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Progestational Effectiveness of 19-nor-Ethinyl-Testosterone* by Oral Route in Women. (22281)

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Tullner and Hertz(1) have previously demonstrated that 19-nor-progesterone is 4 to 8 times as active as progesterone by injection in the Clauberg rabbit test. Hertz, Tullner, and Raffelt(2) also showed that 19-nor-ethinyl-testosterone is likewise about 5 times as active as ethinyl testosterone when tested for progestational activity by oral administration in the Clauberg rabbit and that it is also highly active in the ovariectomized monkey pretreated with estrogen(2,3).

This report presents observations on the progestational effectiveness of 19-nor-ethinyl-testosterone[†] upon oral administration in 4 women.

Case 1: S.J.M. 14-year-old white female; proven by biopsy of ovarian anlagen to have ovarian agenesis (October, 1953). She was maintained on cyclic estrogen therapy with monthly withdrawal bleeding until January, 1954. Then after 23 days on 0.1 mg ethinyl estradiol daily she received 10 mg 19-nor-ethinyl-testosterone[†] twice daily for 12 days. Suction curettement of the endometrium

showed marked progestational effects with numerous polyhedral as well as spindle cells in the stroma. Menses ensued 2 days after cessation of therapy.

Case 2: A. H. 21-year-old white female; ovarian agenesis proven by biopsy of both ovarian anlagen in November, 1953. She was maintained on cyclic estrogen therapy until January, 1954, when she was given 5 mg of 19-nor-ethisterone twice daily in addition to her usual daily estrogen dosage of 0.1 mg ethinyl estradiol for 2 days followed by 12 days more of the nor-ethisterone alone. She began menstruating at this point and all treatment was discontinued for 3 months. This bleeding indicated that although 5 mg of nor-ethisterone twice daily was sufficient to markedly prolong her usual latent period for withdrawal bleeding, nevertheless it was not sufficient to maintain the endometrium. Accordingly, about 2 weeks later another course of estrogen followed by 10 mg of nor-ethisterone twice daily was given for 14 days and a suction curettement performed. The endometrium showed a marked progestational effect with distinct decidual reaction in many areas.

* We are greatly indebted to Chemical Specialties Co., N. Y., for supplies of 19-nor-ethinyl-testosterone.

[†] Also called: "nor-ethisterone."

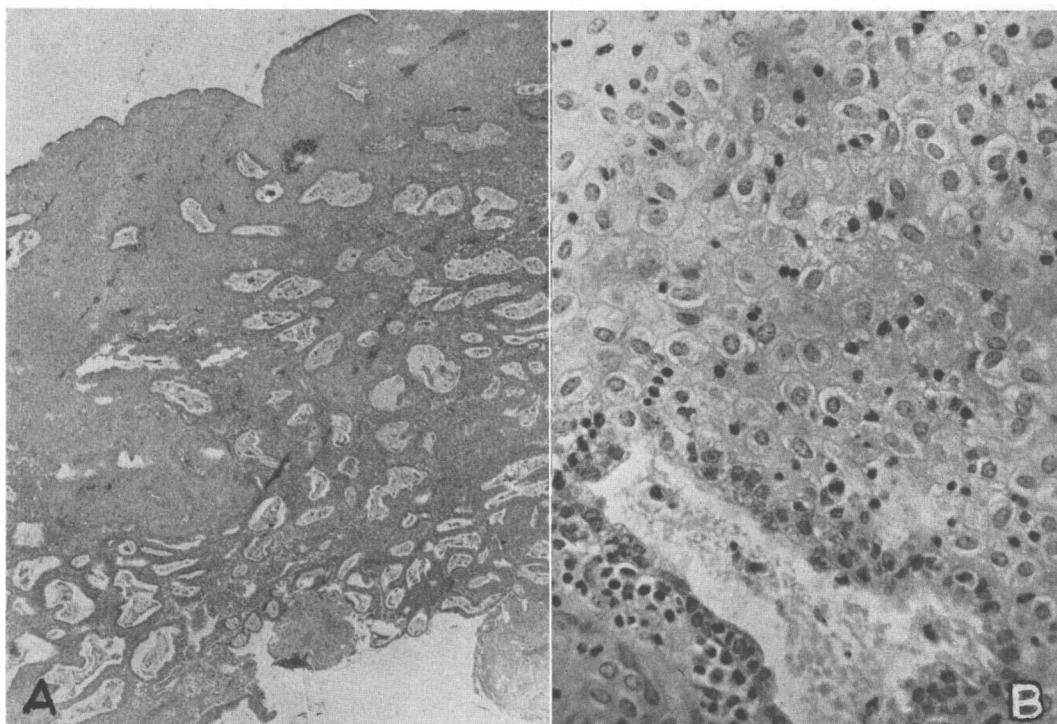


FIG. 1A. Curettage specimen from case 4 after 25 days on 19-nor-ethisterone at 10 mg twice daily.

FIG. 1B. Decidual cells in case 4.

Case 3: M. H. 24-year-old white married female; amenorrhoea of 4 years duration. Menses had been entirely normal (interval 28 days; flow 5 days; napkins 3-4) since 13 years of age. She was given 5 mg of nor-ethisterone twice daily for 5 days and no menses occurred on withdrawal. A second course of 10 mg nor-ethisterone twice daily for 5 days was followed after 3 days by menses lasting about 5 days. Since no spontaneous menstruation occurred during the ensuing 35 days she was given another course of 10 mg of nor-ethisterone twice daily for 5 days and this was followed by menses. Six weeks later she was given ethinyl testosterone at a dose of 40 mg twice daily for 5 days. No bleeding had ensued when the patient was seen 41 days later and further followup was not obtainable.

Although no histological evidence was obtained in this case, 10 mg nor-ethisterone twice daily elicited menses on 2 occasions and half this dose failed to do so. In addition, a

4 times greater dose of ethinyl testosterone also proved ineffective.

Case 4: C.P. 40-year-old white female; carcinoma-in-situ diagnosed by repeated smears and biopsy. She was placed on 10 mg nor-ethisterone twice daily continuously for 25 days while awaiting hysterectomy. No menses intervened during this period. Papanicolaou smears throughout this period remained positive. Quadrant biopsies of the cervix prior to hysterectomy revealed invasive carcinoma of the cervix. Endometrial curettage showed extreme progestational effect with extensive decidual reaction (Fig. 1). Panhysterectomy with node dissection was then carried out.

Conclusions. It is clear from the foregoing observations that 10 mg nor-ethisterone given twice daily represents a reproducibly effective dose in women for the production of marked progestational changes in the endometrium. The data suggest that very probably one half this dose will not be effective. The comparably effective dose of ethinyl tes-

tosterone (ethisterone) would be about 4 times higher(4). Thus the comparative values agree reasonably well in rabbit, monkey, and man(2,3).

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Cytological and Weight Changes in Pituitary Gland of the Severely Stressed Rat.* (22282)

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Numerous cytological studies have been made of the anterior pituitary gland following the application of different types of stress. Finerty and Briseno-Castrejon(1) and Brokaw *et al.*(2) reported an increase in the percentage of acidophils as shown by azocarmine after unilateral adrenalectomy in rats. Daughaday, Perry and McBryde(3) associated the acidophils with ACTH secretion in their studies of increased adrenal function in acromegaly. Finerty, Hess and Binhammer(4) reported no increased percentage of acidophils or basophils at intervals of 1, 3, 12 and 24 hours after stress with the azocarmine staining method but did describe an increase in numbers of acid hematein positive cells. No change in the percentage of the basophils by staining with PAS or with aldehyde fuchsin was found. Recently, Knigge(5) reported an increase in percentage of acidophils and argyrophilic basophils 12 hours after severe stress, and concluded that the latter were most probably associated with ACTH production since response to stress occurs in thyroidectomized animals which are characterized by absence of acidophils. Kraus(6) reported a decrease in the number of basophils in the anterior pituitary of Addison's disease patients. Further evidence for the basophils as the cytological source of ACTH was noted by Koneff(7) who found a decrease in the

basophils after bilateral adrenalectomy and after ACTH injection in rats. D'Angelo *et al.*(8) noted adrenal hypertrophy during prolonged periods of inanition in the guinea pig. This was accompanied by loss of weight of the pituitary and hypertrophy and hyperplasia of the basophils, increasing with the severity of the inanition. Marshall(9) found ACTH antibody coupled with fluorescent dye to be localized in the basophil cells of the hog pituitary. Recently, Wilson *et al.*(10) reported the characteristic Crooke's hyaline cytoplasmic change of the pituitary basophils associated with hyperfunction of the adrenal cortex, and a progressive loss of acidophils in 100 routine human necropsies.

It was the purpose of the present experiments to reinvestigate histological changes and to study changes in weight of the pituitary gland in order to gain further insight into the effects of a severe stress.

Method. Male rats of the Holtzman strain weighing between 110-130 g were used. They were stressed by immersion (except for the head) in water (containing Aerosol) at 70°C for 5 seconds while under Nembutal anesthesia. All animals were sacrificed by decapitation. The pituitary gland was removed immediately and weighed on a Roller-Smith torsion balance. About half of the glands were then placed in appropriate fixative for future histological study. The rest were placed on previously weighed coverslips, dried in an oven at 30°C for 48 hours and re-

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