nated eggs that are passed in the urine are immediately infective. Contaminated cages, unless washed thoroughly with sufficiently hot water, can cause a large proportion of a colony to become infected.

A report by Chapman (*3*) indicates that infection with *T. crassicauda* may increase the incidence of bladder tumors in rats fed the well-known bladder carcinogen 2-acetylaminofluorene. A somewhat dated controversy as to whether *T. crassicauda* is associated, in the absence of exogenous carcinogens, with bladder tumors (*3*, p. 154) need not be invoked.

Thus it would appear desirable that any investigator encountering bladder tumors in rats make a thorough search for this parasite. Methods are available for eliminating the infection and for maintaining a clean rat colony (*4*).

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Reticular Stimulation and Chlorpromazine

Based on the hypothesis that schizophrenics are overaroused as a result of long-term activation of the brainstem reticular formation (*1*), Kornetsky and Eliasson proposed that animals electrically stimulated in the reticular formation are overaroused in a similar fashion (*2*). They postulated an "inverted U" model in which overarousal moves subjects beyond an optimum level of performance and chlorpromazine keeps subjects before the optimum point; therefore the drug reduces the overarousal effects and produces improved performance. They tested their hypothesis on three rats in a test of sustained attention and found fewer errors in performance when intermittent stimulation and chlorpromazine were combined than with either drug or stimulation alone. We have made slightly different tests with rats given chlorpromazine and electrical reticular stimulation and have found similar results at certain doses, but the effect was more marked with a barbiturate combined with stimulation which suggests that the "inverted U" hypothesis is not specific to chlorpromazine.

We used 82 adult male Wistar rats with silver wire electrodes (0.015 cm in diameter) permanently implanted (*3*) in the mesencephalic reticular formation according to the stereotaxic coordinates of de Groot (*4*); experiments were begun at least 1 week after surgery. Square-wave pulses were applied at currents ranging from 25 to 80 μa and at a frequency of 300 hz of 1-msec duration (*5*). At the end of each experiment the animals were killed and the brains perfused for histological examination. The sites of stimulation were in the dorsal lateral area of the mesencephalic reticular formation [A 0.6 to A 2.2 (*4*)].

The first experiment was a maze-running test in which rats deprived of water for 23 hours were taught to run to the end of an arm (35.5 cm long) of a Y-maze to obtain 0.5 ml of water. To get another reward the rats had to run to the end of the next arm of the maze on the right. A manual correction procedure was used in training. In this way rats learned to run a clockwise route around the maze. Errors were scored when rats took the wrong alley, and the total number of entries made gave a measure of general activity. The rats were trained daily, and, when they reached an asymptote level on three consecutive days with the same number of entries ± 2, the test conditions were applied for the following 3 days. Reticular stimulation was given throughout a 5-minute trial session, and drugs were injected 30 minutes before testing. Chlorpromazine was given in doses of 1, 2, and 4 mg/kg, and amylobarbitone in doses of 10, 20, and 40 mg/kg, all subcutaneously. There were 18 saline control animals, 9 of which were stimulated, and 10 rats in each drug dose group, half of which received stimulation. Four rats were eliminated because the electrodes were in the wrong site or because they did not reach the learning criterion. Reticular stimulation significantly reduced activity [$P < .01$ (*6*)] but had no significant effect on the number of errors made. Chlorpromazine produced a decline in activity, but in combination with stimulation there was no significant difference from the nonstimulated condition at a dose of 1 and 2 mg/kg. If we consider the detrimental effect with stimulation alone in the saline group, this result shows a reduction of the stimulation effect. At 4 mg/kg, however, there was a greater decrease in activity when stimulation was given than with the drug alone ($P < .025$). This potentiation of the drug and stimulation is anomalous with the proposed "inverted U" model (*2*). The medium dose plus stimulation was also anomalous in that it produced a significant interference with the accuracy of performance ($P < .025$). The barbiturate alone lowered activity, but in combination with stimulation there was a significant increase in activity above the level produced by the drug alone at all three doses (test of orthogonal contrasts, $t = 2.42$, 1,21 d.f., $P < .05$). The effect seen with amylobarbitone alone on the error score was also offset by the combination of barbiturate and stimulation at a dose of 40 mg/kg ($P < .025$). Thus there was an antagonism between both drugs and stimulation, but the effect produced by the amylobarbitone was greater than that of chlorpromazine.

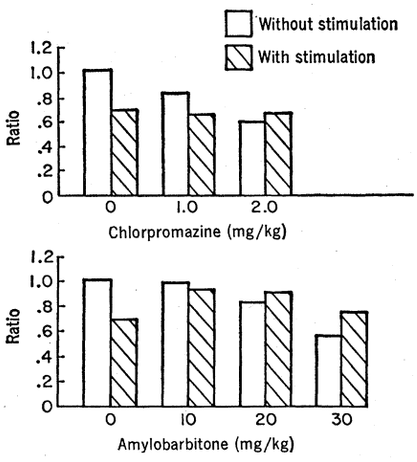

Fig. 1. The effect of drugs and reticular stimulation on discriminated conditioned avoidance responding expressed as a ratio (mean) of the test performance to the criterion performance level.

The next experimental test was set up to require little response activity but to be more a test of accuracy. A discriminated, operant-conditioned avoidance response to a flashing light was established in four rats. At the beginning of a trial the conditioned stimulus (CS) was presented. If a subject pressed the lever within 10 seconds, shock was avoided; if the lever was

not pressed, shock was delivered at 10-second intervals until a press occurred. Pressing the lever changed the CS to a nonflashing light, and a 50-second intertrial interval was timed out. The shock was short (0.3 seconds) and sharp (0.2 to 0.5 ma) (*7*). Electrical reticular stimulation was presented at random in 1- to 2-second trains during the last half of a 60-trial test session. The results were calculated as the percentage of avoidance responses in the last 30 trials. Chlorpromazine was given in doses of 1 and 2 mg/kg and amylobarbitone in doses of 10, 20, and 30 mg/kg, all intraperitoneally administered immediately before the test. Each rat was used as its own control and underwent all treatments with a rest period of at least 3 days between doses and 1 week between drugs (*8*). Two days before each test a control trial was run to establish the rate of responding.

Stimulation alone reduced the number of correct responses ($t = 5.91$, $P < .01$) (Fig. 1). Chlorpromazine alone resulted in lower performance, but, at the dose of 1.0 mg/kg, stimulation counteracted the decrement and at 2 mg/kg there was even a slight, though nonsignificant, improvement with stimulation over the unstimulated condition. Amylobarbitone also produced a decrement with increasing dose, but there was a significant interaction with stimulation ($P < .05$).

Chlorpromazine can offset the effects of direct reticular stimulation (*2*) but the antagonistic effects are even more pronounced when a barbiturate is combined with stimulation. This casts doubt on the specificity of chlorpromazine in the "inverted U" hypothesis. Also chlorpromazine (4 mg/kg) and stimulation potentiated their effects in reducing activity. This suggests that there is not a simple nonmonotonic function relating chlorpromazine effects with arousal. It has been proposed that chlorpromazine has an action related to the sensory input (*9*), and it has been further suggested that the drug facilitates the selection of stimuli which might be deemed the most significant to an organism (*10*). This leads to a lowered rate of responding but responses are made to "significant" stimuli. In the present context this might lead one to suggest that where chlorpromazine is most effective—as in confused, hallucinated, or agitated patients—there is an impairment in sensory evaluation and chlorpromazine facilitates the process of assessment, rather than altering a state of overarousal per se.

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Phillips and Bradley have presented data suggesting that our results (*1*) are correct. Stimulation of the mesencephalic reticular formation or treatment with chlorpromazine impaired the performance of rats trained on a test of attention, and the two treatments together resulted in performance no different from that seen after saline alone. However, they argue that because in their experiments barbiturate effects are also antagonized by reticular stimulation and because barbiturates are not useful in treating schizophrenics our model is not tenable.

Although there are a number of differences in the details of the procedure used by us and that of Phillips and Bradley, there are major differences in the behavioral tasks. Phillips and Bradley used three procedures—locomotor activity, a simple maze, and a conditioned avoidance task. The central factor missing in the Phillips and Bradley experiment that was present in our experiment was a procedure that is analogous to a procedure in which some schizophrenic patients show impairment as compared to normal subjects (*2*). Long-term administration of chlorpromazine to these schizophrenic patients results in improved performance on this test, while not significantly altering performance on a simple test of cognitive ability. Also our behavioral procedure discriminates between the effects of barbiturates and chlorpromazine (*3*).

We have done some preliminary experiments on barbiturates and reticular stimulation on the performance of rats, and we do not find that barbiturates antagonize the deficits caused by reticular stimulation.

We are not denying the interpretation of Bradley (*4*) that chlorpromazine reduces sensory input and that barbiturates, at least in the *encéphale isolé*, decrease behavioral and electroencephalographic arousal at cortical levels to reticular stimulation. We did not state in our paper, as Phillips and Bradley imply, that we were talking about all schizophrenics, nor did we say that all schizophrenics respond to phenothiazine drugs. We said that in some schizophrenic patients there is a putative central hyperarousal which is the result of the inability of the reticular system to adequately inhibit incoming stimuli, be they internal or external. This results in the patient's inability to focus attention and leads to a deficit in performance on an attention task. There are differences between barbiturates and chlorpromazine action on the arousal system, and our data simply state that we have a model for the attentional deficit seen in some schizophrenic patients.

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