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.

9851

Effect of Androgens on Exophthalmos in Rabbits.

DAVID MARINE.

From the Laboratory Division, Montefiore Hospital, New York City.

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.

ments on rabbits using testosterone propionate (Perandren) and androsterone, generously donated by Ciba Products, Inc., and dehydro-androsterone prepared in this laboratory. These hormones were dissolved in sesame oil and injected into the subcutaneous and intramuscular tissues of the abdominal wall. Eighteen experiments have been carried out in a group of 22 rabbits. The principal data of 11 of these experiments are given in Table I.

These experiments include rabbits with thyroid and gonads intact, with thyroids or gonads removed, with partial thyroidectomy and gonadectomy, and with partial thyroidectomy and cryptorchidism. The parenteral administration of large doses of androgens has produced or increased exophthalmos only in those rabbits (1) that had had exophthalmos and recovered (Exp. 1), or (2) that had latent exophthalmos (Exp. 6), or (3) that had definite exophthalmos at the time of the injections (Exp. 7). In no instance was exophthalmos produced by synthetic androgens in rabbits that never had had thyroid deficiency exophthalmos even though they had been subjected to thyroidectomy, thyroid feeding, cryptorchidism or gonadectomy. In experiments Nos. 1, 4 and 5, the same rabbits were used for testosterone propionate (70 mg. in 8 days), androsterone (150 mg. in 8 days) and dehydro-androsterone acetate (533 mg. in 4 days). The degree of exophthalmos produced was greatest with testosterone propionate and least with dehydro-androsterone acetate, despite the enormous differences in dosage used. The exophthalmic reactions obtained were qualitatively similar to the capon's comb, or rat seminal vesicle reactions to these hormones.

Experiment 3 shows the rapid counteractive or curative effect of desiccated thyroid on exophthalmos produced by testosterone propionate. This observation may be correlated with the antagonistic effect of thyroxine or desiccated thyroid on the gonads (depresses ovulation and spermatogenesis in rats and produces hen feathering in male birds). In those rabbits in which exophthalmos was produced or increased by androgens a suggestive increase was often noted about 6 hours after the first injection and was definite on the second day (24-36 hours). Another feature is the rapid regression of the exophthalmos after stopping the injections. This regression was evident in 3 days and sometimes complete in 7 days. The possibility that the sesame oil might have caused the exophthalmos was eliminated by using the oil in the same dose in 2 of our most sensitive rabbits (30 and 99). No rabbit with intact thyroid or in which the thyroidectomy appeared to be complete (no thyroid tissue found at surgical or postmortem examination) developed

TABLE I.

Exp. No.	Rabbit	Sex	Thyroidectomy	Gonadectomy	Cryptorchidism	Androgens injected: Total Amt. (mg.)	Androgens injected: Duration (days)	Degree of Exophthalmos: Before (days) 7	3	1	After (days) 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
						Test. prop.																			
1	30	M	5-1		12-29	70	8	0			0	0	2	4	3	3	3	4	3	2	2	2	1	2	2
	99	M	3-24	11-27		70	8	0			0	2	3	3	4	1	4	4	3	3	1	1	1	0	1
	55	M			2-12	70	8	0			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
						Test. prop.																			
2	30	M	5-1		12-29	40	4	1	0	0	1	2	2	2	3	1	1	1	1	1	0	0	0	0	0
	99	M	3-24	11-27		40	4	1	0	0	0	1	1	3	3	2	1	1	0	0	0	0	0	0	0
						Test. prop.																			
3	30	M	5-1		12-29	160	16	0	0	0	1	2	2	3	2*	3	2	2	1†	0	1	1	2	2	1
	99	M	3-24	11-27		160	16	0	0	0	0	1	1	4	3	4	3	2	2	1	1	1	3	1	2
						Andros.																			
4	30	M	5-1		12-29	150	8		0	0	1	1	2	2		2	2	2	2	2	2	1	0	0	1
	99	M	3-24	11-27		160	9		0	0	1	1	1	2		1	3	1	3	2	2	1	0	0	1
						Dehydro. ac.																			
5	30	M	5-1		12-29	533	4	0		0	0	1	2	1	1		0	0							
	99	M	3-24	11-27		533	4	0		0	0	1	2	0	0		0	0							
						Test. prop.																			
6	87	F	6-10	8-6		50	10	0			0	1	1	1	1	1	2	2	3	4	4	3		4	1
	89	M	8-6	8-6		50	10	0			0	1	2	2	2	3	3	4	4	5	4	5		4	4
	94	F		8-6		40	8	0	0	0	0	0	0	0	1	0	0	0	0	0		0	0	0	0
	95	M		8-6		40	8	0	0	0	0	0	0	0	0	0	1	0	0	0		0	0	0	0
						Test. prop.																			
7	91	M	6-10	8-6		30	3	4	4	4	3	5	4	4	4	4	2	2	4	2	3	4	0	2	0
	92	M		8-6		30	3	0	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0
						Test. prop.																			
8	02	M				40	4		0		0	0	0	0	0	0	0								
	03	M				40	4		0		0	0	0	0	0	0	0								
						Test. prop.																			
9	02	M	11-9		11-9	50	5		0	0	0	0	0	0	0	0	0	0							
	03	M	11-9		11-9	50	5		0	0	0	0	0	0	0	0	0	0							
						Test. prop.																			
10	55	M	8-11		2-12	75	8	0	0		0	0	0	0	0	0	0	0							
	94	F		8-6		55	8	0	0		0	0	0	0	0	0	0	0							
	95	M		8-6		55	8				0	0	0	0	0	0	0	0							
						Sesame Oil																			
11	30	M	5-1		12-29	10 cc.	5	0		0	0	0	0	0	0	0									
	99	M	3-24	11-27		10 cc.	5	0		0	0	0	0	0	0	0									

*First dose desiccated thyroid.

†Last dose desiccated thyroid—total 500 mg.

exophthalmos following the injection of androgens. We have no explanation as to why some rabbits failed to develop exophthalmos. Similar failures, however, occur in guinea pigs with pituitary extracts, as well as in rabbits following partial thyroidectomy. These failures indicate that other unknown factors must be favorable in order to obtain exophthalmos. There is some evidence that one of these factors is a disturbance of mineral metabolism, especially the Ca-P ratio. Four female rabbits received testosterone propionate. In only one—an ovariectomized rabbit with latent exophthalmos—did exophthalmos develop. The two with intact ovaries developed intense oestrus as determined by vaginal and vulval reactions and sexual receptivity.

Summary. The data here reported indicate that thyroid insufficiency associated with increased pituitary and androgenic activity (active or passive) are important factors favoring the development of exophthalmos in rabbits. The androgenic factor is believed to play a rôle in the percentile increase in the incidence of post-thyroidectomy exophthalmos in Graves' disease in males.

9852

Sugar Alcohols XIII. Primulatol and Glycogen Storage in the Rat.

E. P. HIATT, C. JELLEFF CARR, W. E. EVANS AND JOHN C. KRANTZ, JR.

From the Departments of Physiology and Pharmacology, School of Medicine, University of Maryland.

Roe and Hudson[1] demonstrated that β d-mannoheptulose is physiologically available to the rabbit which has a high tolerance for this heptose. In the studies of the fate of the sugar alcohols and their anhydrides in the animal body in which mannitol[2] was shown to be a precursor of glycogen the possible utilization of the corresponding sugar alcohol, β d-mannoheptitol became of interest. The β d-mannoheptitol was extracted from *Primula officinalis* by the method of Bougoult and Allard.[3] The compound melted uncorrected at 153°.

Rats were fasted for 51 hours. After this period the control

1 Roe and Hudson, *J. Biol. Chem.*, 1936, **112**, 443.

2 Carr, Musser, Schmidt, and Krantz, *J. Biol. Chem.*, 1933, **102**, 721.

3 Bougoult and Allard, *Compt. rend.*, 1902, **135**, 796.