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Influence of Methyltestosterone on Metabolism of Normal, Castrate and Thyroidectomized Rats.

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From the general physiological action of sex hormones in eunuchs, consisting in the restoration of the low resilience of a sluggish organism to normal tonus, one would expect *a priori* a certain influence on the metabolic rate. Whether or not hypermetabolic levels could be reached by such treatment was less predictable. Eunuchoids usually give metabolic figures not as low as those found in myxedema, the lowest values reported being −30 and −24.[1, 2] Treatment with moderate doses of methyltestosterone by Byron and Katzen[3] did not result in metabolic rates definitely above normal, and Sandiford, Knowlton and Kenyon[4, 5, 6] obtained in eunuchoids with testosterone propionate (25 mg 3 to 7 times weekly) only moderate metabolic increases, if any at all, but no changes in a normal individual. Only McCullagh, *et al.*,[1, 2] reported definite hypermetabolic rates after prolonged treatment with large doses of methyltestosterone. Eidelsberg and Ornstein[7] found the metabolism not altered by testosterone propionate but the sensitivity to thyroid increased. Experiments with androgens in castrate dogs by Kochakian and Murlin[8, 9, 10] failed to show any metabolic increment, except in one animal after 3-4 weeks' treatment. A supplementary investigation in animals seemed desirable. The present paper reports the results obtained by treatment of rats with methyltestosterone.*

1 McCullagh, E. P., and Rossmiller, H. R., *J. Clin. Endocrinology*, 1941, **1**, 503.

2 Jones, R., McCullagh, E. P., McCullagh, D. R., and Buckaloo, G., *J. Clin. Endocrinology*, 1941, **1**, 656.

3 Byron, C. S., and Katzen, P., *J. Clin. Endocrinology*, 1941, **1**, 359.

4 Sandiford, I., Knowlton, K., and Kenyon, A. T., *J. Clin. Endocrinology*, 1941, **1**, 931.

5 Kenyon, A. T., Sandiford, I., Bryan, A. H., Knowlton, K., and Koch, F. C., *Endocrinology*, 1938, **23**, 135.

6 Kenyon, A. T., Knowlton, K., Sandiford, I., Koch, F. C., and Lotiwin, G., *Endocrinology*, 1940, **26**, 26.

7 Eidelsberg, J., and Ornstein, E. A., *Endocrinology*, 1940, **26**, 46.

8 Kochakian, C. D., and Murlin, J. R., *Am. J. Physiol.*, 1936, **117**, 642.

9 Kochakian, C. D., *Endocrinology*, 1937, **21**, 750.

10 Kochakian, C. D., and Murlin, J. R., *J. Nutrition*, 1935, **10**, 437.

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Male rats, normal, castrate, thyroidectomized and thyroidectomized-castrate, were used. Castration was performed at 60 and 72 days of age, which means either immediately preceding or following maturation; thyroidectomy was always done at an age of 80 days, and in case of additional castration, this was done 20 days preceding or 20-25 days following thyroidectomy, the object being the discovery of any possible difference in the animals caused by the sequence of operations. The metabolic standardization was begun when the rats reached an age of 125-140 days and was carried on until satisfactory agreement was obtained on various days. The determinations were made in a closed Benedict apparatus, as described in a previous publication,[11] and the results were calculated in mg oxygen per hour per kilogram.

Taking, at random, from our record of over 1000 determinations those of 200 thyroidectomized rats, the average oxygen consumption was found to be 975 with a standard deviation of 80.7. Normal rats give an average value of 1500 ± 100. The methyltestosterone was given in daily subcutaneous injections (for this purpose a standard alcoholic solution was diluted with a calculated amount of water preceding use) mostly 500 γ per dose, in some instances only 100 γ, in others 50 γ. The 500 γ dose was proportionately in keeping with the massive doses used by Jones, *et al.* During the treatment the metabolism was determined at convenient intervals. At the end of the test period, the animal was treated with a standard dose of thyroid and the metabolic response observed. For this purpose a purified thyroid powder of 0.65% iodine content was used. From numerous tests we knew that this product, fed at a rate of 80 γ per 10 g body weight daily for 3 days, causes in the thyroidectomized rat on the fifth day an increase in metabolic rate of 32-38% without affecting the heart rate materially. This potency was checked again in 2 thyroidectomized control rats. The metabolic change at the dose of 80 γ per 10 g, was in the first rat from 1000 to 1360 mg oxygen, or 36%, in the second from 985 to $1360 = 38\%$. In normal rats 20 to 25 times that dose is required to produce the same effect, for which reason 1.6 mg was given for each 10 g weight to the normal as well as the non-thyroidectomized castrate rats. While in some of the animals of each group the treatment with the androgen was continued during the thyroid treatment, other animals were left without it for a certain length of time before the thyroid was given to show any influence which the androgen might have on the response to thyroid. The

[11] Meyer, A. E., and Wertz, A., *Endocrinology*, 1939, **24**, 683.

TABLE I.

No. of rats in group	History of group	Daily dose, γ Me-testosterone	B.M.R. mg O_2 per hr per kg before and after days of treatment				Treatment interrupted for days	B.M.R. after standard thyroid dose	% inc. over initial B.M.R.
			Bef.	7 da.	14-20	30			
4	Thyroidectomy at 80 days	50	920	945	900		cont.	1260	+37
4		500	915	950	915		"	1240	+36
4	Thyroidectomy 80 days	500	955	1110	1060		"	1320	+38
4		100	870	910	955		"	1275	+46
2	Castrated 105 days	500	1030	1255	1125		12 days	1495	+44
3	Castrated 60 days	500	930	1080	1020		cont.	1370	+47
3	Thyroidectomy 80 days	500	890	1000	1060		11 days	1275	+43
4	Normal	500	1500	1500		1550	cont.	1920	+28
4	Castrated 72 days	500	1350	1300		1320	"	1840	+36
4	" 60 "	500	1270	1310		1295	"	1725	+36
4	" 60 "	500	1290	1355		1355	10-18* days	1800	+40

*The B.M.R. after this period was 1235.

heart beat was determined routinely, but is not reported in Table I as no change was observed.

The metabolic rates before treatment with the androgen show that the castrate rat has a metabolic rate lower than the normal but higher than the thyroidectomized animal, which is in agreement with the experience in humans. Castration does not reduce the metabolic rate in thyroidectomized animals to still lower levels. Thyroidectomized rats gave no response to the androgen and neither were they influenced in their response to thyroid. Thyroidectomized castrates showed a moderate increase of the metabolic rate under the influence of methyltestosterone, usually, however, without exceeding the limits generally observed in the athyroid animals. This whole group gave an increased response to thyroid; the higher sensitivity to thyroid seems to be a consequence of the castration which is not altered by the methyltestosterone, since there was no difference between animals with continued or discontinued treatment. The sequence of the operations seems to have no influence on the response of the rats.

The normal rats treated with the androgen showed no deviation from the behavior of the untreated rat. The response to thyroid was, perhaps, slightly lower than usual, but normal animals do not give quite as uniform reaction in these tests as thyroidectomized rats, for which reason this lower value cannot be considered as significant.

The castrate rat, contrary to expectation, maintained an un-

changed metabolic rate during the treatment. The final increase in metabolism after thyroid treatment was well within the limits of the normal rat, whether or not the methyltestosterone injections had been continued.

Summary. The oxygen consumption of castrate male rats is lower than that of normal, but higher than that of thyroidectomized rats. In castrate-thyroidectomized rats it is not lower than that found in non-castrate thyroidectomized rats. Treatment with methyltestosterone, within the conditions of these experiments, did not affect the metabolic rate of non-castrate animals, nor that of castrates. It caused a moderate increase in thyroidectomized-castrate rats. The latter rats showed also an increased sensitivity to treatment with thyroid, which, however, was neither caused nor influence by methyltestosterone.

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Effects of Gonadotropic Hormone in the Fish, *Xiphophorus helleri* Heckel.

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The administration of mammalian gonadotropins from pregnancy urine and other preparations to a teleost fish, *Lebistes reticulatus,* has been reported by Berkowitz.[1] These substances stimulated the precocious development of male secondary sex characters, as well as the precocious but normally-patterned development of immature testes. The response of adult male *Lebistes,* if any, was by a decreased gonad size and an interstitial hypertrophy of the stroma. The latter phenomenon persisted only in some but not all of his fish when treatment was prolonged. He reported there was no effect on the secondary sex characters nor gonads of immature female *Lebistes.* The action of the hormones on mature females of this species was not mentioned. Saphir[2] found that injection of *prolan* from urine of pregnant women caused inconstant response of the "wedding dress" in male *Chromosomus erythrogaster.* Owen[3] produced this chromatophore reaction in 75% of male *Phodeus amarus* by employing the prolan in aquarium water, while he failed

[1] Berkowitz, P., *J. Exp. Zool.,* 1941, **86**, 247.