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.

1. Tullner, W. W., and Hertz, R., *Endocrinology,* 1953, v52, 195.

2. Mardones, E., Iglesias, R., and Lipschutz, A., PROC. SOC. EXP. BIOL. AND MED., 1954, v86, 451.

3. Djerassi, C., Miramontes, L., Rosenkranz, G., and Sondheimer, F., *J. Am. Chem. Soc.,* 1954, v76, 4092.

4. Hertz, R., and Tullner, W. W., *Endocrinology,* 1954, v54, 228.

5. Iglesias, R., and Lipschutz, A., *Lancet,* 1946, v2, 488.

6. Lipschutz, A., *Steroid Hormones and Tumors.* Williams & Wilkins, Baltimore, 1950, p138, 147, 148.

7. Fuenzalida, F., *J. Cl. Endocrinol.,* 1950, v10, 1511.

8. Lipschutz, A., and Maass, M., *Cancer Research,* 1944, v4, 18.

Received November 2, 1955. P.S.E.B.M., 1956, v91.

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.

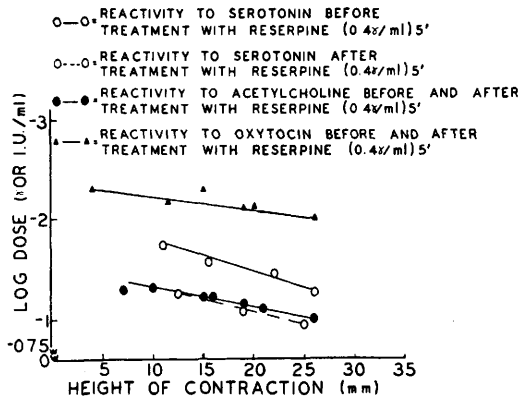

FIG. 1. Diminished contractility of uterus to serotonin after reserpine is contrasted to constancy of response to ACh and oxytocin. The figure discloses that to obtain an equal degree of activity after reserpine it is necessary to use a higher concentration of serotonin.

tranquilizing drug (Frenquel, chlorpromazine, reserpine, Lergigan, mescaline and LSD) had been left in contact with the organ for 3 to 5 minutes.

Results. The tranquilizing agents (Frenquel, reserpine, deserpidine and chlorpromazine) antagonize the serotonin-induced uterine contractions while in the same doses they display no antagonism either toward ACh or oxytocin. Lergigan and Meratran, similar in their chemical structure to chlorpromazine and Frenquel, respectively, do not display anti-serotonin activity in the concentrations at which they antagonize ACh. Successive washing completely reversed the antagonistic effects of Frenquel and of chlorpromazine after intervals of 30 and 60 minutes respectively. With reserpine and its analogue (both in concentration between 0.4 to 1 mg/l), the antagonism was long lasting; the uterine contractility being restored to normal values after 240 minutes.

Fig. 1 shows the uterine response to serotonin, ACh, and oxytocin before and after treatment with reserpine (0.4 mg/l) for 5 minutes. The negative log of concentration (γ/cc) of the contracting agent (serotonin, ACh and oxytocin I.U./cc) was placed on the ordinate axis, and the mean height of contraction (in mm) attained with each dose on the abscissae. Thus we obtained a graphic representation of the reactivity of the uterus to the contracting agent. No changes were observed in the response to oxytocin before and after treatment with reserpine. The graphical expression of uterine reactivity to ACh both before and after treatment practically coincides showing that no changes were induced by the drug. The open circles represent the uterine reaction to serotonin; the upper line showing the pretreatment reactivity, and the lower one indicating the decrease in sensitivity following treatment. The distance between these two lines represents the degree of inhibition exerted by reserpine on the serotonin-induced uterine contractions. Chlorpromazine (0.1 γ/cc for 3 minutes) and Frenquel (0.8 γ/cc for 3 minutes) increased the minimal active dose of serotonin from 12 γ/l to 60 γ/l and from 14 γ/l to 38 γ/l respectively.

Mescaline (Fig. 2) in concentration of 100 γ/l, facilitated the serotonin-induced contractions of the rat uterus. The increase of the serotonin contractions induced by mescaline is a reversible phenomenon. Mescaline alone in concentrations higher (over 0.4 mg/l) than that used in the above experiment evoked a uterine contraction. The contractile effect of mescaline was not modified by 240 γ/l of atropine sulfate. This concentration usually antagonized ACh-induced contractions of the rat uterus.

With LSD we were able to confirm the results of Gaddum(9), Cerletti(11), and Erspamer(5). As a matter of fact, using the comparatively high concentration of LSD of 1 γ/l (left in contact with the uterus for 5 minutes), we obtained a clear inhibition of the serotonin or mescaline-induced contraction,

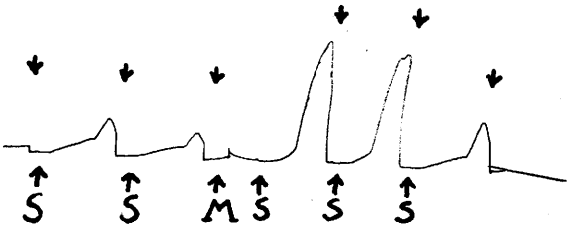

FIG. 2. Mescaline (100 γ/l) produces a transitory augmentation of minimal contraction evoked by serotonin (2γ/l). M and S indicate treatment of uterus with mescaline and serotonin respectively. In the concentration employed in this experiment mescaline by itself cannot cause a contraction.

while the activity of ACh was not affected. In contrast by using minimal effective doses of serotonin, we observed that LSD in low amounts (0.05 to 0.2 γ/l) left in contact with the uterus for 3 minutes increases the uterine response both to serotonin and mescaline. Since the action of LSD is long lasting, with the use of successive doses a summation of effect may occur. Thus inhibitory concentrations can be easily reached which prevent the demonstration of the facilitating action of LSD in low concentration.

Discussion. We were able to demonstrate that reserpine, Frenquel, and chlorpromazine are antagonists of serotonin activity in the rat uterus. Meratran and Lergigan, similar chemically to Frenquel and chlorpromazine respectively, do not exert a tranquilizing action in patients, and do not antagonize the serotonin-induced uterine contraction specifically. Mescaline and LSD, on the other hand, show a great affinity for serotonin receptors and under our experimental conditions, could be considered synergistic with serotonin. If an analogy is possible between the receptors in smooth muscle and the serotonin receptors in the brain, tranquilizing action seems to be associated with serotonin inhibiting properties while the hallucinogenic effect may be related to the facilitation of serotonin.

Summary. Tranquilizing drugs: Frenquel (0.8 mg/l), chlorpromazine (0.1 mg/l) and reserpine (0.4 mg/l), antagonize serotonin-induced uterine contractions, though they do not affect sensitivity of the uterus of the spayed rat either to ACh or oxytocin. The period of antagonism is longer lasting with reserpine than with chlorpromazine and is shortest with Frenquel. Mescaline (0.1 mg/l) causes a facilitation of serotonin activity, and in highest amounts causes a uterine contraction by itself. However, it is not antagonized by atropine (0.24 mg/l). A relatively high concentration of LSD (1 γ/l) antagonizes both serotonin and mescaline-induced uterine activity. In contrast low concentrations of LSD (0.05 to 0.2 γ/l) facilitate the effects of serotonin and of mescaline on the rat uterus.

1. Twarog, B. M., and Page, I. H., *Am. J. Physiol.*, 1953, v175, 157.

2. Amin, A. H. T., Crawford, B. B., and Gaddum, J. H., *Abst. Montreal, XIX Intern. Physiol. Congress,* 1953, p671.

3. Bacq, Z. M., Fischer, P., and Ghiretti, F., *Arch. Internat. Physiol.*, 1952, v60, 154.

4. Welsh, J. H., *Fed. Proc.*, 1954, v13, 162.

5. Erspamer, V., *Pharmacol. Rev.*, 1954, v6, 425.

6. Shaw, E., and Woolley, D. W., *J. Pharmacol.*, 1954, v111, 43.

7. Cerletti, A., and Berde, B., *Experientia,* 1955, v11, 312.

8. Herxheimer, H., *J. Physiol.*, 1955, v128, 435.

9. Gaddum, J. H., and Hameed, K. A., *Brit. J. Pharmacol.*, 1954, v9, 240.

10. Evarts, E., Quoted by Erspamer, V.(5).

11. Cerletti, A., and Rothlin, E., In press, Macy Foundation (Neuropharmacology, II Transaction).

Received November 7, 1955. P.S.E.B.M., 1956, v91.