

THE EFFECT OF CHLORPROMAZINE ON  
AVOIDANCE LEARNING IN RATS

APPROVED:

*Jack R. Hayner*  
Major Professor

*Earl W. Koehler*  
Minor Professor

*Twane Kinger*  
Dean of the School of Education

*Robert B. Toulson*  
Dean of the Graduate School

THE EFFECT OF CHLORPROMAZINE ON  
AVOIDANCE LEARNING IN RATS

THESIS

Presented to the Graduate Council of the  
North Texas State University in Partial  
Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

Thomas Carl Fain, B. S.

Denton, Texas

January, 1968

## TABLE OF CONTENTS

LIST OF TABLES . . . . .	Page iv
Chapter	
I. INTRODUCTION. . . . .	1
II. METHOD. . . . .	19
Subjects	
Apparatus	
Procedure	
Injections	
III. RESULTS . . . . .	24
IV. DISCUSSION. . . . .	27
V. SUMMARY AND RECOMMENDATIONS . . . . .	34
APPENDIX . . . . .	36
BIBLIOGRAPHY . . . . .	37

## CHAPTER I

### INTRODUCTION

Chlorpromazine and other tranquilizing agents have been recommended for the treatment of behavior disorders and the management of anxiety. In an attempt to evaluate drug effects on specific behaviors many investigators have explored the effects of acute chlorpromazine administration on lower animals. Particular attention has been paid to responses motivated by fear or anxiety. Results of several studies involving avoidance conditioning in rats indicate that chlorpromazine disrupts the acquisition and facilitates the extinction of conditioned avoidance responses. One interpretation of these data has been that the drug acts to reduce anxiety and thereby renders the organism more amenable to the learning of new responses. Other researchers have obtained results which suggest that chlorpromazine also interferes with general motivational level, and either directly or indirectly with the learning process itself, particularly when the animal is confronted with a difficult task.

Chlorpromazine, in addition to its gross sedative effects, has been found to produce measurable changes in nervous system activity. Intravenous doses of 0.5 to 6.0 milligrams per kilogram in rabbits have been shown to depress the electroencephalogram alerting reaction normally given after

stimulation of the reticular formation (11). Study of the spontaneous electrical activity of the brain indicated a greater proportion of slow frequencies from the motor cortex of the monkey following doses of 0.5 to 1.5 milligrams per kilogram, intramuscularly. This same research demonstrated that chlorpromazine in the monkey can reduce the threshold for after discharge following electrical stimulation of the amygdala and thalamus (3).

In general, many sources can be cited that comment on how administration of chlorpromazine can slow and affect varied physiological processes. However, no distinct causal relationships have been established. Until fact can be established, hypothesis will, and should, be explored.

Hamister conducted an experiment using twenty-five naive rats, which were given twenty-five consecutive trials concurrent with daily injections of chlorpromazine (ten milligrams per kilogram). Following a thirty-day rest, they received seventeen trials without the drug and then five trials with the drug. Their performance was compared with that of eighteen animals who had followed the same course in the maze, with the exception of not receiving the drug.

Hamister claims the rats learned with daily injections of chlorpromazine, but they learned much more slowly than untreated animals and retention could not be demonstrated. He wrote that the performance of previously drugged animals during retention trials, (one month after discontinuance of

the drug) could not be distinguished from the learning performance of naive animals. When the drug was re-introduced to the experimental animals after seventeen retention (or relearning) trials, they performed about as well as untreated animals following a thirty-day rest after their first twenty-five trials (7).

In a recent study by Doty and Doty, forty naive young rats were used to determine the effects of chronic administration of chlorpromazine in infancy. All experimental group subjects received intraperitoneal injections of two milligrams per kilogram chlorpromazine daily for fifty-three days, beginning at three days of age and terminating at fifty-six days of age. Control group subjects received equal volume injections of saline solution. Mean body weights for experimental and control group subjects were determined at three-day intervals throughout the fifty-three day treatment period in order to determine whether chronic drug treatment affected general physical development.

Testing began when subjects were sixty days of age. The problem used required the animal to make a conditioned delayed discrimination avoidance response. During each acquisition trial the subject was first placed in the restraining compartment for a period of five seconds. Following this period the lamp in one of the compartments at the opposite end of the apparatus was turned on and served as the conditioned stimulus (CS). Five seconds later it was turned off. Five

seconds later the plexiglass screen was raised, allowing the animals to respond by entering the compartment previously illuminated. Five seconds later the unconditioned stimulus (US) consisting of shock to the feet was presented, unless the animal had already entered the correct compartment.

Five days following the last acquisition trial extinction trials were begun. The procedure was identical to that followed during acquisition with the exceptions that (1) the US was never presented and (2) each trial was terminated twenty seconds after the screen was raised.

During the first relearning series, which began sixty days after the original learning, control animals made a mean number of successful avoidances of 99.9 as compared to a mean of 39.8 for animals originally treated with chlorpromazine. This difference is highly significant ( $t=14.04$ ;  $p<.001$ ). During the second relearning series sixty days later, the mean numbers of successful avoidances for control and experimental animals respectively were 108.9 and 46.8. This mean difference is also highly significant ( $t=15.29$ ;  $p<.001$ ).

Representative mean body weights for experimental and control subjects at intervals during treatment period were recorded. Prior to the beginning of drug treatment (three days) mean weights did not differ significantly. Immediately following the beginning of treatment and for a period lasting a little more than two weeks, very small but significant differences in mean weights for the two groups appeared. From

this time until shortly after the termination of treatment no significant differences were found. Also, Doty and Doty found no significant differences between groups in activity, as measured by number of squares (in home cage) crossed during observations of activity level.

Doty and Doty comment that it is of interest that response decrements in experimental animals persisted for as long as 120 days after the termination of drug treatment. It was felt that this indicated a serious interference with later adaptive problem-solving behavior. A key question is how the drug produced this behavior. One immediately tempting explanation is that treated animals simply were not motivated and did not learn as well during the original trials. If this were the case one might expect such animals to perform more poorly during later relearning trials. In view of the relatively short interval between termination of treatment and original testing one might attribute this to residual effects of the drug. If this were the case, however, one might expect significant improvement by the time the second relearning series began 124 days after termination of treatment. Such is not the case: experimental animals made significantly fewer successful avoidances (mean=46.80) during the second relearning trials than did controls (mean=81.00) during the original learning series. A test of significance yields a  $t$  of 8.23,  $p < .001$ .

Other evidence against the simple suppression of motivation is the fact that there were few response failures on the part of treated animals during any of the acquisition series. One might expect that if the animal simply was not motivated he would not respond at all or would respond only after the presentation of shock. Doty and Doty found that while treated subjects did fail to avoid successfully more frequently than controls, the incidence of response failure was very low. Moreover, more than half of the responses scored as errors were made prior to the presentation of shock; yet the animal entered the wrong compartment. Gross observations of activity level during the treatment period yielded no significant differences between the two groups and no differences in general responsiveness or activity level were observed during the testing sessions. Finally, the absence of significant differences in body weight for some time prior to testing would not support a general physically debilitating effect of the drug during the treatment period.

There were no observable differences in the behavior of the two groups in their approach to problem solution. Both groups were very active and responded to the apparatus and test situation in the same way. Nor were there any apparent differences in the approach of good and poor learners within either group. Doty and Doty felt that the results indicated clearly that chronic administration of the drug during infancy exerts a profound and persistent effect on subsequent problem-solving behavior (5).

In an experiment conducted by McMurray and Jaques several different drugs were used to observe their effects on a conditioned avoidance-escape. For the present experiment attention shall be focused only on the results found using chlorpromazine. The subjects were twelve male rats of Wistar stock ranging in weight from 140 to 210 grams. The apparatus consisted of a box made of 5/8 inch plywood with over-all dimensions of 36 1/4 inches by 11 3/4 inches by 8 inches. It was divided into two compartments of equal size by a sheet of aluminum 4 inches high set in metal slots on the side walls. One compartment, which was painted black, had a grid floor of copper wire wound around a plastic insulator at 1/4 inch intervals. The other compartment was painted white, and the floor was of the same smooth plywood as the walls. A power supply delivered sixty cycles per second current at one hundred volts, 1.5 to 2 milliamperes, across the grid whenever a key was closed. The current resulting regularly elicited squealing, rapid foot withdrawals, and other escape movements from a rat in the shock compartment. The box was not covered, but a piece of plate glass was placed over the shock box immediately after the animal had been placed in this compartment.

Each rat was given five minutes to explore the two compartments. The first trial began immediately after, when the animal was placed in the black (shock) compartment and a timer started. At the end of sixty seconds shock was administered through the floor grid until the rat escaped by

jumping over the low hurdle into the white compartment or by perching on the hurdle itself. The timer was stopped, measuring the time of escape, and a second timer was started to measure the thirty-second interval preceding the next trial which began when the animal was picked up and replaced in the black compartment. If the rat avoided shock by leaving the shock box before the end of the sixty-second period, the time of this avoidance response was noted and the next trial started thirty seconds later. In this procedure, escape (E) was the response to shock itself and avoidance (A) the response to stimuli anticipating shock. An animal failing to escape after an arbitrary time limit of 200 seconds was moved across the barrier by the experimenter, and the response recorded as escape failure (EF). The normal course of avoidance learning in this apparatus was studied in ten undrugged rats given thirty-five to seventy trials each.

When drug effects were being tested the rats were trained by the above procedure, given a brief rest period, and then run for fifteen to thirty-five additional trials to ensure the appearance of a normal pattern of avoidance responses. The drug was administered by injection into a tail vein, and fifteen to thirty minutes later trials under drug conditions were begun. Chlorpromazine (one milligram per kilogram) was administered to twelve rats.

A further experiment was done in which rats were not trained prior to drug administration, but were first given the drug and the learning of the escape and avoidance response

studied while the animal was under drug influence. Twelve rats were run fifteen minutes after chlorpromazine injection (one milligram per kilogram).

Normal undrugged animals learned the avoidance response easily. Shocks were usually administered in the first three trials, and subsequently the rat avoided the shock by leaving the compartment before sixty seconds. A group of ten animals with no drug made 93 per cent successful avoidance responses (A) at a median time of 7.1 seconds. This was over a block of thirty-two trials each. These results were repeated in the preliminary training before drug administration when characteristically about 94 per cent avoidance responses were obtained at a median time always under ten seconds and usually under three.

Chlorpromazine very significantly reduced the percentage of avoidance responses (A) (Pre-drug, 94 per cent; Post-drug, 44 per cent) and increased the median time of those that were made (Pre-drug, 5.0 seconds; Post-drug, 14.4 seconds). Although the proportion of successful avoidance responses was much reduced, the rats still responded effectively to shock itself (Post-drug E was 48 per cent). This preservation of an escape response without producing a large percentage of escape failures indicates that the effect on the avoidance response was not due to gross motor or sensory disturbances.

When chlorpromazine was given before training, it was very difficult to establish a conditioned avoidance, and even the executing of a prompt escape pattern was markedly retarded. Apparently, when these drugs are given before the animal has learned to avoid the shock, the acquisition of both avoidance and escape responses is retarded. Their results show that chlorpromazine significantly reduced the number of avoidance responses while leaving the animal capable of behavioral arousal and of escaping the shock (9).

Cook and Weidley used a technique in which rats could avoid shock by climbing a pole at the sound of a buzzer, previously associated with shock. Chlorpromazine and reserpine selectively blocked this avoidance response while the escape response (pole climbing after shock) remained relatively intact (2).

McMurray and Jaques felt that the above results were interpretable in terms of the hypothesis that fear responses are conditioned to stimuli contiguous with shock and this conditioned fear supplies the stimuli which evoke an avoidance response reinforced through reduction of the fear drive. It would be expected then that agents which either reduce the strength of the conditioned fear drive or markedly change and distort the fear response-produced stimuli would result in loss of conditioned avoidance responses. It is possible that chlorpromazine could have such effects on fear (9).

It should be noted, however, that this blocking of conditioned responses is not restricted to responses conditioned to aversive stimuli. Weiskrantz found that reserpine practically eliminated lever-pressing motivated by food reward (13). Olds with a new drug-testing technique showed that chlorpromazine and reserpine reduced lever-pressing which delivered electrical stimulation to hypothalamic and amygdaloid areas. In the undrugged rat such stimulation in these areas acts as a reward, maintaining lever-pressing rates as high as 5,000 per hour (10).

It is noted that Brodie has suggested that reserpine (closely related to chlorpromazine) through the release of serotonin in the brain activates parasympathetic centers in the hypothalamus, allowing them to predominate over sympathetic-like effects (1). Chlorpromazine produces a similar result probably by blocking chemical mediators activating sympathetic centers. Thus, through different mechanisms, it is likely that these drugs markedly change hypothalamic functioning, tending to reduce highly affective-motivational components. McMurray and Jaques feel that it is this action which may markedly depress the performance of responses which are evoked by stimuli associated with motivational conditions, such as fear or hunger (9).

Sidley and Schoenfeld found that chlorpromazine had the effect of slowing the overall rate of responding, and resulting in a greater number of (US) shocks and resulting in a decrease in avoidance efficiency. They considered this to be an

indication that the drug is not simply a general activity depressant, but rather is specific to behavior maintained by avoidance contingencies (12).

It has been suggested by Himwich that chlorpromazine exerts its behavioral effects by reducing the organism's responsiveness to environmental cues, either by blocking input of sensory information or by interfering with its processing in the central nervous system (8).

Doty, Doty, Wise, and Senn conducted an experiment which was designed to determine effects of chronic chlorpromazine treatment in infancy on ability of rats to utilize home environmental cues in subsequent problem solving which required use of these cues. Comparisons of ability at maturity to acquire discriminated avoidance responses were made among: rats treated chronically with chlorpromazine in infancy simultaneously with exposure to geometric forms; rats receiving chronic saline treatment during continuous exposure to identical forms; and rats receiving no treatment and no experience with the geometric shapes.

Ss were sixty male hooded rats of Long-Evans stock. At age three days Ss were randomly assigned to one of three groups of twenty animals each. E group Ss received daily injections of two milligrams per kilogram chlorpromazine hydrochloride intraperitoneally from age three to sixty days. C<sub>1</sub> group Ss received daily injections of physiological saline from age three to sixty days, in a volume equivalent to chlorpromazine

dosages, simultaneously with exposure to the forms. C<sub>2</sub> group Ss received no injections of any kind. They were raised in cages identical to those of the previous groups except that no forms were present.

Visual exposure to geometric forms was accomplished by equipping home cages with two black metal shapes, a circle three inches in diameter and an equilateral triangle with three-inch sides. Forms were placed in cages when Ss were ten to sixty days of age. Shapes were attached to opposite sides of cages and were rotated once weekly.

At age ninety days Ss were required to learn a discriminated avoidance problem. Thirty trials a day were given for four consecutive days. Each trial was twenty seconds in duration. Ten seconds elapsed between trials during which time Ss were placed in the start area of the apparatus. On each trial S was restrained in the start area for five seconds. After five seconds the Plexiglas screen was raised, allowing S to respond by entering either of the two compartments. While S was in the start area, the circle and triangle were affixed to the openings in the two compartments opposite the start area. For one-half the Ss in each group, entry into the compartment affixed with the circle within five seconds after the screen was raised constituted a correct avoidance response. For the other Ss, entry of the compartment containing the triangle within five seconds was the correct response. The location of the forms on any trial followed a random sequence.

If S failed to make a correct avoidance response within five seconds after the screen was raised, shock to the feet was administered. Entry of the correct compartment at any time after S received the shock was recorded as an escape. Failure to enter the correct compartment at all constituted an error. Shock was terminated when S made an escape R, or in fifteen seconds if S failed to enter either compartment.

There were no significant differences in response means of any category between E group Ss (Chlorpromazine-treated) and C<sub>2</sub> group Ss (Ss not exposed to forms in their early environments). However, mean errors and escapes performed by C<sub>1</sub> group Ss (saline-treated with early exposure to forms) were significantly smaller than similar means obtained by other Ss.

Avoidance performance was most impaired by chlorpromazine treatment or lack of exposure to geometric stimuli. Performance of error responses was inversely related to level of avoidance performance. In contrast with avoidances, escape responses were not suppressed among E and C<sub>2</sub> group animals. Doty, Doty, Wise and Senn indicate that under the conditions of this experiment chronic administration of chlorpromazine during early life has a profound effect on later ability to utilize cues present in the infantile environment. Especially revealing is the finding that Ss which received chlorpromazine behaved essentially the same as Ss which had never been exposed to the early environmental cues they were later required to discriminate. In this respect, chlorpromazine-treated Ss

behaved as adults like sensorily-deprived animals. It was felt that the drug may interfere with the organism's ability to receive or process sensory information, thereby producing persistent impairment of learning. Another possible explanation was that brain acetylcholinesterase activity was inhibited by chlorpromazine(6).

In another study by Doty and Doty, concerning response decrements as a function of problem difficulty level, effective avoidance and escape behavior are suppressed both during response acquisition and extinction by acute chlorpromazine administration. They further stated, however, that the degree of suppression is a function of the complexity of the response to be acquired. Attention is called particularly to the fact that the mean decrement in the number of avoidance responses produced by the drug in Group One (required to learn a simple conditioned avoidance response) during acquisition is 3.3 while the mean decrement produced by the drug for Group Two (required to learn more difficult discriminated avoidance response) is 36.0, more than ten times as great.

In this study the effect of increasing problem difficulty on acquisition performance of treated Ss was to cut the mean number of successful avoidances almost in half and to increase avoidance failures by a factor slightly less than three.

The authors indicated that, under the conditions of this experiment, the drug in question is not simply acting to reduce fear, but in some undetermined manner is interfering with

processes necessary for problem solution (4).

In agreement with Doty and Doty, it is believed that the drug, chlorpromazine, does do more than reduce fear motivated behavior. It is thought that the drug possibly breaks down some chemical connection preventing the "normal" learning process. This does not mean that the effect of the drug does not also allay anxiety, but that it disrupts important processes in learning.

Several studies have indicated that chlorpromazine disrupts the acquisition and facilitates the extinction of conditioned avoidance responses. One interpretation of these data has been that the drug acts to reduce anxiety, and another study considers that chlorpromazine reduces the fear drive. Other researchers have suggested that the drug interferes with general motivational level, and either directly or indirectly with the learning process.

It was hypothesized that (a) those organisms trained under the influence of chlorpromazine will perform a learned task (when tested) with more incorrect responses than a comparable group trained under "normal" conditions; (b) those organisms tested under the influence of chlorpromazine will perform a previously learned task with more incorrect responses than a comparable group of organisms tested under "normal" conditions.

## CHAPTER BIBLIOGRAPHY

1. Brodie, B. B. and P. A. Shore, "A concept for a Role of Serotonin and Norepinephrine as Chemical Mediators in the Brain," Annals of the New York Academy of Science, LXVI (1957), 631-642.
2. Cook, L. and E. Weidley, "Behavioral Effects of Some Psychopharmacological Agents," Annals of the New York Academy of Science, LXVI (1957), 740-752.
3. Delgado, J. M. R. and L. Mihailovic, "Use of Intracerebral Electrodes to Evaluate Drugs that Act on the Central Nervous System," Annals of the New York Academy of Science, LXIV (1956), 644-666.
4. Doty, L. A. and B. A. Doty, "Chlorpromazine-Produced Response Decrements as a Function of Problem Difficulty Level," Journal of Comparative and Physiological Psychology, LVI (1963), 740-745.
5. \_\_\_\_\_, "Chlorpromazine-Produced Response Decrements Resulting from Chronic Administration in Infancy," Canadian Journal of Psychology, XVII (1963), 45-51.
6. Doty, L. A., B. A. Doty, M. Wise, and R. K. Senn, "Effects of Postnatal Chlorpromazine on Discrimination in Rats," Perceptual and Motor Skills, XVIII (1964), 329-332.
7. Hamister, R. C., "Chlorpromazine in Maze Learning and Retention," Psychological Reports, II (1956), 331.
8. Himwich, H. E., "Viewpoints Obtained from Basic and Clinical Symposia on Tranquillizing Drugs," Tranquillizing Drugs, I (1957), 183-192.
9. McMurray, G. A. and L. B. Jaques, "The Effects of Drugs on a Conditioned Avoidance Response," Canadian Journal of Psychology, XIII (1959), 186-192.
10. Olds, J., K. F. Killam, and P. Bach-Y-Rita, "Self-Stimulation of the Brain Used as a Screening Method for Tranquillizing Drugs," Science, CXXIV (1956), 265-266.
11. Rinaldi, F. and H. E. Himwich, "Drugs Affecting Psychotic Behavior and the Function of the Mesodiencephalic

Activating System," Disorders of the Nervous System, XVI (1955), 133-141.

12. Sidley, N. A. and W. N. Schoenfeld, "Effects of Chlorpromazine and D-Amphetamine on Escape and Avoidance Behavior Under a Temporally Defined Schedule of Negative Reinforcement," Journal of the Experimental Analysis of Behavior, VI (1963), 293-295.
13. Weiskrantz, L. and W. A. Wilson, "The Effects of Reserpine on Emotional Behavior of Normal and Brain-Operated Monkeys," Annals of the New York Academy of Science, LXI (1955), 36-55.

## CHAPTER II

### METHOD

#### Subjects

A total of twenty-four white rats were used for this study. There were nineteen male and five female rats, all naive. All animals were between sixteen and twenty weeks old at the time of testing, and all subjects were maintained on ad libitum food and water.

#### Apparatus

A three compartment T-maze was used for Phase I and Phase II (see appendix). The maze was resting on a pinewood floor measuring thirty-six inches by thirty-six inches. On the pinewood floor of the maze was the grid, consisting of small copper strips  $1/8$  inch apart, charged with 1.2 milliamperes of current by a power supply. There were three compartments in the maze, two goal boxes (at both ends of the arms of the maze) and a start box. All three compartments were of identical measurements and construction. They measured ten inches by eight inches by six inches, and were made of mesh wire with a small door for entrance. The walls and roof of the alleys, connecting the compartments, were made of clear Plexiglas, measuring five inches by six inches. The alley which connected the start box to the arms of the "T" was

twenty-seven inches long. The alley connecting the two goal boxes was twenty inches long. Entrance into the compartments from the alleys was by way of a sliding Plexiglas door, five inches by six inches.

### Procedure

Preliminary training consisted of familiarizing all rats with the maze. Each subject was allowed to explore the maze for five minutes before actual training began.

### Phase I

During this phase each subject was given ten trials in which he was trained to avoid shock by entering the goal box opposite to the one the rat chose first during his exploration. The subject was put in the start box, restrained for five seconds, then a Plexiglas screen was raised, allowing the subject to respond by entering either of the two compartments. If the subject chose the correct compartment within five seconds after the Plexiglas screen was raised no shock was administered and it was scored as an avoidance (A). If the subject entered the correct goal box after the administration of the shock it was scored as an escape (E). If the subject failed to enter the correct goal box or failed to make a response he was subjected to ten seconds of shock and scored as an escape failure (EF). After the subject entered either goal box the Plexiglas screen was closed behind him until the trial was over. If it had not been necessary to administer shock, the subject would wait

until fifteen seconds had expired before he was removed. All subjects were in the maze for twenty seconds on all trials, regardless of whether a correct or incorrect response was made. Twenty-four subjects were used and they were divided into three groups of eight (two experimental groups and one control group).

### Phase II

The subjects used in Phase I were also subjected to Phase II trials. The difference in the two phases was that the two experimental groups received a different injection under Phase II than they had received under Phase I. The number of trials (ten), and all other aspects of the procedure were the same under both phases.

### Injections

All injections were made according to the ratio of one milligram per kilogram of body weight. The injections were done with a one cubic centimeter tuberculin syringe and needle. The drug used was chlorpromazine hydrochloride (Smith, Kline, and French), and a placebo of distilled water. All animals were injected intraperitoneally.

A single classification Analysis of Variance design was used to test for significance of the drug effect upon performance of the learning task, and a Duncan's Range Test was used to determine in what respect the groups differed. Injections were made before both phases. The order of injection for

experimental group one ( $E_1$ ) was distilled water before Phase I, and chlorpromazine hydrochloride before Phase II. The order for experimental group two ( $E_2$ ) was chlorpromazine hydrochloride before Phase I, and distilled water before Phase II. The control group (C) received distilled water for both phases of the procedure.

The experimental sequences of time, temperature, and place were held constant, and every effort was made to keep the interexperimental intervals identical for all animals. A one day interval between injections was allowed to permit complete drug dissipation.

A standard procedure was followed for all injections (1). The experimental drug and placebo were injected intraperitoneally over a period of thirty seconds. Both drug and placebo were injected in the same volume relationship. The subject was then returned to the home cage for thirty minutes to allow for the drug to take effect.

## CHAPTER BIBLIOGRAPHY

1. Barnes, C. D. and L. G. Eltherington, Drug Dosage in Laboratory Animals, Berkeley and Los Angeles, University of California, 1954.

## CHAPTER III

### RESULTS

The result of Phase II for the three groups can be interpreted as important in terms of the effect of the drug upon performance of a learning task. The unit of measure was the number of responses made in each category. Experimental group two had a little under nine times as many escape failures (incorrect responses) as did the control group. Experimental group one had almost three times as many escape failures as did the control group. The control group had more than eight times as many avoidance (correct) responses as experimental group two, and more than four times as many as experimental group one. The results of Phase II trials can be quickly noted in Table I.

TABLE I  
NUMBER OF RESPONSES PER  
CATEGORY FOR THE  
THREE GROUPS

Phase II	E <sub>1</sub>	E <sub>2</sub>	C
Avoidance	11	6	49
Escape	50	13	24
Escape Failure	19	61	7

Each category of response was assigned a value, so a statistical analysis of variance could be applied to the data. Each avoidance response was assigned the value of three. Escape responses were given the value of two. Each escape failure was assigned the value of one. Each subject's result was based on the combined values of his responses.

The application of a single classification of the Analysis of Variance to the significance of chlorpromazine hydrochloride's effect upon performance of the learning task, yielded an F-value of 11.18. It was found that an F-value of 9.77 or larger resulted in significance at the .001 level. These results are to be seen in Table II.

TABLE II  
SINGLE CLASSIFICATION ANALYSIS OF VARIANCE  
BASED ON THE THREE GROUPS

Source of Variation	df	SS	MS	F
Treatments	2	495.58	247.79	11.18
Within-Groups	21	465.38	22.16	. . .
Total	23	960.96	. . .	. . .

The importance of this level of significance is that it indicates that the results of the experiment could be due to chance only once out of a thousand occurrences. These data can be seen to confirm that the drug does have a definite effect on performance of a learning task.

The statistical analysis thus far has supported the contention that chlorpromazine hydrochloride affects performance on a learning task. Duncan's Range Test was administered to determine the significance of group differences. This test was used to discover whether the drug, and its order of injection with water, is significantly related to the difference of the pattern of responses made by each group. The results of the Duncan's Range Test are in Table III.

TABLE III  
DUNCAN'S RANGE TEST FOR THE  
THREE GROUP'S DIFFERENCES

Groups	Level to be Significant	Level Achieved
C-E <sub>2</sub>	5.12	11.125
C-E <sub>1</sub>	4.87	5.25
E <sub>1</sub> -E <sub>2</sub>	4.87	5.875

All three groups differ significantly (at the .05 level) from each other. This means that each group's pattern of responses differed from the other significantly at a chance of only five times out of a hundred.

## CHAPTER IV

### DISCUSSION

It was found by visual observations, as well as statistical analysis, that chlorpromazine hydrochloride did affect not only motivation, but also problem solving behavior. Considering observations first, it was noticed that the rats injected with water first would exhibit inquisitive and exploratory behavior. Whereas the animals given chlorpromazine tended to remain in the start box rather than explore. Also the rats that were injected with the drug would often sit on the grid, not attempting to move, but plainly jerking from the discomfort of the shock.

The statistical data also indicate the effect of administration of chlorpromazine hydrochloride. Table I in Chapter III can be seen to contain the record of responses for each group under Phase II conditions. The control group (C), which received the placebo under both Phase I and Phase II conditions has the greatest number of avoidance (correct) responses and the fewest number of escape failure (incorrect) responses. Experimental group two (E<sub>2</sub>) had the most escape failure responses, and the fewest avoidance responses (the few avoidance responses made in this group were made by a single rat, which did not seem as affected by the drug as the remaining members of the group).

Of key importance is the fact that experimental group two on more than half of the trials (56 per cent) did not even attempt to escape the shock and attempt to enter either goal box, but endured the pain of the shock (this and all following percentages are based on the eighty possible responses an individual group has made during a particular phase). Experimental group one had only 10 per cent of its trials with no entrance of a goal box. When this occurred usually the rat would sit on the grid squeaking but making no attempt to escape the shock. Experimental group one made escape responses on 62.5 per cent of its trials. But experimental group two rats did not even attempt an escape on 56 per cent of their trials when shock was administered. In contrast the control group did not have an escape failure as a result of non-entry into a goal box.

There is a possibility that the drug reduced the effect of pain. In contradiction to this possibility, experimental group one made escape responses on 62.5 per cent of the trials, after the administration of shock.

The control group had 61 per cent of their responses in the avoidance category. Only 9 per cent were escape failures. This puts the predominance of the control group's responses in the avoidance category. Whereas experimental group one had 63 per cent of its responses in the escape category, and experimental group two had 76 per cent of its responses in the escape failure category.

Experimental group one's pattern of responses can be seen as a possible motivational problem. The majority (62.5 per

cent) of the rats knew which goal box to enter to avoid the shock, but did not enter without the inducement of shock. Immediately after administration of shock they would make an escape response. Little effort was asserted to make an avoidance response, giving rise to the impression that little motivation was present. The subjects would calmly sit immobile until shock was administered. Experimental group one received water in training and reacted in a similar manner to the control group. In testing trials experimental group one received the drug injection, which was accompanied by a drop in avoidance and escape failure responses. The drug, in this group, produced motivational problems, but did not hinder the rats' ability to retain the knowledge of how to escape the unpleasant shock.

Experimental group two, which received the drug under Phase I and placebo during Phase II trials, gave evidence of not only little motivation, but even less knowledge of the correct response. This group exhibited little problem-solving behavior and in 56 per cent of the trials made no attempt to escape the shock. This lack of response could be the result of the subjects not knowing how to respond, besides not being motivated. It has been noted that experimental group one seemed to know the correct response, but could be induced to respond (making escape responses in 62 per cent of the trials) only by shock. It is possible that under Phase I (drug) experimental group two was not motivated to make a response other than just sitting on the grid. When this same group was

subjected to Phase II (water) the only response previously learned was sitting on the grid waiting for the shock to stop. In experimental group one and two, motivation could be a key factor.

The results of a test of significance to find if the three groups differed in regards to responses made can be found in Table II, in Chapter III. It was found that the test was significant at the .001 level. From this it can be assumed that the drug had an effect upon the performance of the learning task.

The application of Duncan's Range Test (Table III in Chapter III) was used to find if the three groups differ from one another significantly. The three possible comparisons of the groups were found to be significant at the .05 level. This means the order of injections (drug and water) for the three groups was significant. Consequently, the hypothesis that subjects trained under the influence of chlorpromazine will perform a learned task (when tested) with more incorrect responses, than a comparable group trained under "normal" conditions, is confirmed. The second hypothesis, that those subjects tested under the influence of chlorpromazine will perform a previously learned task with more incorrect responses than a comparable group tested under "normal" conditions, is also confirmed.

In disagreement with a study by Doty and Doty it was felt that chlorpromazine did exert a suppressive effect upon

motivation, for the animals would in 86 per cent of the trials (for  $E_1$ ) respond only to shock, or not respond at all (2).

McMurray and Jaques found, in a similar study, that normal undrugged animals learned the avoidance response easily, and made 93 per cent successful avoidance responses. It was found in their study that chlorpromazine very significantly reduced the percentage of avoidance responses (Pre-drug, 94 per cent; Post-drug, 44 per cent).

McMurray and Jaques also found that although the proportion of successful avoidance responses was much reduced, the rats still responded effectively to shock itself (E). The authors felt this preservation of an escape response without producing a large percentage of escape failures indicates that the effect on the avoidance response was not due to gross motor or sensory disturbances.

In agreement, the present study had very similar results. McMurray also achieved similar results as the present study did with  $E_2$ . When chlorpromazine was given before Phase I, it was very difficult to establish a conditioned avoidance response, and even the execution of a prompt escape pattern was markedly retarded. In close agreement with McMurray and Jaques it is felt that when chlorpromazine is given before the animal has learned to avoid the shock, the acquisition of both avoidance and escape responses is retarded. Results of both studies show that chlorpromazine significantly reduced the number of avoidance responses while leaving the animal capable of behavioral

arousal and of escaping the shock (4).

Cook and Weidley in their study found that chlorpromazine selectively blocked the avoidance response while leaving the escape response relatively intact (1). This finding is not only in agreement with the present study, but it also gives support to the findings of McMurray and Jaques.

McMurray and Jaques considered this change in response patterns to be the result of some action of the drug causing a reduction of the fear drive (4). It is felt that this may be a possibility, but more important is the possibility noted by Doty and Doty that the drug may cause some chemical breakdown of the learning process (3). Seemingly, the drug does hinder learning ability, possibly disrupting important learning processes by disrupting some process affecting motivation. Based on this, and past experimental evidence, it is concluded that chlorpromazine hydrochloride can have a definite aversive effect on new learning, and possibly negate the effects of initial learning.

## CHAPTER BIBLIOGRAPHY

1. Cook, L. and E. Weidley, "Behavioral Effects of Some Psychopharmacological Agents," Annals of the New York Academy of Science, LXVI (1957), 740-752.
2. Doty, L. A. and B. A. Doty, "Chlorpromazine-Produced Response Decrements as a Function of Problem Difficulty Level," Journal of Comparative and Physiological Psychology, LVI (1963), 740-745.
- 3. \_\_\_\_\_, "Chlorpromazine-Produced Response Decrements Resulting from Chronic Administration in Infancy," Canadian Journal of Psychology, XVII (1963), 45-51.
- 4. McMurray, G. A. and L. B. Jaques, "The Effects of Drugs on a Conditioned Avoidance Response," Canadian Journal of Psychology, XIII (1959), 186-192.

## CHAPTER V

### SUMMARY AND RECOMMENDATIONS

#### Summary

Twenty-four white rats were used in this study. All subjects were trained to shock avoidance and the procedure consisted of two phases, both consisting of ten trials. The trials were conducted in a T-maze with a grid charged by 1.2 milliamperes of current by a power supply. The rats were divided into three groups of eight, two experimental groups and one control group. In Phase I experimental group one received distilled water, and in Phase II they received chlorpromazine hydrochloride. Experimental group two received chlorpromazine hydrochloride during Phase I, and received distilled water during Phase II. The control group received distilled water under both phases. All injections were made thirty minutes prior to the trials. The injection ratio for the chlorpromazine was one milligram per kilogram of body weight. This study was an attempt to test the theory that chlorpromazine hydrochloride would affect the rats' ability to learn.

The hypothesis were (a) those organisms trained under the influence of chlorpromazine will perform a learned task (when tested) with more incorrect responses than a comparable group trained under "normal" conditions; (b) those organisms

tested under the influence of chlorpromazine will perform a previously learned task with more incorrect responses than a comparable group of organisms tested under "normal" conditions. A significant difference was found, and the hypothesis was accepted.

Statistical analysis of the data (Duncan's Range Test) revealed that all groups were significantly different from each other. No specific conclusions were made as to the cause of the results. It was felt to be a possibility that chlorpromazine hydrochloride caused some pharmacological change affecting motivation and thereby affecting learning.

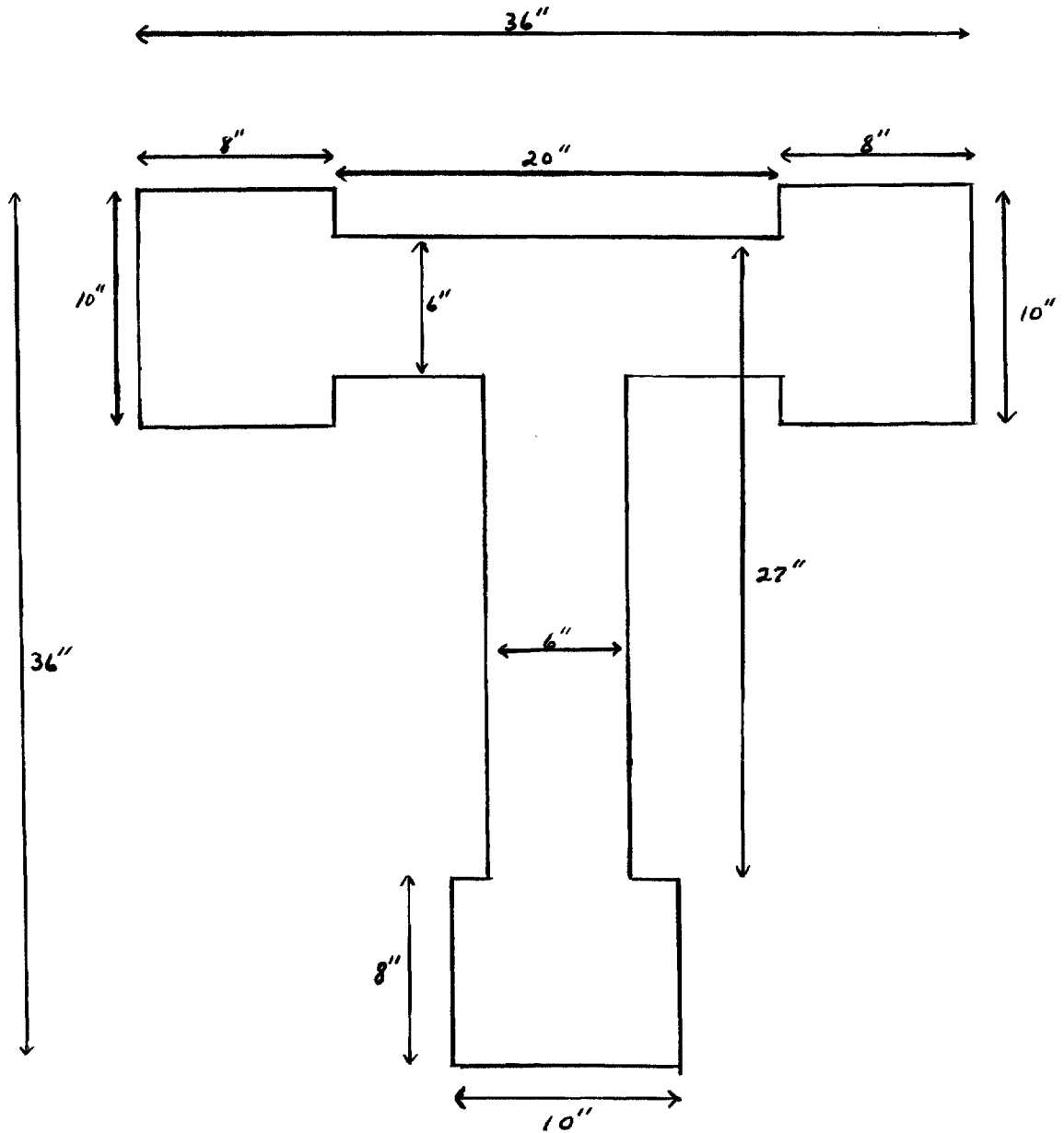
#### Recommendations

Based on the results and conclusion of this investigation, several additional related conditions require further experimentation and exploration.

1. The number of trials under both Phase I and Phase II should be increased to allow for a more stable pattern of responses.
2. Future research efforts in similar studies should have various injection ratios to find how different amounts of chlorpromazine hydrochloride will affect the subjects.
3. Future investigations directly related to the present study should modify procedure by allowing the subject to exit an incorrect goal box when he attempts to do so.

APPENDIX

DIAGRAM OF MAZE



## BIBLIOGRAPHY

### Book

Barnes, C. D. and L. G. Eltherington, Drug Dosage in Laboratory Animals, Berkeley and Los Angeles, University of California, 1954.

### Articles

Brodie, B. B. and P. A. Shore, "A Concept for a Role of Serotonin and Norepinephrine as Chemical Mediators in the Brain," Annals of the New York Academy of Science, LXVI (1957), 631-642.

Cook, L. and E. Weidley, "Behavioral Effects of Some Psychopharmacological Agents," Annals of the New York Academy of Science, LXVI (1957), 740-752.

Delgado, J. M. R. and L. Mihailovic, "Use of Intracerebral Electrodes to Evaluate Drugs that Act on the Central Nervous System," Annals of the New York Academy of Science, LXIV (1956), 644-666.

Doty, L. A. and B. A. Doty, "Chlorpromazine-Produced Response Decrements as a Function of Problem Difficulty Level," Journal of Comparative and Physiological Psychology, LVI (1963), 740-745.

---

"Chlorpromazine-Produced Response Decrements Resulting From Chronic Administration in Infancy," Canadian Journal of Psychology, XVII (1963), 45-51.

Doty, L. A., B. A. Doty, M. Wise, and R. K. Senn, "Effects of Postnatal Chlorpromazine on Discrimination in Rats," Perceptual and Motor Skills, XVIII (1964), 329-332.

Hamister, R. C., "Chlorpromazine in Maze Learning and Retention," Psychological Reports, II (1956), 331.

Himwich, H. E., "Viewpoints Obtained From Basic and Clinical Symposia on Tranquilizing Drugs," Tranquilizing Drugs, I (1957), 183-192.

- McMurray, G. A. and L. B. Jaques, "The Effects of Drugs on a Conditioned Avoidance Response," Canadian Journal of Psychology, XIII (1959), 186-192.
- Olds, J., K. F. Killam, and P. Bach-Y-Rita, "Self-Stimulation of the Brain Used as a Screening Method for Tranquillizing Drugs," Science, CXXIV (1956), 265-266.
- Rinaldi, F. and H. E. Himwich, "Drugs Affecting Psychotic Behavior and the Function of the Mesodiencephalic Activating System," Disorders of the Nervous System, XVI (1955), 133-141.
- Sidley, N. A. and W. N. Schoenfeld, "Effects of Chlorpromazine and D-Amphetamine on Escape and Avoidance Behavior Under a Temporally Defined Schedule of Negative Reinforcement," Journal of the Experimental Analysis of Behavior, VI (1963), 293-295.
- Weiskrantz, L. and W. A. Wilson, "The Effects of Reserpine on Emotional Behavior of Normal and Brain-Operated Monkeys," Annals of the New York Academy of Science, LXI (1955), 36-55.