TWO SPONTANEOUS UTERINE TUMORS IN A RABBIT: AN HORMONAL INVESTIGATION

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There have been recorded in the literature between 90 and 100 spontaneous tumors in the rabbit, of which 42 were located in the uterus. The present report of two spontaneous uterine neoplasms in a female rabbit brings this latter number to 43. The literature has been reviewed and references are given by Cutler (1), Heiman (2), and, most recently, by Orr and Polson (3).

The uterine tumors here described were observed June 9, 1937, in a mature female black and white rabbit between eight months and one year old, weighing 2520 gm. The past history of the rabbit was not obtainable. The animal was being used for immunological sera studies, and as it was thought to be pregnant, since two masses could be felt in its abdomen, it was discarded for that purpose and operated upon to obtain some fetal tissue. Upon opening the abdomen two tumors were encountered. One was located at the bifurcation of the uterine horns, extending more to the right side than to the left. It was of a deep purplish color with dilated veins on its surface; it measured $5 \times 3 \times 3$ cm. and on section showed extreme proliferation of the endometrium, which completely obliterated the lumen. The second tumor was at the mid-point of the left horn and measured about $2 \times 2 \times 2$ cm. When the uterine wall over this tumor was cut through, an endometrial mass, attached to the wall of the horn by a sessile base, extruded itself. On gross examination both ovaries showed fresh corpora lutea. No metastatic nodules were present in the retroperitoneal lymph nodes and lungs, nor was any abdominal organ invaded by neoplasm. Unfortunately neither adrenal glands, breasts, nor the hypophysis were removed for microscopic study. Grossly there was no evidence of pregnancy in either uterine horn.

The extensive endometrial proliferation of the tumors is illustrated in Fig. 1 (A) as compared with the usual endometrial hypertrophy found in the uterine horn of a twelve-day pregnant rabbit (B). It is readily seen how markedly the tumor endometrial proliferation exceeds that of normal pregnancy. A section through a twelve-day pregnant uterus in the rabbit (Fig. 2), showing a small embryo and the implantation area, presents only limited decidual proliferation and almost no endometrial proliferation as compared to that in the tumors.

Upon microscopic study of the tumors there appear certain areas which are obviously to be interpreted as a benign hyperplasia even though it be of a highly proliferative type. Other areas are seen in which mitotic figures are plentiful and which at first sight suggest adenocarcinoma (Fig. 3), but on closer study the cells can be observed to change back into the type found in
the benign hyperplasia. Whether this phenomenon can be looked upon as metaplasia of a highly proliferative hyperplasia is a conjecture. The main point under consideration is whether such a cellular metaplasia can be brought about by hormonal stimulation and, if so, what evidence there is in the histologic study of these tumors and the animal's organs to suggest this cellular conversion by hormonal stimulation?

Anatomical evidence suggesting extreme hormonal activity is to be found in (1) the decidual-like reaction of the stromal tissue of the benign hyperplasia of the tumor and (2) the complete luteinization of both ovaries except for one atretic follicle. Figs. 4 and 5 offer a comparison between the decidual-like reaction of the stroma of the tumor hyperplasia with that occurring in the implantation area of a twelve-day rabbit pregnancy. Histologically the cells are identical. Such similarity suggests that the tumor animal is under the same hormonal control—that of the corpus luteum hormone, progesterone—with the associated estrogenic hormonal effects, as the twelve-day pregnant rabbit. That such hormonal stimulation is possible is attested by the extensive luteinization changes found in both ovaries of the animal.

The important question in regard to the tumors under consideration is whether or not the cellular areas suggestive of malignancy can be called adenocarcinoma. Undoubtedly malignant tumors of the uterine fundus occur
Fig. 2. Section through a twelve-day pregnant rabbit uterus, showing small embryo in center of field, implantation area, and limited endometrial proliferation in surrounding tissue. × 8

Fig. 3. Uterine tumor: area of benign hyperplasia on right, fusing into a field suggestive of malignancy on left. × 140
Figs. 4 and 5. Decidual-like reaction in the stroma of the endometrium of the tumors (above) and decidual reaction from an endometrial implantation area in a twelve-day pregnant rabbit (below). × 240

Note the similarity of the reaction in the two sections. A large syncytial mass is present in the center of the section from the pregnant uterus.
in the rabbit, as illustrated by the case of Rusk and Epstein (4), in which the neoplasm had extended into many adjacent organs and had metastasized to others. On the other hand Case 13 of Polson (5), reported by him as an adenocarcinoma of the uterus, is less suggestive of malignancy than the tumors under discussion. Polson's report is illustrated by two sections showing the tumor divided by a fibrous septum; a definitely benign hyperplasia, but less proliferative than that in our tumor, is seen on the right side, and a "more malignant area on the left." Even this "malignant area," however, is much less suggestive of adenocarcinomatous changes than that shown in our Fig. 3.

Any theory advanced to explain the origin of the above tumors must include not only the possible malignant process but should explain also the highly proliferative generalized hyperplasia of the endometrium so frequently associated with it.

The hypothesis offered here is that of hormonal influence. That endometrial hyperplasia in animals or man is the result of excessive estrogenic stimulation is generally accepted at the present time. Such excessive estrogenic stimulation would explain the highly proliferative but benign hyperplasia of the endometrium here observed. If this strong estrogenic impulse were maintained and, through some unknown mechanism, a still more powerful corpus luteum influence were brought into play, as attested by the complete luteinization of both ovaries and the decidual reaction in the stroma of the endometrium of the tumors, might we not have an explanation for the metamorphic changes associated with the endometrial hyperplasia? Evidence favoring or against such an hypothesis could have been obtained by complete castration of this rabbit. It is the conjecture of the author that regression of the tumors would have followed, in association with the genital atrophy accompanying castration.

The association of benign endometrial hyperplasia and malignant-like changes in the uterus of a rabbit suggests the possibility of similar cellular reactions in the endometrium of woman. The interrelation of menopausal endometrial hyperplasia and uterine fundal carcinoma has long been discussed. The present reports may be of interest from this point of view.

CONCLUSION

Two spontaneous uterine tumors in a rabbit are described. The histology of the tumors was complex in that it varied from definitely benign endometrial hyperplasia and highly proliferative areas to fields that were suggestive of adenocarcinoma. No metastases were found in the retroperitoneal lymph nodes or lungs nor were metastases noted in any of the abdominal organs.

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BIBLIOGRAPHY