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Androgenic Action of Desoxycorticosterone Acetate?

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It is generally assumed that under certain circumstances the adrenals exert an androgenic action. Clinical evidence may be seen in the high excretion of androgens in women with tumors of the adrenal gland as well as in the fact that both excretion of androgens and clinical symptoms of virilism regress after removal of the adrenal tumor. In the young rat and mouse, castration is not followed by complete atrophy of the prostate and seminal vesicles[1, 2] unless the adrenals are also removed.[4, 5] The X zone of the mouse adrenal is considered to be androgenic[5] but this interpretation has been doubted and the X zone was thought to represent a "reserve zone of the adrenal".[6]

Reichstein has isolated andrenosterol from the adrenal cortex and has proved its androgenic action.[7] This, however, is probably not the only androgenic steroid compound of the adrenal cortex. Progesterone, one of the sterols found in the adrenal cortex, is androgenic.[8] It was, therefore, planned to examine sterols of the cortex for their androgenic activity. In this paper we report on desoxycorticosterone acetate. Other sterols are to be studied if and when sufficient quantities become available to us. Desoxycorticosterone has been studied previously with conflicting results. Hooker and Collins[9] have found this compound to be active, whereas Greene and Burrill[10] failed to find any androgenic activity.

Our interest in the possible androgenic action of various cortical steroid compounds was also stimulated by the question whether

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1 Price, D., *Am. J. Anat.*, 1936, **60**, 79.

2 Howard, E., *Am. J. Physiol.*, 1937, **119**, 339.

3 Burrill, M. W., and Greene, R. R., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 327.

4 Burrill, M. W., and Greene, R. R., *Endocrinology*, 1940, **26**, 645.

5 Howard, E., *Am. J. Anat.*, 1939, **65**, 105.

6 Gersh, T., and Grollman, A., *Anat. Rec.*, 1939, **75**, 131.

7 Reichstein, T., *Helv. Chim. Acta.*, 1936, **19**, 223.

8 Greene, R. R., Burrill, M. W., and Ivy, A. C., *Endocrinology*, 1939, **24**, 353.

9 Hooker, Chas. W., and Collins, V. J., *Endocrinology*, 1940, **26**, 269.

10 Greene, R. R., and Burrill, M. W., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 382.

cases of virilism, in which no disturbance of salt and water metabolism or of carbohydrate metabolism could be detected, might be explained on the basis of "dissociated hyperfunction" of the adrenal cortex (unpublished observations).

Methods and Results. For assay of androgenic activity, two methods were used: (a) stimulation of mitosis in the prostate and seminal vesicle of castrate rats as described by Fleischmann,[11] and (b) the comb growth of the immature chick (Frank,[12] modified by Rakoff[13]).

Twenty adult male rats weighing between 200 and 250 g were castrated. Adult instead of immature rats as employed by Fleischmann were used in order to exclude any possible influence of the animals' own adrenals (see above). Three and one-half weeks were allowed for complete atrophy of the accessories (prostate, seminal vesicles). Desoxycorticosterone acetate* was then injected subcutaneously in two divided doses (first half dose at 2 p. m., second half dose at 8 a. m. on the following morning). Two tenths mg colchicine were injected simultaneously with the second half dose, but at a different site. Eight hours after the injection of the colchicine, *i. e.*, 26 hours after the first injection of hormone, the animals were killed. The prostate and seminal vesicle were fixed in Bouin's solution, imbedded in paraffin, sectioned and stained with hematoxylin and eosin. From each animal a specimen from the small intestine was treated in the same way in order to serve as a control for the effectiveness of the colchicine to arrest mitoses.

The animals were divided into 4 groups, one group serving as control and receiving colchicine only, the 3 others receiving desoxycorticosterone acetate in total doses of 0.6, 1.0, 5.0 mg, respectively.

There was no stimulation of mitosis in the prostate or seminal vesicle at either of the 3 dosage levels employed. Mitoses were very plentiful in the intestinal epithelium, thus indicating normal response of the animals to colchicine.

Comb Growth Promoting Potency. It is well known that some androgens, such as testosterone and its esters, are relatively more potent in repair of the rodent's accessories; whereas others, such as androsterone, have a relatively higher comb growth promoting po-

[11] Fleischmann, W., *Endocrinology*, 1939, **25**, 798.

[12] Frank, R. T., Klempner, E., and Hollander, F., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 853.

[13] Rakoff, A., unpublished.

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tency. Since the experiments on the castrated rat had revealed no androgenic potency, the following experiments on one-day-old chicks were carried out. Thirty chicks were used. The hormones were injected into the comb. Six chicks received 0.025 mg desoxycorticosterone daily for 6 days, a total of 0.15 mg; 6 chicks received 0.125 mg daily for 6 days, a total of 0.75 mg. Six animals received no treatment (untreated controls); 5 were treated with androsterone, receiving 6 daily doses of 0.005 mg, a total of 0.03 mg; 6 received 6 daily doses of 0.0005 mg of androsterone, a total of 0.003 mg (androsterone controls). Whereas treatment with androsterone produced an increase of comb growth of 20 and 32% respectively with the dosage levels employed, there was no increase in comb growth with desoxycorticosterone acetate; rather the desoxycorticosterone acetate seemed possibly to impair comb growth. The comb weight in the desoxycorticosterone-treated animals was 9 and 12% lower than that of the untreated controls. These figures are probably not significant.

No androgenic activity of desoxycorticosterone acetate was found either in the castrate rat or in the chick. These findings are in agreement with the results of Green and Burrill.[10] These authors gauged the androgenic activity by maintenance of secretion of the ventral prostate of the castrate rat, as judged by histologic appearance. In our experiments stimulation of mitosis in the castrate rats' accessories was used as indicator of androgenic activity. This is probably a more sensitive test. The question of specificity of this test need not be discussed since the results were negative. Howard[14] has shown that even large doses of desoxycorticosterone fail to produce atrophy of the X zone of the adrenal gland of the mouse. Atrophy of the X zone is the typical reaction of the adrenal gland of the mouse to androgens. Hooker and Collins[9] have based their statement of androgenic activity of desoxycorticosterone acetate on increase of seminal vesicle weight in 2 desoxycorticosterone-treated rats over that of one control. In addition they report on 6 capons treated with varying dosage levels. In our experiments desoxycorticosterone acetate failed to stimulate comb growth in 12 chicks.

Summary. Desoxycorticosterone is not androgenic.

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[14] Howard, E., *Anat. Rec.*, 1940, **77**, 181.