loop strangulation. In the animals in which the loop had been denervated the early suppression did not occur.

Conclusions. (1) Distention of an isolated loop of bowel to the point of strangulation, when caused either by the spontaneous accumulation of fluids therein, or by the distending of an indwelling balloon, produces an early temporary suppression of the combined digestive secretions. (2) The suppression of secretion does not occur when the loop has been denervated. (3) The similarity of the changes produced by balloon distention with those seen in spontaneous loop distention would seem to argue against the hypothesis that strangulation intestinal obstruction is associated with hypersecretion of the digestive juices.

10214

Nature of the Action of Testosterone on Genital Tract of the Immature Female Rat.*

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Opening of the vagina and estrus in the immature rat with the use of various androgens has been reported by Butenandt and Kudzus.[1] Deanesley and Parkes[2] noted, in addition, that testosterone and other androgens produced not only vaginal opening but also uterine enlargement in the ovariectomized as well as in the intact immature rat. This suggested, therefore, a direct action upon the uterus and vagina. Nelson and Merckel[3] described the uterine reaction of adult rats to androgens and found enlargement after the administration of testosterone, androstenedione, cis-androstenedione and dehydroandrosterone; the latter producing the response even in the absence of the pituitary. McKeown and Zuckerman[4]

* We are indebted to Dr. Joseph C. Aub for valuable suggestions in the preparation of the paper and to Dr. Shields Warren for reviewing the histological sections.

1 Butenandt, A., and Kudzus, H., *Hoppe-Seyler's Z.*, 1935, **237**, 75.

2 Deanesley, R., and Parkes, A. S., *Brit. Med. J.*, 1936, **1**, 527.

3 Nelson, W. O., and Merckel, C. G., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 825.

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

stated that the uterine response to testosterone differed in intact and ovariectomized animals. Brooksby[5] from other experiments concluded that the uterine response to testosterone differed qualitatively from that of progesterone and that of the estrogens. Recently, Salmon[6] with the use of testosterone propionate and androstenediol noted vaginal opening, uterine enlargement, and follicle stimulation with corpus luteum formation in the ovaries of the intact immature rat. He suggested that the vaginal opening may have resulted from a gonadotropic effect exerted upon the ovary, either directly or indirectly through stimulation of the hypophysis.

This study was undertaken to ascertain the mode of action of testosterone propionate† upon these various genital organs. All of the experiments listed below were carried out on immature white stock rats, weighing between 55 and 65 g. The animals mature generally at a weight of from 110 to 120 g.

Experiment 1. Ten intact immature female rats were given a single injection of testosterone propionate in sesame oil in doses varying from 2.5 to 10 mg. Five other animals were injected with equivalent amounts of sesame oil to serve as controls for this and subsequent experiments.

Results: (a) Vaginal opening occurred within 96 hours in all animals which received testosterone. The time of opening varied directly with the dosage employed. The controls showed no change. Vaginal smears within 12 hours after vaginal opening revealed complete or partial cornification in every instance (5 animals). Histologic sections of the vagina showed different stages of cornification (5 animals). This was not found in the control animals. (b) Ovaries removed within 24 hours after vaginal opening were enlarged and showed moderate to marked follicle stimulation (judged by mitotic activity and size of the follicle) in every instance (3 animals). In 2 cases, early luteal changes were seen. In ovaries examined 48 to 168 hours after vaginal opening more pronounced follicle stimulation was noted and corpora lutea in all stages were present in practically every ovary (7 animals). Here, too, the degree of change varied directly with the dosage employed. The ovaries from control animals showed no or only mild follicular activity. (c) The uteri in all animals were enlarged and exhibited moderate to marked edema. On microscopic section there was an increase in stroma, vascularity, and glands. Mitotic activity and

[5] Brooksby, J. B., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 235.

[6] Salmon, U. J., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 352.

† We are indebted to Doctors Gregory Stragnell and Erwin Schwenk of the Schering Corporation for a generous supply of testosterone propionate.

very slight secretory activity were noted in uteri which were removed 24 hours after vaginal opening (3 animals). In uteri removed when corpora lutea were present, there was marked secretory activity, with a marked increase in the number of glands (7 animals). The uteri of the control animals were small and showed no activity. (d) Tubes: When corpora lutea were present in the ovary, there was slight evidence of activity in the tubal epithelium, manifested by mitoses. This was not seen in any other group.

Experiment 2. Eight immature white rats were ovariectomized and 72 hours later were injected with testosterone as in experiment 1.

Results: (a) Vaginal opening and estrus (confirmed by smear and histologic examination of the vagina) occurred as in the intact animals. (b) The uteri removed at intervals of 24 to 168 hours after vaginal opening were enlarged and edematous. Microscopic examination showed an increase in stroma, vascularity and edema. There was also an increase in the number of glands, which, however, was not so marked as in the intact animal treated with testosterone. Secretory changes were not seen. (c) Tubes—no change.

Experiment 3. Eight immature animals were hypophysectomized by the parapharyngeal route, using a technic previously described.[7] Seventy-two hours later the animals were injected with testosterone as above. At the completion of the experiment the pituitary fossa of each of the animals was examined with a magnifying loupe to verify the fact that hypophysectomy had been complete.

Results: (a) Vaginal opening and estrus occurred as before. (b) The uteri resembled those of experiment 2. (c) The ovaries were small and showed only small, inactive follicles on histologic examination. (d) Tubes—no change.

Experiment 4. Five immature animals were hypophysectomized and, thereafter, at intervals varying from 72 to 240 hours were subjected to bilateral ovariectomy. Testosterone was administered approximately 72 hours after ovariectomy.

Results: The changes noted were the same as those in experiments 2 and 3.

From the results obtained it appears that the action of testosterone on the female genital tract of the immature rat is as follows:

1. A direct action upon the vagina, since the changes noted occurred in the absence of either or both the ovaries and hypophysis. Vaginal opening probably occurs as a result of an estrin-like action in the immature female rat. Warren[8] expresses the opinion that

[7] Franseen, C. C., Brues, A. M., and Richards, R. L., *Endocrinology*, 1938, **23**, 292.

[8] Warren, Shields, personal communication.

immature tissue is more labile and, therefore, may respond to a weaker estrous stimulus than adult tissue. This is based purely on speculation, although somewhat supported by other observations in vitamin deficiencies. Since other androgens have been shown to have moderate to marked estrogenic activity, it therefore remains a distinct possibility that testosterone, which belongs to the same series, may also have this same property, but to a much less degree, *i. e.,* it is not sufficient to evoke estrus in adult tissue in the doses commonly employed. It is possible, however, that testosterone is converted into an estrogen by the immature animal. Deanesley and Parkes[2] suggested that the ovary may be responsible for this change. Since the effect was also obtained in ovariectomized animals, this thesis seems unlikely. Changing of the chemical structure by the adrenal remains a possibility, but proof for this is lacking.

2. A direct action upon the uterus. In the absence of either the hypophysis or the ovary, changes in the uterus occur after testosterone is administered. This response, however, differs in the intact and ovariectomized immature animal. It seems significant that secretory changes were seen only in the intact animal and this when corpora lutea were present in the corresponding ovaries. The effect of testosterone on the uterus, therefore, in the intact and the ovariectomized animal seems to differ qualitatively as suggested by McKeown and Zuckerman[4] and Brooksby.[5] The secretory changes may occur as a result of the combined action of the ovarian hormones and testosterone; the ovarian hormones being elaborated as a consequence of the gonadotropic action of the hypophysis, which is stimulated by testosterone.

3. Changes in the tubes were noted only when corpora lutea were present in the ovary. This, therefore, can be attributed to an indirect action of testosterone.

4. An indirect action upon the ovary due to direct stimulation of the anterior hypophysis, which in turn elaborates the gonadotropic hormones to elicit follicle growth, maturation, and corpus luteum formation.

Conclusions. Testosterone stimulates directly the growth of the uterus and the vaginal epithelium of the immature rat. There is a qualitative difference only in the uterine response in the intact and ovariectomized animal. It does not act directly on the ovary but stimulates it indirectly by way of the anterior hypophysis, resulting in follicle maturation and corpus luteum formation. As a result of corpus luteum formation from hypophyseal stimulation, the Fallopian tubes may show growth activity.