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Antifibromatogenic Activity of 19-Nor-α-ethinyltestosterone in the Guinea Pig.* (22162)

DUSAN JADRIJEVIC, ELVIRA MARDONES, AND ALEXANDER LIPSCHUTZ.

Instituto de Medicina Experimental, Servicio Nacional de Salud, Santiago, Chile.

Both the progestational and antifibromatogenic potencies of 19-nor-progesterone (19-nor-P) are greatly superior to those of progesterone (P)(1,2). Likewise, the progestational potency of (19-nor-α-ethinyltestosterone (19-nor-ET)(3) has been found to be 5 times that of α-ethinyltestosterone (ET) (4). ET also is antifibromatogenic though about 15 times less than P(5,6). Because of the clinical importance of 19-nor-ET which is active by mouth(4) its antifibromatogenic activity was studied.

Methods previously described(2) were used. Because of slow absorption of ET (0.2 to 0.4 μg/sq mm of the pellet) 4 to 8 pellets were implanted subcutaneously. Absorption rate of 19-nor-ET was 1.6 μg/sq mm. Absorption rate of 19-nor-P also was greater than that of P (7 against 3 μg/sq mm(2,5,7).

Results with ET and 19-nor-ET are summarized in Table I. No prevention of estrogen-induced abdominal fibroids was obtained with the quantities of ET used. On the contrary, with the same quantities of 19-nor-ET the fibrous reaction was greatly diminished; the same occurred even with as little as 50 to 70 μg/day (see individual values in parentheses). With ET values of 4 to 7 may still occur with 150 to 210 μg/day(5). Thus the antifibromatogenic potency of 19-nor-ET is probably more than 4 times that of ET. It is noteworthy that the increase from ET to 19-nor-ET is of the same quantitative order as from P to 19-nor-P(2). However, 19-nor-ET is far less potent than 19-nor-P and even than P.

There was also a very pronounced increase in prevention of abnormal uterine weights

TABLE I. Antifibromatogenic and Antihysterotrophic Activities of ET and 19-nor-ET in Castrated Female Guinea-Pigs with Subcutaneously Implanted Pellets of Estradiol (Absorption: 47 to 50 μg/day). Duration of experiment: 3 mo. For classification of results see (6,8).

Steroid tested		No. of	Fibrous		
Compound	μg/day	animals	tumoral effect*	Q_{2-3}†	Uterine wt, g
ET	71 (35–127)‡	10	6 ± .9‖	1.9	6.0 (2.7–8.7)
19-nor-ET	80 (49–126)§	14	2 ± .2¶	.3	2.6 (1.5–4.0)

* Arbitrary values for number and size of tumors, ranging from zero to 12(6).
† " " " *large* tumors only, per animal (8).
‡ 4 to 8 pellets.
§ ½ to 1 pellet.
‖ Individual values: 2–2.5–3–4–5.5–6.5–7.5–7.5–8.5–11.
¶ " " : (1.5–1.5)–1.5–1.5–1.5–1.5–1.5–(2–2)–2–2.5–(3–3)–3. In parentheses: animals receiving only 50-70 μg/day of 19-nor-ET.

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which dropped from 6 g with ET to 2.6 g with 19-nor-ET.

Summary. The antifibromatogenic potency of 19-nor-ET is about 4 times that of ET. 19-nor-ET is also greatly superior to ET in antihysterotrophic potency, *i.e.*, in preventing uterine increase due to estrogen.

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Effects of Hallucinogenic and Tranquilizing Drugs on Serotonin Evoked Uterine Contractions. (22163)

E. COSTA.* (Introduced by H. E. Himwich.)

Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital, Galesburg, Ill.

Evidence has been presented to support the hypothesis that serotonin (5 hydroxytryptamine) which has been found in extracts of mammalian brain(1,2) plays a role in the physiology of the nervous system of invertebrates(3,4). While many physiological properties of serotonin have been characterized (5), its action on the central nervous system has not been defined. Shaw and Woolley(6) think that serotonin injected in the mouse cannot reach the brain. Since the hallucinogen, d-lysergic acid diethylamide (LSD), has been shown to antagonize the effects of serotonin, both *in vivo*(7,8) and *in vitro*(9), it has been suggested that serotonin antagonism may be important in the mechanism of LSD induced psychosis(9). However, mescaline and bufotenine(10) which are also hallucinogenic, do not antagonize serotonin activity *in vitro* (9,5). Furthermore, while many lysergic acid derivatives are not hallucinogenic, they retain the ability to antagonize serotonin-induced uterine contractions(7).

Methods. In the present experiments we used the uterus of spayed rats brought into oestrus by the injection of ovarian hormone. The rat uterus was suspended (at 28.5-29.5°C) in aerated de Jalon fluid (NaCl 9.0 g; KCl 0.42 g; $CaCl_2$ 0.06 g; $NaHCO_3$ 0.5 g; glucose 0.5 g/l). We studied the reactivity of the organ to serotonin creatinine sulfate, acetylcholine (ACh) and oxytocin before and after treatment with Frenquel (alpha-4-piperidyl diphenyl carbinol hydrochloride), chlorpromazine (10-(3-diethylaminopropyl), 2-chlorophenothiazine hydrochloride), reserpine, desmethoxy reserpine, Lergigan (N (2-dimethylamino-2-methyl-1-ethyl) phenothiazine hydrochloride), mescaline (3,4,5 trimethoxyphenyl ethylamine sulfate) and LSD (d-lysergic acid diethylamide). To make a comparative evaluation of the antagonistic powers as well as to compare the specificity of each drug tested, we determined the uterine reactivity to a series of increasing concentrations of contractile agents, (serotonin, ACh and oxytocin) starting from a minimally active concentration then increasing it until the maximal uterine contraction was reached. Each dose was given 3 times. We accepted, as the stabilized value, the mean height of contraction when the variation between the 3 contractions was not greater than 10%. Then we again tested the reactivity of the uterus to the contractile agents after the hallucinogenic or

* Fulbright Fellow on leave from Institute of Pharmacology, University of Cagliari, Italy.