by the animals with the angled mammillary body lesion is likely due to the electrode track piercing fibers in this area.

The region of the zona incerta has intimate connections with the globus pallidus and extrapyramidal structures. In this connection Brady and Conrad (*4*) have already shown that when monkeys work for electrical stimulation of the globus pallidus on a reinforcement schedule where responses must be spaced 20 seconds apart, there is a marked shifting in the interresponse times towards the shorter time periods. This is fairly well localized, since electrical self-stimulation in other structures does not produce a comparable effect. These observations raise the possibility of the significance of extrapyramidal or basal ganglia structures in behaviors where temporal factors play a mediating role.

The observations presented in this report, together with our previously reported findings concerning the septum and hippocampus, de-emphasize the contribution of rhinencephalic structures to the temporal patterning of behavior. Moreover, it is suggested that the functional system principally involved in the temporal patterning of behavior appears to be extrapyramidal, as evidenced by the present results implicating the zona incerta, and the results of others implicating the globus pallidus (*5*).

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26 June 1963

Acetophenazine and Fighting Behavior in Mice

Abstract. *Assuming fear to be a variable of importance in the inhibition of aggressive behavior, we used acetophenazine to try to facilitate fighting in mature male C57BL mice. Drugged pairs did not differ significantly from controls in fighting latency; however, the time lapse from the first fight to submission and the actual fighting time to submission were significantly longer for drugged pairs. An attempt is made to relate what is known of the action of the drug with research on the neural correlates of aggressive behavior.*

A number of studies can be interpreted to support the hypothesis that fear is an important inhibitor of aggression. Hall and Klein (*1*) found that nonemotional rats were markedly more aggressive than an emotional strain. Seward (*2*) has emphasized "the conditioning of fear to stimuli associated with the fighting" in the reduction of aggression in male rats. King (*3*) observed long fighting-response latencies in mice raised in social isolation and concluded that they likely resulted from some inhibitory mechanism due to the strangeness of the social situation. Previous work by Knight (*4*) has indicated that rats which were raised in social isolation from weaning showed both physiological indications of stress and fought less when first caged together as adults.

Hess's success in extending the imprinting period by reducing fear with a phenothiazine (*5*) suggested to us that fighting behavior might also be facilitated by reducing the emotional response of laboratory mice with such a drug. Acetophenazine dimaleate (*6*) was selected because it was the most recently introduced phenothiazine derivative.

The phenothiazines depress the midbrain reticular formation, diminishing alertness. They also increase recruitment, that is, the sleep pattern mediated by the thalamocortical fibers, thus further diminishing alertness.

Both effects are additive and together tend to reduce emotional responses to stimuli. The phenothiazines depress the sympathetic function of the hypothalamus and also appear to block the action of the neurohormones, serotonin and noradrenaline (*7*). These drugs do not appear to affect the neocortex or the learning process (*8*). In our laboratory acetophenazine has been shown to reduce the rate of bar pressing for water by rats on a variable ratio schedule, without affecting acquisition (*9*).

It is hypothesized that if fear is an inhibitor of fighting, and if acetophenazine reduces fear without other significant effects upon behavior, acetophenazine is an agent which increases or prolongs fighting behavior.

Sixty-four male mice were used from the C57BL stock of Rockland Farms, New City, N.Y. Animals had been obtained at 8 weeks of age and caged in such a way that no subject could see another mouse.

The fighting cages consisted of a series of wire and wood-frame compartments about 30 by 15 by 15 cm. These compartments were arranged in a double row so that when a guillotine partition between two compartments was removed for the actual contest, each cage was about 61 by 15 cm. Food and water were available at all times.

When the mice were 10 to 12 weeks old, they were randomly paired and assigned to either the drug or the control treatment. On the fourth day after being placed into the contest cages, the mice were weighed and injected. Experimental pairs received 2.4 mg of acetophenazine per kilogram (*10*) and control pairs were injected with saline. All animals were injected subcutaneously with 0.1 ml of solution per 10 g of body weight.

One hour after injection the paired contests were undertaken and the following three measures recorded: (i) latency of the first fight; (ii) time lapse between the onset of the first fight and the first submissive posture of one member of the pair (latency to submission); and (iii) total time during which the mice were actually engaged in fighting before the first submission (duration of fighting). This final measure was not available on four of the total 160 pairings, owing to a failure in the timing device. A fight was said to have taken place when aggressive contact involving nipping occurred. Tail rattling and other threats were not recorded. It was assumed that both members of a pair were aggressive until a clear submission by one of the mice had occurred. The submissive posture is a stereotyped response which is easily recognizable and has been illustrated by Scott (*11*). Two observers were present for all contests, and in no instance did they disagree as to the response

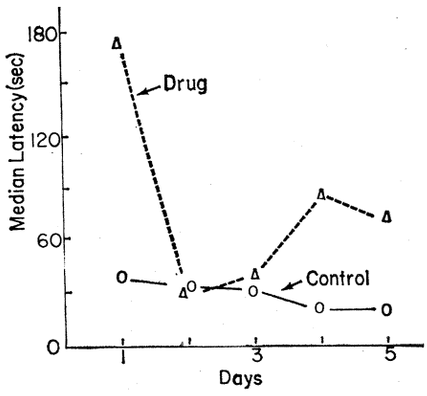

Fig. 1. Median latencies to the first fight for drugged and control pairs on five consecutive days of contests.

which had occurred. The contest was terminated when the first submissive posture occurred or at the end of 15 minutes.

This procedure was repeated on five consecutive days with mice being injected daily and fought in the same pairs 1 hour later. The data were gathered in four successive replications.

Not all of the 16 pairs of subjects in each treatment fought in the 15-minute contests. On the first day 12 of the drugged pairs and 10 of the control pairs fought. On the third day one member of a drugged pair and one member of a control pair died before injection. By the fifth day 12 of the remaining 15 drugged pairs and 11 of the 15 remaining control pairs had fought.

Although no attempt was made to quantify general activity, it was observed that general locomotor activity was markedly reduced in drugged animals.

From the hypothesis that mice with fear reduced by drugs would show increased aggression, it was predicted that experimental pairs would have shorter fighting latencies. Figure 1 fails to confirm this prediction. In general, the differences appear in the opposite direction. If a two-tailed Mann-Whitney U test is applied to the data for each day, none of the differences reach the .05 level of significance.

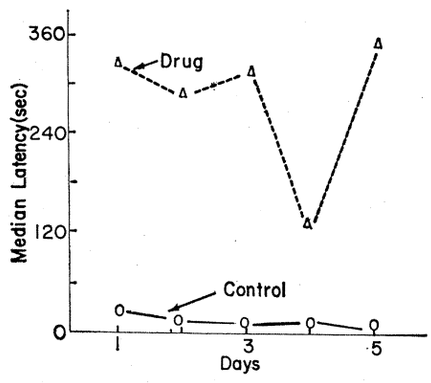

Fig. 2. Median latencies to submission from the onset of the first fight for drugged and control pairs on five consecutive days of contests.

The other two measures provide highly significant differences in the direction predicted. The median latencies to submission for experimental and control pairs on the five consecutive days are presented in Fig. 2. The two treatments differed beyond the .001 level on days 1 through 4 and at the .01 level on the fifth day (one-tailed Mann-Whitney U). The medians of the actual fighting durations, as measures of aggressive response level, are shown in Fig. 3. The drugged and control pairs differed at the .025 level on the first day and at the .001 level on each of the four remaining days.

The failure of the drugged pairs to demonstrate a higher level of aggressiveness as measured by the latency of the first fight could be attributed to the reduction in general activity level which was observed. The general exploratory behavior of the experimental subjects was less than that of control subjects, and thus reduced the social exploration which normally precedes fighting. Once fighting began drugged pairs fought more continuously and longer than control pairs, as indicated in the other two outcome measures.

Hess (*12*) has shown by electrical stimulation that there are independent areas in the hypothalamus for attacking and fleeing. Presumably, these separate centers stimulate different neurohormones and are physiological correlates of states which are commonly referred to as anger and fear. Lesions in the septal region increase aggressive responses while lesions in the amygdaloid area eliminate aggression in rats (*13*). There is some suggestion that the hypothalamus is inhibited or excited by the two regions, respectively.

In view of these generalizations as to the neural mechanisms of aggressive behavior and the observation that acetophenazine prolongs fighting, one might suspect an important subcortical locus of the drug's activity to be the septal region or, more directly, Hess's "flight" center in the hypothalamus, or both. Of course, such inferences are speculative and simply suggest further work.

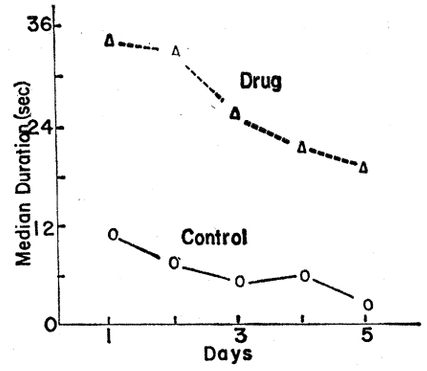

Fig. 3. Median duration of fighting before submission for drugged and control pairs on five consecutive days of contests.

The findings of the present study would seem to conflict with those of Walaszek and Abood (*14*), who report the suppression of pugnaciousness in Siamese fighting fish by a phenothiazine derivative. The difference between the effects on fish and on mice may reflect a phylogenetic difference in the subcortical neural organization of the two species.

These drugs may have a greater specificity of action at the mammalian level, affecting only the inhibitory centers for fighting. Perhaps these conflicting results can be explained more simply by a difference in dosage. Since Walaszek and Abood indicate a "strong depression" of general action in the fish, the lack of fighting may have been an artifact of this more general outcome (*15*).

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26 June 1963