ON THE PRODUCTION OF ENDOMETRIAL MOLES WITH
STEROID HORMONES

HANS SELYE AND SIDNEY FRIEDMAN
(From the Department of Anatomy, McGill University, Montreal, Canada)

It is well known since the investigations of Loeb (1) that the uterus, if it is traumatized while under the influence of an active corpus luteum, responds by the formation of a structure not unlike the maternal portion of the placenta. This growth may become quite large and assume the appearance of a decidual tumor. It has, therefore, been termed a deciduoma. The hormonal mechanisms controlling deciduoma formation have been studied by Selye and McKeeown (2) and it appears well established that the presence of corpus luteum hormone is indispensable for the production of the tumor, while large doses of estrogens prevent its formation.

Another type of abnormal response of the endometrium to trauma has been seen in spayed rats pretreated with estrogens. In such animals large, succulent tumors develop in the endometrial stroma at the site of trauma. Macroscopically and microscopically these tumors are rather similar in appearance to hydatidiform moles; they are translucent and of a pinkish color, and upon histologic examination prove to consist mainly of a gelatinous connective tissue with much intercellular substance. In order to emphasize their similarity to hydatidiform moles, and at the same time to point out their endometrial origin, they have been termed "endometrial moles" (2-4).

The object of this communication is to report on some recent experiments which indicate that steroid hormones other than progesterone and estrogens may likewise so modify the responsiveness of the endometrium that tumor-like masses develop at the site of mechanical stimulation.

Twenty-two female albino rats weighing 137 to 172 gm. were divided into four groups on the day after their ovaries were removed. Six animals received daily injections of 100 gamma of estradiol, 6 were treated with 3 mg. of testosterone propionate, and 6 with 3 mg. of pregneninolon, also referred to as ethinyl testosterone, pregneninol or anhydro-oxy-progesterone. The remaining four served as untreated controls. The daily dose of each of the sterol preparations employed was dissolved in 0.4 c.c. of peanut oil and was injected subcutaneously. On the ninth day of treatment, the left uterine horn of each animal was slit longitudinally in order to traumatize the endometrium. Five days later, a portion of the traumatized uterine horn was removed together with a part of the intact horn for inspection and histologic study. In all groups of experimental animals there developed macroscopically visible, gelatinous, hyperemic endometrial tumors; no such growths were detectable in the controls. Upon histologic examination these tumors showed the characteristic features of endometrial moles. The connective-tissue cells, which in most cases appeared to be star-shaped with many processes, rather than
FIG. 1. **Endometrial Stroma in the Intact Horn of the Uterus of a Rat Treated with Ethinyl Testosterone**

Note the dense collagenous connective tissue. The connective-tissue cells are fusiform and have relatively small dense nuclei.

FIG. 2. **Stroma of an Endometrial Mole Which Developed in the Traumatized Horn of the Uterus in a Rat Treated with Ethinyl Testosterone**

Note the loose arrangement of the connective-tissue cells, which here, as in the other endometrial moles shown in this series, are somewhat enlarged, with irregular processes which lose themselves in the well developed intercellular tissue.

FIG. 3. **Endometrial Mole in the Traumatized Uterine Horn of a Rat Treated with Testosterone Propionate**

FIG. 4. **Endometrial Mole in the Traumatized Uterine Horn of a Rat Treated with Estrin.**
fusiform, were separated from one another by large quantities of a light intercellular substance. Since the cell boundaries were extremely indistinct, it was almost impossible to determine how much, if any, of the homogeneous substance was located intracellularly. The striking resemblance between the stroma of these tumors and that of hydatidiform moles is illustrated in Figs. 1–5.

It is of interest to note that testosterone propionate, a highly active typical androgen, sensitizes the endometrium to trauma in the same manner as do the estrogens, and that the same is true of pregneninolon, a compound closely related to progesterone. This is all the more remarkable since pregneninolon causes progestational transformation of the endometrium both in experimental animals and in women (5–7). It might consequently have been expected that an endometrium prepared by this substance would respond to trauma by deciduoma formation just as an endometrium in which progestational proliferation was elicited by progesterone.

The endometrial tumors described above never showed signs of malignancy, but their close resemblance to myxomatous growths is undeniable and they furnish a further example indicating the importance of local trauma and of a predisposing humoral medium for tumor formation.

It is perhaps worth emphasizing that throughout the animal kingdom, gelatinous connective tissue develops almost invariably under the influence of sex hormones. In support of this statement we may mention the mucoid connective tissue in the comb of the cock, which is under the control of androgens (8–9), the mucoid stroma of the sexual skin of monkeys which develops during estrus and after estrin administration (10–13), and the mucoid connective tissue responsible for the enlargement of the cloaca during the breeding season in tritons and lampreys (8–9). The connective tissue in the walls of the ejaculatory ducts and the ampullae of the vas deferens likewise shows myxoma-like
transformation under the influence of estrin treatment in the mouse (14–15). More recently, Selye (16) observed that in very young rats treatment with testosterone propionate causes transformation of the wall of the oviduct into gelatinous connective tissue (Fig. 6). All these examples seem to indicate that a close correlation exists between the sex hormones and this particular type of tissue.

Because of the conflicting results of studies, by different investigators, of the action of androgens on the vagina of the spayed rat, it may be mentioned that in our ovariectomized females treated by testosterone propionate there was a slight increase in the number of nucleated epithelial cells in the vaginal smear and cornified cells appeared in all cases during the first two or three days following initiation of the injections. The smears were never free of leukocytes, however, and could not be regarded as characteristic of estrus. Later during the experiment the cornified cells disappeared and the nucleated epithelial cells became extremely scarce. The appearance of such an intermediate type of smear during the first days of treatment may explain perhaps that while some authors (17–18) claimed to have obtained full vaginal estrus with testosterone, others (19–20) observed only an increase in vaginal weight and mucification of the epithelium. It is noteworthy that those who observed estrus examined the vaginal smears soon after initiation of treatment, while those who found no cornification of the vaginal epithelium made their studies after a more prolonged period of injections. It appears very probable that the investigators who reported positive results interpreted the transitory appearance of a few

![Fig. 6. Gelatinous Connective Tissue in the Wall of the Oviduct in a Testosterone-treated Immature Rat](image)
cornified and nucleated epithelial cells as sufficient evidence of an estrous smear.

In our pregneninolon-injected series, full vaginal cornification was observed between the second and third day of treatment so that in this case the production of vaginal cornification was undeniable. This observation is in agreement with the findings of Emmens and Parkes (21) and shows beyond doubt that this compound, which is a weak androgen and has a fairly strong progesterone-like action, must also be regarded as an estrogen. Our experiments indicate, however, that in spite of continued treatment with pregneninolon the cornified cells disappear from the vaginal smears within two days after the onset of estrus and the smears assume a mucous appearance. It appears, therefore, that unlike the typical estrogens the vaginal cornification caused by pregneninolon is only transitory.

Summary

The uteri of postpubertal ovariectomized rats treated with daily doses of 100 gamma of estradiol, 3 mg. of testosterone propionate, or 3 mg. of pregneninolon are sensitized to local trauma in such a manner that gelatinous tumors of the endometrial mole type develop at the site of injury. No such tumors were produced in the traumatized uteri of untreated control animals. These observations give further support to the concept that both local injury and an appropriately prepared humoral medium are essential for tumor production.

As an incidental observation, it was noted that the vaginal smears indicated only a transitory partial cornification during the first days of testosterone propionate administration, and even this inconspicuous change vanished within a few days. Pregneninolon caused full cornification of the vaginal epithelium within two or three days after the beginning of injections but continued treatment failed to maintain vaginal estrus.

Acknowledgments: The expenses of this investigation were defrayed in part by a grant in aid received by the senior author from the Schering Corporation of Bloomfield, N. J., through the courtesy of Dr. G. Stragnell. The hormone preparations used were supplied by Dr. E. Schwenk of the above Corporation.

Addendum

After completion of this paper the authors' attention was drawn to a recent publication, in which McCahey and Rakoff (J. Urol. 42: 372, 1939) reported their observation of vaginal cornification in spayed mice after 96 hours' treatment with testosterone propionate.

Bibliography

PRODUCTION OF ENDOMETRIAL MOLES WITH STEROID HORMONES 563