31.25% ($P<.001$) and 43.75% (P .001) in 2 separate experiments. There was no evidence of glycyrrhetinic acid toxicity.

Uterotrophic response of immature rats to endogenous steroids.

Glycyrrhetinic acid did not antagonize the uterotrophic response to endogenous sex steroids regardless of the source of gonadotropins or the dose. Six and 16 mg of glycyrrhetinic acid was not anti-estrogenic in immature female parabiont recipients nor PMS stimulated animals. However, 16 mg produced a 16.78% increase ($P<.01$) in uterine weights of the parabiont recipients but not the PMS stimulated animal. There was no apparent increase in ovarian weight.

Discussion. The estrogen antagonism with glycyrrhetinic acid does not depend upon gonads nor adrenals(1), but does appear to depend upon the presence of the hypophysis. The anti-hysterotrophic action is restricted to exogenous estrogens, but the anti-estrogenic effect is not limited to the uterine target organ. The vaginal mucosa is less sensitive than the uterus to the estrogen antagonism and the minimum effective ratio of drug to estradiol benzoate was 5 times the minimum anti-hysterotrophic ratio(1).

The lack of antagonism of endogenous steroids may infer that the mechanism of action of glycyrrhetinic acid lies in interference with absorption or metabolism of exogenous estrogen rather than through altering target organ response. This effect may be mediated through the hypophysis.

Augmentation of the uterotrophic response of female parabionts may have been due to a pituitary-adrenal inhibition during prolonged drug administration such as has been observed with glycyrrhizin(3,4). This lowering of the adrenal cortical hormone level can augment the estrogen response(5). However, the adrenal cortical hormone level of the PMS stimulated rat may not have been changed due to the effect of PMS on the adrenal gland itself(6).

Summary. Beta glycyrrhetinic acid restricted the response of the female accessory reproductive tract to exogenous steroidal estrogens (estradiol benzoate, estrone and estriol). It antagonized the uterotrophic and vaginal estrous response of ovariectomized rats to estradiol benzoate, but had no effect in hypophysectomized rats. It did not interfere with the response to other exogenous uterine stimulating steroids nor to endogenous steroids. High doses of glycyrrhetinic acid, increased the uterine response of immature parabiont recipients though similar doses had no effect in the PMS stimulated animal.

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Chlorpromazine Inhibition of the Positive Intermediary Potential.* (27094)

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Gasser and Graham(1) described a positive potential of long duration recorded from spinal cord. They termed this the positive intermediary potential and associated it with alterations in the central excitatory state. Using different technics, Lloyd and McIntyre (2) reinvestigated the positive intermediary potential and found that it resulted from an increased negativity which originated in secondary neurons of the spinal cord as a resid-

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TABLE I. Mean Amplitudes of Positive Intermediary Potentials (DR V) after Injection of Chlorpromazine Hydrochloride in Decerebrate Cats. Values of the potentials are expressed as % of pre-drug controls. Doses of chlorpromazine represent avg of cumulative amounts given.

	Exp. group	No. of animals tested	Dose CPZ (mg/kg) mean and range	DR V (% of control amplitude) mean ± S.D. and range
I	Spinal cord intact	5	4.57 (1.75-12.5)	68.6 ± 3.8 (38-84)
II	Lumbar 1 section	11	4.25 (1.0 - 9.0)	61.7 ± 6.8 (0-92)

ual alteration of membrane potential. These authors, recording from a dorsal root, renamed this potential DR V.

A previous report from this laboratory(3) and others(4,5,6) showed that chlorpromazine is capable of inhibiting spinal reflexes in the decerebrate cat, although Preston(7) did not observe this same phenomenon. DeMaar *et al.*(8) concluded that chlorpromazine produces a selective depression of the frequency response of the reticular formation to stimulation of the sciatic nerve. These observations would indicate that chlorpromazine depresses the fidelity with which the central nervous system can respond to peripheral stimuli, and that these changes might be reflected in alterations of the positive intermediary potential of spinal cord.

Method and materials. Sixteen decerebrate cats were used. Of these, 11 had spinal cord transections of the lumbar (L1) level. The technics used to study the positive intermediary potential were essentially those of Lloyd and McIntyre(2). A complete description has been given elsewhere(9). Briefly, it consists of stimulating a dorsal spinal rootlet and recording the electrotonic current flow in an immediately adjacent dorsal rootlet. Conventional electrophysiological technics were used. Stimuli were biphasic and maximal. They were maintained constant for the duration of the experiment at a frequency of 0.5 per second.

Cats were decerebrated under ether anesthesia which was discontinued at least one hour prior to initiation of the experiment. The experiment was started only after the positive intermediary potential had been seen to remain constant for at least 30 minutes. Blood pressure was monitored from the femoral artery in the absence of any anticoagulant. Respiration was noted, but not measured. Chlorpromazine was administered in divided doses *via* a polythene cannula inserted in the femoral vein.

Results. Immediately after injection of chlorpromazine there was an increase in the positive intermediary potential which lasted for about 2 minutes. This change in amplitude correlated with a fall in blood pressure. The blood pressure and positive intermediary potential returned to control values simultaneously.

When adequate doses of chlorpromazine were given, the initial increase in amplitude of the positive intermediary potential was followed by a decrease (Table I, Fig. 1). The decrease lasted at least 30 minutes, and was continuous with the previous increase in amplitude. After the decrease in amplitude there was no further change, *i.e.*, any change that took place, did so in the first 10 minutes and lasted more than 60 minutes. There were no consistent changes in respiration or blood pressure that could account for the prolonged alterations in positive intermediary potential. The same results were obtained in both decerebrate and decerebrate-spinal cats.

Discussion. These data show that chlorpromazine causes an initial increase of the positive intermediary potential, followed

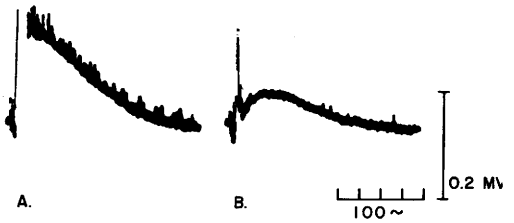

FIG. 1. Trace A illustrates the qualitatively typical positive intermediary potential during control period. Chlorpromazine, 4 mg/kg, was then inj. Trace B indicates this positive intermediary potential 5 min. after inj.

after sufficiently large doses by a fall in positive intermediary potential. Since the enhancement correlates well with changes in blood pressure it is probably secondary to cardiovascular changes. The depression, however, would appear to be due to an action of the drug directly on the spinal cord since it was not correlated with alterations in blood pressure. Furthermore, it would not appear to be due to an action of the drug higher in the neuraxis since it was found in both decerebrate and decerebrate-spinal cats.

The inhibitory action of chlorpromazine on the positive intermediary potential described here probably does not account for the depression of spinal reflexes described previously(3,4,5,6). The reason for this conclusion is 2-fold. First, the dose of chlorpromazine necessary to inhibit the positive intermediary potential is much greater than that required to inhibit the spinal reflex. Second, whereas the reticular formation would appear to be necessary for the actions of chlorpromazine on spinal reflexes it would not appear to be necessary for the actions of chlorpromazine described here.

The observations reported here may explain those of DeMaar *et al.*(8) that chlorpromazine inhibits activation of the reticular formation by stimulation of the sciatic nerve. This correlation would be based on the relation between the positive intermediary potential and excitability of the spinal cord(1,10) and the fact that the dose of chlorpromazine required to depress the positive intermediary potential is approximately that required to inhibit activation of the reticular formation. Obviously, these data do not preclude the existence of chlorpromazine action higher in the neuraxis, or that such action may better explain DeMaar *et al.*'s observations. On the other hand, even if this is the case, the action of chlorpromazine on a spinal level may indicate the mechanism of its action higher in the neuraxis.

Summary. It was found that intravenous injection of chlorpromazine produces an initial brief period of enhancement of the positive intermediary potential of the cat's spinal cord. This is followed by a prolonged period of depression of the positive intermediary potential. The period of enhancement is probably associated with alterations in blood pressure. The period of depression would appear to be due to a direct action of chlorpromazine on the spinal cord.

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Mechanism of the Antidiuretic Action of Reserpine.* (27095)

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Antidiuresis has been reported to follow the administration of several agents which depress the central nervous system(1), such as reserpine(2,3) and chlorpromazine(4). The reports have suggested that, subsequent

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