10233

Biphasic Effect of Male Sex Hormone on the Pituitary of the Female Rat.

S. C. FREED, J. P. GREENHILL AND S. SOSKIN.

From the Department of Metabolism and Endocrinology, Michael Reese Hospital, Chicago, Illinois.*

It is known that testosterone and testosterone propionate are capable of suppressing the cyclic activity of the ovaries in several species of animals.[1-4] Because rats which were treated with these substances presented ovaries with large corpora lutea, it was suggested that the androgenic hormones caused a release of the luteinizing principle from the anterior pituitary. This, in turn, gave rise to the persistent corpora lutea as in the diestrus of pregnancy or lactation. In monkeys and humans, on the other hand, similar treatment resulted in a cessation of ovulation and some degree of ovarian atrophy. This apparent species difference in the response to testosterone was also reflected in the uterus. The uteri of rats and rabbits developed progestation-like changes,[5, 6] while the uteri of the primates underwent involution.[3, 7]

It seemed to us to be significant that Hertz and Meyer,[8] who used 1/10 to 1/20 of the amounts of testosterone propionate which had been employed by others to induce persistent corpora lutea, showed that these small doses effectively inhibited the secretion of the follicle-stimulating hormone in parabiotic rats. This suggested that a qualitative difference in pituitary response to large and small doses of androgen might account for the confusing variation in the results which had been obtained. The increasing clinical use of androgenic therapy for certain ovarian dysfunctions lent practical as well as theoretical importance to further investigation.

Groups of adult female rats, showing regular estrous cycles, were given daily subcutaneous injections of testosterone propionate for

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

1 Robson, J. M., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 49.

2 Browman, L. G., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 205.

3 Zuckerman, S., *Lancet*, 1937, **2**, 676.

4 Papanicolaou, G. V., PROC. SOC. EXP. BIOL. AND MED., 1938, **37**, 689.

5 Klein, M., and Parker, H. S., *Proc. Roy. Soc. Lond. s. B.*, 1937, **121**, 574.

6 Brooksby, J. B., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 235.

7 Gaines, J. A., Salmon, U. J., and Geist, S. H., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 779.

8 Hertz, R., and Meyer, R. K., *Endocrinology*, 1937, **21**, 756.

16 days. A different daily dose was used for each group, and vaginal smears were made on each animal every day. In the groups of rats receiving 1.0 mg and 0.1 mg per day vaginal cornification was completely suppressed throughout the injection period. The group which received 0.05 mg daily, showed only an occasional estrus smear. All the animals were autopsied on the 17th day. The ovaries and uteri were weighed, and examined both grossly and microscopically.

Table I shows the marked difference in ovarian and uterine weights which resulted from the different dosages employed. Except for the slight difference in vaginal cornification mentioned above, the results obtained with 0.1 mg per day resembled those obtained with the smallest dosage and need not be described separately. It may be seen that as little as 0.05 mg of testosterone propionate per day caused severe ovarian atrophy, and uteri significantly below normal in weight. The ovaries of the rats treated with 1.0 mg doses were much larger, though still somewhat below normal weight. Their uteri showed pronounced growth, as previously reported by others.

TABLE I.

Effect of Administration of Testosterone Propionate for 16 Days in the Adult Rat.

Daily dose, mg	No. of rats	Avg wt of ovaries, mg	Avg wt of uterus, mg
1.0	7	56	570
0.1	8	32	298
.05	8	.24	262
Control	6	74	370

Gross and microscopic examination of the ovaries and uteri showed just as marked differences in the effects of small and large doses of the androgen. The small ovaries of the rats treated with 0.05 mg doses, failed to show any normal structures on gross examination. Under the microscope, a few small follicles were seen, while corpora lutea were entirely absent. The uteri of these animals were much smaller in diameter than the normal diestrus uterus, though not quite as small as the castrate uterus. Microscopically, the uterine endometrium was atrophic, with low cuboidal epithelium and poorly developed glands, although there were some slight decidua-like changes in the stroma. In contrast to the foregoing, the ovaries of the rats which had received the 1.0 mg dosage contained numerous large corpora lutea, which were evident grossly as well as microscopically. The large uteri of these animals exhibited an endometrium with progestation-like appearance. The glands

were well developed and actively secretory. There were decidua-like cells in the stroma.

Our results show that both the effects previously found in rodents and those reported in primates, can be obtained in the same species (rats) by varying the dosage of testosterone propionate. This explains the apparently contradictory results which have been obtained with this hormone, and obviates the necessity for postulating a species difference in its action. The estrus-suppressing effects in our rats were obtained with much smaller doses of testosterone propionate than have hitherto been used. It seems likely that the similar results which others have obtained in primates, were due to the arbitrary choice of a relatively small dosage for those experiments.

The different effects of the large and small doses of the androgen may be explained by the different actions of these doses on the anterior hypophysis, and by the direct effects of the amount of androgen injected. Both large and small doses depress the elaboration of follicle-stimulating hormone by the pituitary, as judged by the cessation of estrous cycles. Large doses, however, also cause a release of luteinizing hormone, as indicated by the numerous large corpora lutea in the ovaries. This difference in the effects of large and small doses on the pituitary is similar to that which is known to occur with the estrogens.[9] Thus a small dose of testosterone results in cessation of the estrous cycles, ovarian atrophy, diminished estrin and involution of the uterus. A large dose results in cessation of the estrous cycles, persistent corpora lutea and diminished estrin. But uterine involution does not occur because the larger amount of androgen present acts directly on the uterus to prevent the atrophy and to produce the progestation-like changes.[5, 6]

10234

Utilization of Carbohydrate by the Phlorhizinized Dog.*

SAMUEL SOSKIN, R. LEVINE AND W. LEHMANN.

From the Metabolic Laboratory of the Department of Physiology, Michael Reese Hospital, and the Department of Physiology, University of Chicago.

The glycosuria produced by the administration of phlorhizin has served as an experimental tool in the study of carbohydrate metabo-

[9] Hohling, W., *Klin. Wchnschr.*, 1934, **13**, 97.

* Aided by the Max Pam Fund for Metabolic Research.