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Maintenance of Spermatogenesis in Hypophysectomized Mice with Androgenic Substances.*

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It was shown by Walsh, Cuyler and McCullagh[1] and confirmed by Nelson and Gallagher[2] that spermatogenesis could be maintained in hypophysectomized rats by the administration of male hormone extracts. These studies were extended by Nelson and Merckel[3] and Nelson[4] through the use of various crystalline androgens. Since these studies had been confined to rats it was of interest to extend them to other species. This report deals with results obtained upon mice. Studies upon guinea pigs are in progress.

Adult male mice were hypophysectomized by the parapharyngeal approach. The effect of hypophysectomy upon the reproductive organs in the mouse have been described by Leblond and Nelson.[5] Injections of androgenic hormone† were begun on the second day after hypophysectomy and continued for 20 days. The animals received the routine colony ration with the addition of sugar in their drinking water. In the averages only those animals are included that survived through the experimental period and in which hypophysectomy was shown to have been complete by serial section of their sellæ turcicæ. At the time of autopsy the testes, seminal vesicles, prostate, and adrenals were weighed. These and the epididymis, Cowper's glands, vas deferens and thyroid were fixed for histological study. Smears of the epididymal head and tail as well as of the vas deferens were studied for the presence and motility of sperm.

Table I includes the data of studies thus far completed and is given in the form of averages. In the table a group of 5 animals

* Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1 Walsh, E. L., Cuyler, W. K., and McCullagh, D. R., *Am. J. Physiol.*, 1934, **107**, 508.

2 Nelson, W. O., and Gallagher, T. F., *Science*, 1936, **84**, 230.

3 Nelson, W. O., and Merckel, C. G., Proc. Soc. Exp. Biol. and Med., 1937, **36**, 825.

4 Nelson, W. O., *Cold Spring Harbor Symposia on Quantitative Biology*, 1937, **5**, 123.

5 Leblond, C. P., and Nelson, W. O., *Compt. rend. Soc. biol.*, 1937, **124**, 9.

† Generously supplied by Dr. Erwin Schwenk of the Schering Corporation.

TABLE I.

Male Mice Hypophysectomized for 22-23 Days and Treated for 20-21 Days with Androgenic Substances. Weights Are Given as Averages.

No. of Animals	Body weights (first) g	Body weights (last) g	Treatment Daily dose in mg	Organ weights (g) Testes	Seminal Vesicles (full)	Seminal Vesicles (empty)	Prostate	Sperm Motility
15	28.5	29.6	Normal controls	.211	.243	.118	.048	++++
9	27.7	22.3	Hyp. controls	.031	—	.017	.012	No Sperm
3	27.6	22.4	Androstanedione, 0.8	.198	.149	.087	.041	++++
4	27.0	22.3	" 0.6	.186	.128	.074	.039	++++
4	27.0	21.8	" 0.4	.140	.114	.057	.029	++++
4	27.5	22.4	Androstanediol, 0.8	.175	.263	.135	.052	++++
3	28.2	23.1	" 0.4	.123	.205	.121	.044	++++
3	28.3	23.4	Testosterone propionate, 0.8	.168	.579	.158	.085	++++
5	28.6	23.6	" " 0.4	.120	.409	.118	.067	++++
4	26.3	21.5	Testosterone, 1.0	.116	.218	.107	.049	++++
3	28.1	23.4	" 0.5	.109	.189	.095	.043	++++
5	27.4	26.9	Androgenic hormone*	.164	.198	.091	.053	++++

*Three animals received androstanedione, one received testosterone propionate, and one received testosterone.

are included in which small fragments of anterior lobe tissue were found. It will be noted that although the body weights of these animals were about the same at the close of the experiment as they had been at the beginning, thus indicating the presence of sufficient anterior lobe tissue to maintain body weight, this residual tissue did not enhance the effect of the treatment with androgenic substance. This is noteworthy since Gomez, *et al.*,[6] have indicated that small fragments of pituitary will entirely alter the effect of estrogenic substance in the mouse. We have been unable to detect any evidence of such enhancement in these studies.

It is apparent from the table that the results on mice confirm those previously obtained with rats. Androstanedione proved to be the most effective of the androgens in maintaining spermatogenesis as well as testis weight, although it is much less active than testosterone or testosterone propionate in androgenic potency. Androstanediol was slightly less effective than androstanedione. The results have not been quite as striking, even with androstanedione, as in the rat, but the use of somewhat larger amounts of androgen may result in responses entirely comparable to those observed in the latter animal.

The microscopic findings were similar to those previously re-

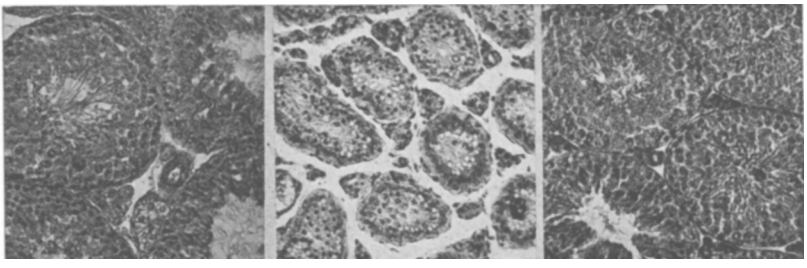

FIG. 1 FIG. 2 FIG. 3

FIG. 1.

Testis of normal adult mouse. Note particularly the large interstitial cells. × 116.

FIG. 2.

Testis of hypophysectomized untreated mouse. Note the extensive damage to the seminiferous tubules and the shrunken interstitial cells. × 116.

FIG. 3.

Testis of hypophysectomized mouse which had received 0.8 mg of androstanedione daily. The tubular diameter is slightly decreased, but spermatogenesis is normal. The condition of the interstitial cells is not improved by the treatment. × 116.

[6] Gomez, E. T., Turner, C. W., Gardner, W. U., and Hill, R. T., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 287.

ported for the rat. The testes of all animals injected with androgens showed spermatogenesis in progress, although the degree of tubular maintenance varied with the particular androgen. The latter was most marked in cases where androstanedione or androstanediol had been used. Even here, as is true of the rat, occasional tubules that show degenerative changes are encountered. The striking degeneration of the interstitial cells which follows hypophysectomy in the mouse is not prevented by treatment with androgens. Nor are the damaged adrenals and thyroid altered. As would be expected the male accessory organs present a normal or hypertrophied histological picture in animals which had received treatment. Figures 1 to 3 represent typical areas in the testes of normal, hypophysectomized-control, and hypophysectomized-treated animals.

Summary. The injection of crystalline androgenic hormones will prevent the marked degenerative changes in the seminiferous tubules of hypophysectomized mice for at least 23 days. The most effective substance used has been androstanedione. The degenerative changes in the interstitial cells, adrenals and thyroid were not altered.

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Toxicity of $MnCl_2.4H_2O$ when Fed to Rats.

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Findlay[1] claims that addition of manganese chloride to the "ordinary" diet of rats produces cirrhosis of the liver and death in from 6 to 10 weeks. He fed 0.3 to 0.4 g manganese chloride per rat per day but failed anywhere to indicate the composition of the diet used. McCarrison[2] fed rats 0.889 mg of MnO per day. He compared their weights with those of a similar group receiving no manganese other than that contributed by the salt mixture and the other constituents of the diet. He states, "There was no difference in the percentage weight curves of the 2 groups up to the 32nd day. Thereafter the curves diverged gradually and increasingly; that of the group receiving manganese being at the lower level." The experi-

[1] Findlay, G. M., *Brit. J. Exp. Path.*, 1924, **5**, 92.

[2] McCarrison, R., *Ind. J. Med. Res.*, 1926-27, **14**, 641.