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Neutralization of Ovarian Follicular Hormone in Women by Simultaneous Administration of Male Sex Hormone.*

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Recent experiments from this laboratory, in which the vaginal smear was used as an index, have shown that the menstrual cycle can be inhibited in the human by the male sex hormone.[1] This is in accord with previous findings in rodents[2] and primates.[3] The vaginal smear reverts to the atrophic or menopausal type,[4] and can be kept at that level by continued administration of adequate amounts of hormone. Menstrual function returns spontaneously after cessation of treatment.

The present study was concerned with the possibility that the male hormone might have a direct antagonistic action on the ovarian follicular hormone, in addition to its suppressive effect on menstrual function. It was stimulated by our findings in a case in which the menstrual cycle was interrupted by the administration of testosterone propionate. Four weeks after the last definitely established ovulatory phase, and during a period in which the vaginal smear remained typically menopausal, there was observed an increased excretion of ovarian follicular hormone which reached the same high levels as during the previous follicular phase, and lasted for 3 days. The question arose whether the persistence of the menopausal smear during this period might have been due to neutralization of the effect of endogenous estrogen on the vaginal epithelium by the administered male hormone. The experiments of Robson[5] on ovariectomized mice in which vaginal cornification by oestrone was prevented by concomitant administration of testosterone, suggested that this might be the case.

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1 Papanicolaou, G. N., Ripley, H. S., and Shorr, E., PROC. SOC. EXP. BIOL. AND MED., 1938, **37**, 689.

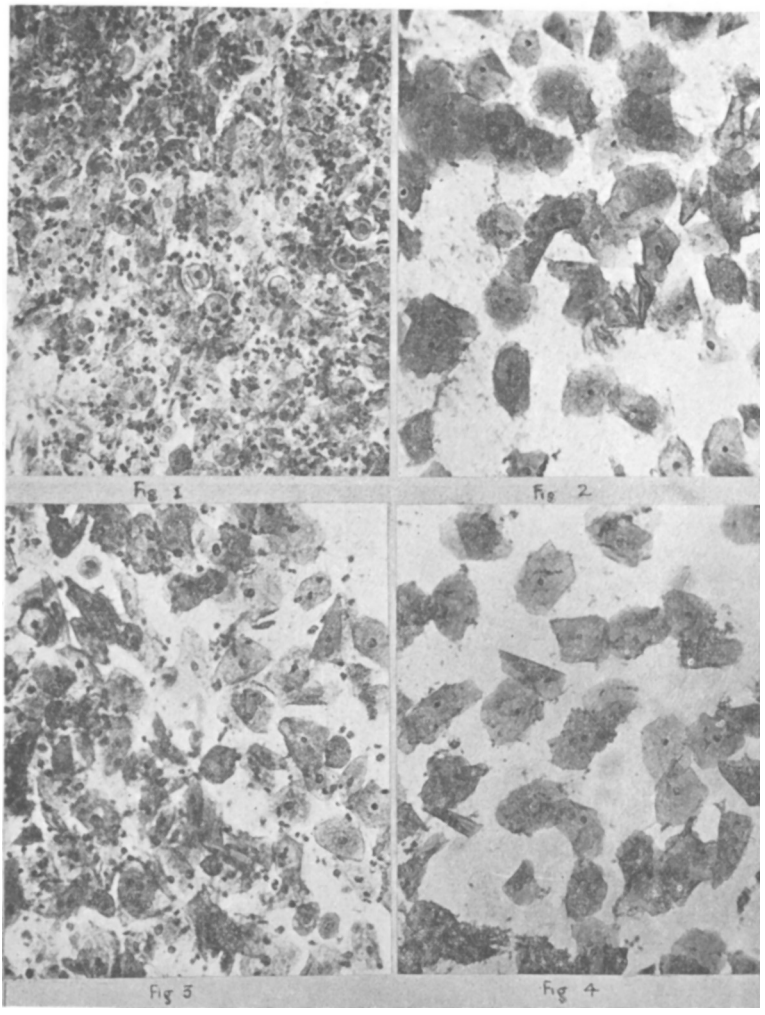
2 Robson, J. M., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 49.

3 Zuckerman, S., *Lancet*, 1937, **233**, 676; Hartman, C. G., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 87.

4 Papanicolaou, G. N., and Shorr, E., *Am. J. Obs. and Gyn.*, 1936, **31**, 806.

5 Robson, J. M., *J. Physiol.*, 1937, **90**, Proc. Physiol. Soc., 15 P.

Experimental. With this in mind, estradiol benzoate (progynon-B) was administered to women with the menopausal syndrome in amounts sufficient to produce and maintain a follicular smear.[4] At



Vaginal Smears of Case C.

FIG. 1. Control smear before treatment (menopausal type).

FIG. 2. Follicular smear following treatment with estradiol benzoate (3,000 R.U. daily), prior to administration of testosterone propionate.

FIG. 3. Smear after daily administration of 25 mg of testosterone propionate for 27 consecutive days and 50 mg for 7 days, combined with 3000 R.U. of estradiol benzoate daily throughout this period. Note disappearance of cornified cells, reappearance of deep cells, with regression towards the menopausal type of smear.

FIG. 4. Reappearance of follicular smear with continuance of daily treatment with 3000 R.U. of estradiol benzoate, 14 days after stopping testosterone propionate.

this stage, the injections of estradiol were continued, and, at the same time, testosterone propionate (Oreton)† was also given. The effects of the simultaneous administration of these hormones was followed by means of vaginal smears, vaginal biopsies, and hormonal assays.

The subjects were 3 women whose menopause was well established. Patients A and B had intact pelvic organs. Patient C had had a hysterectomy. In all 3, control smears were typically menopausal (Fig. 1). Prior to treatment, urinary estrogen assays in each case indicated a daily excretion of less than 90 International units, and the urinary prolan was above normal levels.

A daily dose of estradiol benzoate sufficient to establish a typical follicular smear (Fig. 2) and symptomatic relief was administered. This was, for A, 1,500 R.U., and for B and C, 3,000 R.U. Then testosterone propionate was given as follows: to A, 25 mg daily in oil for 17 days (total 425 mg); to B, 25 mg daily for 10 days, 50 mg for 3 days, and 25 mg for the next 3 (total 475 mg); and to C 25 mg on 27 consecutive days, and 50 for the following 7 (total 1,025 mg). Estradiol benzoate, in the doses given above, was administered throughout the period of study.

In all 3 women, with the administration of male hormone together with estradiol benzoate, there was a gradual disappearance of cornified cells, a reappearance of deep cells, and the smears lost their typical follicular character (Fig. 3). Biopsies of the vaginal mucosa at this time showed a loss of the cornified zone which had been built up by the previous injections of estradiol benzoate. The level of the urinary prolan fell to below 10 mouse units per 24 hr and remained within these normal values throughout the period of combined treatment. The symptomatic improvement achieved with estradiol alone persisted when both hormones were given. During the period in which the male hormone was given, libido and sexual response were definitely greater than that experienced with estradiol alone. The voice was perceptibly lowered, and there was a marked vulval hyperemia, as well as moderate enlargement of the clitoris in all 3 subjects.

In B and C, the administration of estradiol benzoate was continued after the testosterone propionate was stopped, and the vaginal smears again became follicular (Fig. 4). Patient C received a second course of 25 mg of testosterone daily for 14 days, along with

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3,000 R.U. of estradiol benzoate. This resulted in a second transition from a follicular smear to one devoid of cornified cells.

A second group of 5 menopausal women, including 2 castrates, received testosterone propionate alone (25 mg daily). Symptoms were relieved with this dose in 4, and prolan excretion diminished, with no changes in the smear picture or the vaginal epithelium, which remained menopausal throughout. In neither of these 2 groups of subjects was there observed the development of a follicular smear with male hormone alone as has been recently reported by Salmon.[6]

Comment. There are several possible modes of action of male hormone in women. One is a direct effect upon the ovary to suppress menstrual function. An example of this may be the amenorrhea which follows the prolonged administration of the hormone to menstruating women.[1] Another possibility is that the action is primarily on other endocrine organs, most likely the hypophysis, and the effect on the ovary is secondary. This is suggested by the diminution in prolan excretion we and others[6] have observed. A third is a direct peripheral effect antagonistic to the estrogens, such as we have shown for vaginal cornification in humans, and Robson in mice. Finally, all these mechanisms may function in varying degrees and at different times.

A calculation of the neutralizing capacity in humans of the male hormone on estradiol is of interest. One mg of estradiol benzoate is equivalent to about 6,000 R.U. In these experiments, 25 mg of testosterone propionate was able to neutralize 0.5 mg of estradiol. The ratio is therefore 50:1. Using ovariectomized mice, Robson found a ratio of 300:1 between testosterone and estradiol.

These results may have some bearing on the interpretation of the observation that androgens and estrogens are both present in the normal male and female. It may be that some such mechanism of neutralization serves to preserve the fundamental characteristics of each sex, in the presence of both types of hormones, and that the different concentration in which they exist in men and women is the expression of the proper balance between them which will achieve this end.

Conclusion. Studies of vaginal smears and biopsies indicate that the male hormone (testosterone propionate) is able to neutralize, in women, the effects of estradiol on the cornification of the vaginal epithelium.

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[6] Salmon, U. J., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 488.