Hormonal Relationships of the Endometrium in Animals

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SUMMARY

This paper serves as a brief preface to a discussion of the endocrine aspects of endometrial cancer by enumerating certain salient features of the hormonal relationships of the endometrium in animals.

This communication aims to describe briefly certain features of the hormonal relationships of the endometrium in experimental animals with special emphasis on those aspects which appear to have some pertinence to clinical phenomena.

The endometrium may be defined as that tissue which lines the uterus. In such lower forms as the dogfish the endocrine control of this tissue provides the stimulus for the secretion of nutrient fluids which are directly utilized by the developing young. In higher forms the hormonal effects upon the endometrium regulate the estrus or menstrual cycle so as to condition the endometrium for the implantation and retention of the developing embryo. In some species these effects involve complex neuroendocrine relationships which may also be included in the present discussion.

For example, in such forms as the rabbit and the cat, ovulation occurs only following copulation. This response is mediated through a chain of events beginning with the sensory stimulation of mating and ultimately involving the hypothalamus which controls the release of luteinizing hormone from the anterior pituitary. The consequent shift from estrogen production to progesterone formation in the ovary induces in the uterus a modification from the proliferative type of endometrium to the progestational or secretory type. The latter is capable of responding to the presence of a fertilized ovum by formation of decidua, which is essential for complete implantation of the embryo.

In other forms, in which ovulation occurs cyclically without relation to copulation, the neuroendocrine mechanisms operate through completely endogenous control during the estrus or menstrual cycle. However, through mechanical stimulation of the cervix in such forms as the rat and the mouse the cycle may be prolonged to constitute a pseudopregnancy. In these species it is only under such special conditions that the endometrium proves capable of decidua formation. However, in other species such as the guinea pig and in primates the corpus luteum of each ovulatory cycle transforms the endometrium into a completely functional progestational phase fully prepared to respond by decidua formation to the developing embryo.

These observations serve to emphasize the highly varied patterns of endometrial hormonal conditioning seen among various species. It is, accordingly, quite essential that these species differences be kept in mind in any analysis of the nature of hormonal effects on the endometrium.

The primates, in particular Macaca mulatta, exhibit a menstrual cycle so comparable to that seen in women that special emphasis on these species is warranted.

It is particularly noteworthy that in one of the more widely studied primates, Macaca mulatta, both anovulatory cycles and ovulatory cycles occur as part of the normal menstrual phenomena. Thus Corner (1) observed the frequent occurrence of anovulatory cycles in this form during the summer months. This seasonal occurrence suggests that external environmental factors probably play a vital role in the normal elaboration of the complete or ovulatory cycle. What has already been said about the marked dependency of the luteal phase on neuroendocrine factors in lower forms would support this inference. However, the environmental factors involved in Macaca mulatta are apparently not the obvious ones of temperature and light exposure, which are known to play such a vital role in lower forms. We have observed in our own laboratory the same high incidence of anovulatory cycles during the summer months even under artificially controlled conditions of light and temperature. Such influences seem to have a counterpart in the numerous subjective factors related to the onset of amenorrhea and possibly ovulation failure in women.

The essential significance of these considerations is that the presumably spontaneous luteal phase of the pituitary-ovarian cycle in such complex forms as the monkey and human is intimately affected by neural mechanisms subject to environmental factors.

Such phenomena become of even more immediate pertinence to the problem of neoplasia when it is appreciated that endometrial carcinoma in women is noted to be excessively frequent in patients with such conditions as the Stein-Leventhal syndrome or long-standing adenomatous endometrial hyperplasia (6, 7). In such instances the protracted action of endogenous estrogen, unopposed by the presumed neutralizing effect of normal progesterone secretion, seems to play a pathogenetic role in the frequently associated endometrial malignancy.

However, when one reviews the available data pertain-
ing to the experimental production of endometrial abnormalities by prolonged estrogen therapy in the monkey, certain discrepancies become apparent. Although initial estrogen stimulation dramatically increases the mitotic activity in the glandular epithelium of the monkey endometrium, refractoriness to such stimulation is seen after about 20 days of such estrogenization. This is followed by endometrial atrophy despite continued massive dosage, and the expected picture of adenomatous hyperplasia is not regularly observed (10).

Moreover, data as to the carcinogenic potential of exogenous estrogen in the monkey are highly inadequate to date. Such experiments, which have ranged in duration from 3 months to 10 years, have involved only 25 monkeys in all, and only 4 of the monkeys were treated for 4 years or more. Although no actual malignancies were described, the monkeys almost uniformly exhibited profound metaplastic changes in the cervix and endometrium, and 1 of them showed a marked endometrial hyperplasia and polypsis (2, 3, 8, 12-14).

It seems appropriate to conclude that such studies are as yet by no means conclusive for the primate.

In the rabbit, however, several lines of experimental evidence implicate ovarian hormones as vital factors in the pathogenesis of endometrial carcinoma. Greene (4) described a strain of rabbits which exhibited both "hyperestrinism" and carcinoma of the uterus. Meisner and Somers (11) produced endometrial carcinoma in the rabbit after prolonged estrogenization. More recently Griffiths et al. (5) have demonstrated that the expected carcinogenic response of the endometrium of the rabbit to implantation of a methylcholanthrene-impregnated thread is estrogen dependent. They also observed that simultaneous progestin administration will neutralize the procarcinogenic effect of administered estrogens. The pertinence of these and other findings in the rodent to the limited observations in the primate remains to be determined by further study of the higher experimental forms. However, the lack of genetic standardization of primate species for experimental study on carcinogenesis imposes a serious handicap on such investigations. Also the relatively long life expectancy of primates necessitates more prolonged periods of experimental observation than have proven practicable in most laboratories to date.

The distinctive effects on the primate endometrium of both naturally occurring and synthetic progestogens merit further discussion. Progesterone itself halts mitotic activity in the glandular epithelium and induces a secretory function in this tissue. It also conditions the epithelium to respond to traumatization by forming "implantation plaques" comparable to those seen during the normal implantation process. Stromal changes in response to progesterone are minimal (10).

In marked contrast, such synthetic progestogens as 17-ethynyl-19-nortestosterone regularly induce a marked decidual reaction in the stroma of the monkey uterus quite comparable to that seen in women after certain dosages of this and related steroids (9, 16). It is clear, then, that these newer progestogens exert an endometrial effect which differs not only quantitatively but qualitatively from the classically observed effects of progesterone itself.

In this same vein, Pincus et al. (15) have emphasized the relative progestational potencies of several of the newer progestogens and their capacity to maintain pregnancy in the rat.

Exactly which of these biologic properties is most directly related to the capacity of progestogens to induce regression of endometrial cancer in women is not yet determined. Further extensive correlation of the laboratory findings with the clinical effects are urgently needed.

The foregoing is by no means an exhaustive treatment of the assigned topic. However, it is hoped that these brief remarks will provide some experimental orientation to the clinical problem which will be discussed this morning.

REFERENCES

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