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Gonadotropic Effect of Androgens upon the Immature Rat Ovary.

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Butenandt and Kudzus[1] have reported that androgenic substances administered to immature female rats cause premature opening of the vagina. The present study was undertaken to determine whether the androgens produce this effect directly upon the genital tract or indirectly through the ovary.

Eighteen rats (comprising 5 litters), varying in age from 27 to 30 days, were used in this study. Twelve were given a single injection of androgen in sesame oil; 6 controls were given an equal quantity of pure sesame oil. Seven of the animals were injected with testosterone propionate and 5 with androstenediol,† the dosage varying from 1 to 5 mg.

The time of the opening of the vagina was noted in each case. Laparotomies were performed and one ovary removed at intervals varying from 60 to 96 hours after the administration of the androgen. The animals were sacrificed at periods varying from 96 to 228 hours after the injection and the remaining ovary was then removed. At corresponding intervals, the ovaries were removed from the control animals. The ovaries were examined microscopically in serial sections.

Opening of the vagina occurred in all androgen-injected animals within 72 hours after the injection. Follicle stimulation was noted as early as 60 and 72 hours after the injection. Corpora lutea were found as early as 96 hours and as late as 192 hours after androgen administration. The ovaries of all the 12 injected animals exhibited some gonadotropic effect, either follicle stimulation, luteinization or both. The uteri in all these animals were markedly enlarged. In the 6 control rats, the vaginas remained closed and the ovaries were negative.

It appears from this study that testosterone propionate and androstenediol produce follicle growth and corpora lutea in the ovaries

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1 Butenandt, A., and Kudzus, H., *Hoppe-Seyler's Z.*, 1935, **237**, 75.

† For the testosterone propionate and androstenediol used in this experimental study, I am indebted to Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J.

of immature rats. The premature opening of the vagina which occurs following the administration of androgens is apparently brought about through a gonadotropic effect exerted upon the ovary. Whether this gonadotropic effect is produced by direct action of the androgen upon the ovary or indirectly through stimulation of the hypophysis has not been determined. To ascertain this point, similar experiments with hypophysectomized animals would have to be performed. However, in view of the fact that Hohlweg and Chamono[2] have been able to produce corpora lutea in the ovaries of intact immature rats with an estrogen (estradiol benzoate) but not in hypophysectomized animals, it seems likely that the androgens act in a similar fashion, stimulating the hypophysis to secrete the follicle stimulating and luteinizing hormones.

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Effect of Androgens on Exophthalmos in Rabbits.

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In earlier papers[1, 2] we have reported (a) that exophthalmos developed more frequently in male rabbits (60 vs. 40%), (b) that this sex difference was independent of the exophthalmos-promoting effect of thyroid insufficiency, (c) that castration in the male greatly inhibited the development of exophthalmos, and caused gradual regression of an existing exophthalmos,[3] and (d) that cryptorchidism with complete degeneration of the germinal epithelium did not cause regression of exophthalmos in rabbits.[4]

From these observations it appeared highly probable that the interstitial cells of the testis were producing some hormone which, in association with reduced thyroid secretion, increased pituitary activity and perhaps other endocrine and mineral imbalances, was capable of maintaining an existing exophthalmos.

On the basis of these observations we have carried out experi-

2 Hohlweg, W., and Chamono, A., *Klin. Wchnschr.*, 1937, **16**, 196.

1 Marine, D., Rosen, S. H., and Cipra, A., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 649.

2 Marine, D., Rosen, S. H., *Am. J. Med. Sci.*, 1934, **188**, 565.

3 Marine, D., Rosen, S. H., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 354.

4 Marine, D., Rosen, S. H., *Am. J. Physiol.*, 1938, **121**, 620.