

Effects of Administration of Testosterone on Vitamin A-Deficient Rats. (17460)

JEAN MAYER AND ALDO P. TRUANT (Introduced by P. K. Smith)

*From the Department of Pharmacology, The George Washington University School of Medicine,
Washington, D. C.*

It has been shown by Mason¹ in particular that the effect of vitamin A deficiency on the male rat amounts to a virtual castration. This phenomenon can lead to two main hypotheses. One, vitamin A deficiency may interfere either with the synthesis of testosterone, directly (chemically) or indirectly (*e.g.* secondary effect due to pituitary atrophy in deficient animals). The second probability is that the response of target organs to circulating male sex hormones is affected. To elucidate this point, it was decided to examine and compare the effect of testosterone administration on castrated and non-castrated vitamin A deficient male rats and their controls.

Method. The animals used were male Wistar albino weanlings, 23 days of age. Their average weight was 55 g. Castrated animals had been operated at the age of 21 days and subsequent autopsies showed that all operations had been successful. Prior to the weaning of the experimental animals, their mothers had been put on a vitamin A-poor, "depletion" diet. The animals were kept at room temperature (about 70° F) and were alternately 12 hours in darkness and 12 hours in artificial light. They were fed water and food *ad libitum*. The diet used was the U.S.P. XII diet for vitamin A assay (casein 18%, salt mixture 4%, yeast 8%, starch 65% and vegetable oil 5%) to which was added 100 mg per kg of α -tocopherol. With a yeast-containing diet and a slow growing strain of animals, secondary vitamin C deficiency does not develop as a complicating factor.^{2,3} Control animals received orally 1200 I.U. vitamin A every 8 days.*

The animals receiving testosterone were injected every day subcutaneously with 2 mg

of testosterone propionate ("Perandren") dissolved in 0.04 cc of sesame oil.[†] Other animals received a control daily injection of 0.04 cc of pure sesame oil. Thirty-one animals were used. They were divided into the following 8 groups:

- a) 6 non-castrates, vit. A deficient
- b) 6 non-castrates, vit. A deficient receiving testosterone
- c) 3 non-castrates receiving vit. A
- d) 3 non-castrates receiving vit. A and testosterone
- e) 4 castrates, vit. A deficient
- f) 4 castrates, vit. A deficient receiving testosterone
- g) 3 castrates, receiving vit. A
- h) 2 non-castrates receiving vit. A and testosterone

All animals were weighed every other day. They were sacrificed by decapitation after they had been 64 days on the experiment. By that time most deficient animals showed ocular symptoms of vitamin A deficiency and had lost some weight.

Results and discussion. Table I gives the average weight gains as well as significant average organ weights found. As most groups of animals were too small to permit legitimate statistical treatment and comparison, Table II gives the values of all ratios $\frac{\text{organ weight}}{\text{body weight}}$ found so as to show the distribution of results.

Selye⁴ conducted a systematic study of the

* The authors are indebted to Dr. E. L. Sevringhaus, medical director, Hoffmann-LaRoche, Nutley, N. J., for gifts of vitamins.

† The authors are indebted to Dr. Roy Hertz and to Dr. K. W. Thompson of the Roche-Organon Co., for gifts of "Perandren."

⁴ Selye, H., *PROC. SOC. EXP. BIOL. AND MED.*, 1941, **46**, 142.

¹ Mason, K. E., *Am. J. Anat.*, 1933, **52**, 153.

² Mayer, J., and Krehl, W., *Arch. Biochem.*, 1949, in press.

³ Mayer, J., *Rev. Can. Biol.*, 1949, in press.

TABLE I.
Effect on Body and Organ Weight. Gain in weight during experimental period.

	a. No vit. A No testost.	b. No vit. A + testost.	c. + vit. A No testost.	d. + vit. A + testost.
1. Non-castrates				
Final* wt gain	44 g	44 g	104 g	84 g
Max. wt gain	54 g	50 g	id.	id.
Testes*	1068 mg	932 mg	2247 mg	1833 mg
Seminal vesicles†	107 mg	1727 mg	193 mg	1749 mg
Kidneys	1149 mg	1448 mg	1769 mg	2187 mg
	e. No vit. A No testost.	f. No vit. A + testost.	g. + vit. A No testost.	h. + vit. A + testost.
2. Castrates				
Final wt gain	46 g	47 g	104 g	105 g
Max. wt gain	52 g	57 g	id.	id.
Seminal vesicles†	— ‡	1417 mg	— ‡	1720 mg
Kidneys	1083 mg	1560 mg	1517 mg	2429 mg

* The difference between "Final" and "Maximum" gain weights is due to the fact that when the animals were sacrificed, the degree of deficiency reached was such that most animals had already lost weight.

† Prostates and epididymes showed size changes in the same directions as seminal vesicles.

‡ Not detectable by macroscopic examination.

effects of various doses of testosterone on the weight of the body and of certain organs of the male albino rat. He found particularly striking effects for doses of 1.0 to 10 mg daily. This is an analogous dosage to that used here. The experiment was continued for only 20 days—approximately one-third of the duration of the present experiment. In these conditions, he observed that accessory sex organs, the seminal vesicles in particular were very much enlarged, while the size of the testes was decreased. In this particular series of his no significant effect was observed on the weight of the kidneys, in contradistinction with some other of his own observations⁵⁻⁷ and those of other investigators.⁸⁻¹⁰

In the present work, the deficient animals, castrates as well as non castrates conformed to the general pattern established and verified for the control animals: testosterone administration was followed by extreme hypertrophy of accessory sex organs, seminal vesicles in

particular; by a definite hypertrophy of the kidneys and by a decrease of the size of the testes. As far as the effect on the overall body weight is concerned, while the decrease in weight gain of normal animals under the influence of testosterone administration noted by Selye was confirmed, deficient animals behaved like castrates in that they were not affected.

Particularly significant is the fact that the extreme hypertrophy of accessory sex organs was maintained by testosterone even in the face of acute deficiency. Animals showing marked periocular symptoms and which had sustained severe losses of weight extending over a period of two weeks still showed seminal vesicles, prostates and epididymes 10 times larger, in absolute values, than control animals not receiving testosterone. This differential reaction is in itself quite striking.

This experiment seems to establish definitely the fact that any "castration effect" observed as a result of vitamin A deficiency in the rat is not due to the lack of response of target organs but to lack of circulating androgens. Because of previous results indicating the apparent "piling up" of cholesterol, in Vitamin A deficiency,¹¹⁻¹³ a possible explana-

⁵ Selye, H., *J. Urol.*, 1939, **42**, 637.

⁶ Selye, H., *Canad. Med. Assn. J.*, 1940, **42**, 113.

⁷ Selye, H., *J. Endocrinol.*, 1939, **1**, 208.

⁸ Korenchevsky, V., and Ross, M. A., *Brit. Med. J.*, 1940, **1**, 645.

⁹ Paschkis, K. E., Shay, H., Gershon-Cohn, J., and Fels, S. S., *Am. J. Physiol.*, 1940, **129**, 191.

¹⁰ Pfeiffer, C. A., Emmel, V. M., and Gardner, W. U., *Yale J. Biol. Med.*, 1940, **12**, 493.

¹¹ Balli, E. P., and Waterhouse, A., *Proc. Soc. Exp. Biol. and Med.*, 1933, **30**, 519.

TABLE II.
Organ weight
Body weight Relationship. Distribution of Values.

	a. No vit. A No testost.		b. No vit. A + testost.		c. + vit. A No testost.		d. + vit. A + testost.	
Non-castrates								
Testes	10.4	11.5	8.5	10.8	14.3	14.2	12.9	13.4
$\frac{\text{---}}{\text{body}} \times 10^3$	11.2	9.8	8.5	12.2	14.4		14	
	10.2	12.8	10.8	8.5				
	Avg 11		Avg 9.9		Avg 14.3		Avg 13.4	
Seminal vesicles	0.002	1.78	15	18.4	1.7	0.8	10	12.5
$\frac{\text{---}}{\text{body}} \times 10^3$	0.64	0.8	17.2	23.2	1.4		17.8	
	2	1.47	17.7	18.8				
	Avg 1.1		Avg 18.4		Avg 1.2		Avg 13.4	
Kidneys	14.7	15	13.6	15	13.4	9.8	16.3	16
$\frac{\text{---}}{\text{body}} \times 10^3$	13.8	12.9	19.8	14.8	10.5		14.3	
	13.3	12.2	13.4	13.2				
	Avg 13.7		Avg 15.0		Avg 11.2		Avg 15.6	
Castrates								
Seminal vesicles	—		12.9	12.5	—		10.3	10.9
$\frac{\text{---}}{\text{body}} \times 10^3$			13.1	12.7				
			Avg 12.8				Avg 10.6	
Kidneys	12.1	12.8	14	14.2	9.3	9.2	14.2	15.8
$\frac{\text{---}}{\text{body}} \times 10^3$	14.1	13.4	14.1	14.4	9.5			
	Avg 13.1		Avg 14.2		Avg 9.3		Avg 15.0	

tion is that vitamin A deficiency prevents chemical transformation of cholesterol into testosterone. Indirect mechanisms, such as intervention of vitamin A in the synthesis or release of gonadotrophic hormones cannot, however, be eliminated without further experimental work.

Summary. 1. In an effort to find whether the "virtual castration" of vit. A deficient male rats is due to prevention of the synthesis of androgens or to the lack of response of target organs, the effects of administration of testo-

sterone in deficient non-castrates and castrates were compared with the effects on their controls.

2. The response of the deficient animals was found to be essentially normal. The accessory sex organs in particular were extraordinarily hypertrophied under the influence of testosterone administration even in the face of severe losses of weight.

3. The evidence obtained suggests that vitamin A deficiency interferes with the synthesis or release of androgens.

¹² Smith, M. E., *J. Nutrition*, 1934, **8**, 675.

¹³ Mayer, J., unpublished observations.