rats receiving DOCA, thiouracil, or a combination of both drugs. There are 3 rats in each group and all are littermates.