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Uterine Reaction to Testosterone in the Rat.

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The administration of testosterone to the female animal leads to an enlargement of the uterus, which has been described in the rabbit by Robson[1] and by Klein and Parkes[2] as a progestational proliferation. McKeown and Zuckerman[3] have recently described the reaction of the rat uterus to testosterone, and noted that the effect is not obtainable in ovariectomized animals, the deduction being that the uterine effect is due to increased production of the normal ovarian hormones under the influence of testosterone. The work of Selye and McKeown[4] on the reaction of the uterus to trauma by the formation of deciduoma under the influence of progesterone, or of an endometrial mole under the influence of oestrone and progesterone suggested the use of traumatization as an index of the state of the endometrium, and the following experiments were undertaken to examine the uterine growth produced by testosterone and, if possible, to arrive at the nature of this growth.

In connection with experiments on lactation, testosterone propionate was given in doses of 500 γ in 0.25 cc. oil daily for the first 10 days of lactation to 6 rats. Another group of 6 rats remained untreated and a third group received one mg. of crystalline progesterone daily in 0.25 cc. oil. At the end of 10 days the animals were killed and the uteri examined. Those of the testosterone group were markedly enlarged and hyperemic, showing on histological examination an endometrium resembling the type termed by Selye, Collip and Thomson[5] "second progestational proliferation" with a loose fibrous stroma. The epithelium, however, was lower than would be expected in this type of endometrium and the ridges of epithelium so often seen were not marked. The uteri of the progesterone-treated group were only slightly enlarged and were in the stage of "first progestational proliferation," while the control group differed from the progesterone-treated group only in the smaller size of the uterus.

1 Robson, J. M., *Quart. J. Exp. Physiol.*, 1937, **26**, 355.

2 Klein, M., and Parkes, A. S., *Proc. Roy. Soc. B.*, 1937, **121**, 574.

3 McKeown, T., and Zuckerman, S., *Proc. Roy. Soc. B.*, 1937, **124**, 362.

4 Selye, H., and McKeown, T., *Proc. Roy. Soc. B.*, 1935, **119**, 1.

5 Selye, H., Collip, J. B., and Thomson, D. L., *Endocrinol.*, 1935, **19**, 151.

A group of 6 rats was ovariectomized on the first day of lactation and given 500 γ testosterone daily. Examination of the uteri on the 10th day showed them to be larger than normal and hyperemic. Histologically the uterus was of the dioestrous type with, however, considerable cell proliferation under the epithelium, suggesting that testosterone was capable of inhibiting to some extent the castration regression of the uterus, particularly with regard to the stroma.

The effect of testosterone in conjunction with uterine trauma was investigated in 20 rats, 10 normal and 10 castrate, which received 500 γ daily. After 5 days' treatment, biopsy specimens of the uterus were taken from 5 animals of each group, and the uterus subjected to trauma by slitting of the uterine horns in all 20 animals. After a further 5 to 7 days' treatment with testosterone, the rats were killed and the slit horn of the uterus taken for histological examination. Control animals, 6 normal and 6 castrate, were subjected to the same operative interference but remained untreated. The biopsy specimens after 5 days' testosterone treatment showed the normal animals, testosterone-treated, to have uteri of the type of second progestational proliferation with a lining of tall columnar cells thrown into folds over a loose and mostly fibrous stroma. The ovariectomized treated animals, on the other hand, showed small uteri of the post-castration type with a low cubical epithelium and a stroma of fibrous tissue with no dividing cells.

Examination of the slit uterine horn of both normal and castrate testosterone-treated animals showed absence of either deciduoma or endometrial mole. In normal testosterone-treated animals the uterus was of the same type as at biopsy. The edges of the slit horn were covered by tall columnar epithelium and the stroma under this was markedly proliferated, of loose fibrous character, and showed slight oedema and marked leucocytic infiltration. In the castrate testosterone-treated animals the uteri were similar to the testosterone-treated normals but were much smaller. The epithelium was low, the oedema and leucocytic infiltration of the stroma less marked. The uteri of the intact and castrate controls were small and reacted to the slitting only by loosening of the stroma and infiltration with leucocytes. It would seem that the reaction to slitting the uterine wall is the same in the 4 groups studied, *viz.*, some proliferation and loosening of the stroma with leucocytic infiltration. The larger and more active uterus of the testosterone-treated intact animal reacts more obviously, though in essentially the same way as that of the testosterone-treated castrates or that of the untreated animal.

The absence of alteration by testosterone of the reaction to uterine

trauma found in the experiments suggested investigation to determine if testosterone had an inhibiting effect on formation of deciduoma when these would normally occur. Six rats were taken on the first day of lactation and given 500 γ testosterone daily. By the fourth day the litters of 2 of these rats had died, though the mammary gland was found to be well developed and secreting, and these 2 animals were removed from the group. On the fifth day biopsy specimens of the uterus were taken and the uterine horn slit in the remaining 4 rats. The biopsy specimen showed the uterus to be in the state of second progestational proliferation, with a lower epithelium than is usual in this condition. Five days later the rats were killed. Histological examination of the slit uterus showed in 3 cases typical deciduomata and in the fourth case a typical endometrial mole. The animal in which mole formation occurred failed to rear its litter. Seven young were born and in 6 days the number was reduced to 3, and in 7 days to *nil*. It is suggested, though direct proof is lacking, that the animal was passing, at the time trauma was performed, into a state of post-lactation oestrus, and that the oestrin in circulation at this time resulted in formation of the endometrial mole. This chance occurrence affords evidence that, in addition to failing to inhibit deciduoma formation, testosterone does not prevent the formation of an endometrial mole.

Summary. From traumatization experiments on the rat uterus, it is concluded that the action of testosterone* differs qualitatively both from that of progesterone and from that of oestrogens.

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Hemolytic Properties of Indol.

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Rhoads and his collaborators[1, 2, 3] have recently established that the administration of indol to dogs on a deficient (Goldberger) diet results in a severe anemia which can be cured by adding the lacking

* The author is indebted to Dr. Erwin Schwenk of the Schering Corporation for the testosterone used in these experiments.

1 Rhoads, C. P., and Barker, W. H., *J. Exp. Med.*, 1938, **67**, 267.

2 Rhoads, C. P., and Miller, D. K., *J. Exp. Med.*, 1938, **67**, 273.

3 Rhoads, C. P., Barker, W. H., and Miller, D. K., *J. Exp. Med.*, 1938, **67**, 299.