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The modification of schizophrenic performance by drugs and by positive reinforcement

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BOSTON UNIVERSITY

GRADUATE SCHOOL

Dissertation

THE MODIFICATION OF SCHIZOPHRENIC PERFORMANCE

BY DRUGS AND BY POSITIVE REINFORCEMENT

by

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TABLE OF CONTENTS

| CHAPTER | PAGE |
|--|------|
| List of Tables | vi |
| List of Figures | vii |
| I INTRODUCTION | 1 |
| II HISTORICAL SURVEY | 6 |
| A. The Neuropsychological Dimension of Activation | 6 |
| B. The Effect of Reinforcement on the Perfor- mance of Chronic Schizophrenics | 14 |
| C. Barbiturates | 23 |
| 1. Site of Action | 23 |
| 2. Effect on Sustained Attention | 24 |
| 3. Effect on Psychomotor Performance | 25 |
| D. Chlorpromazine | 26 |
| 1. Site of Action | 26 |
| 2. Effect on Sustained Attention | 29 |
| 3. Effect on Psychomotor Performance | 30 |
| E. The Selective Effects of Chlorpromazine on Sustained Attention | 32 |
| III METHOD AND PROCEDURE | 33 |
| A. Statement of Hypotheses | 33 |
| B. Independent Variables | 34 |
| C. Dependent Variables | 35 |
| D. Subjects, Training Procedures and Experi- mental Controls | 37 |
| E. Schedule | 38 |
| F. Operational Hypotheses | 41 |
| G. Statistical Treatment | 42 |
| IV RESULTS | 44 |
| A. The Effect of Reinforcement | 44 |
| B. The Effect of the Drugs | 46 |
| C. The Dissimilar Effects of the Drugs | 51 |
| D. The Effect of the Drugs in the Presence of Reinforcement | 60 |

| CHAPTER | PAGE |
|--|------|
| V DISCUSSION. | 71 |
| A. The Effect of Reinforcement | 71 |
| B. The Effect of the Drugs | 74 |
| C. Relation to Activation Theory | 80 |
| D. Suggestions for Further Research. | 84 |
| VI SUMMARY | 87 |
| APPENDICES | 91 |
| Appendix A. Description of Apparatus. | 92 |
| Appendix B. Statistical Models. | 96 |
| Appendix C. Analysis of Variance Results. | 99 |
| Appendix D. Comparison Data With the Performance of Normals On the CPT. | 105 |
| LIST OF REFERENCES | 107 |
| ABSTRACT | 117 |
| AUTOBIOGRAPHY | 121 |

LIST OF TABLES

| Table | Page |
|--|------|
| 1 Experimental Drug Schedule. | .39 |
| 2 Effect of Reinforcement on Mean Performance Scores. . | .45 |
| 3 Effect of Drug Conditions on Mean Performance Scores. | .48 |
| 4 Dunnett's Test of Differences Between Placebo and Active Drug Conditions. | .50 |
| 5 Orthogonal Tests of Differences Among Drug Con- ditions | .52 |
| 6 Tabular Summary: Results of the Analyses of Vari- ance, the Orthogonal Comparisons and the Dunnett's Test. | .70 |

LIST OF FIGURES

| Figure | | Page |
|--------|--|------|
| 1 | Errors of Omission. Drug X Hour Interaction. . | 54 |
| 2 | Errors of Commission. Drug X Hour Interaction. | 55 |
| 3 | Response Latency. Drug X Hour Interaction. . . | 56 |
| 4 | Number of Responses (SPT), First Period Drug X Hour Interaction. | 57 |
| 5 | Number of Responses (SPT), Second Period Drug X Hour Interaction. | 58 |
| 6 | Mean and t Test Comparisons Between the Peak Effects of 100 mg Chlorpromazine and 100 mg Secobarbital. | 61 |
| 7 | Mean and t Test Comparisons Between the Peak Effects of 200 mg Chlorpromazine and 200 mg Secobarbital. | 62 |
| 8 | Number of Omission Errors as a Function of the Experimental Conditions | 64 |
| 9 | Number of Commission Errors as a Function of the Experimental Conditions | 65 |
| 10 | Response Latency as a Function of the Experi- mental Conditions | 66 |
| 11 | Number of Responses (SPT) as a Function of the Experimental Conditions | 67 |

CHAPTER I. INTRODUCTION

Although it is generally recognized that relative to normal persons, the attentive and psychomotor functioning of chronic schizophrenic patients is impaired, there is substantial disagreement as to the relative effectiveness of various experimental variables in modifying such performance. Two general classes of variables whose effects on the behavior of different populations, including chronic schizophrenics, have been extensively investigated are reinforcement and drugs.

Psychological investigations of schizophrenic performance utilizing reinforcement variables explicitly or implicitly make the assumption that the impaired performance of schizophrenics is intrinsic to a general motivational deficit, and therefore is subject to change consequent to changes in the motivational level due to the presence of reinforcement. A large number of studies have investigated the effectiveness of various positive and negative reinforcement parameters with generally inconclusive results. A review of some of the pertinent studies follows in a later chapter. It has to be emphasized, however, that due to the great variability in experimental procedure and the possible heterogeneous nature of "schizophrenia," comparisons across studies are difficult and have a limited value only.

Within the last decade the relationship between drugs and behavior in general and that of psychotropic drugs and behavior in particular have received increased attention in the psychological literature. The great increase in knowledge in what became known as the discipline of "psychopharmacology" has been accompanied by an increased realization of the complexity of factors, which in inter-relationship with each other determine the end result of a drug's effects. For example, it is becoming increasingly clear that the effect of a given drug on a given person's behavior will depend not only on the age, sex, and health of the subject, but also on his personality, although the specific relationships are not yet fully understood. Experimenters are also increasingly cognizant of the fact that the effects of a given drug will vary depending on the frequency and route of administration, and also on such extra-drug factors as the presence or absence of other subjects taking the medication and the subject's motivation to perform the required tasks.

A question of considerable importance in drug research is the selectivity of a drug's action. In several published experiments, Mirsky and associates and Kornetsky and associates note that in normal adults the effects of acutely given chlorpromazine relative to acutely given barbiturates are more selective with respect to sustained attention, while the reverse is true for cognitive functioning, even though

both drugs cause impairment in performance. The results from several experiments bearing upon the dissociation of the effects of chlorpromazine and barbiturates are summarized in an unpublished report by Mirsky and Kornetsky.

The clinical literature suggests that as therapeutic agents in schizophrenia, the phenothiazines (chlorpromazine being the prototype of this class of drugs) are superior to barbiturates. In experimental settings, however, the acute administration of these drugs produce similar results according to some reports and dissimilar results according to others. Again, as in the case of the previously mentioned reinforcement studies, most studies are sufficiently different from one another with respect to sampling and design that comparisons across studies can at best be of limited value. Since the evidence from normal persons suggests that the relative effects of chlorpromazine and barbiturates might be quite specific to the behavior under investigation, it is of great interest to investigate whether this would also be true in a chronic schizophrenic population. The comparative evaluation of the effects of chlorpromazine and a barbiturate on specific behaviors has, albeit indirectly, neurophysiological significance, since the two drugs are found to act most strongly on closely related yet separate midbrain structures.

A large number of studies utilizing operant conditioning techniques have demonstrated that drug effects are dissimilar

depending on the schedules of reinforcement used. In human subjects, the simultaneous investigation of drug and reinforcement effects has received less attention. The available evidence indicates, however, that drug effects can be altered by the appropriate manipulation of incentive conditions. The results from several experiments on post-addicts prompted the following statement by Wikler:

. . . but there can be no doubt that, regardless of theoretical niceties, behavior is modified by reinforcement . . . and that the effects of drugs on behavior are dependent to some extent at least upon the previous history of reinforcements and the rewarding and/or punishing conditions that prevail at the time and in the situation in which administered. (1959, p. 221)

A theoretical formulation which parsimoniously accounts for diverse behavioral findings and for which there is neurophysiological evidence is the activation theory. The basic psychological postulate of this theory states that there is a lawful relationship between the level of activation or arousal and performance, and that this relationship is characterized by an inverted U-shaped curve. On a given task, that is, performance is optimal at a moderate level of arousal and impaired at low or high arousal levels. Since behavioral arousal is sustained by the reticular formation which, due to its widespread neural connections, is subject to stimulation from external and internal sources, a large number of variables are capable of modifying a given person's level of arousal.

The literature suggests that the effect of reinforcement is to raise the level of activation while the effects of chlorpromazine and secobarbital is to lower it. The present study investigates the effects of these variables on the performance of chronic schizophrenics. Further, it is the aim of this study to determine whether or not the reported selective effects of chlorpromazine on sustained attention in normals can be demonstrated in chronic schizophrenics.

CHAPTER II. HISTORICAL SURVEY

Experimental findings and theoretical formulations from several diverse areas provide the historical background for the present study. In the present chapter, the relevant literature is reviewed pertaining to activation theory, the effects of reinforcement upon attentive and psychomotor performance of chronic schizophrenics, the localization of action of chlorpromazine and barbiturates, and their effect on attention and psychomotor performance.

A. The Neuropsychological Dimension of Activation

Various theoretical formulations have been employed by psychologists to explain the events which intervene between antecedant conditions and performance and the observed performance differences between different population groups, such as normals and schizophrenics. Although a large number of behavioral phenomena are explicable in terms of the more accepted psychological theories, they are still relatively circumscribed in their ability to generate precise behavioral predications whether in real life or in the laboratory. Among the many reasons for this limitation, two are outstanding: the large number of variables that affect behavior singly and in interaction, and the great difficulty in measuring and understanding the organismic events which mediate between stimuli and responses.

Activation theory attempts to integrate a large number of behavioral phenomena with recent neurophysiological findings in order to provide a comprehensive and parsimonious theory of behavior. Although the experimental literature based on this theory is still relatively small, it contains references to verified predictions which were adduced from the general theory.

Activation theory, in its present form, has evolved from the work on generalized drive by learning theorists of the Hull School, from the work of the "energetics" group, and from EEG work. The "energetics" group (Duffy 1934, 1941, 1951, 1957) argued that energy mobilization is a basic component of and lawfully related to behavior, and that the degree of energy mobilization reflects a central, excitation-inhibition continuum. Duffy felt that physiological indices hold promise for the quantifiable measurement of behavior.

A similar position was expounded by D. B. Lindsley (1951) who, after reviewing the behavioral studies which utilized electroencephalographic recordings, concluded that such diverse phenomena as emotional behavior, sleep-wakefulness, and certain behavioral abnormalities can all be explained by one concept which he named "activation." The primary index of activation is degree of EEG desynchronization, which is different in each of the above states. This, according to Lindsley, indicates that such behavioral phenomena are dependent upon the activity

of the ascending reticular activating system.

In the meantime, neurophysiological evidence has accumulated concerning the importance of the reticular formation as a central integrative system in behavior (Jasper, et al, 1958). The functional importance of the reticular formation stems in part from its numerous connections with other structures. According to Papez (1959), the reticular formation has widespread connections with ascending sensory pathways and descending motor pathways, as well as connections with various brain structures including the cortex.

The work from neurophysiology and psychology was integrated by Hebb (1955) in his paper on the conceptual nervous system in which he elucidated the importance of the nonspecific effects of stimulation on activation and postulated that degree of arousal and excellence of performance are lawfully related. According to Hebb, the "nonspecific projection system" exerts a direct influence upon the cortex and this is instrumental in learning and performance. If the nonspecific projection system is only minimally activated, learning and performance will be sluggish; when the degree of activation is increased, there will be an optimal point for behavior efficiency, beyond this further activation will impair performance; and at very high levels of activation the disturbance characteristic of stress--an inability to learn and a breakdown in discriminative performance--will occur.

The above postulated relationship between level of arousal and behavioral efficiency became known as the inverted U relationship and is one of the major general postulates of the activation theory. Since arousal, according to Hebb (1955), depends on exteroceptive and interoceptive stimulation, including the spontaneous activity of the nonspecific projection system, a person is always characterized by a certain degree of arousal.

Experimental evidence in support of the inverted U relationship between arousal and performance is provided in a study by Fuster (1958). Fuster compared the performance of monkeys on a visual discrimination task with and without the simultaneous application of an electric current to the reticular formation via implanted electrodes. A moderate current, Fuster reports, improves both the speed and accuracy of performance, while higher intensities have an opposite effect.

Evidence from human experimentation is less direct than that provided by Fuster. Stennett (1957) studied the effects of several incentive conditions on the auditory tracking ability of normal, human subjects and took concomitant measures from four muscle groups and conductance from the palm. The low incentive condition consisted of creating the impression that the performance was not being recorded, and the high incentive condition consisted of telling the subjects that their performance would determine whether or not they would receive an electric shock or earn from \$2.00 to \$5.00. All

the peripheral measures were sensitive to the changes in the incentive conditions and the relationship between performance and arousal supported the inverted U hypothesis. Kendler (1959) criticized Stennett's interpretation of the obtained results on the grounds that a causal relationship between arousal and performance had not been demonstrated. Since both performance and arousal were functions of the instructions, it is equally logical to conclude that performance was a function of arousal or that arousal was a function of performance. Although seemingly valid, Kendler's criticism ignores the broad psychological context within the activation theory is cast; namely, that mediating between the stimulus and response are the organismic variables, the so-called S-O-R formula (Woodworth and Schlosberg, 1956). Looked at in this way, the instructions, in Stennett's study, were part of the stimulus configuration which brought about a change in the organismic state of arousal. Physiologically, this change was reflected in the electromyographic and palmar conductance recordings; behaviorally, it was reflected in the improved performance on the auditory tracking task.

Bartoshuk (1955) reports that the slope of electromyographic gradients is related to reported interest in the task, and to the magnitude of altered incentives. He also reports that the inverted U relationship holds between **EMG** recordings

and performance. According to Malmo and Davis (1956) speed of performance in a mirror tracing task is reliably correlated with EMG, heart rate, and blood pressure--all of which vary with different incentive conditions.

The effect of pentobarbital on reaction time was found by Hill, et al, (1957) to depend on the motivational state of the subjects: in a group of minimally motivated subjects, pentobarbital impaired reaction-time performance, while in a group of highly motivated subjects the same drug dose improved reaction-time performance. Although the authors do not invoke the activation theory to explain their results, such findings illustrate the usefulness and parsimony of the activation theory in accounting for complex results. Activation theory would predict that, holding all else constant, performance would be relatively impaired under conditions of both minimal and high motivation, since the former would cause too little and the latter too much arousal. Therefore, when a drug such as pentobarbital, which depresses the level of activation, is administered to subjects minimally aroused, their activation level and performance level should be further depressed; but when the same drug is given to subjects too high on the activation continuum, their level of arousal should drop and their performance should improve.

These studies illustrate that: (a) the inverted U relationship between arousal and performance characterizes many types

of behavior including attention and speed of performance;
(b) that the level of arousal depends on exteroceptive and interoceptive stimulation including incentive variables; and
(c) that a variety of peripheral physiological indices are reflected in the state of activation.

The literature contains references to other behaviors which have proven sensitive to changes in activation level, and to a wide variety of variables that affect the level of activation. Of particular relevance to this study are the reviews by D.B. Lindsley (1957, 1958) in which he summarized the experimental evidence for the importance of activation upon attention and reaction time, and the book by Berlyne (1960) which evaluates the relationship between reinforcement and activation as well as the general status of the concept of activation in psychology.

Berlyne writes:

. . . psychologists are beginning to recognize degree of arousal as a dimension or continuum, as one of the variables that would have to be assigned a value if the psychological condition of a human being or higher animal at any particular time were to be adequately described. (p. 48)

. . . it has been repeatedly demonstrated experimentally that negative reinforcement causes heightened arousal. Rewarding stimuli also heighten arousal, although probably less sharply. (p. 174)

It follows from the earlier discussion and the quotation from Berlyne that in order to predict whether a given variable which is known to elevate or depress the level of activation

will bring about an improvement or decrement in performance, the subject's activation baseline has to be known. More specifically, in order to predict whether the performance of chronic schizophrenics--the subjects of this study--will improve in the presence of reinforcement and be impaired in the presence of the drugs, the baseline activation level of chronic schizophrenics has to be known. Although references in the literature to this specific issue are meager, it would seem from the clinical and experimental literature about schizophrenia that chronic schizophrenics are normally in a state of hypoactivation. Arieti (1955), for example, notes that all classical theories of schizophrenia agree that one characteristic of this disorder is a reduced responsivity to the physical and social environment. Experimental studies have consistently shown schizophrenics to be impaired relative to normals on a wide variety of psychological tasks (Jackson, 1960). Chronic schizophrenics were also found to be hypo-reactive to metabolic, autonomic, and central nervous system stimulation (Angyal, et al, 1940). Hypoarousal among chronic schizophrenics is not, however, a uniform finding. Malmö, et al (1951) present evidence from their own work and from that of others that certain indices of activation show chronic schizophrenics to be as high, and at times higher than normals on the activation continuum. These authors conclude that the impaired performance of chronic schizophrenics cannot be taken

by itself as evidence of hypoarousal, since interfering thought processes are more likely to occur among chronic schizophrenics than among normals. They further maintain that chronic schizophrenics, unlike normals, are more prone to show a dissociation between "purposive", voluntary behavior and involuntary, physiological activity. They illustrate this contention by the finding that in a pain-stress test chronic schizophrenics showed a higher level of muscular tension and a higher heart rate than did normals, but they did not press a button to signal pain as often as did the normals.

The present study does not utilize physiological measurements of activation, but since the same subjects will be tested under conditions designed to increase and decrease the the arousal level, the changes in performance will provide an estimate, albeit an indirect one, of the level of activation in chronic schizophrenics.

B. The Effect of Reinforcement on the Performance of Chronic Schizophrenics

The previous section reviewed some of the experimental findings indicating that incentive conditions raise the level of arousal and consequently affect performance. It was also emphasized that the effects of incentive conditions on performance depend on the pre-experimental arousal level of the subjects and the strength of the incentive condition. The studies so far reviewed used normal, human adults as their

subjects and were mostly designed within the framework of activation theory.

The present section will review the literature pertinent to the effect of reinforcement upon the performance of chronic schizophrenics; and especially, performance on tasks similar to the ones utilized in the present study. The most common theoretical position taken by experimenters in this area has been that the impaired performance of chronic schizophrenics is due to a motivational deficit which may be corrected at least partially by the administration of reinforcement. The controversial findings are usually analyzed within such a framework, and references to activation theory are very few.

There is general agreement that relative to normals, chronic schizophrenics are impaired on attention and psychomotor tasks. There is disagreement, however, about the modifying effects of reinforcement on this impairment. The experimental literature does not contain references to studies which have investigated the effects of reinforcement on tasks of sustained attention and response latency specifically. Most relevant to response latency are studies of reaction time. Reaction time studies, however, which utilize preparatory intervals, test not only reaction time but also the ability to maintain attention.

The effects of preparatory intervals upon reaction time were explored three decades ago by Huston, et al, (1937).

These authors found that not only were schizophrenics slower than normals on both simple and complex reaction time measures, but the magnitude of the difference between the two populations increased when a preparatory interval was introduced, i.e., a warning stimulus preceding the stimulus to which the subjects were required to respond. The same results were obtained by Rodnick and Shakow (1940), who on the basis of these findings, constructed a measure which they called the "set index" and which differentiated schizophrenics from normals without overlap.

Some ten years later in a discussion of the various psychological defects in schizophrenia, Shakow elaborated on the "set index" concept:

An examination of these varieties of conduct reveals that in one respect they appear to involve one or another aspect of expression of a single but complex type of difficulty: namely, the inability to keep a major set. By this I mean the inability to maintain a state of readiness to respond to a coming stimulus, a state which facilitates the particular type of activity called for. (1950, p. 384)

Shakow's explanation of set as "a state of readiness to respond" is indeed similar to Berlyne's (1951) definition of attention as the "momentary effective reaction potential of the perceptual response", and to Dember and Earl's definition of attention as "any behavior, motor or perceptual, which has as its end state contact between the organism and selected portions of its environment" (1957, p. 91).

In reviewing the subject, Winder states: "simple reaction time is quite clearly slower and more variable among schizophrenics

than among normals. The defect is more pronounced if the reaction time procedure is made more demanding of continuous attention and effort" (1960, p. 206).

According to Jenkins (1950), the withdrawal from and inattention to social and physical stimuli as seen in schizophrenia is the outcome of prolonged frustration beyond tolerance in the interpersonal relationships of the people who become schizophrenics. He maintains that impaired schizophrenic functioning is reversible through an increase in motivation, and makes the specific prediction that positive reinforcement will bring about an improvement in the performance of schizophrenics on a given task in which they are ordinarily found to perform less well than normals.

In the case of subjects below the level of arousal optimal for best performance, an analogous prediction would derive from Berlyne's statement that "It has been repeatedly demonstrated experimentally that negative reinforcement causes heightened 'arousal'. Rewarding stimuli also heighten arousal, although probably less sharply. . ." (1960, p. 174).

A comprehensive critical review of the relationship between reinforcement and performance in schizophrenia was presented by Rodnick and Garnezy (1957) at the Nebraska symposium on motivation. They presented evidence that negative symbolic reinforcement which cannot be avoided, i.e., the word "wrong", has a deleterious effect upon schizophrenic

performance, and that positive reinforcement has a beneficial effect. They have also shown that the degree of vulnerability to negative reinforcement is correlated with the patient's premorbid adjustment.

The results of extensive experimentation in this area is summarized in a monograph by King (1954). King compared the performance of several populations on a variety of psychomotor tasks, and on the basis of the results concluded that there is a high and positive correlation between severity of illness and degree of psychomotor impairment. Not only were schizophrenics more impaired than pseudoneurotic schizophrenics, who were in turn more impaired than neurotics and normals, but within the schizophrenic group itself there were gradations of impairment linearly related to clinical status.

In these studies, King did not employ reinforcement procedures, but the fact that there was a linear relationship between performance and degree of pathology and that the learning curves of the different populations were similar argues, King feels, against the hypothesis that increased motivation would tend to equate the performance levels of the schizophrenics and normals.

Stotsky (1957) repeated some of King's (1954) studies in order to test his contention that psychomotor impairment is primary in schizophrenia. He tested schizophrenics and normals under control conditions and under conditions of positive

verbal reinforcement that consisted of praise and encouragement. There were two schizophrenic groups: a regressed group and a relatively intact, or remitted group. The task consisted of having each subject hold a finger of his right hand on a finger rest, and use the same finger to depress a telegraph key 10.5 inches to the right or left depending on whether the signal was a buzzer or a bell. The buzzer and bell were preceded by a ready signal from one to four seconds. The results of the study showed the normals to be superior to the schizophrenics, and the remitted patients to be superior to the regressed under control conditions. Under reinforcement both normals and patients improved, the greatest improvement occurring in the regressed patients' group. Although under reinforcement the difference between the two groups diminished, the normals were still faster. Stotsky feels that this last finding could be interpreted to mean that schizophrenics need a greater number of reinforcements. He agrees, however, that his results as they stand could not account for the schizophrenic impairment in motivational terms alone.

Results similar to those of Stotsky are reported by Benton, et al (1960). In this study there was a significant improvement in the schizophrenic group when they were retested under "urging-to-do-better" conditions. But there was a similar improvement in the normals, so that the discrepancy in favor of the normals under standard conditions did not appreciably change.

Cohen (1956) used electric shock as the experimental technique for increasing motivation and compared its effects in normals and schizophrenics on complex reaction time tasks. The results were inconclusive. On some tasks the patients improved significantly relative to the normals, on others they did not.

Rosenbaum, et al (1957a, 1957b) also used avoidance of electric shock as a reinforcer. In this study, the variability and the reaction time of the schizophrenics decreased under the experimental conditions. However, while the decreased variability was statistically significant, the decreased reaction time was not. The performance of the normals also improved, but to a lesser extent. Among the schizophrenics, the females and older subjects improved less, while the more intact patients performed at a level comparable to that of the normals.

Cavanaugh (1958) investigated the effects of white noise on the reaction time performance of normals and schizophrenics. He reports that the schizophrenics improved under the experimental conditions, and that this improvement made their performance comparable to that of the normals. Cavanaugh feels that the results of his experiment support the view that the performance deficit of schizophrenics is due to impaired motivation.

It is evident from the preceding review that there is

agreement among psychologists that the performance of chronic schizophrenics is impaired, relative to normals, on a variety of tasks including attention and reaction time. There is disagreement, however, about the effects of reinforcement on the performance of chronic schizophrenics. It is difficult to draw conclusions from the various studies because they are not strictly comparable. Differences which exist in subject characteristics such as age, sex and degree of pathology, in the type and intensity of stimulation used, and in the tasks employed, make it difficult to reach any firm conclusion. Results from experiments that utilize normals as controls might be confounded by the differential stimulating value of the experimental arrangements for the two populations. Intuitively, it would be expected that such might be the case when verbal encouragement and "urging-to-do-better" are the reinforcing conditions. But there is also an experimental demonstration for such a contention in a study cited by Sands and Rodnick (1950) which has shown that following the presentation of a visual stimulus, "READY", there was a considerable difference in the GSR readings between normals and schizophrenics--the former showing the larger values--but that this difference disappeared when the GSR was recorded during a sound stimulus which followed the "READY" signal.

Despite the controversial findings, however, there seems to be strong evidence that under positive reinforcement the

performance of both chronic schizophrenics and normals improves, but that the improvement is greater for the patients. There is also evidence that the performance of chronic schizophrenics deteriorates when presented with negative reinforcement which they can neither avoid nor escape.

In a general way, these findings are explicable in terms of the activation theory. The performance of chronic schizophrenics is impaired, relative to normals, because they are in a state of lower activation. Positive reinforcement raises the level of activation in both populations, but the performance improvement of the normals is smaller because they are near their optimum arousal to start with. Since negative reinforcement has a higher arousal potential than does positive reinforcement, it impairs performance when it is sufficiently strong because it is overarousing.

These are post hoc explanations, but they can be experimentally investigated. The present study evaluates the effect of positive reinforcement on the performance of chronic schizophrenics in the absence and presence of drugs which are known to depress the level of arousal. It is reasonable to expect that if chronic schizophrenics are characterized by a low level of arousal, their performance should improve under reinforcement, regardless of the presence or absence of other conditions which depress arousal.

C. Barbiturates

This section will review the literature in support of the contention that barbiturates depress the level of activation. The evidence rests on the observation that barbiturates depress brain structures hypothesized to be instrumental in the maintenance of arousal, and also on the reported impairment in behavior which follows the administration of barbiturates.

1. Site of Action

Brazier (1954), Rinaldi and Himwich (1955), and Himwich (1960) emphasize that the cortex is an important site for the action of barbiturates. According to Brazier, barbiturates act upon cortical neurons, and this action is reflected in an increase of EEG activity in the cortex. Rinaldi and Himwich provide evidence that the electrical responses of the cortex of rabbits to environmental stimuli have abnormal characteristics after the administration of barbiturates. Himwich writes:

. . . barbiturates depress functions of the cortical regions concerned with the analyzing mechanisms of vision, audition, and other perceptive functions--the fine co-ordination of motor movements as well as thought and memory (1960, p. 58-59).

The effects of barbiturates upon the reticular system were reported in a study by French, et al (1953). They found that ether and pentobarbital sodium depressed the reticular system of monkeys regardless of whether the stimulation was central or peripheral in origin. According to Magoun (1955), EEG

desynchronization which follows reticular system stimulation is inhibited by barbiturates.

Bradley (1958) and Bradley and Key (1958) confirmed and extended the findings of French and co-workers. Cats with implanted electrodes were stimulated centrally within the reticular system and peripherally by hand clapping, blowing on the face, etc. EEG and behavioral arousal which followed such stimulation were completely blocked by pentobarbitone at doses higher than 3.5 mg/kg, the effect being more pronounced after peripheral stimulation. Lower doses had no effect. Since, with the proper dose, inhibition of arousal followed afferent and central stimulation, the authors conclude that the effect of barbiturates is within the reticular system and not on the collaterals from ascending sensory pathways as is the case with chlorpromazine.

Killam and Killam (1957; 1960) in experiments with cats obtained results similar to those of Bradley. They report that consequent to the administration of pentobarbital, in doses well below anesthetic levels, stimulation within the reticular system failed to produce the normal effects upon the auditory system. They conclude that barbiturates exert a direct depressing effect upon the reticular system.

2. Effect on Sustained Attention

The effect of single doses of barbiturates upon the performance of normal subjects on a task of sustained attention

was investigated by Mirsky, et al (1959), Mirsky and Rosvold (1960), and Townsend and Mirsky (1960). According to Mirsky and his associates, secobarbital, pentobarbital and phenobarbital, each at several doses, brought about an impairment in performance.

There are few published experimental studies about the influence of barbiturates on sustained attention in schizophrenics. Wynne and Kornetsky (1960) failed to confirm a previous report by Huston and Singer (1945) that a barbiturate improved the "maintenance of set" in a reaction-time study. The analogy between "maintenance of set" and "sustained attention" was discussed earlier.

3. Effect on Psychomotor Performance

That barbiturates impair the psychomotor performance of normal subjects is reported by Lehman and Csank (1957), Kornetsky and Humphries (1958), Kornetsky (1960), and Loomis and West (1960). Results similar to the ones obtained with normals are reported for chronic schizophrenics by Kornetsky, et al (1959) on several psychomotor tasks. The reaction time performance of chronic schizophrenics was not, however, appreciably affected by either 100 or 200 mg of secobarbital (Wynne and Kornetsky, 1960).

Shatin, et al (1956) found that sodium amobarbital adversely affected the performance of schizophrenics on several psychomotor tasks. Similar results were obtained by Lehman and Hanrahan (1954) with secobarbital on a variety of psychomotor tasks including reaction time.

The above quoted studies have all employed single dose administration. The effects of chronic administration are reported to be in the same direction. Thus, according to Lehman and Hanrahan (1954), Klugman (1962), and Pearl (1962) the chronic administration of secobarbital, amobarbital and phenobarbital have a depressant effect upon the psychomotor performance of chronic schizophrenics.

D. Chlorpromazine

This section will review the literature in support of the contention that chlorpromazine depresses the level of activation. As is the case with barbiturates, the evidence rests on the observation that chlorpromazine depresses brain structures hypothesized to be instrumental in the maintenance of arousal, as well as on the reported impairment in behavior which follows the administration of chlorpromazine.

1. Site of Action

Although the results are not uniform, there is growing agreement that the reticular system is one of the major loci for the action of chlorpromazine (Hoch, 1958; Jorgsen and Wulff, 1958; Margolis, 1957; Martin and Eades, 1960; Wikler, 1959).

There is disagreement as to whether the action of chlorpromazine is primarily within the reticular system or primarily upon the afferent collaterals that feed into the reticular system from the classical sensory pathways.

When an animal is stimulated within the reticular system or peripherally, its EEG is activated. Chlorpromazine, when administered prior to central or peripheral stimulation, will inhibit such activation. It is inferred, therefore, that chlorpromazine acts within the reticular system (Unna, 1957). Working with implanted electrodes in rabbits, Himwich and Rinaldi (1957) obtained results similar to those of Unna. On the basis of his own work and that of others, Himwich (1960) feels that there is strong evidence in support of the hypothesis that chlorpromazine depresses the reticular system centrally.

This position is challenged by other investigators, notably by Killam and Killam (1957) and E.K. Killam (1959). These authors report that in cats, doses of from 1 to 8 mg/kg had practically no depressant effect upon the reticular system. These are opposite to Himwich's results and, according to the authors, might be due to species differences.

From a series of experiments on the central effects of chlorpromazine in the cat, Killam and Killam (1958; 1960) and Killam, et al (1957) conclude that the effect of chlorpromazine on the reticular formation is small, but that its effect upon the diffuse thalamic projection system is considerably more marked. Within the diffuse thalamic projection system there is a dissociation in the effect of chlorpromazine upon behavioral and EEG arousal, i.e., for a given dose the effects are more marked on behavioral arousal.

The experimental procedure of these studies was as follows: electrodes were implanted in the reticular formation and in the diffuse thalamic projection system of cats. Consequent to implantation, voltage thresholds for behavioral and EEG arousal were determined. Following chlorpromazine administration, the voltage needed to bring about EEG and/or behavioral arousal was noted. The effect on the reticular formation was slight. The threshold for EEG arousal from the diffuse thalamic projection system was raised by about 4 to 5 volts, but a 7 to 13 volt increase was necessary to bring about behavioral arousal. It is interesting that while the above authors do not find the effects of chlorpromazine upon the activating functions of the reticular system to be very impressive, they report a much stronger interaction between chlorpromazine and the inhibitory effects of the reticular system upon responses in the auditory system. Chlorpromazine enhances such inhibition (Killam and Killam, 1958).

Killam and Killam (1960) speculate that the depressant effect of chlorpromazine on behavior is due to its selective facilitation of the inhibitory, downstream effect that the reticular formation has on afferent input.

The experimental findings by Bradley (1958) and Bradley and Key (1958) are in general agreement with the findings of Killam, Killam and co-workers. In cats small doses of the order of from 0.1 to 0.3 mg/kg of chlorpromazine, often had a facilitatory effect, causing EEG and behavioral arousal.

When the dose levels were increased up to 0.8 mg/kg, EEG and behavioral arousal returned to their threshold levels. With doses of from 2.0 to 4.0 mg/kg, there was a slight rise in the arousal threshold of the EEG and behavior under central reticular system stimulation, but almost complete blocking of afferent auditory stimulation. Increases in dose level did not enhance the effect, and at no dose level was the rise in threshold from central stimulation larger than 50%. The authors conclude that chlorpromazine acts on the afferent collaterals rather than within the reticular system itself.

In a recent review of the literature, Brodie, et al (1961) state that the experimental findings suggest that chlorpromazine acts neither on the classical sensory pathways nor on the reticular system but rather on the afferent collaterals between the two. According to these authors, chlorpromazine depresses the activity of the afferent collaterals by its depleting action on norepinephrine, which normally controls the activating effect of the afferent collaterals on the reticular system.

2. Effect on Sustained Attention

Primac, et al (1957), Mirsky, et al (1959) and Mirsky and Rosvold (1960) report that single 100 and 200 mg doses of chlorpromazine cause significant impairment in the performance of normal subjects on a task of sustained attention.

A search of the literature did not reveal similar studies with chronic schizophrenics. The chronic administration of

chlorpromazine has, according to Daston (1959), a beneficial effect on the attention of chronic schizophrenics. Daston's conclusion is based on the observation that the performance of chronic schizophrenics on the Immediate Recall and Paired Associates subtests of the Wechsler Memory Scale improved after they have been receiving daily doses of 400 mg of chlorpromazine for several months. The improvement on the Paired Associates subtest was statistically significant. Daston's conclusion, however, is open to the criticism that "attention" is not the only nor the primary psychological function underlying performance on a Paired Associates test.

3. Effect on Psychomotor Performance

The evidence indicates that chlorpromazine impairs the performance of normal subjects on various psychomotor measures. According to Brodie (1958), the reaction time performance of normal adults was impaired by chlorpromazine at several dose levels. Progressively higher doses had later peak effects, and the duration of effect was directly related to dose magnitude. Brodie reports that he could not collect data for doses higher than 150 mg because his subjects were unable to maintain sufficient alertness to perform the task.

In recent reviews of their experimental findings, Kornetsky (1960) and Loomis and West (1960) have summarized evidence that chlorpromazine in single doses impairs performance on a variety of psychomotor tests. There are few experimental

reports in the literature on the effects of chronic chlorpromazine administration on the performance of normal subjects. According to Schneider (1960) the performance of normal subjects on reaction time was impaired after daily doses of 100 mg of chlorpromazine for four days.

Although the findings are not uniform, there is strong evidence that single doses of chlorpromazine of sufficient strength impair the psychomotor performance of chronic schizophrenics, but that repeated administration has a much smaller effect. Furthermore, it seems to be the case that under conditions of single dose administration, the performance of normal subjects is impaired by chlorpromazine doses too small to produce an equal impairment in chronic schizophrenics. Thus, according to Wynne and Kornetsky (1960), 100 mg of chlorpromazine had no effect on the performance of chronic schizophrenics on a reaction time task very similar to the one used by Brodie; and according to Kornetsky and Humphries (1958) and Lehman and Csank (1957), the tapping speed of normal subjects was impaired by 100 mg of chlorpromazine, but the performance of chronic schizophrenics on an identical task was not impaired by the same drug and dose level, according to Kornetsky, et al, (1959).

Kornetsky, et al (1959) report that a single 100 mg dose of chlorpromazine had no appreciable effect upon the psychomotor performance of chronic schizophrenics. The performance

of the same subjects, however, was significantly impaired after the ingestion of 200 mg doses of chlorpromazine. After two weeks of daily 200 mg doses of chlorpromazine, no impairment in the performance of the same subjects could be detected.

Heilizer (1959) reports that the reaction time performance of chronic schizophrenics did not appreciably change after three months of daily chlorpromazine administration. Similar results were obtained by Wynne and Kornetsky (1960).

According to Lehman and Hanrahan (1954), Klugman (1962), and Pearl (1962), the psychomotor performance of chronic schizophrenics slightly improved after the chronic treatment with chlorpromazine.

E. The Selective Effects of Chlorpromazine on Sustained Attention

The literature review in the preceding sections concerned itself with the sites of action of barbiturates and chlorpromazine and with the changes in performance which follow the administration of these drugs. It was indicated that the research findings suggest that barbiturates have a depressing effect upon the cortex and the reticular formation, and that chlorpromazine depresses the activity of the diffuse thalamic projection system, as well as the collaterals between the reticular formation and the ascending sensory pathways. The above neural structures are implicated in the maintenance of

activation. Although the evidence is not uniform, it appears that single doses of barbiturates and chlorpromazine impair performance on tasks of sustained attention and reaction time in normals and chronic schizophrenics. In general, then, the neurophysiological and psychopharmacological literature are in agreement.

More recently, Kornetsky and associates (Kornetsky, 1960) and Mirsky and associates (Mirsky and Rosvold, 1960) have reported that although both chlorpromazine and barbiturates impair the sustained attention of normal subjects, the effect of chlorpromazine is more pronounced. The experimental evidence for this contention is more fully summarized in an as yet unpublished paper by Mirsky and Kornetsky. Essentially, these authors and their associates have compared the effects of chlorpromazine and barbiturates on a task of sustained attention, the Continuous Performance Test (CPT) and on a subtest of the Wechsler Intelligence Scale for Adults, the Digit Symbol Substitution Test (DSST). They report that both drugs impair performance on both tasks, but chlorpromazine has a greater effect on the CPT while barbiturates have a greater effect on the DSST.

Whether the more pronounced effect of chlorpromazine on sustained attention, as compared to a barbiturate, is also evident in chronic schizophrenics will be investigated in the present study.

CHAPTER III METHOD AND PROCEDURE

A. Statement of Hypotheses

The present study was designed to test the general hypotheses that:

1. Reinforcement improves sustained attention, augments psychomotor output, and decreases response latency in chronic schizophrenics.

2. Chlorpromazine and secobarbital impair sustained attention, decrease psychomotor output, and increase response latency in chronic schizophrenics.

3. Relative to secobarbital, the effect of chlorpromazine in chronic schizophrenics is more pronounced on sustained attention; less pronounced on psychomotor output and response latency.

4. In the presence of reinforcement the effects of these drugs in chronic schizophrenics are reduced.

The experimental arrangements were designed to provide a controlled comparison of the performance of chronic schizophrenics on measures of sustained attention, response latency, and psychomotor output under conditions which would show the effects of reinforcement and the effects of two drugs at two dosage levels. Eight patients, on a balanced schedule were rotated through all conditions, so that each patient served as his own control. In the course of twelve testing days, each patient had two testing days each on chlorpromazine

100 mg, chlorpromazine 200 mg, secobarbital 100, secobarbital 200 mg, an inert placebo, and no medication. The testing involved repeated administration of the Continuous Performance Test and the Subject-Paced Test, given under conditions of reinforcement and no-reinforcement.

B. Independent Variables

The effects of three independent variables were studied: positive reinforcement and two drugs, at two dose levels each. The time interval between medication and testing sessions was also subject to analysis.

Since O.R. Lindsley (1957) found that candy was a better reinforcer than a number of other agents in schizophrenics, chocolate bars were used as rewards. To avoid too much of the same reinforcer, and since many patients smoke but are short of cigarettes, it was decided to use both chocolate bars and cigarettes. The drugs used were chlorpromazine and secobarbital, which were administered orally in identical gelatin capsules at doses of 100 and 200 mg. The choice of chlorpromazine was dictated by one of the aims of the study, i.e., the specific evaluation of the effect of this drug in relation to barbiturates on the behaviors under investigation. Secobarbital was chosen as the barbiturate because data on its effects in a normal population is available. This same consideration, namely comparison data from a normal population, also dictated the choice of dosage. Furthermore, the literature indicates that these

two doses are in the range of clinical use and experimental usefulness, i.e., not too low to produce no observable effects, and not high enough to be toxic or anesthetic.

C. Dependent Variables

Three behavioral parameters were investigated in this study: the maintenance of sustained attention, response latency, and psychomotor output.

"Attention" has been variously defined conceptually, but for the purpose of this study, Denber and Earl's definition of "attention" as ". . . any behavior, motor or perceptual, which has as its end state contact between the organism and selected portions of its environment" (1957, p. 91) seems most adequate. "Sustained attention" merely refers to the temporal dimension, i.e., when ". . . contact between the organism and selected portions of its environment" is demanded not once, but over a given period of time. Operationally, sustained attention was evaluated by means of the Continuous Performance Test (CPT), which was designed by Rosvold, et al (1956) and used as a test of sustained attention by these and other investigators. The basic performance requirement on the CPT is that the subjects respond by pressing a button or pulling a lever to only one of a series of letter stimuli, which are randomly and repeatedly exposed, one at a time. In this study the letter X served as the critical stimulus, and it appeared on the average every fifth letter. Subjects were required to respond to the letter X by

pulling a lever. All stimuli were presented at intervals of 1.10 seconds, and were exposed for 0.10 second. A more detailed description of the test apparatus is given in Appendix A. A subject's capacity for the maintenance of sustained attention was evaluated by the frequency of his omission errors (failure to respond to the critical stimulus), and by the frequency of his commission errors (responses to stimuli other than the critical stimulus), and by the frequency of his commission errors (responses to stimuli other than the critical one).

"Response latency" refers to the time interval between the presentation of a stimulus and the completion of the required response. In this study the evaluation of response latency was also derived from the CPT. The time interval between the onset of the critical stimulus and the response, constituted the response latency. The mean response latency for a given trial, i.e., the cumulated response latencies of all the responses during a trial divided by the number of such responses, served as the raw score for the statistical analyses.

Psychomotor output is conceptually ill defined, since it generally refers to relatively gross performance which might include several more refined psychomotor movements. In this study psychomotor output was evaluated by means of the Subject-Paced Test (SPT), a test designed to include many of the CPT components, but one less dependent on sustained attention.

The basic difference between the two tests is that on the SPT stimulus presentation is under the subject's control. The apparatus was so programmed that pulling the left of two

levers exposed a letter in the stimulus window which remained exposed until the same lever was pulled again. When the letter X appeared in the stimulus window, it remained exposed until the right of the two levers was pulled. Two scores were derived from this test: the number of lever pulls, and the number of errors, i.e., pulling the left lever when an X was exposed or pulling the right lever for letters other than X. The total number of pulls, including the right and left levers, served as the operational measure of psychomotor output.

D. Subjects, Training Procedure, and Experimental Controls

Eight male, chronic schizophrenic subjects, in the age range of 25 to 50 were used in this experiment. Each subject had been hospitalized continuously for no less than three years. None of the subjects was mentally deficient nor did they have any known organic impairment. Each subject had a medical examination to assure that his blood pressure was within normal range, that he was not obese, or otherwise unfit to serve as a subject on medical grounds.

The training period lasted about two months. During this period subjects were tested without drugs but with and without reinforcement. During the training period, an attempt was made to establish the time interval during which approximately 50% of any given subject's responses to the critical stimulus occurred under reinforcement. The apparatus was then calibrated

for each subject individually. This procedure assured a more nearly equal number of reinforcements to all subjects.

In order to minimize the possible effects of extra-experimental variables, certain controls were instituted. Subjects were housed in the hospital's research ward, which assured a more uniform environment. The training period gave the subjects a chance to familiarize themselves with the laboratory environment and apparatus. This served to minimize the possible effects of stress, anxiety or exploratory behavior associated with the above factors. For all subjects all medication, other than experimental drugs, was discontinued for the duration of the training period and experimentation.

On a testing day the ward nurse gave the medication to the subjects to be tested and was present while they ingested the capsules. The nurse made sure that the subjects scheduled for testing did not eat breakfast, and that they were accompanied to the laboratory if they had no parole. Neither the ward nurse nor the other personnel were aware of the nature of the drugs, nor did they know whether a subject was receiving a placebo or an active agent. For the duration of testing subjects were not allowed to smoke or eat.

E. Schedule

The drugs were administered according to a modified Latin Square design. Each subject served as his own control and was given medication once weekly for 12 weeks. Table 1 illustrates

TABLE 1
EXPERIMENTAL DRUG SCHEDULE

| Subject | Weeks | | | | | | | | | | | |
|---------|-------|----|-----|----|---|----|-----|------|----|---|----|-----|
| | I | II | III | IV | V | VI | VII | VIII | IX | X | XI | XII |
| A | | 1 | 2 | 0 | 3 | 4 | 3 | 1 | 0 | 4 | 2 | |
| B | | 2 | 1 | 0 | 4 | 3 | 4 | 2 | 0 | 3 | 1 | |
| C | | 3 | 4 | 0 | 1 | 2 | 2 | 4 | 0 | 1 | 3 | |
| D | | 4 | 3 | 0 | 2 | 1 | 1 | 3 | 0 | 2 | 4 | |
| E | | 4 | 3 | 0 | 1 | 2 | 2 | 3 | 0 | 1 | 4 | |
| F | | 3 | 2 | 0 | 4 | 1 | 4 | 1 | 0 | 3 | 2 | |
| G | | 1 | 4 | 0 | 2 | 3 | 1 | 2 | 0 | 4 | 3 | |
| H | | 2 | 1 | 0 | 3 | 4 | 3 | 4 | 0 | 2 | 1 | |

No entry = no drug

0 = placebo

1 = chlorpromazine 100 mg

2 = chlorpromazine 200 mg

3 = secobarbital 100 mg

4 = secobarbital 200 mg

the drug schedule. The table shows that all the active drugs were administered to each subject twice, and that the order is completely balanced, i.e., each active drug condition followed any other drug condition an equal number of times. Placebos were given to each subject in the fourth and ninth testing days. As is seen from Table 1, no subject received medication on the first and last days of the experiment. The no-medication condition was introduced for two reasons: it provided a baseline of performance against which the performance under placebo could be evaluated, and it allowed for the determination of practice effects.

The order in which the tests and the reinforcement were administered was also balanced. Half of the subjects were tested on the CPT first and the SPT second during testing days 1 to 6 and were tested on the SPT first and CPT second during testing days 7 to 12. For the other half of the subjects the order of test administration was reversed.

During each testing session, one trial each on the CPT and SPT was reinforced, and one trial each on the CPT and SPT was not reinforced. For half of the subjects the first trial on the CPT and SPT was reinforced during testing days 1 to 6, while during testing days 7 to 12 the second trial on each test was reinforced. For the other half of the subjects, the order was reversed.

A testing day consisted of four sessions, every hour on

the half hour after drug administration, i.e., testing began one-half hour after a subject received medication, and the last session began three and a half hours after drug administration. A session lasted approximately half an hour and consisted of two CPT trials and two SPT trials, one of each being reinforced. A visual stimulus indicated to the subject whether or not the trial would be reinforced. Fifty critical stimuli were presented during a CPT trial, this number remaining invariant for all occasions. An SPT trial lasted three minutes.

F. Operational Hypotheses

The independent and dependent variables, and the operational procedures to measure the relationships between the two having been defined, the following operational hypotheses were formulated:

On the CPT:

1. Under reinforcement the number of omission errors and the number of commission errors is smaller than under no reinforcement.

2. Under reinforcement the response latency is shorter than under no reinforcement.

3. Under the active drug conditions the number of omission and commission errors is greater than under placebo; the larger doses have the greater effect; and the effect of chlorpromazine and secobarbital are alike.

On the SPT:

1. Under reinforcement the number of responses is greater

than under no reinforcement.

2. Under the active drug conditions the number of responses is smaller than under placebo; the larger doses have the greater effect; and the effects of chlorpromazine and secobarbital are alike.

G. Statistical Treatment

Two analyses of variance for correlated scores were performed on each dependent variable.

The first analysis evaluated the possible effect of placebo, as compared to the no-drug condition, as well as the variance associated with repeating the no-drug and placebo conditions twice. In this analysis the reinforced and non-reinforced trials were evaluated separately. Table 1, Appendix B, shows the model for this analysis. It should be noted that the error term is based on all the pooled interactions involving "subjects". However, in order not to inflate the significance values, the number of degrees of freedom used to enter the F Table were based on the number associated with "subjects".

If the statistical comparison between the placebo and no-drug conditions was found to be non-significant, the latter was excluded from further statistical analysis. When the difference between the two testing periods proved to be statistically nonsignificant, the scores from the two testing

periods for all drug conditions were pooled and the mean of the pooled scores for each subject served as the raw score for further analysis.

The second analysis served to evaluate the reinforcement and drug effects, as well as the interactions between them. Table 2, Appendix B, shows the model for this analysis. As in the previous model, the sums of squares of all the interactions involving the subjects term were pooled to form the error term. Consequently, the mean square for error is based on 273 degrees of freedom. Entries into the F table, however, were made with the number of degrees of freedom associated with the particular source of variance and its interaction with the subject term, thus avoiding inflated significance values.

CHAPTER IV. RESULTS

The statistical tests of the differences in performance under the placebo and no-drug conditions revealed no significant differences between the two conditions on any dependent variable of the experiment. The scores from the no-drug condition were, therefore, excluded from further statistical treatment.

In the case of all the dependent variables, except number of responses on the SPT, there was no significant difference in performance between the two periods. In the further analyses, therefore, the SPT scores from each period were analyzed separately, while the scores from both periods of the other dependent variables were pooled.

The results from the analyses of variance of each dependent variable are reported in Appendix C.

A. The Effect of Reinforcement

The findings confirm the hypothesis that in chronic schizophrenics reinforcement improves sustained attention, decreases response latency, and augments psychomotor output.

Table 2 presents the mean values for the reinforced and non-reinforced trials and the F and P values for reinforcement as a source of variance from the analyses of variance. Each mean was arrived at by summing over all drug conditions and over the four test sessions per day, for the reinforced and non-reinforced trials separately, and dividing each sum by 160.

TABLE 2

Effect of Reinforcement on Mean Performance Scores

| | Reinforced Trials | Non-Reinforced Trials | F (1 & 7df) | P |
|-------------------------------|----------------------|--------------------------|----------------|--------|
| Mean Number Omission Errors | 6.14 | 9.09 | 14.31 | <.01 |
| Mean Number Commission Errors | 2.61 | 1.90 | 14.96 | <.01 |
| Mean Response Latency in Sec. | .58 | .63 | 43.62 | <.0005 |
| Mean Number of Response (SPT) | | | | |
| 1st Period | 21.34 | 19.87 | 27.59 | <.0005 |
| 2nd Period | 22.34 | 20.92 | 25.34 | <.0005 |

As Table 2 shows, in the presence of reinforcement, the average number of omission errors is smaller than in the absence of reinforcement; the average response latency is shorter in the presence of reinforcement; and the average number of responses on the SPT is larger for the reinforced trials. Furthermore, Table 2 shows that the differences between the reinforced and non-reinforced trials for each of the above dependent variables are statistically significant. This supports the conclusion that under reinforcement the performance of chronic schizophrenics improves.

It will be noted, however, that in the case of commission errors, the results are opposite to the prediction. The mean number of commission errors is larger for the reinforced rather than the non-reinforced trials, and the difference between the two is statistically significant. This negative finding, however, may be reconciled with the confirmation of the hypothesis if it is assumed that during reinforcement the subjects were more highly motivated, and therefore pulled the lever at times when only a partial cue of the critical stimulus was perceived.

B. The Effect of the Drugs

The findings in general confirm the hypothesis that in chronic schizophrenics, chlorpromazine and secobarbital impair sustained attention, increase response latency, and decrease

psychomotor output--the higher doses having the greater effect.

These findings are most clear with respect to the chlorpromazine effects. As will be discussed more fully later, secobarbital had a much shorter duration of action; consequently, the effects of this drug are more evident when it is compared to placebo during its peak effect rather than over the four post-drug testing sessions.

Table 3 presents the mean values of the dependent variables for each drug condition and the significance values associated with the "drug" term in the analyses of variance. Each mean was arrived at by summing over the two reinforcement conditions and over the four test sessions per day and dividing the sum by 64, which is the total number of cell entries for each drug condition. An inspection of Table 3 shows that in the case of each dependent variable, performance was best during the placebo condition; or conversely, the table shows that all drug conditions impaired performance on all the measures that were taken. Thus, the number of omission and commission errors is greater under each of the active drug conditions than it is under placebo, the response latency is longer under the active drug conditions than under placebo, and the number of responses on the SPT during both periods is smaller for the active drug conditions than for placebo.

That the differences in performance under placebo and the other drugs are not due to chance is revealed by the

TABLE 3

Effect of Drug Conditions on Mean Performance Scores

| | <u>Placebo</u> | <u>CPZ 100 mg</u> | <u>CPZ 200 mg</u> | <u>Seco 100 mg</u> | <u>Seco 200 mg</u> | <u>F (4 & 28 df)</u> | <u>P</u> |
|----------------------------------|----------------|-----------------------|-----------------------|------------------------|------------------------|------------------------------|----------|
| Mean Number Omission Errors | 4.8 | 8.9 | 12.0 | 5.3 | 7.2 | 11.26 | < .0005 |
| Mean Number Commission Errors | 1.8 | 2.0 | 2.8 | 2.0 | 2.7 | 4.65 | < .01 |
| Mean Response Latency in Seconds | .56 | .60 | .65 | .59 | .64 | 20.00 | < .0005 |
| Mean Number of Responses (SPT) | | | | | | | |
| 1st Period | 21.84 | 20.82 | 19.63 | 21.33 | 19.39 | 11.75 | < .0005 |
| 2nd Period | 22.79 | 21.66 | 20.67 | 22.12 | 20.92 | 7.59 | < .001 |

significant F values associated with the "Drug" term of each dependent variable. In order to determine whether performance under each individual drug condition was significantly different than performance under placebo, significance tests were performed with Dunnett's Test for comparisons with a control (Edwards, 1960). Table 4 presents the results of these comparisons. Since the hypotheses predicted that the drugs will impair performance, all comparisons are based on a one-tailed test. As this table indicates, some of the comparisons did not reach statistical significance. The 100 mg dose of secobarbital did not significantly differ from placebo in its effect on sustained attention and psychomotor output, but did significantly affect response latency. The 100 mg dose of chlorpromazine did not significantly differ from placebo on commission errors, but differed significantly on all other measures. The 200 mg dose of secobarbital significantly impaired psychomotor output and response latency, but differed significantly from placebo on only one of the two measures of sustained attention, i.e., commission errors. The difference, however, approached the .05 level of significance on the omission errors: the numerical difference between this condition and placebo was 2.40 and the value required for significance is 2.78. The 200 mg dose of chlorpromazine was significantly different from placebo on all dependent variables.

TABLE 4

Dunnett's Test of Differences Between Placebo
and Active Drug Conditions

| <u>Source</u> | SPT | | | | |
|-------------------------|------------------------|--------------------------|-------------------------|--------------------------|-----------------------------|
| | <u>Omission Errors</u> | <u>Commission Errors</u> | <u>Response Latency</u> | <u>Number 1st Period</u> | <u>Responses 2nd Period</u> |
| Placebo- CPZ 100 mg | <.01 | -- | <.01 | <.05 | <.05 |
| Placebo- CPZ 200 mg | <.01 | <.01 | <.01 | <.01 | <.01 |
| Placebo- Seco 100 mg | -- | -- | <.05 | -- | -- |
| Placebo- Seco 200 mg | -- | <.01 | <.01 | <.01 | <.01 |

The data summarized in Tables 3 and 4, then, support the hypothesis that both chlorpromazine and secobarbital impair the performance of chronic schizophrenics on the measures under study. Table 3 also shows that for each dependent variable, the larger dose of each drug had a greater effect than the smaller dose. For example, while the mean number of omission errors under 100 mg of chlorpromazine is 8.9, the comparable value for 200 mg of chlorpromazine is 12.0. The significance of the differences between the effects of both doses of both drugs was evaluated by means of the method of orthogonal comparisons (Edwards, 1960). Since four degrees of freedom are associated with the "Drug" term, four orthogonal comparisons are permissible. Table 5 presents the results of these comparisons. As is seen from the table, in all cases but one (omission errors) the differences between the 100 and 200 mg doses for both drugs are statistically significant. Reference to Table 3 shows that in all cases the greater impairment in performance occurred under the higher doses.

C. The Dissimilar Effects of the Drugs

The findings in general support the hypothesis that relative to secobarbital, the effect of chlorpromazine in chronic schizophrenics is more pronounced on sustained attention, but not on psychomotor output and response latency.

TABLE 5

Orthogonal Tests of Differences Among Drug Conditions

| <u>Source</u> | SPT | | | | |
|------------------------------|------------------------|--------------------------|-------------------------|--------------------------|-----------------------------|
| | <u>Omission Errors</u> | <u>Commission Errors</u> | <u>Response Latency</u> | <u>Number 1st Period</u> | <u>Responses 2nd Period</u> |
| Placebo- All Drugs | <.0005 | <.025 | <.0005 | <.0005 | <.0005 |
| Chlorpromazine- Seco. | <.0005 | -- | -- | -- | -- |
| CPZ 100 mg - CPZ 200 mg | <.05 | <.01 | <.0005 | <.025 | <.05 |
| Seco 100 mg - Seco 200 mg | -- | <.05 | <.0005 | <.0005 | <.025 |

In comparing the effects of chlorpromazine and secobarbital, however, the different time-response curves of the two drugs must be considered. Figures 1, 2, 3, 4, and 5 illustrate the time-response curves of the two drugs with respect to the dependent variables of this study. The statistical significance of these relationships is evident from the tables in Appendix C which show that the Drugs X Hours interaction is significant for each dependent variable, except errors of commission.

Figure 1 shows that with respect to omission errors, secobarbital has its maximum effect 1/2 hour after administration, that chlorpromazine is approaching its peak effect 3 1/2 hours after administration, and that the effect of placebo does not appreciably change from hour to hour. This figure also shows that both doses of each drug have a similar time course although they differ in magnitude of effect at each hour.

Figure 2 shows a basically similar relationship between the drugs with respect to commission errors, except that the 100 mg dose of either drug does not vary much from placebo. As is seen from this figure, 200 mg of secobarbital has its maximum effect 1/2 hours after administration and declines thereafter; while 200 mg of chlorpromazine has very little effect 1/2 hour after administration, but its effect increases steadily thereafter.

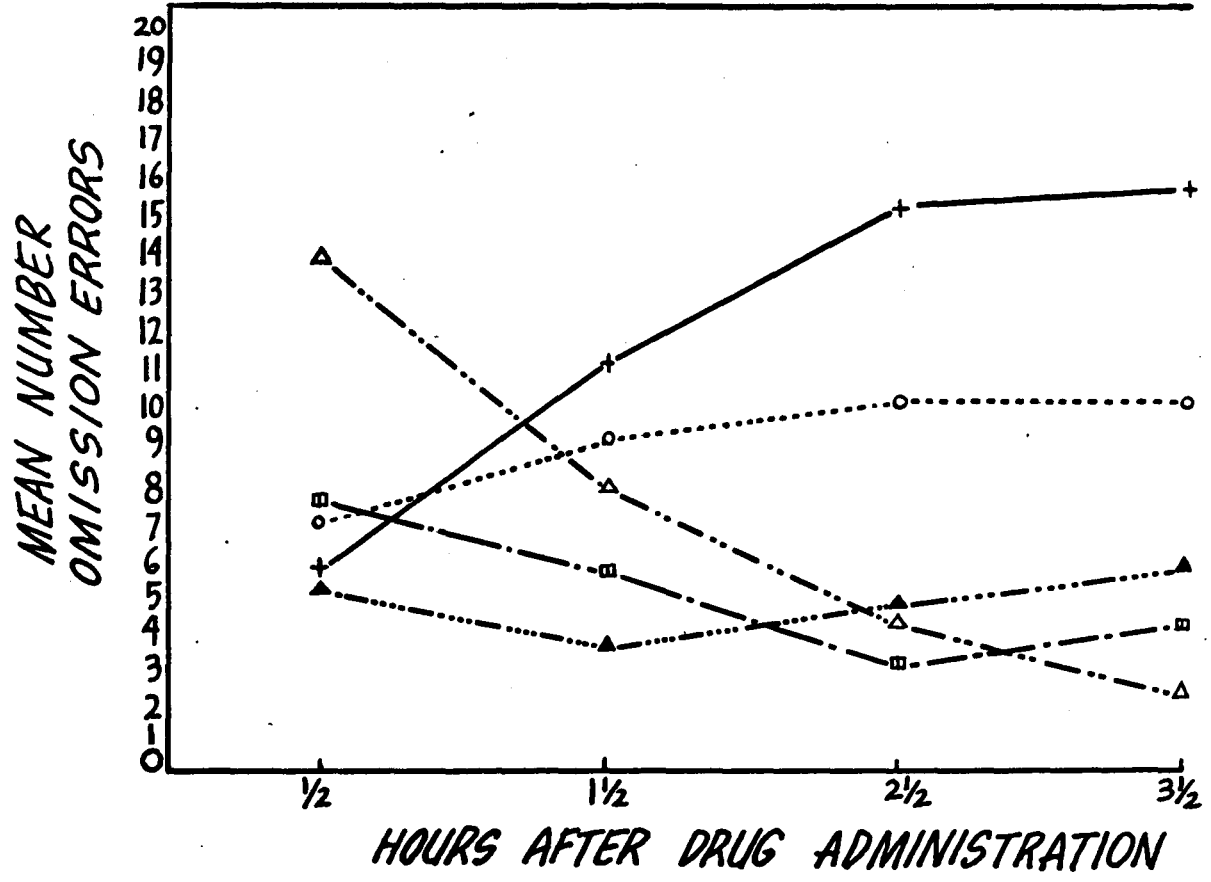


FIGURE 1. ERRORS OF OMISSION. DRUG X HOUR INTERACTION

PLACEBO ▲.....▲
CHLORPROMAZINE 100 mg ○.....○
CHLORPROMAZINE 200 mg +.....+
SECOBARBITAL 100 mg ◻.....◻
SECOBARBITAL 200 mg △.....△

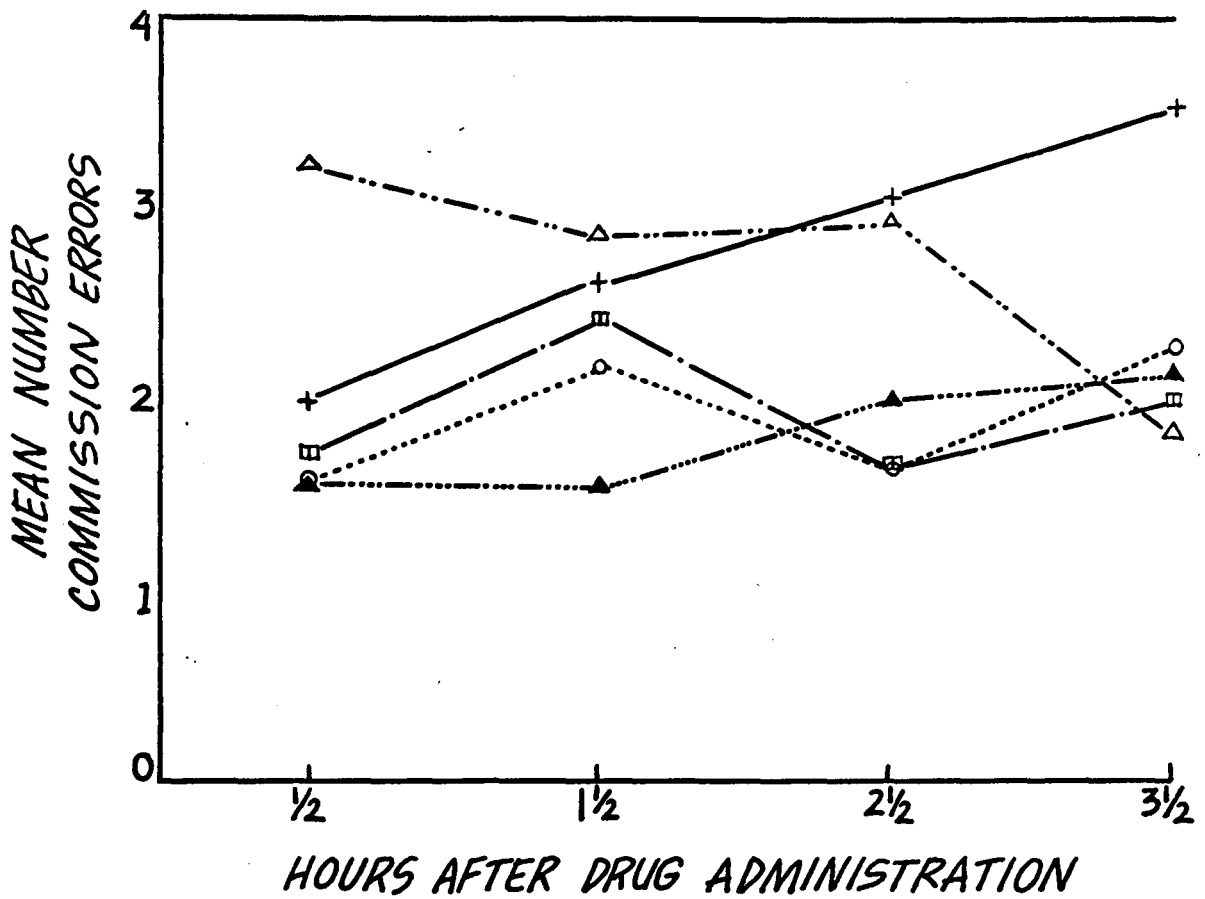


FIGURE 2. ERRORS OF COMMISSION. DRUG X HOUR INTERACTION

| | | | |
|----------------------|---|-------|---|
| PLACEBO | ▲ | | ▲ |
| CHLORPROMAZINE 100mg | ○ | | ○ |
| CHLORPROMAZINE 200mg | + | ———— | + |
| SECOBARBITAL 100mg | ◻ | | ◻ |
| SECOBARBITAL 200mg | △ | | △ |

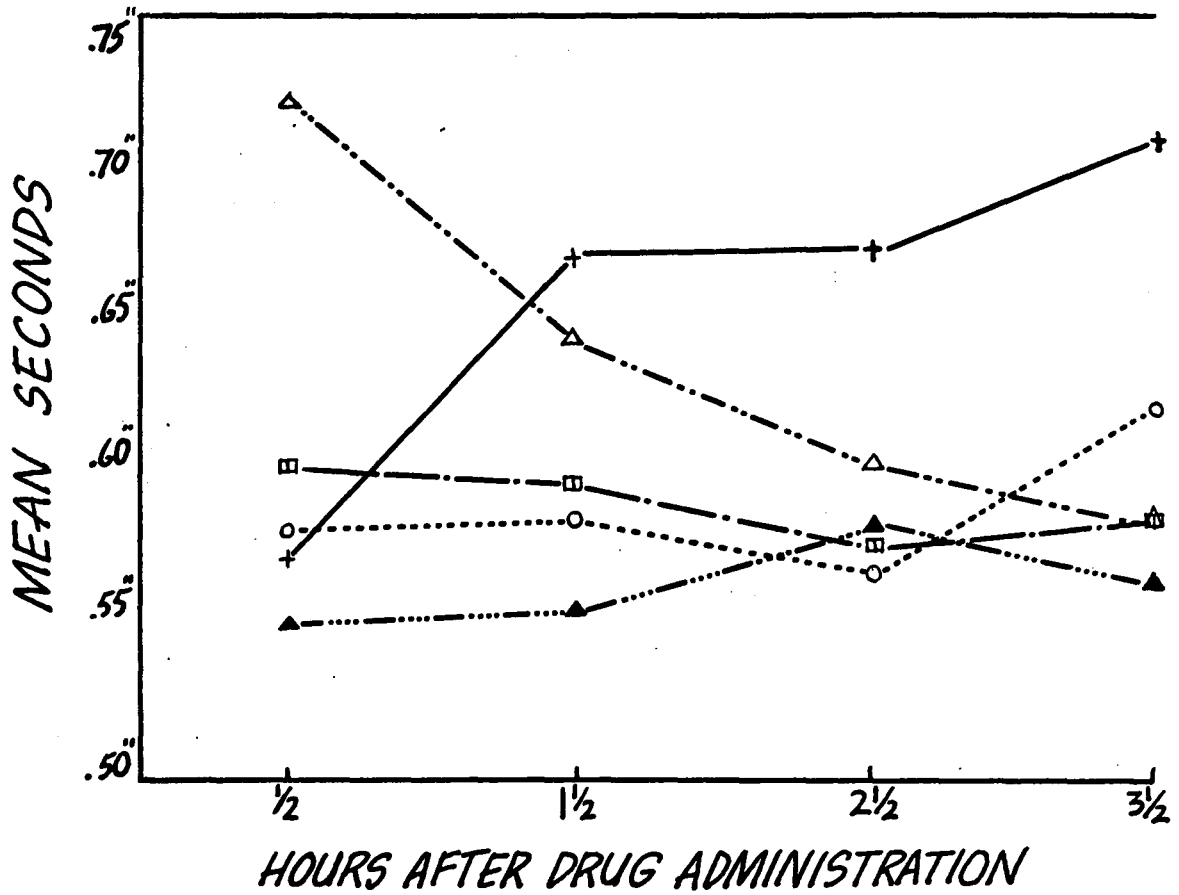


FIGURE 3. RESPONSE LATENCY. DRUG X HOUR INTERACTION

PLACEBO ▲-----▲
 CHLORPROMAZINE 100mg ○-----○
 CHLORPROMAZINE 200mg +-----+
 SECOBARBITAL 100mg ◻-----◻
 SECOBARBITAL 200mg △-----△

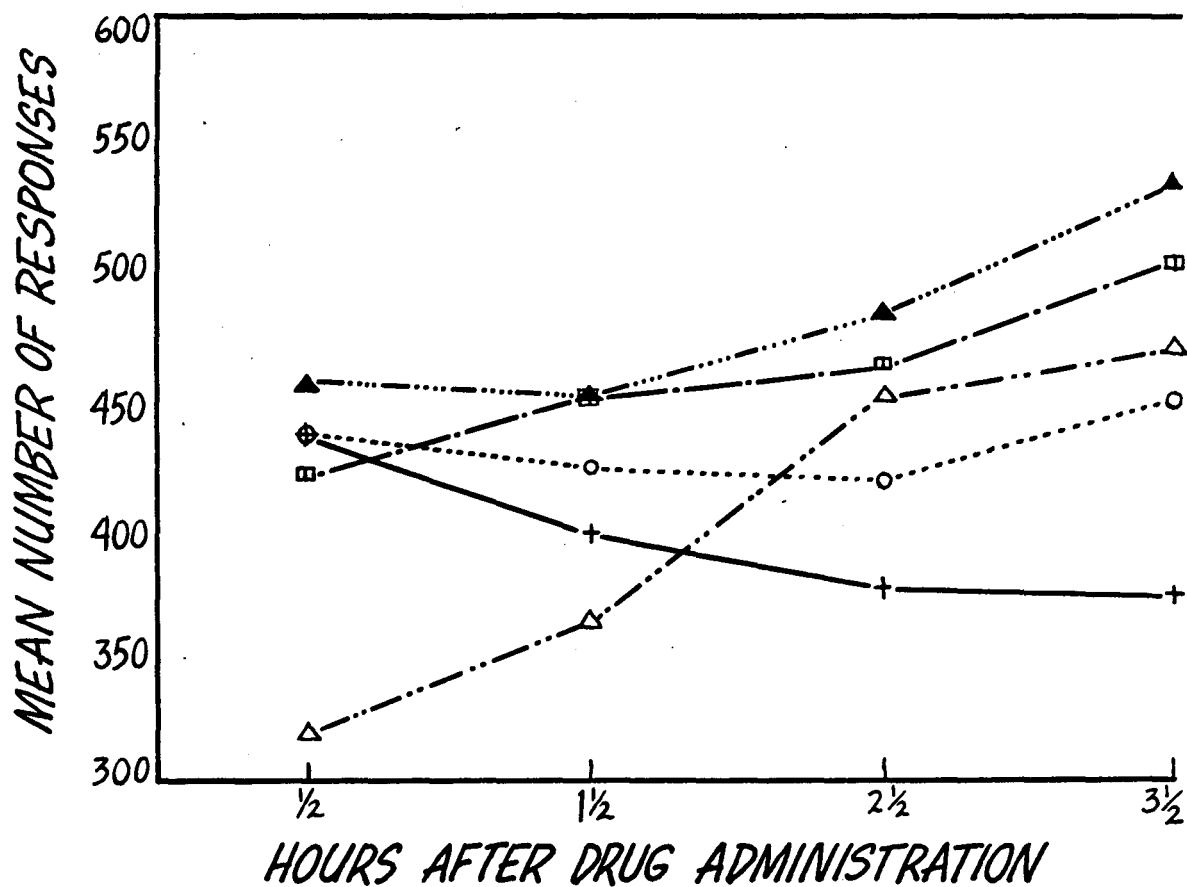


FIGURE 4. NUMBER OF RESPONSES (SPT), FIRST PERIOD
DRUG X HOUR INTERACTION

| | | | |
|----------------------|---|-------|---|
| PLACEBO | ▲ | | ▲ |
| CHLORPROMAZINE 100mg | ○ | | ○ |
| CHLORPROMAZINE 200mg | + | ———— | + |
| SECOBARBITAL 100mg | ◻ | | ◻ |
| SECOBARBITAL 200mg | △ | | △ |

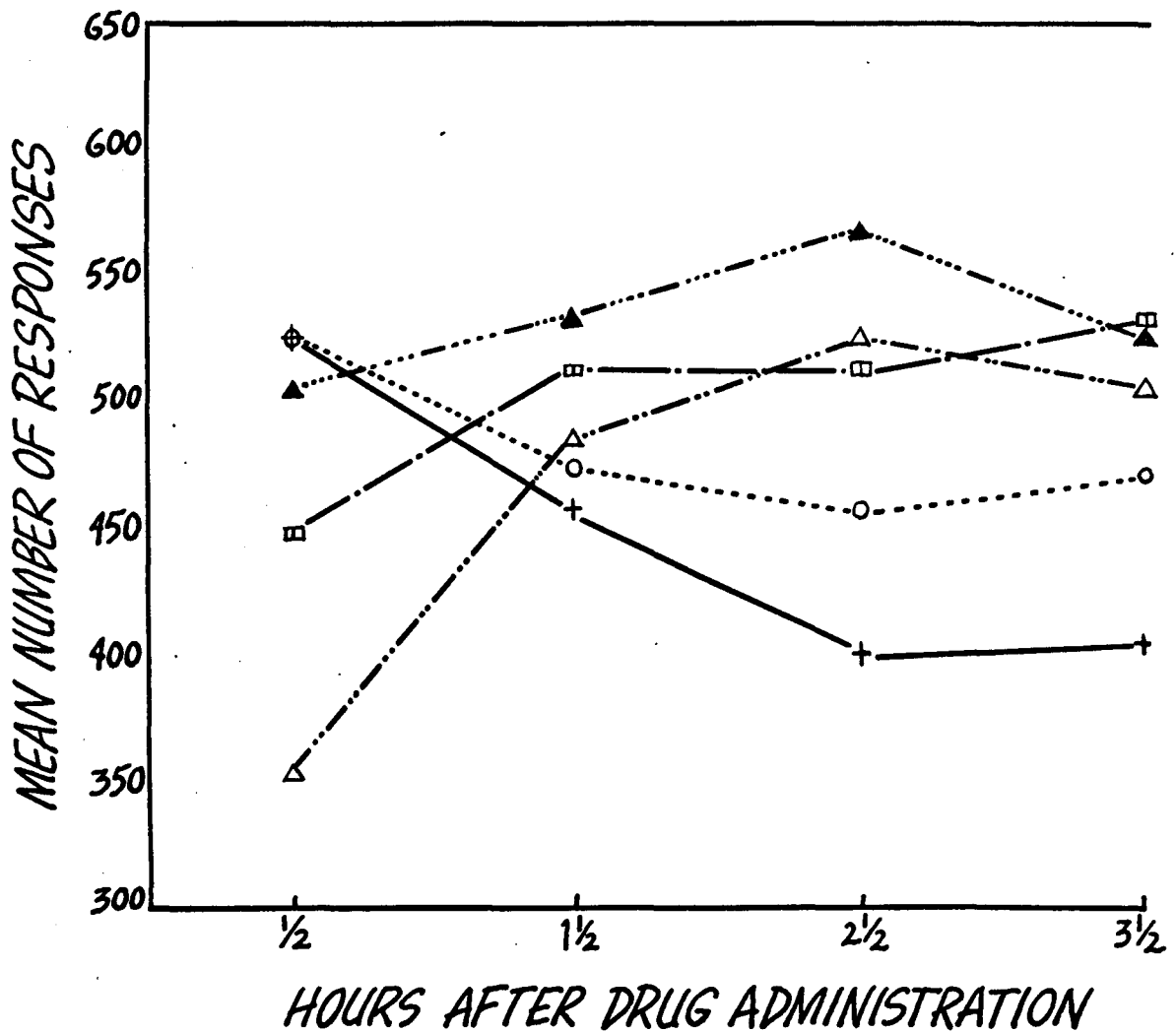


FIGURE 5. NUMBER OF RESPONSES (SPT), SECOND PERIOD
DRUG X HOUR INTERACTION

| | | | |
|----------------------|---|-------|---|
| PLACEBO | ▲ | | ▲ |
| CHLORPROMAZINE 100mg | ○ | | ○ |
| CHLORPROMAZINE 200mg | + | ———— | + |
| SECOBARBITAL 100mg | ◻ | | ◻ |
| SECOBARBITAL 200mg | △ | | △ |

Figure 3 shows the time-response curve of the drugs with respect to the response latency measure. Again, the peak effect of secobarbital is evident 1/2 hour after administration; while the effect of chlorpromazine is negligible 1/2 hour after administration, but increases steadily thereafter. During the last post-drug testing session, the chlorpromazine effect is approaching its peak. Figure 3 also shows that both doses of each drug have similar time courses, and that performance under placebo changes little from hour to hour.

As is seen from Figures 4 and 5, the peak effect of secobarbital with respect to the number of responses on the SPT, as in the case of all other measures, is 1/2 hour after drug administration; chlorpromazine, however, reaches its peak 2 1/2 hours after drug administration, which is earlier than in the case of the other measures. It will be noted in Figure 4 that the placebo curve shows an acceleration from the first to the fourth testing session. This increase is significant, as indicated by the significant P value for Hours on this measure in Table 4, Appendix C, and it is the only case where placebo performance was significantly different between any two testing sessions during the same day.

Since the time-response curves of the two drugs are different, the evaluation of their relative effects on the behaviors under study is based on the comparison between their

peak effects. Figures 6 and 7 show the results of these comparisons. In Figure 6, the effects of the 100 mg doses of both drugs on the dependent variables are compared, while Figure 7 presents the comparisons between the 200 mg doses of both drugs.

Figure 6 shows that at its peak, the effect of 100 mg of chlorpromazine was more pronounced on omission errors and response latency, and that both drugs had an identical effect on the other dependent variables. As is seen from Figure 6, none of the comparisons are statistically significant.

The selective effects of chlorpromazine on sustained attention are more pronounced with the higher doses (Figure 7). Although none of the differences in Figure 7 are statistically significant, they clearly demonstrate the dissimilar effects of the drugs. Thus, the effect of the 200 mg chlorpromazine dose is greater on omission and commission errors, and the reverse is true for number of responses on the SPT and response latency.

D. The Effect of the Drugs in the Presence of Reinforcement

The findings confirm the hypothesis that in chronic schizophrenics the effects of chlorpromazine and secobarbital are reduced in the presence of reinforcement.

As was noted earlier (See Table 2), reinforcement significantly improves performance on all dependent variables except

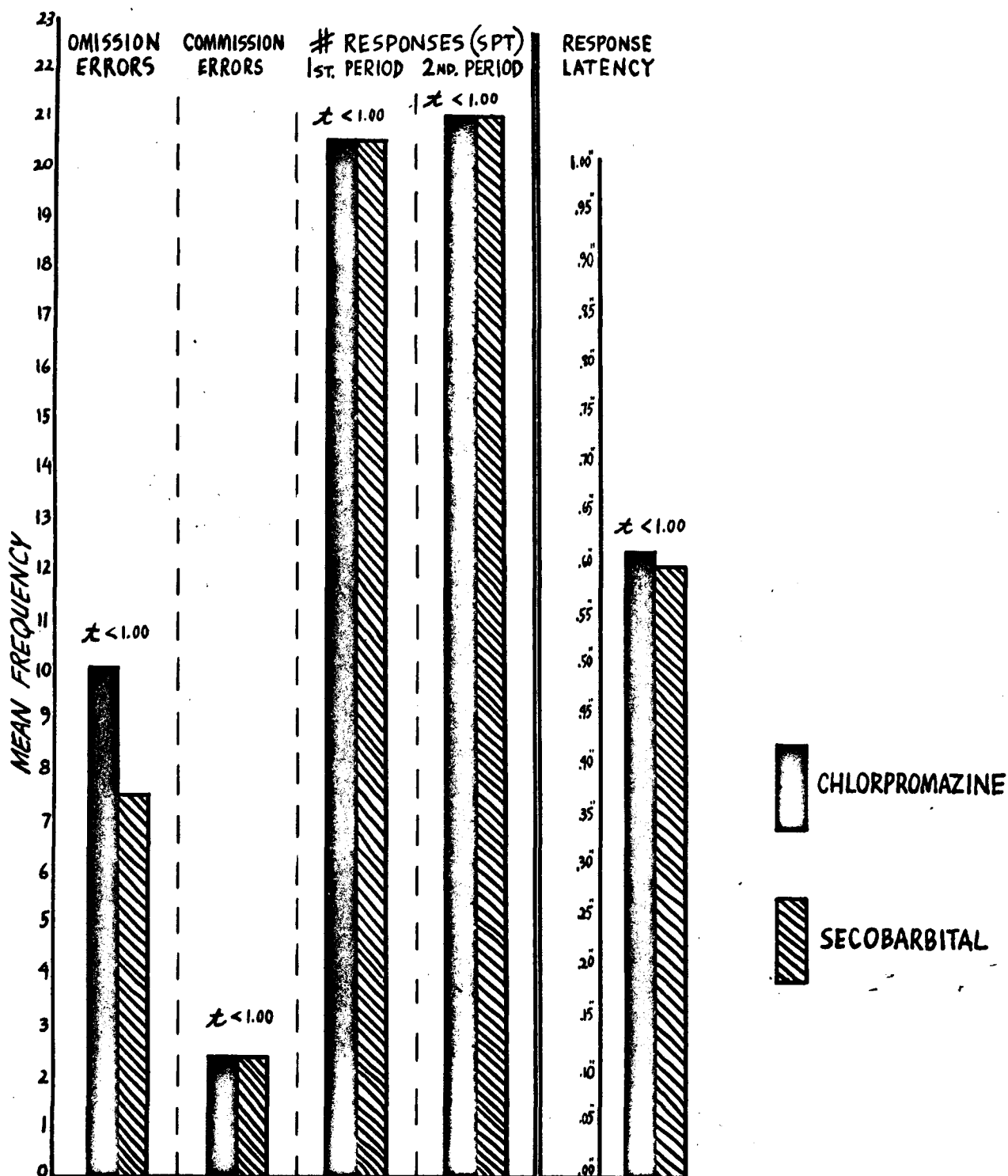


FIGURE 6. MEAN AND t TEST COMPARISONS BETWEEN THE PEAK EFFECTS OF 100_{mg} CHLORPROMAZINE AND 100_{mg} SECOBARBITAL

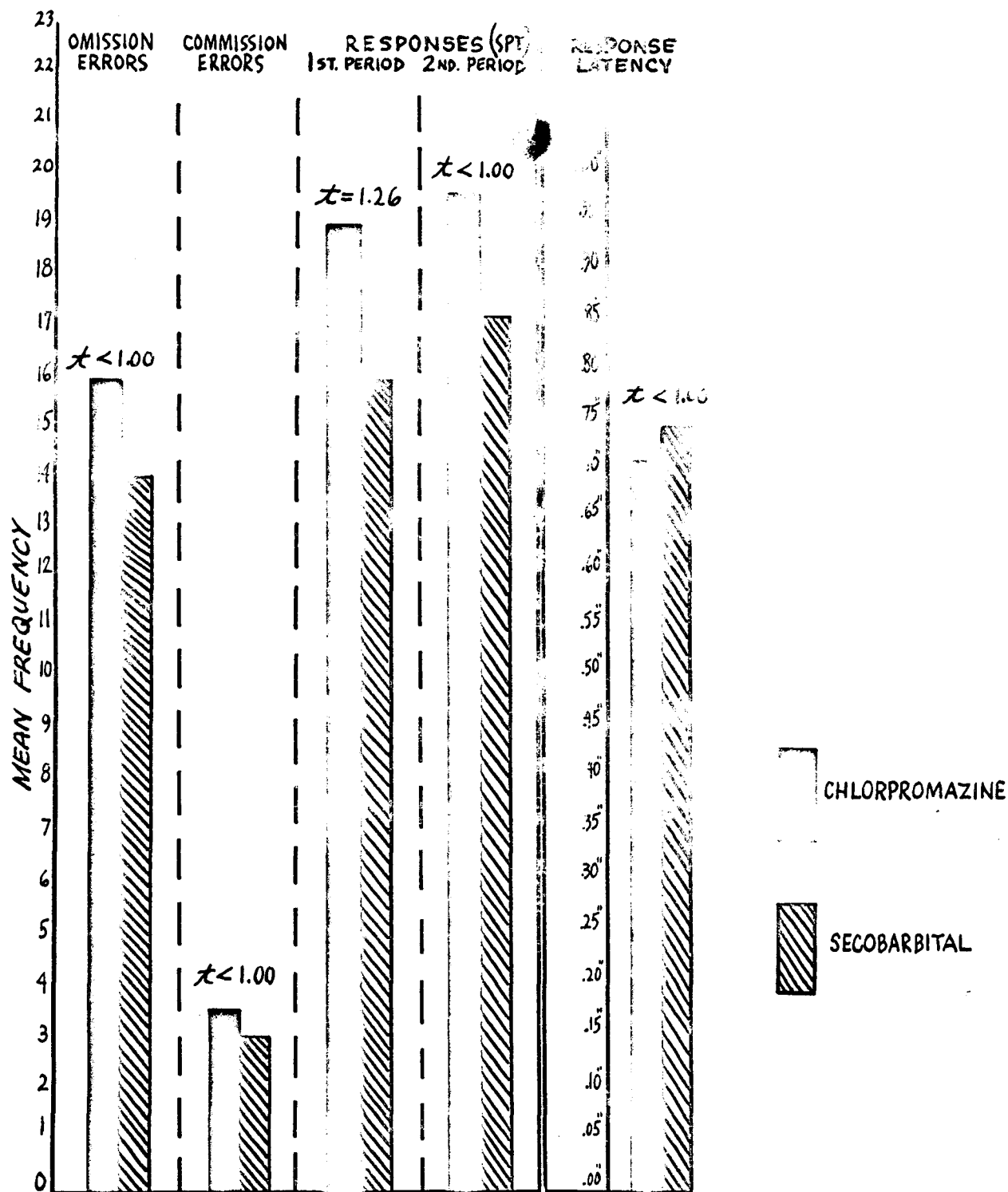


FIGURE 7. MEAN AND t TEST COMPARISONS BETWEEN THE PEAK EFFECTS OF 200_{mg} CHLORPROMAZINE AND 200_{mg} SECOBARBITAL

errors of commission. That the reinforcement effect is similar over all the experimental drug conditions is evident from the absence of a significant Drug X Reinforcement interaction (See Table 8). Figures 8, 9, 10, and 11 give a graphic illustration of the changes in the mean performance scores of the dependent variables under the experimental conditions. Table 8 summarizes the statistical results from the analyses of variance and the multiple comparison tests. In all figures the experimental conditions are plotted along the horizontal baseline, and the means along the vertical. As is evident from these figures, the overall effect of the active drugs is to impair performance; and the overall effect of reinforcement is to improve performance. Furthermore, the reinforcement effect is independent of the particular experimental conditions, having a nearly identical effect in the presence of all the active agents.

Table 8 indicates the significance values associated with the different sources of variance, as well as the significance values associated with the interaction terms for each dependent variable. The effect of "Drugs" and "Reinforcement" on performance is significant on all measures taken. The interaction between these two terms is not significant. The absence of a significant interaction between drugs and reinforcement indicates that both effects are independent of each other, i.e.,

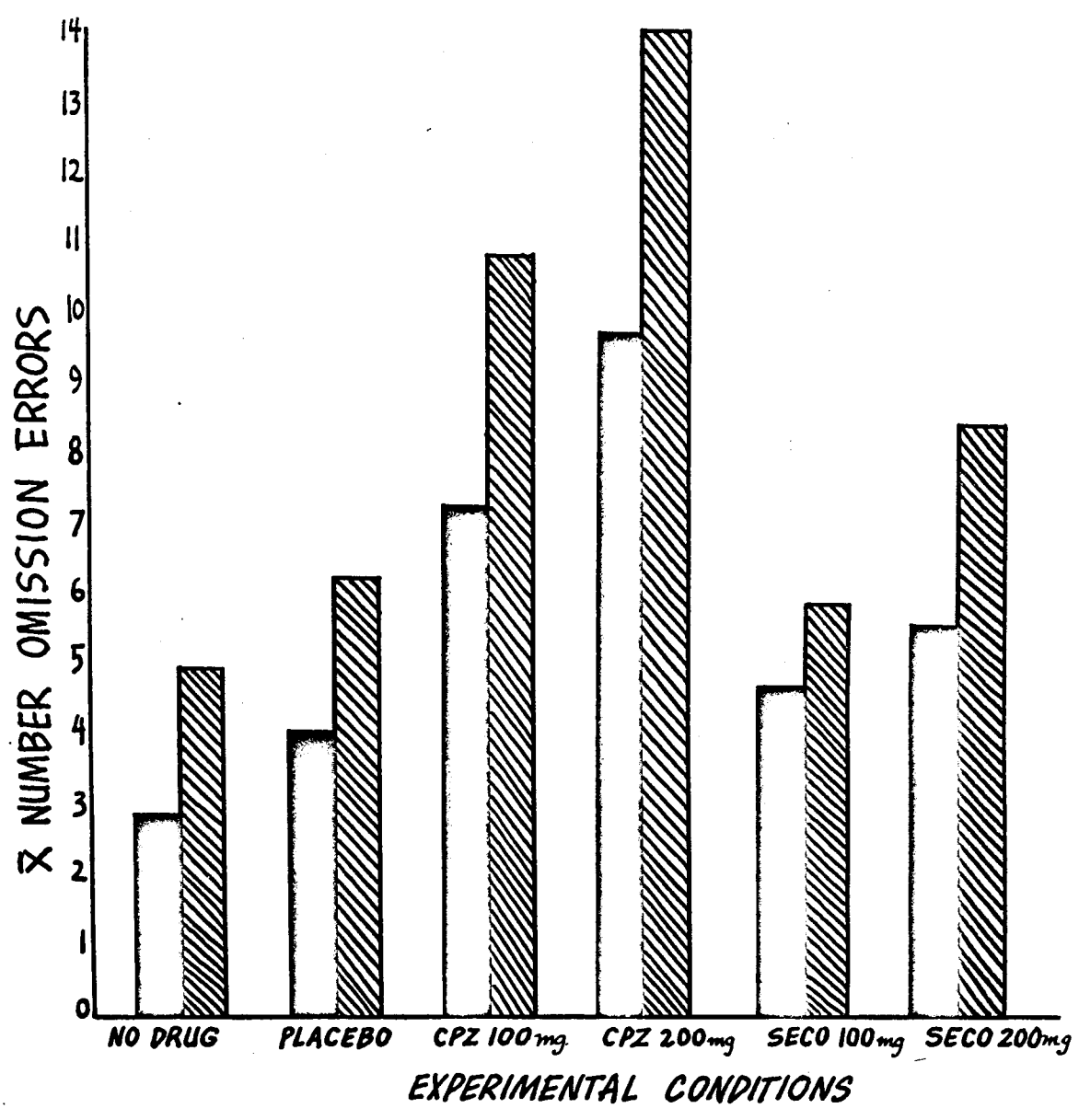


FIGURE 8. NUMBER OF OMISSION ERRORS AS A FUNCTION OF THE EXPERIMENTAL CONDITIONS

REINFORCED TRIALS  NON-REINFORCED TRIALS 

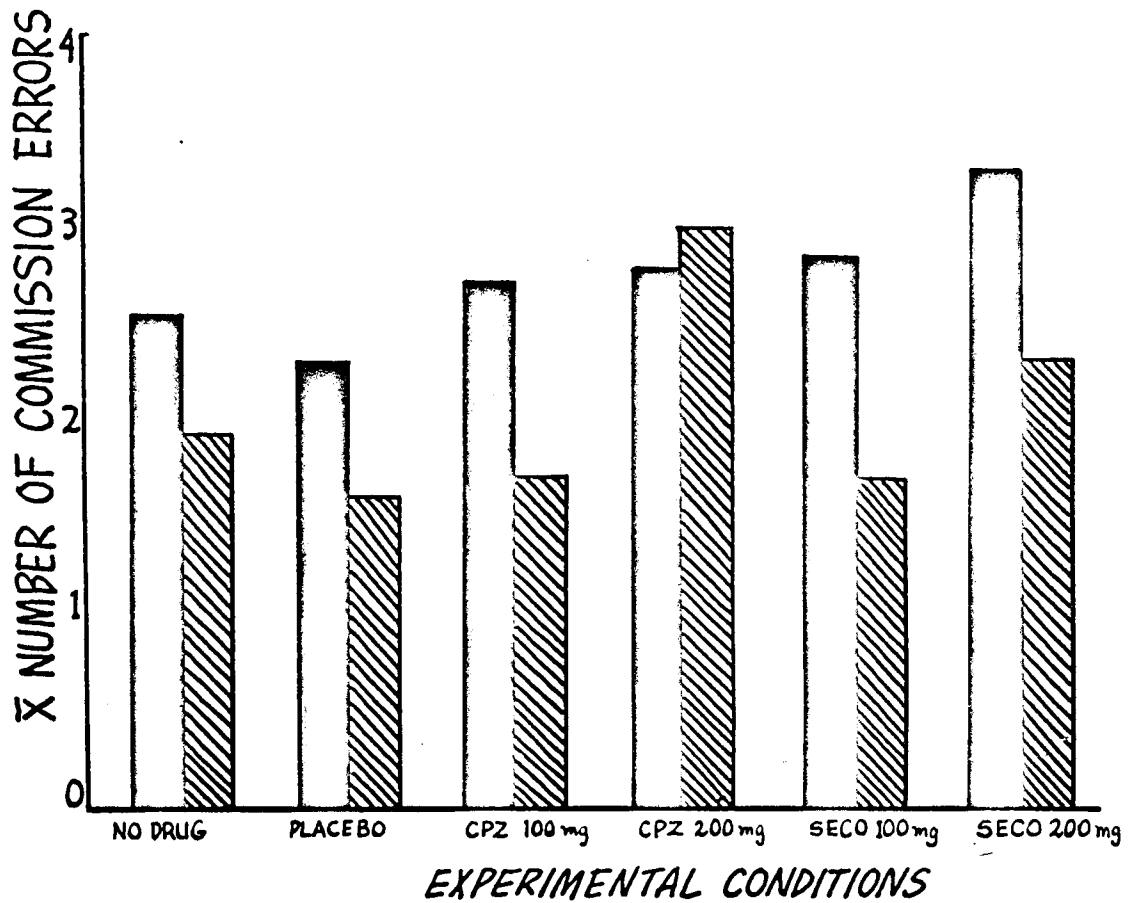


FIGURE 9. NUMBER OF COMMISSION ERRORS AS A FUNCTION OF THE EXPERIMENTAL CONDITIONS

REINFORCED
TRIALS



NON-REINFORCED
TRIALS



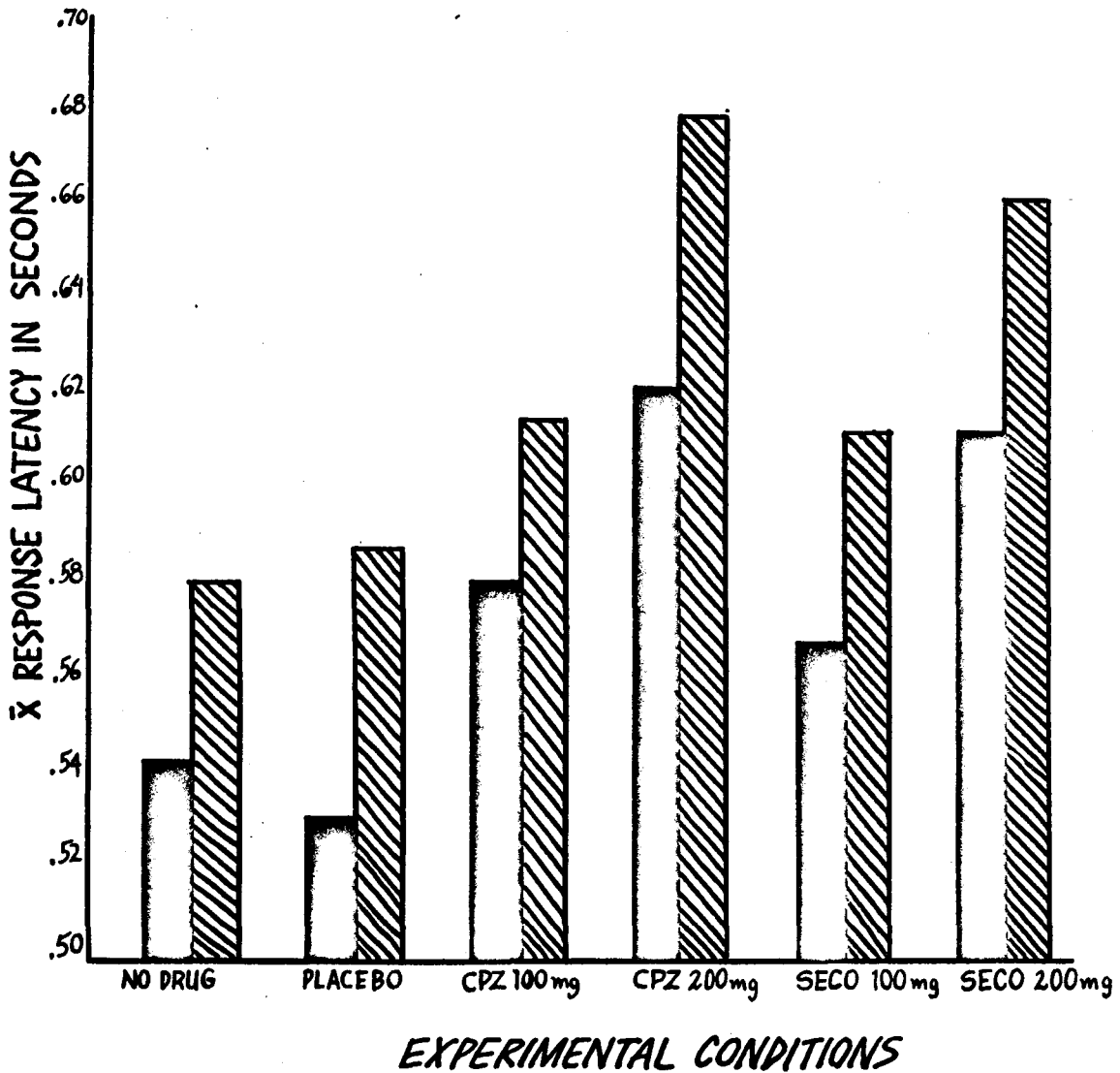


FIGURE 10. RESPONSE LATENCY AS A FUNCTION OF THE EXPERIMENTAL CONDITIONS

REINFORCED
TRIALS



NON-REINFORCED
TRIALS



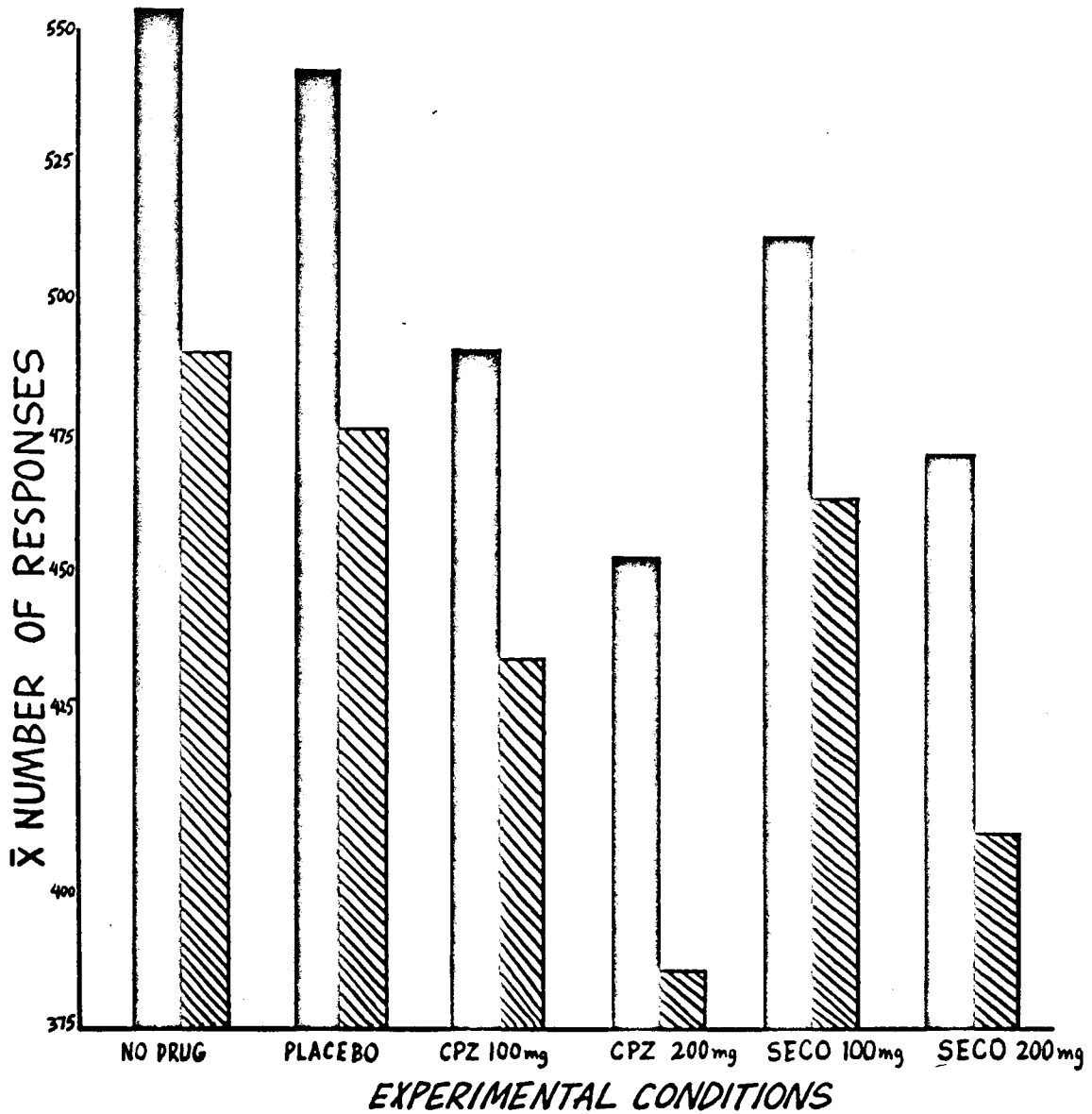


FIGURE 11. NUMBER OF RESPONSES (SPT) AS A FUNCTION OF THE EXPERIMENTAL CONDITIONS

REINFORCED TRIALS  NON-REINFORCED TRIALS 

the drugs impair performance on all measures in the presence of reinforcement and in the absence of reinforcement, while reinforcement improves performance in the presence and absence of the active drugs.

In the case of all measures but one, repeated testing during the same half day has no significant effect on performance. This is evident from the non-significant "Hour" effect. The one exception is the first period of the number of responses (SPT). In this case performance during the fourth post-drug session, independent of all other conditions, was significantly better than during the first post-drug session.

While the effect of "Hours" is not significant, the interaction between "Hours" and "Drugs" is significant in all cases but one. This indicates that except in the case of commission errors, the time-response curves of the different drug conditions are significantly different from each other. As was discussed earlier (See Figures 1 to 5), within the time limits of this experiment, the effect of secobarbital was greatest 1/2 hour after administration and declined fairly rapidly thereafter; while chlorpromazine had no detectable effect 1/2 hour after administration, but its effect increased steadily thereafter to a peak at 3 1/2 hours after administration.

The effect of reinforcement is not significantly different during any of four testing sessions of the same day. This

is evident from the absence of a significant interaction between "Reinforcement" and "Hours".

The triple interaction between "Drugs", "Reinforcement", and "Hours" is not significant.

Table 8 also summarizes the results of the Orthogonal Comparisons and Dunnett's Test. The table shows the significance value of the differences in the various comparisons. Absence of an entry indicates that the two conditions did not differ significantly in their effect on the particular measure. Thus, as the table shows, performance on all measures under 200 mg of chlorpromazine is significantly different from performance under placebo, while performance under 100 mg of secobarbital is significantly different from performance under placebo only in the case of response latency.

TABLE 6

Tabular Summary: Results of the Analyses of Variance,
The Orthogonal Comparisons and the Dunnett's Test

| Source | SPT | | | | |
|-------------------------------|--------------------|----------------------|---------------------|----------------------|-------------------------|
| | Omission Errors | Commission Errors | Response Latency | Number 1st Period | Responses 2nd Period |
| Drugs | <.0005 | <.01 | <.0005 | <.0005 | <.001 |
| *CPZ 100 mg - CPZ 200 mg | <.05 | <.01 | <.0005 | <.025 | <.05 |
| *Seco 100 mg - Seco 200 mg | -- | <.05 | <.0005 | <.0005 | <.025 |
| *Placebo - All Drugs | <.0005 | <.025 | <.0005 | <.0005 | <.001 |
| **Placebo - CPZ 100 mg | <.01 | -- | <.01 | <.05 | <.05 |
| **Placebo - CPZ 200 mg | <.01 | <.01 | <.01 | <.01 | <.01 |
| **Placebo - Seco 100 mg | -- | -- | <.05 | -- | -- |
| **Placebo - Seco 200 mg | -- | <.01 | <.01 | <.01 | <.01 |
| Reinforcement | <.01 | <.01 | <.0005 | <.0005 | <.0005 |
| Hours | -- | -- | -- | <.01 | -- |
| Drugs X Reinf. | -- | -- | -- | -- | -- |
| Drugs X Hours | <.0005 | -- | <.0005 | <.0005 | <.0005 |
| Reinf. X Hours | -- | -- | -- | -- | -- |
| Drugs X Reinf. X Hours | -- | -- | -- | -- | -- |

*Orthogonal Comparisons

**Dunnett's Test

CHAPTER V. DISCUSSION

This chapter will relate the findings from the present study to those reported by other investigators. For ease of exposition, the findings relating to each of the general hypotheses (p. 33) will be discussed in a separate section. A section will be devoted to the relation of the present findings to the activation theory, and a final section to suggestions for further research.

A. The Effect of Reinforcement

There is almost universal agreement that attention and psychomotor performance are impaired in schizophrenia. With respect to psychomotor impairment, the conclusion is derived from the comparison of the performance of chronic schizophrenics and normals on a large number of simple and complex psychomotor tasks. Although there is some evidence that the degree of impairment may be task specific, chronic schizophrenics are generally impaired relative to normals on almost all psychomotor tasks. The conclusion with respect to attention is based on clinical observations and indirect measurements, since tests designed to measure attention specifically are rare. As previously stated, reaction time studies which utilize preparatory intervals provide a good measure of sustained attention, and the concept of "preparatory set", which is invoked as essential in such performance, is very similar if not identical

to the definition of "sustained attention." Such reaction time studies have repeatedly demonstrated that relative to normals, the performance of chronic schizophrenics is impaired.

The results are inconclusive as to whether these performance deficits of chronic schizophrenics are modifiable in the presence of reinforcement. It is reported that positive verbal reinforcement, material rewards, and the cessation of shock or noise bring about an improvement in the performance of chronic schizophrenics. Improvement is also reported to take place when the tasks are made more interesting or when the experimenter urges the patients to perform better. Negative reinforcement, on the other hand, and tasks which are perceived as ego threatening are reported to impair the performance of chronic schizophrenics. Other studies, however, report no improvement in the performance of chronic schizophrenics in the presence of positive reinforcement, while others report improvement on some tasks only, or by some subjects only or both.

It is not possible to draw firm conclusions from the literature because the different studies are not strictly comparable. The studies vary with respect to the experimental arrangements, including such variables as sex, age, degree of pathology, and years of hospitalization of the subjects, as well as nature of the tasks, nature of the reinforcement conditions, and types of controls. The findings in general

suggest that the effect of positive reinforcement may be task specific, having a more pronounced effect on the performance on simple tasks. It also seems that reinforcement effects interact with subject characteristics. For example, positive, verbal reinforcement seems to improve the performance of more intact patients to a greater extent than it does the performance of more deteriorated patients, while the reverse seems to hold for the deleterious effects of negative reinforcement.

The effect of reinforcement upon the tasks of this study was not previously investigated. Since the literature indicates that the effects of reinforcement upon the performance of chronic schizophrenics may be task specific and may depend on the nature of the subjects, generalizations from the present findings may have to be somewhat limited. In the most general case, the findings from the present study permit the inference that in the presence of positive reinforcement, the sustained attention and psychomotor performance of chronic schizophrenics improves.

There are several implications in the present findings with respect to the effect of reinforcement. On a theoretical level, the general relationships between reinforcement and performance established for various populations are found in chronic schizophrenics as well. This point will be elaborated

upon more fully in a later section where the relationship between the present findings and the activation theory are discussed. The findings also imply that the behavior of chronic schizophrenics can be modified by the manipulation of incentive conditions, or conversely, that the behavior of chronic schizophrenics in a given situation may not be fully understood unless the reinforcement characteristics of that situation are known.

This last point is demonstrated in the present study. As was earlier shown, the effect of reinforcement was evident to the same degree in the presence of placebo and the active drugs. Studies in animals have repeatedly demonstrated the importance of reinforcement schedules in the modification of the observable effects of drugs. Similar studies with chronic schizophrenics are rare. But the present findings suggest that the toxic behavioral effects of psychoactive drugs in chronic schizophrenics may be reduced in the presence of reinforcement.

B. The Effect of the Drugs

It was emphasized in the previous section that due to sampling variability and differences in experimental design, it is difficult to draw valid conclusions from studies of chronic schizophrenics or explain discrepant findings. The same considerations apply to drug studies. These objections are less pertinent with regard to drug studies of normal persons, since

they usually employ samples from more homogeneous populations; namely, volunteer, male college students or attendants in mental hospitals. Drug studies of normals and chronic schizophrenics differ with respect to another very important variable, i.e., the duration of drug administration. On the whole, the reported experiments with normals are single dose studies; while those with chronic schizophrenics are chronic drug studies. There is ample pharmacological evidence that the single dose effects of many compounds are unlike those of chronic administration.

These considerations limit the extent to which valid comparisons can be made concerning the effects of drugs on normal persons and chronic schizophrenics. Evidence, however, has been accumulating that barbiturates impair the performance of normal persons and chronic schizophrenics whether given once or over time. Single doses of chlorpromazine also impair the performance of normal persons and chronic schizophrenics, but upon repeated administration, the toxic behavioral effects of chlorpromazine are less evident in chronic schizophrenics. This suggests that chronic schizophrenics develop tolerance to chlorpromazine but do not develop tolerance to barbiturates. From the limited evidence available, it appears that normal persons do not develop tolerance to either chlorpromazine or barbiturates.

Uhr (1960) arrived at a similar conclusion with respect to the effects of chlorpromazine. He writes:

The relatively few studies of chronic drug effects on patients in which laboratory tests, rather than the more traditional diagnostic batteries, have been used give a picture of minimal behavioral toxic effects from the tranquilizers tested. There are indications that these are smaller for patients than for normal subjects . . . (p. 623).

Some studies have reported that not only did chronic schizophrenics develop tolerance to the effects of chlorpromazine after repeated administration, but that their performance on psychomotor and other tasks improved. It has to be emphasized, however, that any reported improvement in performance as a result of the repeated administration of a drug cannot, by itself, be interpreted as due to the drug's specific action on the behavior studied, since the results may be confounded with clinical improvement.

The present findings show that the sustained attention and psychomotor performance of chronic schizophrenics is impaired under single doses of chlorpromazine and secobarbital. The findings also indicate that the impairment in performance is a function of the dose, the higher doses having a larger effect, and the time elapsed after the administration of the drug. The effects of secobarbital are evident only a short time after administration and decline relatively rapidly thereafter. The effects of chlorpromazine are small up to about one and a half hours after administration, but

are quite evident for two hours thereafter.

When the results from the present study are compared with findings in normals, it appears that on similar tasks the performance decrements produced by barbiturates are similar in normals and chronic schizophrenics, but that the performance decrement caused by chlorpromazine is more pronounced in normals. Such a comparison, with respect to omission errors on the CPT, appears in Appendix D.

As is seen from the table in Appendix D, 200 mg of secobarbital produced a very similar decrement in the performance of normal subjects and the subjects of the present study, but the chlorpromazine effects, especially for the higher dose, were much more pronounced in the normal subjects.

It appears, then, that chronic schizophrenics are as vulnerable as normals to the toxic behavioral effects of barbiturates, but that they are less vulnerable to the toxic behavioral effects of chlorpromazine. This dissociation in the effects of the two types of drugs in the two populations may be explained in neurophysiological terms or in more behavioral-psychological terms. It is likely that the receptor sites for chlorpromazine in the central nervous system are in some way altered in chronic schizophrenics as compared to normal persons. Ultimately, neurophysiological research may provide direct evidence on this question. But it is of interest to note that the midbrain receptor sites for both drugs, although

within the reticular system, are thought to be anatomically distinct (Killam and Killam, 1957; 1958; 1960; Bradley and Key, 1958).

The dissociation in the effects of the drugs, may also be explained in terms of a difference in the psychological reaction of normal persons and chronic schizophrenics to the pharmacological activity of the drugs. In a review of the pharmacological literature, Pelikan and Kensler (1958) have concluded that the peripheral changes which are induced by chlorpromazine are more extensive than are the peripheral effects of barbiturates. They write:

Sedative agents can also produce side effects referable to actions on peripheral systems. In therapeutic doses, such sedative agents as the barbiturates . . . seldom produce effects on systems other than the central nervous system (p. 12).

According to these authors, the incidence of side effects, such as tachycardia, hypotension, hepatotoxicity and dry mouth are more common after the administration of chlorpromazine.

The behavioral deficits, then, which are produced by chlorpromazine and secobarbital may be conceptualized as having two components: a central component and a peripheral one. Normals and chronic schizophrenics are affected by both, but chronic schizophrenics react to a lesser degree to the peripheral changes than do normals.

This less pronounced psychological reaction of chronic

schizophrenics to induced alterations in their internal environment may be understood in terms of the different life histories of chronic schizophrenics and normal, young adults (as are most subjects in psychopharmacological experiments). Even on a superficial level, the differences are great: the patients have had a variety of physical treatments and years of regimented conformity to a mental hospital environment, to mention just two factors.

The present finding that inert capsules (placebos) do not significantly affect the performance of chronic schizophrenics is in agreement with other published reports. Identical results were obtained in another acute study (Wynne and Kornetsky, 1960) as well as in studies with a six-week-placebo condition (Pishkin, 1962), and a twelve-week-placebo condition (Pearl, 1962). It is of interest to note that in the above-mentioned study by Pishkin, the test employed was the CPT. The findings reported by him together with those of the present study indicate that the CPT is a reliable measure even with chronic schizophrenics who are known to display considerable inter- and intra-subject variability.

As was earlier discussed, Kornetsky (1960) and Mirsky and Rosvold (1960) report that in normal subjects chlorpromazine has a selective effect on a test of sustained attention, while barbiturates have a selective effect on a more cognitive-type test. Mirsky and Kornetsky (unpublished) have summarized electroencephalographic, neuropharmacological, and behavioral evidence to show that there are different neural organizations which mediate performance on these two types of tests. It is

suggested that these neural organizations are differentially sensitive to the effects of chlorpromazine and barbiturates.

Findings from the present study indicate that the selective effect of chlorpromazine on sustained attention is also present in chronic schizophrenics. In the present study, the comparison between the action of chlorpromazine and secobarbital is based on their selective effects on sustained attention, response latency and psychomotor output. These findings indicate that when evaluating the effects of chlorpromazine on a given task, the possible role of sustained attention in the performance on the given task has to be considered.

C. Relation to the Activation Theory

The findings from the present study suggest that chronic schizophrenics are normally at a level of hypoactivation. The evidence for this suggestion rests on the data from this experiment which show that in the presence of the drugs performance was impaired, while in the presence of reinforcement performance improved. The evidence that chlorpromazine and secobarbital lower the level of arousal, and that reinforcement heightens the level of arousal was reviewed in an earlier chapter. Since the placebo-drug differences in this study were in most cases more pronounced than the differences between the reinforced and non-reinforced trials (whether during placebo or drug sessions), it would appear that the effects of the drugs on arousal are more pronounced than the reinforcement effects. It need be emphasized, however, that such

quantitative comparisons cannot be generalized but have specific reference to the exact variables of this study, i.e. it is quite possible that other reinforcement conditions would have an effect different from that of the present study.

A further note of caution with regard to the above conclusion stems from the absence of physiological measures of activation in the present study. Although it is reasonably well established by techniques independent of behavioral measurement that chlorpromazine and secobarbital cause a drop in the level of arousal, such independent confirmation of the effects of reinforcement is less extensive. Despite the absence of independent physiological confirmation, conceptualizing the data within the activation theory is of value in that it can be related to a systematic body of knowledge and theory. This is especially true for the present finding that when present together the drugs and reinforcement counteract each other's effects, as would be predicted by the activation theory.

If reinforcement raises the activation level of chronic schizophrenics, why is this not reflected in improved performance in some of the studies which investigated the effects of reinforcement? One explanation rests on the possibility that intended reinforcers had no such value. It can also be explained in terms of sample differences. Given the heterogeneous nature of schizophrenics, it is possible that some schizophrenics are normally in a state of high arousal. Consequently, further increases in arousal would tend to impair

performance rather than improve it. In one study, for example, Malmo, et al (1951) found that a group of chronic schizophrenics had a higher degree of spontaneous central nervous system activity than a group of normal controls. This explanation would apply to reports that the performance of chronic schizophrenics improves after the acute administration of chlorpromazine. Patients who are normally highly aroused should perform better when their level of activation is decreased towards a more optimum middle level. Studies, however, which report no improvement under reinforcement, or improvement under single doses of chlorpromazine, are the exception rather than the rule.

From a comparison of the present findings with those reported from studies of normal subjects, it appears that chronic schizophrenics are characterized by a lower level of arousal than are normals. It has been repeatedly demonstrated by many workers that the performance of chronic schizophrenics relative to normals is impaired on a large number of tasks. By reference to the postulated relationship between performance and arousal, chronic schizophrenics could be inferred to be either overaroused or underaroused. Since the present findings indicate that chronic schizophrenics function at a level of activation below that for best performance, the inference seems justified that they are characterized by a lower level of activation than are normals.

The foregoing discussion is based on the assumption that

the theoretical model provided by the activation theory applies to chronic schizophrenics as well as to normals. Although the present findings support such an assumption, in the absence of physiological measures they are only suggestive. In normals, for example, Mirsky and Cardon (1962) have shown that errors of omission, after sleep deprivation or 200 mg of chlorpromazine, were associated with a slowing of the EEG, increased finger pulse amplitude, and an increase in the length of the respiratory cycle. It would be of value to study schizophrenics in an analogous fashion for there are some indications that under certain conditions the correlation between behavioral measures and performance may be different for chronic schizophrenics than for normals. A study by Fedio, et al (1961) illustrates this point. These authors compared the performance of normal and chronic schizophrenic subjects on a reaction time test during which EEG recordings were made. There was no difference in the speed of reaction of the two groups when EEG alpha activity was present, but when alpha was blocked by an auditory stimulus, the reaction time of the normals improved whereas the reaction time of the schizophrenics became even slower. In this case, then, there was a dissociation between a physiological and behavioral response. The authors suggest that their findings support the hypothesis that EEG activation and behavioral arousal might be mediated by two different neural systems, and that the neural system which mediates behavioral arousal may be altered in chronic schizophrenics.

It is also likely, however, that the effect of a given auditory stimulus is not the same for normals and chronic schizophrenics. That the meaning of a stimulus may measurably affect the level of activation, and that a given stimulus may have a different meaning or differential reinforcing characteristics for normals and chronic schizophrenics was previously illustrated and discussed. It is possible, therefore, that the chronic schizophrenic subjects in the study by Fedio, et al were highly aroused by the auditory stimulus and that consequently their performance was impaired.

D. Suggestions for Further Research

The present findings show that in the presence of positive reinforcement, the performance of chronic schizophrenics improves. The results also show that the impairment in performance under chlorpromazine and secobarbital is reduced in the presence of positive reinforcement. It is reported in the literature that negative reinforcement impairs the performance of chronic schizophrenics. It would be of value to investigate the effects of the simultaneous presentation of negative reinforcement and psychoactive drugs.

Studies with normal subjects report that there is a lawful relationship between level of activation and excellence of performance. Whether such a relationship is characteristic of chronic schizophrenics is not known. The present findings suggest that the performance of chronic schizophrenics improves in the presence of agents which heighten the level of arousal

and is impaired in the presence of agents which lower the level of arousal. However, in the absence of physiological indices of arousal, such evidence is indirect and merely suggestive. For a more direct test of the relationship between arousal and performance, chronic schizophrenics should be tested under agents known to affect arousal, while physiological measures of arousal are concomitantly employed. Such studies would shed further light on the hypothesis that in chronic schizophrenics, there is a dissociation between behavioral and physiological arousal.

The present findings show that chlorpromazine has a selective effect on sustained attention; it is not known, however, whether this is peculiar to chlorpromazine or is characteristic of all the phenothiazines.

From a comparison of the present findings with those of research on normal persons, it appears that the performance of chronic schizophrenics is less affected by chlorpromazine than is that of normal subjects, but that the performance of the two populations is impaired to about the same extent by barbiturates. It was suggested that as compared to normals, chronic schizophrenics respond to a lesser degree to the peripheral effects of psychoactive drugs, but that they respond to the same degree to the central effects. Further experimentation with pharmacological agents which are known to affect primarily the central nervous system and agents which do not have such an effect would seem like a valuable research effort for the

determination of response differences between normals and chronic schizophrenics to the effects of drugs.

CHAPTER VI. SUMMARY

The purpose of the present study was to determine whether positive reinforcement, chlorpromazine and secobarbital alter the ability of chronic schizophrenics to maintain sustained attention and whether these affect their psychomotor functioning.

Neurophysiological and psychological findings indicate that the effect of reinforcement is to raise the level of activation, and that the effects of chlorpromazine and secobarbital are to lower the level of activation. Activation theory postulates that there is a lawful relationship between the level of activation or arousal and performance, and that this relationship is characterized by an inverted U-shaped curve. That is, on a given task performance is optimal at a moderate level of arousal and impaired at low or high arousal levels.

It is a further postulate of activation theory that variables which affect the level of activation will cause an impairment or an improvement in the performance of a given subject depending on the subject's pre-experimental level of arousal. That is, the performance of a subject in a high state of arousal will be impaired if his arousal level is depressed. Conversely, if a subject is normally in a state of low arousal, a moderate increment in his level of arousal will improve his performance and a depression of his arousal level will produce a further performance impairment.

The literature suggests that chronic schizophrenics are characterized by a state of hypoarousal. On the basis of these considerations the following general hypotheses were formulated:

1. Reinforcement improves sustained attention, augments psychomotor output, and decreases response latency in chronic schizophrenics.

2. Chlorpromazine and secobarbital impair sustained attention, decrease psychomotor output, and increase response latency in chronic schizophrenics.

3. Relative to secobarbital, the effect of chlorpromazine in chronic schizophrenics is more pronounced on sustained attention; less pronounced on psychomotor output and response latency.

4. In the presence of reinforcement the effects of these drugs in chronic schizophrenics are reduced.

The third hypothesis derives from recent findings that chlorpromazine, as compared to barbiturates, has a selective effect on sustained attention in normal persons.

Eight male, chronic schizophrenic patients, with an age range of 25-50 and in good physical health, served as the subjects. All subjects had been hospitalized continuously for at least three years. Medication was discontinued for all subjects two months before the study started.

In the course of twelve testing days, each patient had two testing days each on chlorpromazine 100 mg, chlorpromazine 200 mg, secobarbital 100 mg, secobarbital 200 mg, an inert placebo, and

no medication. The patients were rotated through all conditions, so that each patient served as his own control. A testing day consisted of four sessions: 1/2, 1 1/2, 2 1/2 and 3 1/2 hours post-medication. The time interval, thus, between medication and testing sessions was also subject to analysis.

The testing involved repeated administration of the Continuous Performance Test (CPT) and the Subject-Paced Test (SPT), given under conditions of reinforcement and no-reinforcement. Candy and cigarettes served as the reinforcers.

On the CPT, a test of sustained attention, a subject was required to respond, by pulling a lever, to one of twelve letters which were randomly exposed at the rate of 1.10 sec. for a period of .10". In this study the letter x served as the critical stimulus, and it appeared on the average every fifth letter.

The following measures were available from the CPT: a) errors of omission: missed responses to the critical stimulus; b) errors of commission: responses to stimuli other than the critical stimulus; and c) response latency: the time that elapsed between the onset of the critical stimulus and the response to it. The errors of omission and commission scores served as the indices of sustained attention.

The SPT was similar to the CPT except that the rate of stimulus presentation was controlled by the subject. Pulling one of two levers changed the stimuli till the critical stimulus appeared and stayed on unless the other lever was pulled. The number of total lever pulls served as the index of psychomotor output.

Two analyses of variance for correlated scores were performed on each dependent variable.

The first analysis evaluated the effect of placebo, as compared to the no-drug condition, as well as the variance associated with repeating the no-drug and placebo conditions twice. The second analysis evaluated the main drug, reinforcement and hour effects, as well as the interactions between them.

The statistical tests of the differences in performance under the placebo and no-drug conditions revealed no significant differences between the two conditions on any dependent variable of the experiment. The scores from the no-drug condition were, therefore, excluded from further statistical treatment.

In the case of all the dependent variables, except number of responses on the SPT, there was no significant difference in performance between the two periods. In the further analyses, therefore, the SPT scores from both periods were analyzed separately, while the scores from both periods of the other dependent variables were pooled.

In the presence of reinforcement, performance on all the dependent variables except commission errors was significantly better than in the absence of reinforcement. In the presence of the drugs, performance on all the dependent variables was significantly impaired. The effects of the drugs and reinforcement were found to be independent. The absolute impairment caused by the drugs was reduced when it was present simultaneously with

reinforcement. For each drug, the higher dose caused the greater impairment.

The time-response curves of the two drugs were dissimilar: the peak effect of secobarbital occurred 1/2 hour after administration, while chlorpromazine approached its peak 3 1/2 hours after administration. At their peaks, chlorpromazine had a greater effect on sustained attention, while secobarbital had a greater effect on both response latency and psychomotor output, but these differences were not statistically significant.

It is concluded from the results of the experiment that:

a) chronic schizophrenics are characterized by a level of activation below the optimum middle for best performance; b) positive reinforcement improves the sustained attention and psychomotor performance of chronic schizophrenics; c) chlorpromazine and secobarbital impair the sustained attention and psychomotor performance of chronic schizophrenics; d) the effects of chlorpromazine on sustained attention are larger than the secobarbital effects, and e) in the presence of reinforcement, the absolute impairment caused by chlorpromazine and secobarbital is reduced.

A comparison of the present findings with studies on normals suggests that: a) the effect of secobarbital is similar in both populations; b) the effect of chlorpromazine is more pronounced in normals; and c) the selective effect of chlorpromazine on sustained attention is present in both populations. Possible reasons for the dissimilar effects of these drugs in the two populations are discussed.

APPENDICES

APPENDIX A

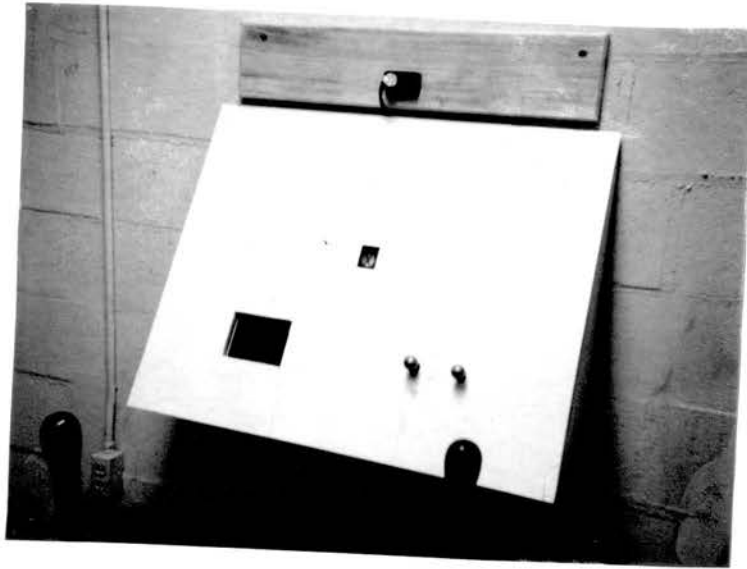
DESCRIPTION OF APPARATUS

Description of Apparatus

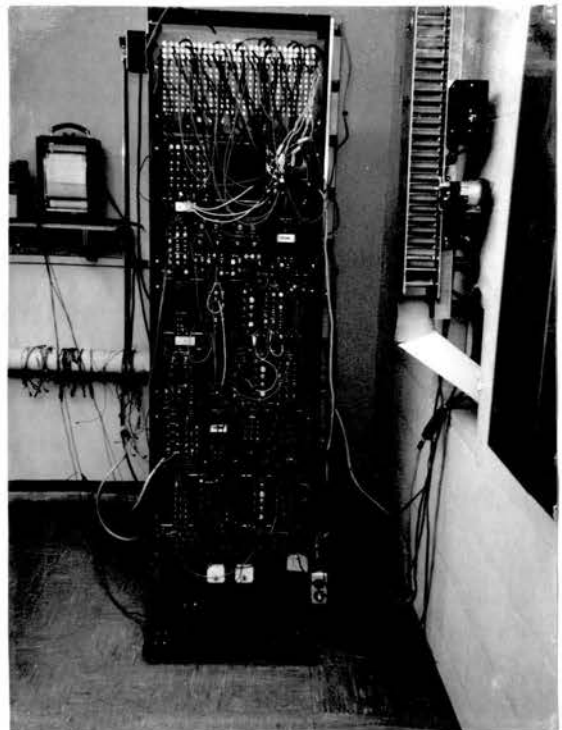
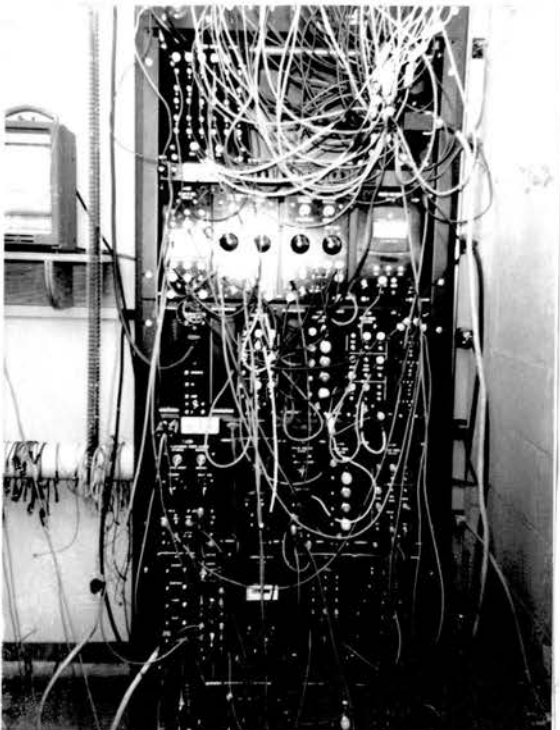
The apparatus employed was a combination of the operant conditioning machine, as used for humans, and the Continuous Performance Test (CPT), a test of sustained attention, described by Rosvold, et al (1956). A subject was seated before a manipulandum containing two pull-levers, a little window for the presentation of visual stimuli and a magazine receptacle for reinforcements (Photo A). A dim, small bulb illuminated the room which was bare otherwise. During testing, a subject was alone in the room, but the experimenter was able to observe him through a one-way mirror. In an adjacent room were the recording devices, the reinforcement magazine, and the machine that scheduled the presentation of stimuli and reinforcements. (Photo B). One at a time, twelve letters (A, C, E, H, K, L, N, P, S, V, X, Z) were randomly presented in the stimulus window at the rate of 1.10 seconds, and were exposed for 0.10 seconds. The letter X, the critical stimulus, appeared on the average once in every five stimuli. Each series consisted of 72 stimuli. The order of the stimuli within a series was changed from time to time, thus preventing the learning of an order and anticipating the critical stimulus.

In addition to the two timers which controlled the interval between stimuli and the duration of stimulus exposure, a third timer activated the reinforcement magazine, during

A



B



reinforced trials, for a fraction of the time between the onset of the X and the next stimulus. If a response occurred during this interval, it was reinforced. For each subject the time value represented the interval during which 50% of his responses to the X occurred under reinforcement and while in training.

The recording devices consisted of: a) four counters which recorded the number of total stimuli presented, number of critical stimuli presented, number of reinforced responses, and total number of responses; b) an Esterlyne-Angus Event Recorder which recorded the presentation of the critical stimuli, as well as all responses separately and those made to the critical stimulus; c) a clock which cumulated over a session the actual time that elapsed between the presentation of an X and the subject's response. The onset of an X activated this clock and a subject's response or the next stimulus if the subject did not respond, stopped it. For each session, then, it was possible to compute the mean-response latency by subtracting from the cumulated-response latency the time value of the unresponded-to X's, if such occurred, and dividing the remainder by the number of responses to the letter X.

APPENDIX B**STATISTICAL MODELS**

TABLE 1

Analysis of Variance Model For The Evaluation of
Placebo and Repeated Testing Effects

| <u>Source of Variance</u> | REINFORCED TRIALS | | NON-REINFORCED TRIALS | |
|------------------------------|-------------------|---------------------------|-----------------------|---------------------------|
| | <u>df</u> | <u>df for sig. test**</u> | <u>df</u> | <u>df for sig. test**</u> |
| Treatments (Placebo-No Drug) | 1 | 7 | 1 | 7 |
| Periods (1st - 2nd) | 1 | 7 | 1 | 7 |
| Hours | 3 | 21 | 3 | 21 |
| Subjects | 7 | | 7 | |
| Treatment X Periods | 1 | 7 | 1 | 7 |
| Treatment X Hours | 3 | 21 | 3 | 21 |
| Hours X Periods | 3 | 21 | 3 | 21 |
| Treat. X Hours X Per. | 3 | 21 | 3 | 21 |
| Error | 105* | | 105* | |

* The 105 degrees of freedom for error represent the value from the pooled interactions which was used for finding the error mean square.

** The values in this column, rather than the df associated with the pooled interactions, were used to enter the F table.

TABLE 2

Analysis of Variance Model For The Evaluation of the
Drugs, Reinforcement and Hour Effects

| <u>Source of Variance</u> | <u>df</u> | <u>df for Significance test**</u> |
|---------------------------|----------------|---------------------------------------|
| Drugs | 4 [†] | 28 |
| Reinforcement | 1 | 7 |
| Hours | 3 [‡] | 21 |
| Subjects | 7 | |
| Drugs X Reinforcement | 4 | 28 |
| Drugs X Hours | 12 | 84 |
| Reinforcement X Hours | 3 | 21 |
| Drugs X Reinf. X Hours | 12 | 84 |
| Error | 273* | |

[†] The 4 degrees of freedom are associated with the 5 drug conditions: placebo; 100 mg chlorpromazine; 200 mg chlorpromazine; 100 mg secobarbital; 200 mg secobarbital.

[‡] With 4 testing sessions on each test day, 3 df are available for the evaluation of hour effect.

* The 273 degrees of freedom for error represent the value from the pooled interactions which was used for finding the error mean square.

** The values in this column, rather than the df associated with the pooled interactions, were used to enter the F table.

APPENDIX C

ANALYSIS OF VARIANCE RESULTS

TABLE 1

Analysis of Variance: Errors of Omission

| <u>Source</u> | <u>Sums of Squares</u> | <u>Degrees of Freedom</u> | <u>Mean Square</u> | <u>F</u> | <u>P</u> |
|------------------------|------------------------|---------------------------|--------------------|----------|----------|
| Drugs | 2195 | 4 | 549 | 11.26 | <.0005 |
| Reinforcement | 698 | 1 | 698 | 14.31 | <.01 |
| Hours | 18 | 3 | 6 | < 1.00 | |
| Subjects | 9899 | 7 | 1414 | | |
| Drugs X Reinf. | 96 | 4 | 24 | <1.00 | |
| Drugs X Hours | 2606 | 12 | 217 | 4.45 | <.0005 |
| Reinf. X Hours | 7 | 3 | 2.3 | <1.00 | |
| Drugs X Reinf. X Hours | 95 | 12 | 8 | <1.00 | |
| Error | 13305 | 273 | 49 | | |

TABLE 2

Analysis of Variance: Errors of Commission

| <u>Source</u> | <u>Sums of Squares</u> | <u>Degrees of Freedom</u> | <u>Mean Square</u> | <u>F</u> | <u>P</u> |
|------------------------|------------------------|---------------------------|--------------------|----------|----------|
| Drugs | 50 | 4 | 12.50 | 4.65 | < .01 |
| Reinforcement | 40 | 1 | 40.25 | 14.96 | < .01 |
| Hours | 6 | 3 | 1.91 | < 1.00 | |
| Subjects | 708 | 7 | 101 | | |
| Drugs X Reinf. | 20 | 4 | 5 | 1.90 | |
| Drugs X Hours | 53 | 12 | 4.40 | 1.64 | |
| Hours X Reinf. | 8 | 3 | 2.73 | 1.01 | |
| Drugs X Hours X Reinf. | 17 | 12 | 1.40 | < 1.00 | |
| Error | 736 | 273 | 2.70 | | |

TABLE 3

Analysis of Variance: Response Latency

| <u>Source</u> | <u>Sums of Squares</u> | <u>Degrees of Freedom</u> | <u>Mean Square</u> | <u>F</u> | <u>P</u> |
|------------------------|------------------------|---------------------------|--------------------|----------|----------|
| Drugs | .3762 | 4 | .0940 | 20.00 | <.0005 |
| Reinforcement | .2050 | 1 | .2050 | 43.62 | <.0005 |
| Hours | .0017 | 3 | .0006 | < 1.00 | |
| Subjects | 8.8689 | 7 | 1.2670 | | |
| Drugs X Reinf. | .0082 | 4 | .0020 | < 1.00 | |
| Drugs X Hours | .4336 | 12 | .0361 | 7.68 | <.0005 |
| Hours X Reinf. | .0004 | 3 | .0001 | < 1.00 | |
| Drugs X Reinf. X Hours | .0162 | 12 | .0014 | < 1.00 | |
| Error | 1.2846 | 273 | .0047 | | |

TABLE 4

Analysis of Variance: Number Responses (SPT), 1st Period

| <u>Source</u> | <u>Sums of Squares</u> | <u>Degrees of Freedom</u> | <u>Mean Square</u> | <u>F</u> | <u>P</u> |
|------------------------|------------------------|---------------------------|--------------------|----------|----------|
| Drugs | 289 | 4 | 72 | 11.75 | <.0005 |
| Reinforcement | 169 | 1 | 169 | 27.59 | <.0005 |
| Hours | 99 | 3 | 33 | 5.39 | |
| Subjects | 2444 | 7 | 349 | | |
| Drugs X Reinf. | 7 | 4 | 1.7 | < 1.00 | |
| Drugs X Hours | 251 | 12 | 21 | 3.41 | <.0005 |
| Hours X Reinf. | 5 | 3 | 1.7 | < 1.00 | |
| Drugs X Hours X Reinf. | 13 | 12 | 1.06 | < 1.00 | |
| Error | 1676 | 273 | 6.14 | | |

TABLE 5

Analysis of Variance: Number Responses (SPT), 2nd Period

| <u>Source</u> | <u>Sums of Squares</u> | <u>Degrees of Freedom</u> | <u>Mean Square</u> | <u>F</u> | <u>P</u> |
|------------------------|------------------------|---------------------------|--------------------|----------|----------|
| Drugs | 193 | 4 | 48 | 7.59 | <.001 |
| Reinforcement | 161 | 1 | 161 | 25.34 | <.0005 |
| Hours | 12 | 3 | 4 | <1.00 | |
| Subjects | 3239 | 7 | 463 | | |
| Drugs X Reinf. | 5 | 4 | 1.18 | <1.00 | |
| Drugs X Hours | 495 | 12 | 41 | 6.48 | <.0005 |
| Hours X Reinf. | 1.22 | 3 | .41 | <1.00 | |
| Drugs X Hours X Reinf. | 8 | 12 | .64 | <1.00 | |
| Error | 1738 | 273 | 6.36 | | |

APPENDIX D

COMPARISON DATA WITH THE PERFORMANCE
OF NORMALS ON THE CPT

Average Number of Omission Errors Associated
with Placebo, Chlorpromazine, and Secobarbital
in Normals and Chronic Schizophrenics

| | PRESENT Reinforced Trials | STUDY Non-Reinf. Trials | Mirsky et al, [‡] 1959 | Mirsky and Cardon, 1962 | Primac, et al, [‡] 1957 |
|----------------------|---------------------------------|-------------------------------|---------------------------------------|----------------------------------|--|
| Placebo | 3.6 | 5.9 | 2.5 | 1.0 | 4.4 |
| CPZ 100 (2 1/2 hr) | 7.4 | 12.0 | 9.4 | | |
| (CPZ 100 - Placebo) | 3.8 | <u>6.1</u> | <u>6.9</u> | | |
| CPZ 100 (3 1/2 hr) | 8.1 | 11.8 | | | 10.6 |
| (CPZ 100 - Placebo) | 4.5 | <u>5.9</u> | | | <u>6.2</u> |
| CPZ 200 (2 1/2 hr) | 12.9 | 17.6 | 17.5 | | |
| (CPZ 200 - Placebo) | 9.3 | <u>11.7</u> | <u>15.0</u> | | |
| CPZ 200 (3 1/2 hr) | 13.4 | 18.4 | | 29.0 | 27.1 |
| (CPZ 200 - Placebo) | 9.8 | <u>12.5</u> | | <u>28.0</u> | <u>22.7</u> |
| Seco 200 - (30'-50') | 11.8 | 16.6 | 13.1* | | |
| (Seco 200 - Placebo) | 8.2 | <u>10.7</u> | <u>10.6</u> | | |

[‡] Both male and female subjects

* This is the median score for the group and is the omission error associated with the AX task (a response is demanded whenever X follows A) which is a more difficult task and produces more omission errors than the X task (a response is demanded to X regardless of the letter stimulus that precedes it).

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THE MODIFICATION OF SCHIZOPHRENIC PERFORMANCE
BY DRUGS AND BY POSITIVE REINFORCEMENT

Abstract of a Dissertation

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The purpose of the present study was to determine whether positive reinforcement, chlorpromazine and secobarbital alter the ability of chronic schizophrenics to maintain sustained attention and whether these affect their psychomotor functioning.

Eight male, chronic schizophrenic patients, with an age range of 25-50 and in good physical health, served as the subjects. All subjects had been hospitalized continuously for at least three years. Medication was discontinued for all subjects two months before the study started. In the course of the study, each subject was tested twice under all of the following conditions: no-drug, placebo, chlorpromazine 100 mg, chlorpromazine 200 mg, secobarbital 100 mg, secobarbital 200 mg. The drugs were given once weekly in single doses. A testing day consisted of four sessions: 1/2, 1 1/2, 2 1/2, and 3 1/2 hours post-medication. The different drug conditions were administered according to a modified Latin Square design with each active drug following each other active drug an equal number of times. Half of the trials in each session were reinforced by candy and cigarettes and the other half were not.

Two tests were employed: The Continuous Performance Test (CPT), and the Subject Paced Test (SPT). On the CPT, a test of sustained attention, a subject is required to respond, by pulling a lever, to one of twelve letters which are randomly exposed at the rate of 1.10 sec. for a period of .10 second.

The following measures were available from the CPT:

a) errors of omission: missed responses to the critical stimulus; b) errors of commission: responses to stimuli other than the critical stimulus; and c) response latency: the time that elapsed between the onset of the critical stimulus and the response to it. The errors of omission and commission scores served as the indices of sustained attention.

The SPT is similar to the CPT except that the rate of stimulus presentation is controlled by the subject. Pulling one of two levers changes the stimuli until the critical stimulus appears and stays on unless the other lever is pulled. The number of total lever pulls served as the index of psychomotor output.

An analysis of variance for correlated data revealed that the variances associated with "Drugs", "Reinforcement", and "Drugs X Hours" were significant for all dependent variables, but the "Drug X Reinforcement" interaction was not. In no case was placebo different from the no-drug condition. The effect of 100 mg of secobarbital was significantly different from placebo on response latency only, but the effect of the other drug conditions was significant on all three behavioral measures. For each drug, the higher dose caused the greater impairment.

The time-response curves of the two drugs were dissimilar: the peak effect of secobarbital occurred 1/2 hour after administration, while that of chlorpromazine was 3 1/2 hours after administration. At their peaks, chlorpromazine had a greater

effect on sustained attention, while secobarbital had a greater effect on both response latency and psychomotor output.

It is concluded from the results of the experiment that:

1. Reinforcement improves sustained attention, augments psychomotor output, and decreases response latency in chronic schizophrenics.

2. Chlorpromazine and secobarbital impair sustained attention, decrease psychomotor output and increase response latency in chronic schizophrenics.

3. Relative to secobarbital, the effect of chlorpromazine in chronic schizophrenics is more pronounced on sustained attention, but not on psychomotor output and response latency.

4. In the presence of reinforcement the effects of these drugs in chronic schizophrenics are reduced.

A comparison of the present findings with studies on normals suggests that: a) the effect of secobarbital is similar in both populations; b) the effect of chlorpromazine is more pronounced in normals; and c) the selective effect of chlorpromazine on sustained attention is present in both populations.



AUTOBIOGRAPHY

I was born in Utena, Lithuania, on July 1, 1927, the second of three children of Frieda and Nisan Latz. I attended grammar school and one year of high school in Lithuania. My education was interrupted in 1941 when Lithuania was occupied.

At the end of the war I migrated to Israel where I served with the armed forces during and after the War of Independence.

I came to the United States in 1952. From 1954 to 1958 I attended the University of Maine, where I was awarded the B.A. degree. In February of 1958 I entered the graduate program in psychology at Boston University and was awarded the M.A. degree in 1959. After receiving the M.A. degree I proceeded to study in the same institution towards the Ph.D. degree.

While a graduate student I worked as a research assistant in the psychology department and also on a psychopharmacological research study in the Boston University School of Medicine. I served as a trainee in clinical psychology at Medfield State Hospital.

In 1960 I married Elizabeth Davis.