a close correlation between activities in this and uterine growth test.

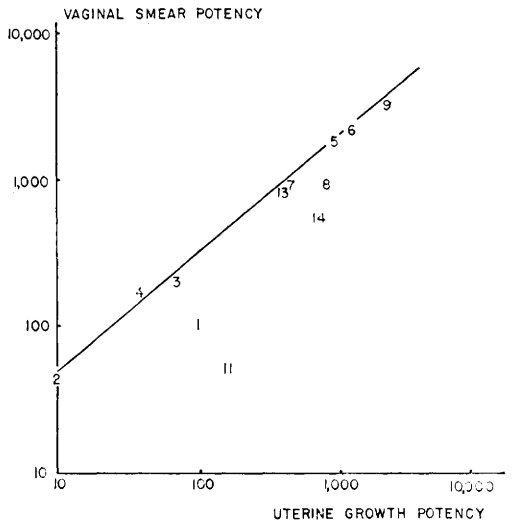

FIG. 1. Relationship of estrogen antagonistic potency in vaginal smear and uterine growth tests. Numbers refer to code numbers of Table I.

Summary. 19-Nortestosterone derivatives are antagonists of estrone in vaginal smear as well as uterine growth tests. Structure-activity relationships among these materials are largely the same in both tests.

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Suppression of LSD-25 Effects in Rats by Steroids.* (26073)

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Unpublished evidence by Resnick in our laboratories indicates that the effects of lysergic acid diethylamide (LSD-25) on smooth muscle contraction in an *in vitro* system may be altered by addition of steroid substances to the bathing medium of the muscle. This apparent antagonism is interesting to us because LSD-25 and steroids are known to affect the function of the central nervous system. Thus LSD-25 in small amounts produces a transient psychotic episode in man(1) and behavioral changes in animals(2). Likewise the balance of steroid hormones may alter mental function, *e.g.*, abnormal behavior may be seen both with adrenal insufficiency (Addison's disease) as well as excess (Cushing's disease)(3). Severe adrenal insufficiency in man is accompanied by a slowing of the electroencephalogram which is restored by cortisone(4). We have noted that adrenalectomy produces a significant decrease of approximately 10% in the dominant EEG frequency in rats and that this condition is corrected not only by most adrenal steroids but by the steroid hormone precursor Δ^5-pregnenolone as well(5). Δ^5-Pregnenolone has been shown to increase the efficiency level of a group of highly skilled motivated workers significantly above a similar group receiving placebos(6).

It occurred to us that investigation of the effects of steroids against behavioral changes produced by LSD-25 might show that steroids are effective anti-LSD agents *in vivo* as well as *in vitro*.

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Materials and methods. The Winter and Flataker rat climbing time procedure was used as the bioassay method for this study (7). Young male Holtzman rats receiving limited food rations are taught to climb a vertical rope 5 ft. high for a food reward. Rats, when placed on a platform near the base of the apparatus learn to run quickly up the rope to a second platform containing dishes of food. After feeding for approximately 10 sec., the rats are returned to the cage. Well trained rats climb the rope in 2-4 sec., and this process can be repeated many times throughout the day with no evidence of decrement in performance as measured by the climbing time(8).

Compounds studied include the adrenal corticoids: desoxycorticosterone (DOC), dehydrocorticosterone, corticosterone, 11-desoxycortisol, cortisone and cortisol, the androgen and androgen metabolites: testosterone, Δ^4-androstenedione, androsterone, dehydroisoandrosterone and etiocholanolone, an estrogen: estradiol, and the C_{21} compounds pregnenolone, progesterone and pregnandiol.

One mg quantities of steroids contained in a vehicle of 25% propylene glycol and 75% physiological saline were injected intraperitoneally for 3 days prior to administration of LSD-25. On the test day the rats were injected with the steroid 1.5 hr prior to intraperitoneal administration of 40 γ LSD. Control rat groups received a similar series of injections of vehicle alone prior to LSD-25 administration. Climbing times for each rat were then obtained at intervals of 5, 10, 20, 30, 45 and 60 min. post injection in an alternating sequence. The performance of each animal injected with a steroid was compared with the performance of a vehicle injected rat. No difference has been noted between response to LSD of rats injected with vehicle and non-injected rats. Usually the group contained 5 rats each. Statistical evaluations were made using Wilcoxon's method for paired replicates(9).

Results. The effect produced by injection of 40 γ LSD-25 on climbing time is shown in Fig. 1. LSD-25 is rapidly absorbed and leads to a sharp rise in climbing time which reaches a maximum in 5-15 minutes followed by a slower return to normal climbing time. Evidences of LSD-25 action may still be apparent after 60 minutes but generally the effect has subsided (Fig. 2).

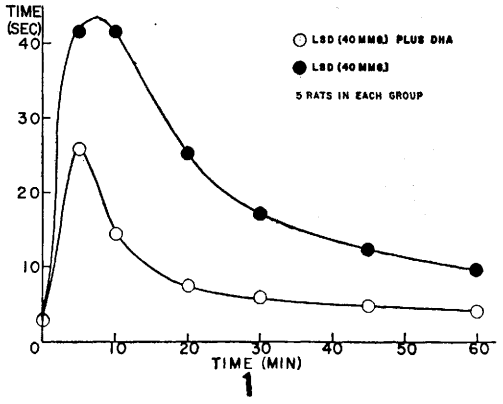
Injections of steroids alone during the 3 day pretreatment period produce no observable changes in climbing time. Mean values plotted in Fig. 1 and 2 for climbing times of a group of 5 rats treated with a steroid and a comparable group injected with the vehicle alone show no differences; pretreated and untreated groups have identical climbing times prior to LSD-25 administration.

Fig. 3 shows ratings of the various steroids tested for ability to suppress the action of LSD-25. Levels of statistical significance range from .05 to $<.001$.

Discussion. The ability of the steroids tested to suppress the LSD-25 effect in rats does not appear to be related to any specific molecular configuration. C_{19} compounds are as effective as C_{21} compounds under the test conditions employed. The negative results obtained with the single C_{18} steroid tested should not militate against the view that other C_{18} steroids may possess anti-LSD-25 activity. Presence or absence of hydroxyl or ketone groups in the molecule does not appear to be related to this activity. Likewise no correlation is evident between hormonal action or potency and anti-LSD-25 action.

The experiments with progesterone and LSD-25 in rats have been extended to a pilot human double blind study to be reported elsewhere. Briefly, 12 male volunteers were subjected to a battery of psychological tests found to be sensitive to LSD-25 in a previous study by Krus and Wapner(10). The test situation was designed to sample sensory-motor, perceptual and conceptual behavior. The results indicate that progesterone counteracts the effects of LSD-25 in some but not all of these tests, and that counteraction is not associated with a single behavior area: aberrations in all 3 behavior areas were corrected.

The mechanism of the action of steroids in rats and in humans has not been determined. The purpose of this study has been to screen



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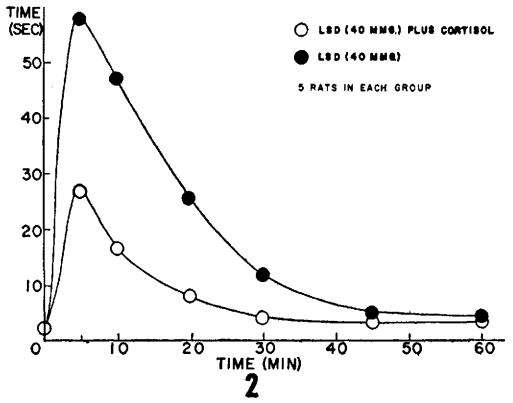

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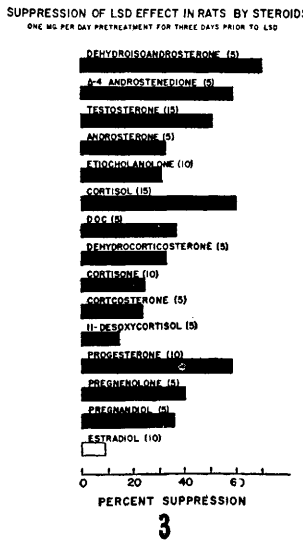

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FIG. 1 and 2. Effect on rope climbing time of rats inj. with LSD alone and in rats inj. with 1 mg dehydroisoandrosterone (DHA), Fig. 1, and cortisol, Fig. 2, for 3 days prior to LSD inj.

FIG. 3. Suppression of LSD effect on rat climbing time by steroids determined by comparison with an identical group of rats tested with LSD alone and tested simultaneously with each drug inj. group. Numbers of rats in each drug group shown in parentheses. An equal number of controls were used. Statistical significance denoted by solid bars, non-significance by open bar.

steroid substances for possible anti-LSD-25 effects. Future experiments will determine dose-response relationships for LSD-25-steroid interaction to obtain quantitative comparisons of the various steroids.

Summary. A series of 15 steroid hormones and metabolites were tested for their effectiveness to suppress LSD-25 induced behavior changes in rats. All produced significant suppression ($p<0.05$) except estradiol. Ability to suppress LSD-25 action does not appear to be related to specific molecular groups or to hormonal potency.

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