Augmentation and Depression of Estriol-Induced Growth of the Uterus By Progesterone.* (22458)

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Progesterone is an important regulator of proliferation of cells whose growth is stimulated by phenolic estrogens; it augments the growth of certain tissues and depresses growth of others. Injected alone, progesterone has no effect on growth of the genital tract(1). When estrone is administered to the ovariectomized rat together with progesterone, the growth of the mammary gland is enhanced while that of the uterus is inhibited. It was found in the present experiments that the action of progesterone on growth of the uterus is different when it is administered with estriol instead of estrone. The effects of progesterone on estriol-induced uterine growth are biphasic, consisting of enhancement of growth followed by depression, depending on the dosage of estriol which is employed.

Methods. The experiments were conducted on 560 albino rats which were maintained under standardized climatic and dietary conditions(2). There were 5 rats in each group at every dose level and the experiments were repeated 5 separate times. Varying quantities of estrone or estriol were administered alone or combined with 1 mg of progesterone. The dosage of steroids refers to the amount injected daily. It had been found earlier(3) that 0.1 mg of progesterone is the smallest quantity to cause maximal depression of estrone-induced growth of the uterus of hypophysectomized rats. The steroids were dissolved in ethyl alcohol which was diluted with sesame oil to make the final alcoholic concentration 10%. Hypophysectomy was performed at age 24 days and the steroids were injected (0.2 ml) subcutaneously daily from age 38 to 44 days. Necropsy was carried out at age 45 days when the uterus was excised, blotted and weighed on a torsion balance. The nitrogen content of the uterus was determined by a micro-Kjeldahl technic. Growth is defined as an increase both of weight and of nitrogen content. It was found in each case that the nitrogen concentration of the uterus was 2.52 $\pm$ 0.08 mg per 100 mg moist weight so that the simple determination of the weight of the uterus had significance.

Results. The results of the 5 experiments were essentially similar. With a dose level of estrone (0.05 μg), just sufficient to initiate growth of the uterus, progesterone exerted no detectable effect on such growth. With increased dosage of estrone (0.1 μg) progesterone exerted an inhibitory effect (Fig. 1) which reached its maximum (32%) when the amount of estrone was 0.15 μg. No augmentation of estrone-induced uterine growth by progesterone was observed.

With reference to the growth of the uterus induced by estriol alone (Fig. 2) progesterone augmented the growth induced by small amounts (1-5 μg) of estriol and inhibited the growth caused by larger doses (25-50 μg). At the 10 μg dosage level of estriol, progesterone did not modify the growth of the uterus. The maximum augmentation of estriol-induced uterine growth by progesterone was 18%; the maximum inhibition was 24%.

Discussion. Estriol is an impeded estrogen (2) belonging to a small class of 1, 3, 5(10)-estratrien-3-ol derivatives with oxygenated functions at specific molecular sites. The impeded estrogens have common physiologic properties that differ from those induced by the majority of estrogenic compounds. 1. Estriol is more potent than estrone(4) in causing opening of the vaginal plate of infantile rats but is less active in evoking vaginal cornification. 2. Whereas estriol in small

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quantity initiates uterine growth, a considerable increase of dosage augments this growth only slightly(5). 3. Hisaw *et al.*(6) discovered that estriol can reduce the effectiveness of estrone in promoting uterine growth when these steroids are injected together.

Evidence has been presented that these physiologic properties of estriol are due to the interaction of its 16α-hydroxyl group with that specific protein surface of the uterine cell which is of critical importance in promoting growth. It would appear from the present experiments that progesterone can block the inhibitory action of this hydroxyl group when small amounts of estriol are present and so enhance the growth promoting activity of the phenolic group in the molecule.

Conclusions. 1. Whereas progesterone inhibits the growth promoting action of estrone on the uterus of hypophysectomized rats, its effects on estriol-induced growth are biphasic. 2. Progesterone depresses uterine growth evoked by large quantities of estriol but *enhances* growth promoting action of small quantities of this impeded estrogen.

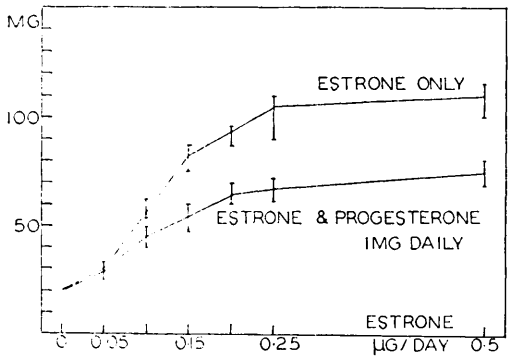

FIG. 1. Effect of progesterone, 1 mg daily, on growth of uterus induced by estrone. Ordinates: wt of uterus. Abscissae: daily dosage of estrone.

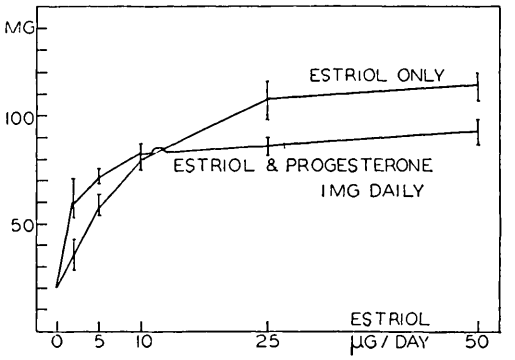

FIG. 2. Effects of progesterone, 1 mg daily, on growth of uterus induced by estriol. With smaller quantities of estriol, growth is enhanced but with larger quantities it is inhibited. Ordinates: wt of uterus. Abscissae: daily dosage of estriol.

1. Hertz, R., Larsen, C. D., and Tullner, W., *J. Nat. Cancer Inst.*, 1947, v8, 123.

2. Huggins, C., and Jensen, E. V., *J. Exp. Med.*, 1955, v102, 335.

3. ———, *ibid.*, 1955, v102, 347.

4. Curtis, J. M., and Doisy, E. A., *J. Biol. Chem.*, 1931, v91, 647.

5. Dorfman, R. I., PROC. SOC. EXP. BIOL. AND MED., 1940, v45, 594.

6. Hisaw, F. L., Velardo, J. T., and Goolsby, C. M., *Fed. Proc.*, 1953, v12, 68.

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Anticonvulsant Effect of Morpholinethylmorphine. (22459)

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Morpholinethylmorphine (MEM)* is an amino alkyl ether of morphine resulting from substitution of morphine's phenolic hydrogen by the morpholinethyl radical. It was prepared by Chabrier, *et al.*(1) and described as an anti-tussive agent which possessed neither the convulsant effect nor the smooth muscle stimulating action of codeine. The close structural relationship of MEM to codeine

* Obtained from Dr. R. Giudicelli, Dausse Laboratories, Paris, France.