METAPLASIA OF UTERINE EPITHELIUM PRODUCED IN RATS BY PROLONGED ADMINISTRATION OF OESTRIN

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In a previous communication from this laboratory (1), it was reported that in a group of 8 female castrate rats which received daily intraperitoneal injections of 30–60 γ of oestrone (ketohydroxy-oestrin, theelin) in oily solution for ten weeks, 4 animals developed a more or less complete metaplasia of the cylindrical uterine epithelium into stratified squamous epithelium with cornification, from which irregular buds penetrated deeply into the stroma. Further studies in this direction are reported in the present paper.

Fig. 1. Uterus of Rat, Distended with Blood and Desquamated Epithelium after Intra-uterine Injection of Oestrone in Oil

The effect of direct application of oestrone to the uterine epithelium received first consideration. A solution of oestrone in corn oil (1 mg. per c.c.) was injected directly into the lumen of one or both uterine horns, by laparotomy, in a first series of 11 castrate female rats. Each injection was pushed until the horn was completely distended and blanched, the amounts introduced varying from 0.05 to 1.25 c.c. Ligatures were applied to prevent escape of the oil. Vaginal smears, which were read daily, showed continuous oestrus (with occasional lapses of one to three days) for long periods. In two cases, lapses of sixteen and twenty days occurred. Four of the animals carried greatly distended uterine horns for as long as 103 days; in one case

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2 An editorial comment on this communication, which referred to the observed changes as "cancer symptoms," was attached without the knowledge of the authors.
the excised uterus measured approximately $60 \times 50 \times 25$ mm., and weighed 75 gm. (Fig. 1). The distention was due to the presence of a dark brownish-red pulp, which was found to be composed of altered blood and desquamated epithelial cells. Metaplasia was found to be present in 5 animals of this series, and to be complete in 3 of these (Figs. 2 and 3).

In a second series of 11 castrate female rats, oestrone in corn oil was administered subcutaneously in doses of 30 $\gamma$ daily; vaginal oestrus was maintained continuously in all cases. Five of these animals were sacrificed on the 132d day of treatment (injections in the six remaining animals being continued), and all of these showed metaplasia of the uterine epithelium into squamous cells. They also displayed some development of the mammary glands and secretion of milk. The hypophyses were enlarged (average 17 mg.), and the adrenal cortex was hyperaemic.

Similar quantities of oestrone were administered to 12 normal male rats. One was killed on the 51st day, one on the 106th, and 4 on the 134th, the rest being kept for further treatment. All the animals sacrificed showed marked atrophy of the penis, testes, seminal vesicles, and prostate, but no metaplasia
METAPLASIA OF UTERINE EPITHELIUM PRODUCED BY OESTRIN

was observed, nor were scrotal herniae detected. The mammary glands showed a slight degree of development, and secretion of milk. The hypophysis was, in most cases, enlarged.

It was of interest to compare the effect of a single large dose of oestrone, given subcutaneously, with the effect of a similar single dose applied directly to the uterine epithelium. Accordingly 6 castrate female rats were injected subcutaneously with oestrone in corn oil in amounts equal to the quantities introduced into the uteri of the animals of the first series. Whereas in this first series vaginal oestrus was maintained for long periods, sometimes over 100 days, and metaplasia was produced in almost half of the animals, equivalent quantities of oestrone given subcutaneously maintained oestrus only for an average of five days (maximum ten days), and histological examination of the uterine horns revealed no metaplasia nor any other abnormality.

It seemed desirable, therefore, to test the effect of direct application of oestrone in the case of male animals. Five castrate male rats received injections of oestrone in oil (1 mg. per c.c.) directly into the seminal vesicles. The fluid was successfully retained in place by ligatures avoiding the main vessels, for periods ranging up to three months. No metaplasia was observed, however. Burrows (2) produced hyperplasia and metaplasia of the prostate in mice by chronically painting oestrin upon the non-epilated skin.

The results obtained with oestrone prompted a study of the effect of direct intra-uterine application of other substances. A solution of 1:2:5:6-dibenzanthracene in olive oil, prepared by the method of Boyland (3), was injected into the uterine horns of 4 normal and 4 castrate female rats. In most cases the injections were repeated several times. The animals were examined at periods ranging up to four and a half months. The uteri showed endometritis, but no other epithelial change. Horizontal-retort gas-house tar was similarly administered to 6 normal and 2 castrate female rats, and at varying periods up to four and a half months was found to have caused obliteration of the uterine lumina, but no metaplasia. A solution of pregnandiol in corn oil (2 mg. per c.c.) was similarly administered to 2 normal and 2 castrate female rats, but was not found to produce any abnormality of the uterine epithelium within seven days; corn oil alone was likewise found to be inert within this period, whereas oestrone in oil, similarly applied, will frequently produce metaplastic changes within four days (1).

SUMMARY

Intra-uterine or continued subcutaneous injections of a solution of oestrone in oil, in castrate female rats, frequently produce squamous metaplasia of the uterine epithelium, with downgrowth into the stroma. The transformation has not progressed beyond the stage previously reported (1), even with experiments continued for several months. Metaplasia of the uterine epithelium did not follow direct application of 1:2:5:6-dibenzanthracene, nor of gas-house tar, nor of pregnandiol, although the two first-named are known to be carcinogenic. Neither subcutaneous injections nor direct application of oestrone produced metaplasia of any sex-gland epithelium in male rats.
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References