jected with the 2 lower doses of reserpine may result from an increased deposition of fat which may occur during a hypothyroid state.

Summary. Reserpine at doses of 5, 10 or 50 μg/100 g/day inhibits thyroid activity in rats. Thyroidal I^{131} output is decreased significantly and thyroid secretion rate is reduced approximately 84-90% below control values. It is suggested reserpine alters thyroid function through inhibition of thyrotropin secretion.

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Effect of Meprobamate on Limbic System of the Brain. (24743)

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During an investigation relating to site of action of meprobamate(1) recordings of brain waves from various cortical and subcortical leads were studied. Spontaneous potentials picked up from thalamus are slowed in frequency and increased in amplitude after administration of small doses of the drug. Larger doses caused similar changes in cerebral cortex but did not affect potentials in the hippocampus, fornix, amygdala and other limbic structures(2). The present study describes effects of meprobamate upon seizure discharges initiated by direct stimulation of the limbic system and upon activation patterns produced by stimulation of the reticular formation.

Methods. Twenty-five adult male cats were prepared under ether anesthesia. Bipolar electrodes were placed stereotaxically in midbrain reticular formation, hippocampus, amygdala, anterior thalamic nuclei, septum and gyrus cinguli, and cortical electrodes were introduced through cranial burr holes. Wound margins and pressure points were infiltrated with xylocaine, the animals immobilized with succinylcholine given intravenously by a slow injection apparatus. Respiration was maintained with respiratory pump. At least one hour was allowed for elimination of ether before start of experiment. Recordings were taken with Grass electroencephalograph, Model IIID, and AEL 104 stimulator supplied the trains of rectangular pulses used. At end of each experiment the brain was removed and electrode positions verified.

Results. The limbic system was stimulated in 2 ways; directly and indirectly. Direct stimulation (1 msec pulse; 150/sec. 4-10 volts; 5-7 sec.) of the hippocampus produced high voltage afterdischarges which usually persisted for 35-50 seconds. These afterdischarges almost always spread to other limbic structures and ended simultaneously and abruptly in all leads. Duration of these elec-

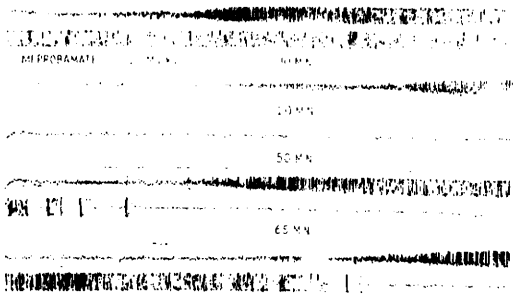

FIG. 1. Effect of meprobamate (20 mg/kg) upon duration of afterdischarges produced in the hippocampus by local stimulation. Control record prior to drug administration and subsequent records 10, 20, 50 and 65 min. after administration of meprobamate 20 mg/kg. Each tracing begins at end of stimulation period.

trical seizures was quite consistent for each animal but showed some variability between different animals. After several consecutive, consistent responses had been obtained, drugs were injected and the stimulation repeated. Meprobamate in doses as small as 20 mg kg i.v. usually attenuated the afterdischarges by one-half or more. Larger doses produced an even greater reduction in duration of afterdischarges observed. Sometimes the seizure was completely suppressed.

An experiment is illustrated in Fig. 1. Prior to administration of the drug, afterdischarges from the hippocampus and amygdala persisted for 54 seconds. Ten minutes after administration of the drug, afterdischarges were reduced in duration to only 18 seconds and failed to appear when stimulation was repeated 10 minutes later. Fifty minutes after administration of meprobamate, afterdischarges, although present, were still markedly shorter in duration than before the drug. Recovery gradually became apparent about an hour after administration of drug. Responses produced by stimulation of the amygdala seemed to be somewhat more sensitive to the effects of meprobamate than the hippocampus.

Electrical stimulation of midbrain reticular formation (0.5 msec pulse; 150/sec; 3-4 volts; 5-7 sec) produced an arousal response and activation pattern in the electroencephalogram characterized by 5/sec high voltage waves in the hippocampus. At the same time high frequency, low voltage rhythm was produced in recordings from the cerebral cortex. Administration of meprobamate in doses of 20 mg kg did not affect this activation response. Larger doses of the order of 40 mg/kg produced only insignificant changes. Barbiturates, on the other hand, suppressed activation in both cerebral cortex and hippocampus as well as afterdischarges in accordance with previous reports(3,4,5).

Discussion. Meprobamate exerts a selective effect upon the limbic system of the brain. This has been previously shown on a behavioral level by Hunt(6) who demonstrated that meprobamate dramatically offset septal irritability in rats. Gangloff(7) has shown that meprobamate does not affect cortical activation responses elicited by stimulation of the reticular formation. Our findings demonstrate that this is also true for hippocampal activation. Meprobamate sharply attenuates afterdischarges in various rhinencephalic areas. This selective effect of meprobamate stands in contrast with the action of barbiturates that suppress both arousal responses in limbic structures and cortex and afterdischarges in limbic structures.

The findings that meprobamate can suppress abnormal activity in the limbic system, known to be intimately associated with emotions(8,9) while leaving unaffected the midbrain reticular formation associated with maintenance of consciousness(10) may provide a neurophysiological substrate for clinical effects of this drug.

Summary. Meprobamate shortened duration of afterdischarges produced in the limbic system of unanesthetized, immobilized cats The drug, however, did not affect the activation patterns evoked in the hippocampus and cerebral cortex by stimulation of midbrain reticular formation.

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Procedure for Detection of Thyrotropin Inhibitor in Human Urine.* (24744)

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A thyrotropin (TSH) inhibitor prepared from human urine has been described(1). This material was shown to repress response to TSH of guinea pig acinar cell height and chick thyroid weight. This paper presents an alternate procedure and further evidence for its presence. Adapting intravenous TSH assay technics(2-5) to the intracardiac route in chicks(6), there was a simplification of TSH-inhibitor assay which was consequently shortened from 2 to 4 days to 4 hours.

Methods. Day-old White Leghorn cockerels are given on arrival at the laboratory an intraperitoneal dose of 5 to 10 microcuries of I^{131} in 0.2 ml saline. A partly purified diet (iodine salts omitted), containing 0.1 mg% of Na-L-thyroxine,† and distilled water supplied *ad lib*. The chicks were screened 3 days later by comparing relative I^{131} uptakes of neck thyroid region (which varied from 4 to 38%) and then distributed into groups. Chicks with I^{131} uptake values of 10 to 13% were used the following day, those with 14 to 19% the next day, and those with 20 to 25% on the next and final day. Food was withdrawn 20 hours before chicks were placed on assay and cockerels distributed into groups of 10. It is of utmost importance that chicks in an assay be equally distributed, balancing in each group the variation in I^{131} uptakes. Determination of blood I^{131} prior to assay was unnecessary since each group had the same distribution of chicks with matched I^{131} uptakes. A solution of inhibitor preparation in 1 ml saline is injected intraperitoneally and one hour later TSH was injected at a different site intraperitoneally or as an intracardiac dose in 0.1 ml of saline. At 4 hours post-injection of inhibitor, aliquots of 0.2 ml of blood were removed by intracardiac puncture with a 3/8 inch #24 needle and dried on aluminum planchets. Blood radioactivity was measured with an end-window-shielded Geiger Tube and Autoscaler (Model SC-lb, Tracerlab). In each assay the blood level I^{131} counts/minute due to highest test dose of TSH reference standard were referred to as 100%; responses to other doses were expressed as per cent of this maximum response. Deviations in blood I^{131} values following TSH stimulation within each group were great, but differences between average values for the groups were significant when using adequate variable TSH doses. After completing assays on chicks with 10 to 13% I^{131} uptakes, seasonal sensitivity to TSH was determined and doses of TSH elevated or decreased to determine seasonal minimal significant dose.

Results. Factors affecting TSH-inhibitor assay. Optimal time interval for assay was determined by selecting an intermediate TSH dose (2 milliunits‡) for intraperitoneal injection, and removing blood samples by intracardiac puncture from chicks with similar I^{131} uptakes at intervals of from 0.2 to 6 hours (Table I). Peak response occurred at 3 hours. Four dose levels were compared using chicks from the same lot and tested simultaneously. The response to 0.75 milliunit of TSH, which

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† Generously supplied by Baxter Labs, Morton Grove, Ill.

‡ This assay, performed in March, represents procedure at its seasonal best.