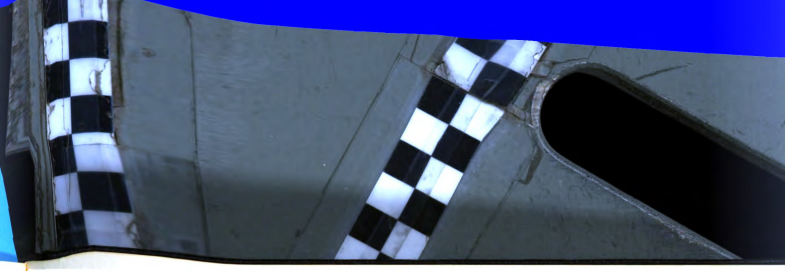

THE EFFECT OF PERPHENAZINE ON FOCUS OF ATTENTION IN SCHIZOPHRENIA

By

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A THESIS

Submitted to the School of Advanced Graduate Studies of Michigan State University of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

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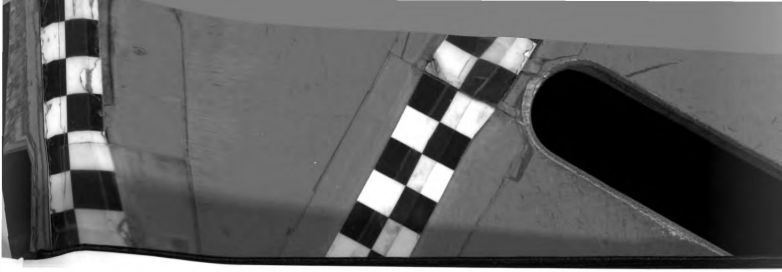


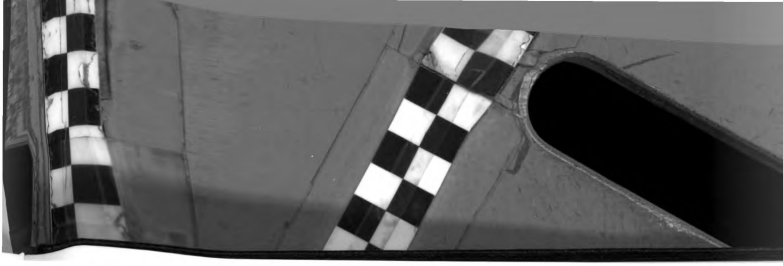
ABSTRACT

The present investigation was designed to explore a physiological activity that is widely held to be involved in attentive behavior and to test the hypothesis that experimental provocation of this activity by the drug perphenazine will be reflected in measurable behavior. Since the present design was not able to demonstrate drug effects on this physiological activity directly, interpretations are necessarily inferential.

Sixty schizophrenic female patients at Kalamazoo State Hospital served as Ss. All patients were medically cleared of physical and sensory involvements. These were divided into three groups of twenty patients each. Medication was administered orally over a period of three consecutive days. The two experimental groups respectively received low-dose perphenazine (12 mg. in divided doses t.i.d.) and high-dose perphenazine (48 mg. in divided doses t.i.d.), whereas the control group received an inactive placebo. The double-blind technique was employed.

Stimulus materials consisted of two tasks designed to measure focus of attention as considered in this investigation. One of these, the narrowed attention task, was a modification of procedures previously used in tests of interference. The second task, the broadened attention task, presented Ss with opportunities to guess which of two possible events will occur.

All materials were presented on No. 74 (heavy weight) Hi-Art hot-pressed, white illustration board.



Experiment I: Narrowed Attention Task

Ss were required to respond to one of two simultaneously presented stimuli each of which was an inherent aspect of the same symbol, a colored geometric figure. In the first instance, Ss were required to name shapes while ignoring colors; in the second, name colors while ignoring shapes. Difference scores between time (in seconds) taken to name one stimulus when presented alone and time taken to name that same stimulus in the presence of the second interfering stimulus served as the basic data for this experiment.

Statistical analyses employing the t test failed to differentiate between the performance of the high-dose group and each of the other two groups in the two separate parts of this task. Analyses of the combined performance scores did differentiate between high drug and placebo in the direction opposite to that hypothesized.

Accordingly, high-dose medication failed to affect performance of the kind called for in this experiment in the predicted direction. The first of the major hypotheses of this investigation is thus considered not confirmed. This hypothesis was stated as follows: Patients treated with perphenazine in dosage amounts presumed to stimulate the brain-stem reticular system will perform better on a task requiring "narrowed attention" (modified Stroop test) than will patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block brain-stem reticular system activity.

The incidence of Parkinsonism in the high-drug group is taken as clinical evidence that 48 mg. of perphenazine a day exceeds that required for optimal functioning.

Experiment II: Broadened Attention Task

Ss were required to guess which of two events (one less likely than the other) would occur. The number of guesses for the "less likely" event over the last eight trials of a ten trial series, served as the basic data for this experiment. Each trial consisted of ten events in which the ratio of less likely to more likely events was 2 to 8.

Analyses of variance over trials between the low-dose drug group and each of the other two groups significantly differentiated behavioral effects of low-dose perphenazine. These effects were in the direction of greater utilization in the use of peripheral cues required for successful performance.

Accordingly, low-dose drug medication may be considered as having a significant effect on performance of the kind called for in this experiment. The second of the major hypotheses of this investigation is thus considered confirmed. This hypothesis was stated as follows: Patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block the brain-stem reticular system will perform better on a task requiring "broadened attention" (guessing game) than will patients treated with perphenazine in dosage amounts presumed to stimulate brain-stem reticular system activity.

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To my constant motivators, Sib, Sudy and Debbie, I offer my thanks for the privilege of being indebted to them.

My greatest debt is to my wife, Helen. This thesis is dedicated to her, to all those above, to the many unmentioned who also helped, and to the patients who taught me much of the meaning of dignity and humility.

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INTRODUCTION

Neurophysiological aspects and bases of behavior have been given increasingly serious consideration during the past decade. A number of important works provide extensive and critical summaries of past and recent developments in this area and present a detailed statement of the current status of this aspect of behavior as viewed from experimental, anatomical, clinical, and psychological approaches (32, 37, 45, 49, 55, 57, 63).

Recent experiments by Calloway and his associates (11, 12, 13) have been directed toward a search for increasingly more measurable details of the relationship between neurophysiological activity and psychological behavior. By observing change in the focus of attention following the experimental provocation of change in neurophysiological activity, these investigators have provided further concrete evidence of the importance of neurophysiological activity as a partial determinant, at least, of behavior. The Calloway studies specifically lend support to the theory that the focus of attention is related to the activity of the brain-stem reticular formation. This brain sub-stratum, considered essential in the control and maintenance of states of consciousness, alertness, and wakefulness in the organism, is seen by Calloway and his group to produce narrowed attention when its activity is stimulated, and broadened attention when inhibited, depressed, or blocked. The focus of attention, narrow or broad, is considered in terms of the extent to which peripheral factors influence or determine behavioral performance. Peripheral

factors are defined as "those relatively current environmental events which are removed from the central focus of attention by space, by time, or by difference of meaning" (12). A decrease in the effects of peripheral factors denotes a narrowing of attention; an increase, a broadening of attention.

Administering drugs known to have specific effects on the brainstem reticular system, these investigators were able to observe changes in the focus of attention in apparently normal, healthy adult subjects. Reticular system stimulants such as amyl nitrite, epinephrine, methamphetamine, and various nerve gases produced narrowed attention (12, 13), while atropine, a reticular system depressant, produced broadened attention (11).

Psychologically, the findings of Calloway and his group have important and crucial implications. If a particular task is facilitated by attention to peripheral factors, then broadening attention will improve behavior. However, performance on a task which calls for a filtering out of distracting, peripheral factors will be impaired. Narrowing attention will of course have opposite effects, improving behavior on a task requiring the filtering out of distracting peripheral factors, while impairing performance on a task calling for attention to contributive peripheral factors.

THE BRAIN-STEM RETICULAR FORMATION

Recent research into mental and psychosomatic disease has pointed more and more clearly to the importance of a region deep within the brain. This region, the rhinencephalon, is the inner and older brain; it lies hidden, most of it near the midline, covered over by the outflow of the new brain, or neocortex, whose culmination in man marks his primary distinction.

Approximately three quarters of a century ago, Jackson (30) theorized that the brain evolved in phyletic layers of which the topmost layer is always highest in command. Accordingly, it was felt that as each new top layer developed, it modified for its own ends the mechanisms of the more primitive brain layers situated beneath it.

In 1933, Herrick (24) oppositionally reasoned that the rhinencephalon served as a non-specific activator for the cortex, facilitating or inhibiting learning, memory, overt behavior and internal attitude. At this time, it was generally accepted that the expression of emotion was mediated by the hypothalamus - not only autonomic reactions that result in pallor or blushing, quickened heartbeat, heightened blood pressure, sweating, or peristalsis, but also responses involving striated muscles, such as grimaces and trembling of rage. It was also felt that subjective experience of emotion quite probably required cortical participation. Obviously stimulated by Herrick's proposal, Papez (48) searched for neural pathways connecting the hypothalamus with the cortex. Based on an analysis of anatomical, experimental, and clinical data,

Papez found such connections by way of rhinencephalic structures. Unexpected support for Papez' physiological explanation of emotion was immediately available. When first announced, the Papez theory was highly speculative and in need of experimental confirmation. The more fruitful methods of exploring brain function involve observation of 1) the effects of removing or destroying a part of the brain, 2) the response to various kinds of stimulation, and 3) correlations between behavior and spontaneous electrical discharges within the brain. Kluver and Bucy (35) unknowingly supplied experimental confirmation of Papez' theory a few months before Papez' paper was published. Extirpation of portions of the rhinencephalon in a series of monkeys resulted in striking effects on emotional behavior. The Papez and Kluver-Bucy reports immediately stimulated widespread interest in the rhinencephalon. It is beyond the scope of this investigation to completely summarize the studies that followed, but the importance of the rhinencephalon in the neuronal organization of emotion has been well verified.

The ready acceptance of the rhinencephalon as an important physiological determinant of emotional behavior led to the investigation of specific areas or regions of this brain substratum. Among the important and interesting of the current research on the rhinencephalon is that being conducted by Heath and his associates at Tulane (21). These studies followed upon Heath's observations as a participant in the Columbia-Greystone lobotomy studies. In examining the effects of lobotomies and related operations, Heath noted that the most consistent reduction in emotional overflow from memories resulted from removal of that part of the prefrontal cortex which was connected with the septal

region of the rhinencephalon. By means of implanted electrodes, the Heath group showed that stimulating the septal region resulted in an alerting response and in behavior which was considered to be more generally favorable. Stimulation of other areas of the brain resulted in the important finding that the same emotional response always accompanied or followed stimulation of a specific region. Such findings lend general support to ideas expressed by Herrick (24), Papez (48), Kluver and Bucy (35), and others who opened up this line of investigation. Heath's interest in the septal region of the rhinencephalon parallels somewhat the investigations of midbrain functions by a number of other workers. Magoun (38, 39) has focused his work on the activating system of the brain stem. This ascending reticular activating system, as Magoun calls it, exerts an over-all effect on consciousness. When activated, it facilitates both behavior and the central alertness that characterizes the waking state. Whereas Magoun's system exerts its effect upon the cortex in a generalized manner without evidence of topographical localization, Jasper (31) has outlined a corresponding system in the thalamus topographically organized to exert an influence upon more restricted areas of the cortex. In addition, Jasper was able to demonstrate that a converse phenomenon characterized the functional aspects of his thalamic reticular system. He found that stimulation of specific areas of the cerebral cortex can modify the activity within the reticular system of the brain stem. Thus, the latter is placed under the control of sensory stimuli from without and cerebral cortical elaboration from within. Himwich (27) and Rinaldi and Himwich (53, 54) have combined the reticular systems of Magoun and Jasper as a unit and call it the mesodiencephalic activating system.

The importance of this system to contemporary speculation and experimentation and its overall contribution to an explanation of the neurophysiology of behavior is reflected in the very recent publications of two symposia, Brain Mechanisms and Consciousness (4) and Reticular Formation of the Brain (50). These volumes represent a landmark in neurophysiological research with respect to behavior and provide an important step toward the integration of the findings of physiologists, psychologists and behavioral scientists into a unified approach to the understanding of behavior with respect to both its neurophysiological and psychological bases.

EXPERIMENTAL AND THEORETICAL BACKGROUND

Recent experiments by Calloway and his associates (11, 12, 13) suggest that changes in attention reflect underlying neurophysiological change. The first of these (13) studied the effect of endogenous sympathetic activity on the perception of size. Stress was produced in apparently normal healthy adults by the inhalation of amyl nitrite. The provocation of sympathetic activity by this method led subjects to increase their estimate of a distant object relative to a near object as compared to results obtained during non-drug performance. Similar findings were obtained with epinephrine and methamphetamine. On the basis of these findings, Calloway and Thompson (13) hypothesized a common neurophysiological factor and called it "central sympathomimetic activity." Since the three drugs used to produce physiological change all mimic the central component of sympathetic discharge, these authors concluded that an increase in central sympathomimetic activity was accompanied by a reduction in the responsiveness of subjects to things (stimuli) outside the immediate scene. This decreased environmental influence was called "narrowed attention."

To test the resulting hypothesized correlation between narrowed attention and central sympathomimetic activity, Calloway and Dembo (12) conducted a number of experiments the results of which confirmed or lent support to the hypothesized relationship. In each experiment, neurophysiological provocation by various sympathomimetic drugs produced narrowed attention reflected in a reduction of the behavioral influence

of peripheral factors. The findings reported by Calloway and Dembo include 1) changes in size matching produced by amyl nitrite, by epinephrine, and by methamphetamine, 2) changes in myographic activity to a tone of 110 decibels following administration of nerve gases, amyl nitrite, and amphetamine, 3) changes in GSR's to various stimuli with amphetamine, and 4) changes in guessing behavior produced by methamphetamine.

The behavioral effects of increased sympathomimetic activity provoked by drugs, in terms of narrowed attention, are likened by the authors to those produced by sudden and strong emotion, anxiety, and panic. Studies by Kinsey (33), Shipman (58), and Kohn (36), are cited as illustrative of the diminution and reduction of attention to peripheral and environmental factors during emotional states. Evidence for grouping the drugs used above and emotions together as sympathomimetic activating provocators is presented by Calloway (9) and Bradley and Elkes (3). A further, and very important common denominator of sympathomimetic activating drugs and emotions is that they both evoke an "alert" EEG by stimulating the brain-stem reticular formation. An immediate suggestion, important to the purpose of the present investigation, is that stimulation of the brain-stem reticular formation will produce a change in attention such that the behavioral influence of peripheral and environmental factors will be diminished or reduced, i.e. it will narrow attention. Conversely, it follows that a blockade of the brain-stem reticular system will result in behavior characterized by an increased influence of peripheral and environmental factors, i.e. the opposite of narrowed attention. In addition, if drugs, emotions and procedures which produce EEG arousal also produce narrowing of attention, then it should follow, according to Calloway and Band (11) that any drug which produces the

opposite of EEG arousal (i.e. EEG drowsiness) should also produce the opposite of "narrowed" attention (i.e. "broadened" attention). To test the broadened attention hypothesis, Calloway and Band (11) selected atropine as the independent variable. Atropine ideally satisfies the requirements for the continued study of attention by Calloway and his associates since it evokes high-amplitude slow-wave activity in the EEG (i.e. a drowsy record) and raises the threshold for EEG "arousal" by inhibiting or blocking reticular-formation activity, attributes which are oppositional to the sympathomimetic stimulant agents used in studying "narrowed" attention.

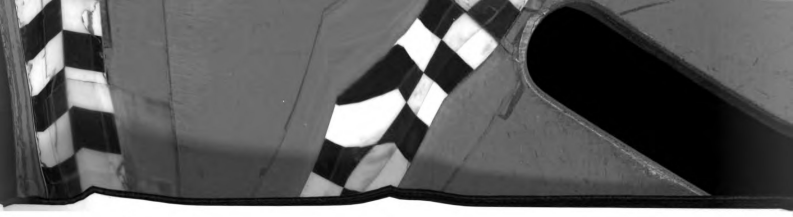
Three procedures were used by Calloway and Band to test the behavioral effects of atropine on normal healthy adults. Two of the procedures, the Stroop and Gottschaldt tests, were selected because successful performance on each required subjects to concentrate and attend only to those stimuli which were within the central focus of attention and to ignore or filter out all intrusive or interfering stimuli peripheral to the immediate focus of attention. These tasks call for operations which are more easily accomplished and performed by narrowly attending subjects whereas the third procedure, the Luchins test, according to this interpretation, is performed more successfully by broadly attending subjects. The results confirm the above implied hypothesis relative to the effects of a reticular substance inhibitor, atropine, in that performance on the Luchins test was improved while that on both the Stroop and Gottschaldt tests was impaired.

These studies by Calloway and his group, conducted over the past few years at the Psychiatric Institute of the University of Maryland, provide not only an important contribution to our understanding of the

neurophysiological basis of behavior, but perhaps more importantly, make more comprehensible and understandable the results of other investigators by applying the concepts of narrowed and broadened attention to these results. As an example, Calloway and Band (11) cite the work of Miles (44) who found that atropine decreased discriminating reaction-time while increasing simple reaction-time. Atropine, by neurophysiologically broadening attention, improved the subjects' capacity to discriminate by enlarging the subjects' field of attention. In a simple reaction-time situation, requiring the filtering out of intrusive and interfering stimuli, subjects did poorly because atropine-provoked broadening of attention seemed to direct subjects' attention to peripheral stimuli which served as detractors and thus impaired performance.

Similarly made more understandable in terms of the Calloway concepts of attention are studies of the effects of psychological provocation of the reticular formation. Pally (47) using threat to create strong emotion and thus stimulating the reticular system with accompanying EEG arousal and increased sympathomimetic activity, provoked narrowed attention in his subjects and obtained impaired performance on the Luchins test. As implied earlier, task success on the Luchins test requires broadened attention - attention to changing details of the earlier problems permitting simpler more economical solution of the last two problems.

As a final example of the application of the Calloway concepts of attention to the understanding and explanation of behavior we utilize the results of one of Klein's (34) most provocative experiments. Very thirsty subjects were divided into what Klein called high interference



and low interference groups (based on Stroop test performance.) On the basis of what has been said here, these groups may be characterized as broadly and narrowly attending groups respectively. These thirsty subjects were shown a series of pictures (exposed tachistoscopically for a very short period of time) in the center of which was an object designed to appeal to a thirsty person. Peripheral to this crucial central object were a number of neutral objects. Recognition of peripheral objects was most difficult for the low interference group of subjects (the narrowly attending group) who were continually drawn to the highly attractive central object. On the other hand, the high interference group of subjects (the broadly attending group) were able to ignore the highly appealing central object and explore more fruitfully the periphery of each picture.

The application of the narrow and broad concepts of attention to an understanding and explanation of the various behaviors observed in normal healthy subjects just considered may be extended to account for much of the behavior currently explained in such diverse terms as those invoked by classical Hullian theory or the dynamic formulations of psychoanalytic psychology. In a simple eyelid conditioning situation (60) high anxiety (increased narrowing of attention) leads to more rapid conditioning since the rather uncomplicated stimulus condition requires little or no participation of peripheral factors for acquisition. On the other hand, if the conditioning situation is increased in complexity, high anxiety causes inferior performance. One would hypothesize that decreasing anxiety, and thus broadening the attention required to cope with the complexity of the situation, would improve performance. Psychoanalytic and other psychodynamic formulations, based on a theory of

threat and fear may be explained and described in part as the consequence of the behavioral response associated with the focus of attention (obviously narrowed in the case of severe emotional states) to environmental stimuli. Characteristically maladaptive, neurotic and psychotic behavior both represent a failure to utilize all relevant environmental cues which would modify the perception of the stimuli considered threatening and thus produce a corresponding change in reaction to such stimuli. Within the laboratory, both narrowed and broadened attention may be required, depending on the situation, for successful performance in specific tasks. Some of these have already been discussed; many more can be suggested. However, realistic adaptation to the requirements of social living demands behavioral responsivity based on a broadened focus of attention. In general, schizophrenic patients suffer from a catastrophic restriction of adaptability, no matter whether this consists of an inability to react to the environment because of their pathological internal stimuli (hallucinations), or because of their inability to realistically integrate external events (delusions), or because of their inability to react at all (withdrawal, stupor) (57). The allowable interpretations of the results of this proposed study might contribute to a further understanding of this disorder in terms of neurophysiological correlates of behavior.

THE DRUG-INDEPENDENT VARIABLE

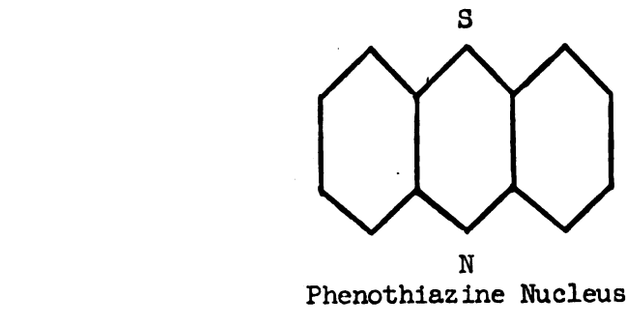
The drug, perphenazine (Trilafon), is an amino-derivative of chlorphenothiazine. Chemically it is 10-(3-(1-(2-hydroxyethyl)-4-piperazinyl)-propyl)-2-chlorphenothiazine. The structural formula is shown in Figure 1.

The core of the molecular structure of perphenazine, as with all the phenothiazine compounds, is the phenothiazine nucleus (Figure 1). It consists of two benzene rings connected by a sulfur atom and a nitrogen atom. Chlorpromazine, the prototype of the phenothiazine compounds by virtue of its early introduction and extensive investigation, has a chlorine atom attached to the nucleus in the 2-position, and a three-carbon "side chain" attached to the nitrogen atom of the nucleus. The third carbon atom in the side chain is followed by another nitrogen atom and the remaining valences of the nitrogen atom are filled by two methyl groups (Figure 1).

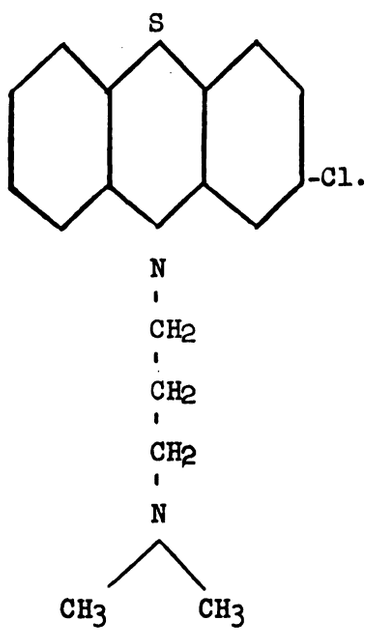
Changes in the structure of chlorpromazine, at the end of the carbon chain and to a lesser extent at the 2-position of the nucleus, have been made in search of compounds possessing increased clinical and therapeutic efficacy concomitant with reduced toxic risks and untoward side effects (18, 26, 28).

Perphenazine, in common with chlorpromazine (Thorazine), promazine (Sparine) and triflupromazine (Vesprin) has a chemical structure which includes three carbons in a straight chain. Freyhan (18) considers this chain to be a characteristic of drugs included in

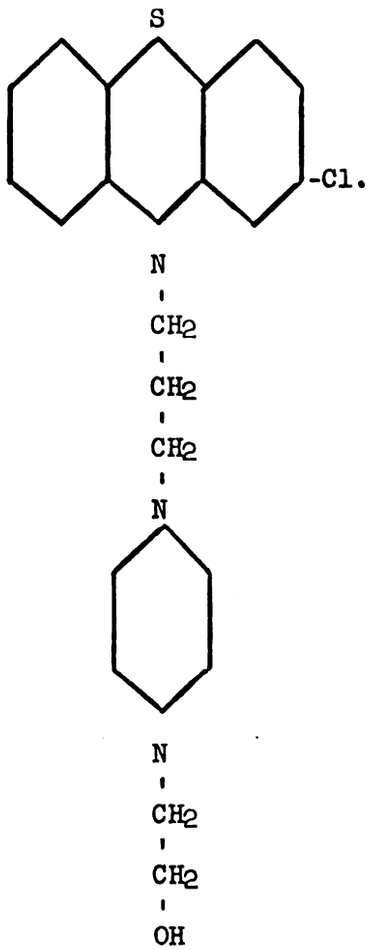
Figure 1



Phenothiazine Nucleus



(Thorazine)
Chlorpromazine



(Trilafon)
Perphenazine

what he calls the "chlorpromazine model." The significance of this chain in blocking mid-brain reticular system activity, was pointed out by Himwich (26). In addition to the three carbon straight chain, the structure of perphenazine includes a piperazine radical and, with prochlorperazine (Compazine) and trifluoperazine (Stelazine), is included in the group of drugs Freyhan has called the "prochlorperazine model." Interesting, and important for the present study, is the observation that drugs possessing the piperazine radical are said to produce alerting, arousal and stimulating effects (25). An equally interesting and provocative observation is the structural similarity of the phenothiazines to the anti-depressive drug imipramine (Tofranil). Himwich (26) regards this drug as a stimulant.

Finally, adding to its intriguing possibilities, perphenazine, when first introduced early in 1957 was heralded as a full-range tranquilizer recommended in various dosages for treating the entire spectrum of emotionally disturbed patients (17).

Preliminary clinical investigations summarized by Schering Corporation established perphenazine as a potent tranquilizing agent with important behavioral effects. Anxiety, tension, apprehension, aggression, psychomotor hyper-activity and fear have been found to be relieved following moderate dosage chemotherapy with this drug. The broad ataractic action claimed for perphenazine is such as to quiet and relax patients without dampening or reducing awareness. Patients are said to exhibit renewed interest in their work and surroundings. The emotional stabilization produced by this chemical compound is reported to increase the patient's capacity to respond to psychotherapy and other therapeutic measures.

Also, at moderate dosage levels, the more serious side and toxic effects have been observed infrequently or not at all. Photosensitivity, despite deliberate attempts to elicit this experimentally, has not been produced. Repeated studies of liver function, blood, urine, and visual fields have not revealed perphenazine-induced abnormalities. Although jaundice, bone-marrow depression and narrowing of visual fields have been associated with the use of various other tranquilizing drugs, they have been notably absent in studies with perphenazine.

The only serious side reactions reported are extrapyramidal symptoms, at times simulating those of the Parkinson syndrome, which occasionally occur following high doses (20 mg. daily) of the drug. A decrease or withdrawal of the drug quickly abolishes this reaction or if medication must be continued, control of these symptoms can be achieved by the concomitant administration of an anti-Parkinson drug such as benztropine methanesulfonate.

Side reactions of a less serious nature from the medical point of view have been observed. These include blurred vision, nasal congestion, and constipation. Only mild hypotensive effects have occurred which in many instances are believed to be associated with relief of anxiety and tension. Mild insomnia and motor restlessness, easily controlled by other means, have been reported in some patients. Hypnotic effects are minimal (18).

Published studies reporting on perphenazine in addition to strictly clinical trials have not yet appeared in large numbers. Ayd (1), treating twenty-five elderly psychiatric patients (age range 60-80

years) whose predominant symptoms were extreme anxiety, agitation and excitement found perphenazine clinically effective in those disorders in which anxiety is paramount.

Cahn and Lehman (8) administered perphenazine to eighty-four female patients and report perphenazine to be a useful and safe agent in the treatment of acute and chronic disorders. As with the Ayd study, lack of controls weaken the interpretative aspects of the study. In both studies, side reactions were mild and when they did occur were quickly abolished by appropriate counter-measures.

In a preliminary report, Mason-Browne (42) presents some tentative findings with perphenazine. A more detailed account of this same study is presented by Mason-Browne and Borthwick (43). They treated seventy-five chronic patients (36 males and 39 females) with a mean age of 41.8 years. All the patients displayed anxiety and over-activity, or were problems in management. The double-blind technique was used with patients divided into three groups of twenty-five. The three groups were each subjected to a different treatment schedule; Group I was given perphenazine 16 mg. t.i.d.; Group II, chlorpromazine 25 mg. t.i.d.; and Group III, an inactive placebo 25 mg. t.i.d. All medication was taken orally in tablets of the same shape, size and color. Duration of the study was thirty days. Urinary, blood, and liver function tests were made before and after the trial. Blood pressure, pulse, respiration, nausea, restlessness, anxiety, alertness, confusion, and insomnia were charted daily. A quantitative evaluation of behavior (acute anxiety cluster of the Wittenborn Rating Scale) was obtained pre- and post-test. Patients were also measured on a battery of tests consisting of tapping, dotting, digit symbol, digits forwards and

backwards, and Porteus Mazes. Perphenazine was significantly effective in alleviating acute anxiety. In addition, tapping and dotting performance was significantly superior than that with either chlorpromazine or placebo. No differences were obtained on other performance tests. All tests, with the exception of the Porteus Mazes, showed the greatest change towards improvement in the group treated with perphenazine. The placebo group showed the least change. In this study, the authors conclude that the drug acts principally on the alerting system of the brain stem. Its potency is placed at five to ten times that of chlorpromazine, and its therapeutic ratio is improved. Side effects were minimal. The term sciotic is substituted for tranquilizer which is considered a misnomer since, in the opinion of these investigators, these drugs affect crude or basic consciousness.

STATEMENT OF THE PROBLEM

The recent convergence of pharmacological and neurophysiological advances, especially with respect to the advent of the tranquilizing drugs and the further clarification of the functions of the mid-brain reticular system, respectively, has opened up new areas of investigation into mental illness. The literature on the tranquilizing drugs will not be reviewed at this time since much of it is not pertinent to our problem. Wikler (63) has provided a recent and painstaking review of the investigations relating pharmacological approaches to the diagnosis, explanation and treatment of psychopathological states. Important for the present investigation is that they all provoke mid-brain reticular formation activity (2, 25, 64). In view of the studies by Calloway and his associates which relate changes in the focus of attention to changes in mid-brain reticular activity, the observations of Himwich (27), Rinaldi (51) and Rinaldi and Himwich (52) are both interesting and provocative. These investigators suggest that the effect on mid-brain reticular activity of low-dose phenothiazine derivative drugs is inhibitory; high-dose, stimulating.

The problem to be investigated in the present study may thus be stated as follows: If different doses of a phenothiazine derivative drug have different effects on the activity of the mid-brain reticular system, and these in turn are reflected in differences in patient behavior, then patients treated with different amounts of the drug should perform differently on tasks calling for either narrowed or broadened

attention and these differences should be applicable to experimental study.

The two major hypotheses to be tested may be stated specifically as follows:

I. Patients treated with perphenazine in dosage amounts presumed to stimulate the brain-stem reticular system will perform better on a task requiring "narrowed" attention (modified Stroop test) than will patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block brain-stem reticular system activity.

II. Patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block the brain-stem reticular system will perform better on a task requiring "broadened" attention (guessing game) than will patients treated with perphenazine in dosage amounts presumed to stimulate brain-stem reticular system activity.

METHOD

Subjects

Sixty female schizophrenic patients at Kalamazoo State Hospital served as subjects in both experiments of this investigation. All were medically cleared of physical and sensory involvements. Each patient was clinically considered capable of comprehending the experimental requirements and of participating cooperatively. A summary of the characteristics of the patients may be found in Table 1 and 2.

Materials

Task I (Narrowed Attention Task)

The materials are modifications of those employed by Stroop (59) to study interference. Described by Thurstone (61) and more recently employed by Klein (34), Calloway and Band (11) and Broverman and Lazarus (6), the procedure involves the simultaneous presentation of two stimulus attributes, color and shape, which are inherent aspects of the same symbol. In the present investigation, the superimposition of one of the four primary colors on one of the four simple geometric figures selected met the criteria of inherency and simultaneity of presentation. The experimental materials for this task consisted of three 15" x 20" test cards and three 3" x 4" corresponding practice cards.

Test Card I (Figure 2) contained ninety-six geometric figures each black-outlined on white and one inch square in size. An equal number (twenty-four) of squares, circles, crosses and triangles were

Table 1

SUMMARY OF CHARACTERISTICS OF RESEARCH POPULATION

Low Drug Group (N = 20)			High Drug Group (N = 20)			Placebo Group (N = 20)		
Age in Years	Length of Hospitalization in Months	Weight in Pounds	Age in Years	Length of Hospitalization in Months	Weight in Pounds	Age in Years	Length of Hospitalization in Months	Weight in Pounds
45	40	157	42	38	160	30	41	110
51	36	124	45	35	206	34	37	149
54	35	145	46	35	121	45	35	129
20	32	130	37	31	186	36	31	135
34	31	206	38	30	189	33	31	127
29	31	215	37	24	113	32	28	106
44	27	138	45	24	200	48	24	181
51	24	165	33	23	143	49	24	113
36	23	140	46	21	100	41	22	112
37	22	113	49	44	149	41	42	120
37	19	118	43	49	171	48	20	161
47	18	143	32	17	144	45	17	141
23	17	112	36	46	125	37	16	127
37	16	194	30	15	163	17	15	155
30	14	109	33	14	202	28	14	145
35	13	101	35	45	121	31	13	114
47	12	143	33	7	168	39	11	133
37	11	146	48	6	139	42	14	126
37	10	157	30	7	116	34	30	158
36	40	209	53	18	149	36	44	185

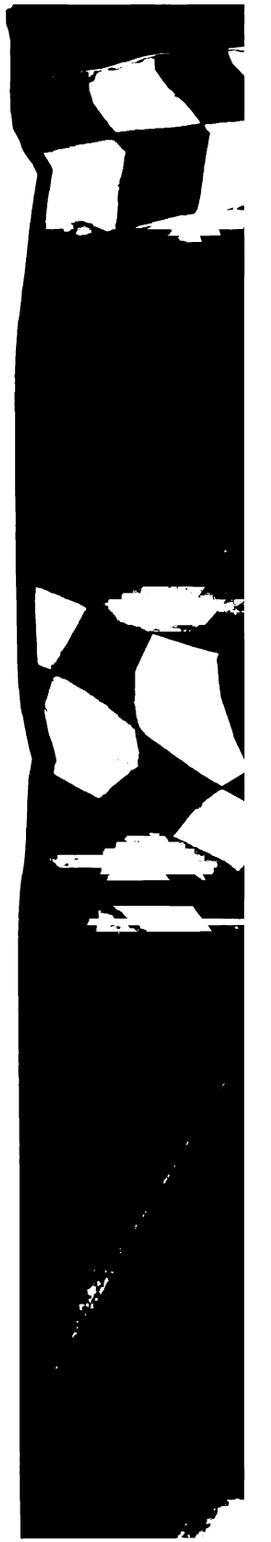
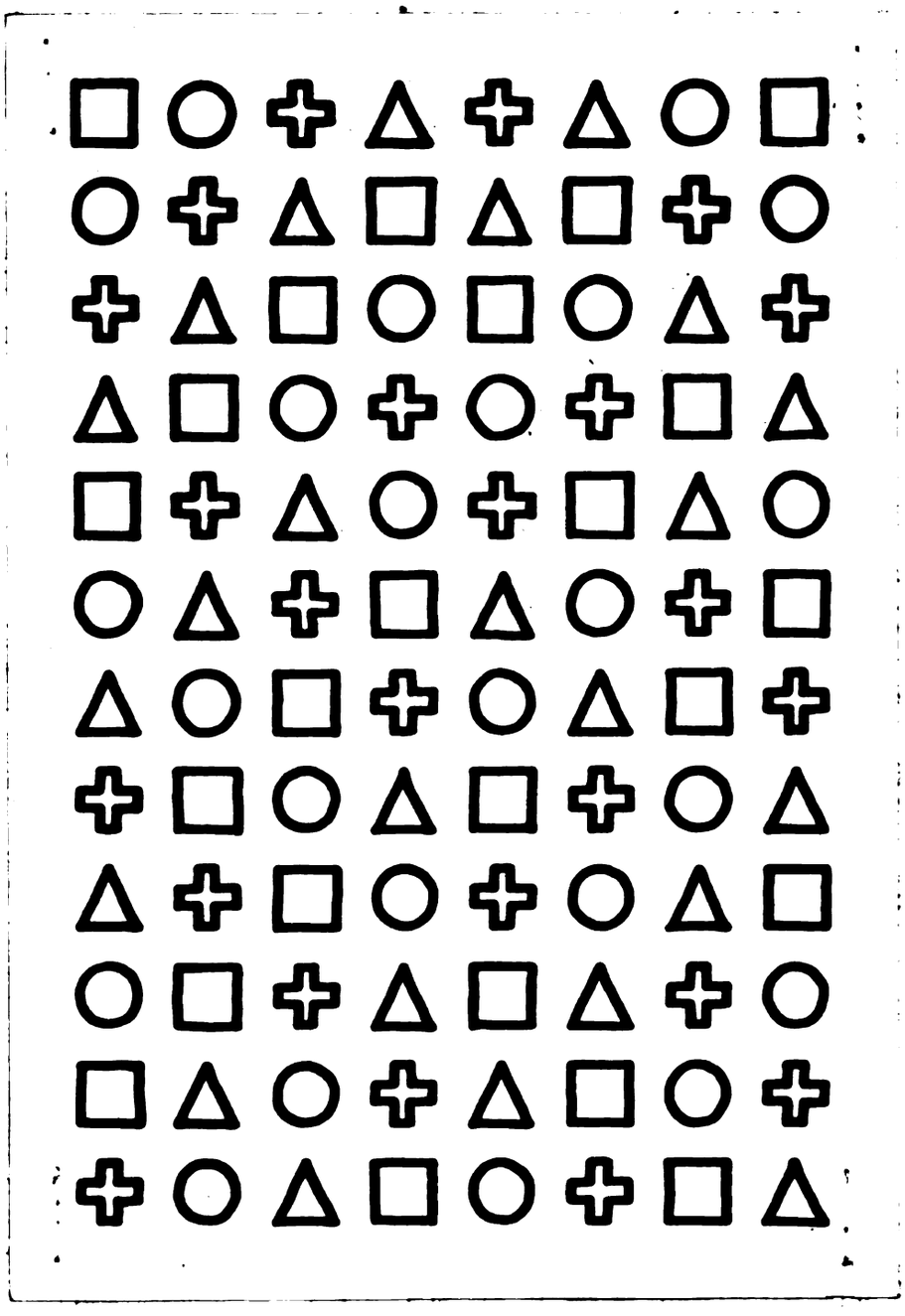


Table 2

COMPARISON OF CHARACTERISTICS OF PATIENT GROUPS USED IN THE PRESENT STUDY

Treatment Group	N	Mean Age in Years	Mean Length of Hospitalization in Months	Mean Weight in Pounds
Low Drug	20	38.35	23.55	148.25
High Drug	20	39.55	26.45	153.25
Placebo	20	37.30	25.45	136.35
Value of F from an analysis of variance between means		.39	.33	1.66
P for 2 and 57 d.f.		N.S.	N.S.	N.S.

Figure 2



arranged in eight columns and twelve rows such that each figure appeared twice in each row and three times in each column. No figure succeeded itself in any row or column. All figures were separated on all sides by one-half inch.

Test Card II (Figure 3) contained a total of ninety-six one-inch circles. An equal number (twenty-four) were tinted in each of the four primary colors: red, yellow, blue, green. Each color appeared twice in each of twelve rows and three times in each of eight columns. No color succeeded itself in any row or column. All colored circles were separated on all sides by one-half inch.

Test Card III (Figure 4) contained a total of ninety-six one-inch colored geometric figures. The figures and colors were identical to those used on Test Cards I and II, respectively. Arranged in eight columns and twelve rows, each color and each figure appeared exactly twenty-four times, twice in each row and three times in each column. No color or figure succeeded itself in any row or column. All colored figures were separated on all sides by one-half inch.

The corresponding practice cards contained one each of the four geometric figures used in Test Card I; four circles each tinted in one of the primary colors used in Test Card II; and one each of the four geometric figures each tinted in one of the four primary colors as in Test Card III.

The stimulus materials were drawn and water-colored by a graduate art student on No. 74 (heavy weight) Hi-Art hot-pressed, white illustration board.

Subjects were presented with the Test Cards in the following order - I, II, III, III. Each was preceded by its corresponding practice

Figure 3

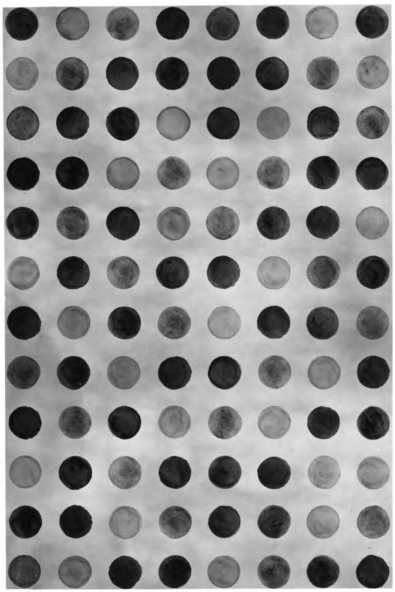
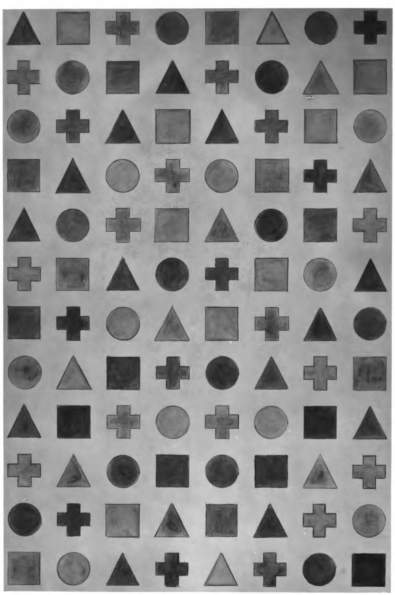
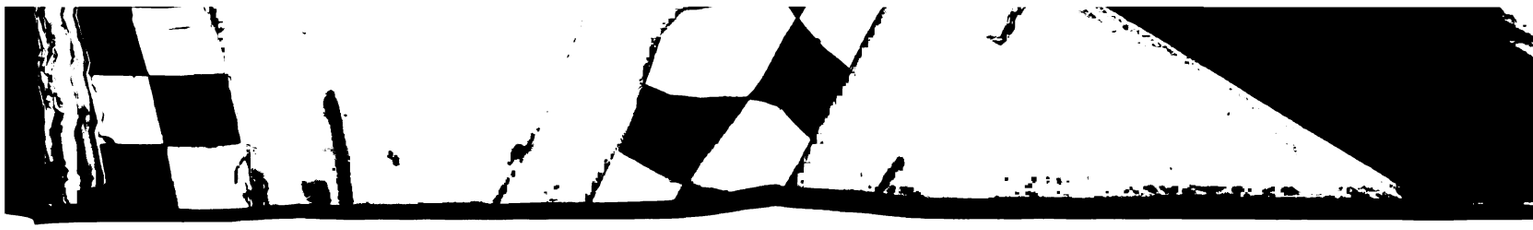


Figure 4



card. Practice cards were placed flat on the table, face-up, directly before each subject. Test Cards were placed upright at slightly more than a 90 degree angle on a stand fifteen inches from the edge of the table and directly in front of each subject. Each Test Card was concealed by a blank card which was removed for the test proper.

Each subject was asked to name the four shapes on the practice card for Test Card I. She was then told, "Underneath this empty card there is another one with lots of shapes on it just like the four on this little card. You are to name these shapes as fast as you can as soon as I take this blank card away. Do the top row first and then, without stopping, do the next row and keep going until you've done the whole card. Are you ready? Go ahead!" The blank card was removed immediately after the directive, go ahead! with the simultaneous activation of a hand-controlled stop watch. Upon completion, Test Card I was removed from the stand and replaced by Test Card II which was covered by a blank card. The practice card for Test Card II was presented to the subject with instructions to name the four colors in which one each of the four circles was tinted. Testing with Test Card II proceeded as with Test Card I. In the instructions to the subject, the word "colors" was substituted for the word "shapes." Upon completion, Test Card II was removed from the stand and replaced by Test Card III which was concealed by a blank card. The practice card for Test Card III was presented to the subject with the following instructions: "On this little card there are four, colored shapes. The colors and the shapes are the same as the ones you named before. I want you to name the four shapes only and pay no attention to the colors. Just tell me the names of the four shapes on this card just like you did before and pay no



attention to the colors." Following the subject's comprehension of the task, she was given the following instructions: "Now I'm going to uncover another big card on which there are many colored shapes. I want you to name only the shapes on this card. Remember, only the shapes and pay no attention to the colors. Just as you did before, do the top row first and then go right on to the next row without stopping. Name all the shapes on the card as fast as you can without stopping. And remember, pay no attention to the colors." The procedure at this point was similar to that employed with Test Cards I and II. Upon completion, Test Card III was retained on the stand and immediately covered by the blank card. The subject was again presented with the practice card for Test Card III and was told: "This time, I want you to name the colors on this little card and pay no attention to the shapes. Remember, just give me the names of the colors." Following the subject's comprehension of the task, she was given the following instructions: "I'm going to show you the same card you saw a little while ago, the one with all the colored shapes on it. This time I want you to name only the colors and pay no attention to the shapes." The remaining instructions and procedure were similar to those used previously with this card with the appropriate interchange of the words "colors" and "shapes."

Task II (Broadened Attention Task)

The materials and procedures for this experiment were suggested by techniques originally used by Humphreys (29) and later by Grant (20), Bruner et al (7), and Calloway and Dembo (12). Subjects are required to guess which of two equally likely events will occur and then observe whether or not the guess was correct by observing the event. After each

event observation, a new guess is made, followed by another observation, etc., throughout a series of trials. The frequency of the two events is then changed such that one of the two events becomes more likely and the other, less likely.

The materials used in this investigation were designed for individual administration and consisted simply of 3 x 4 inch cards cut from No. 74 (heavy weight) Hi-Art hot-pressed, white illustration board. In the center of the face side of each of these cards is a one-inch red or blue circle. Set I consisted of ten cards. Five of these cards contained a red circle; and five, a blue circle. Set II also consisted of ten cards. On eight of these cards, the circle was red; on two, blue.

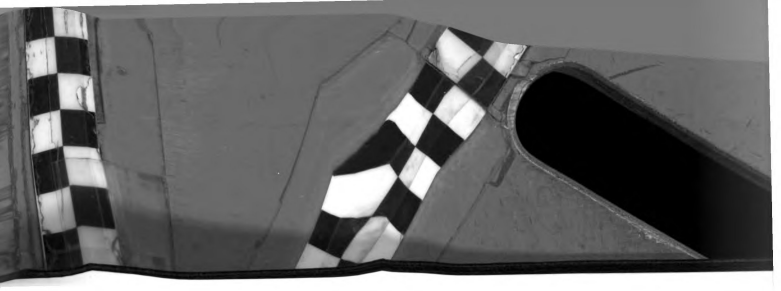
The subjects were first presented with Set I and given the following information and instructions. "Here is a stack of cards. On some of these cards, there is a red circle (subject is shown a card with red circle on it) just like this one, and on some of the cards there is a blue circle (subject is shown a card with a blue circle on it) just like this one. Remember now, some cards are red; and some are blue. I'm going to mix them up just like this (cards are shuffled) so that we don't know which cards are red and which are blue." Cards are then placed in a stack, face down, before the subject. "I would like you to guess which color is on the top card. Remember, it has to be one of two colors. After you guess, I'll turn it over so you can see what the color really is. Now make your guess." As soon as the subject makes her guess, the card is turned over and the examiner says, "it is a (name of color) one" and places it aside, face down. The subject is

asked to make a new guess for each card in the stack after which the card is turned over, named by the examiner, and placed in the discard stack, face down. After completing the series of ten cards, E shuffles them for approximately fifteen seconds during which the subject is informed that the procedure is to be repeated. Three series of guesses are obtained for Set I. After the third series, Set II is substituted for Set I and placed before the subject without comment. Ten series of guesses are obtained with Set II.

Procedure

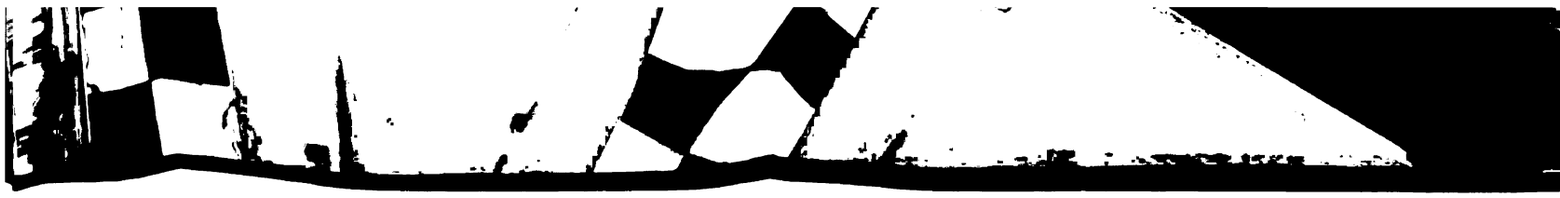
The sixty female schizophrenic patients who participated in this study were randomly assigned to one of three groups of twenty patients each. Each of the groups was then assigned to one of three treatment schedules by a blind randomization procedure. The medication schedule for each of the three groups was determined on medical advice and approval. Group HD (high-dosage perphenazine) received 48 mg. of perphenazine daily; group LD (low-dosage perphenazine), 12 mg. of perphenazine daily; and group P (perphenazine placebo), an inert saline compound. All tablets administered were identical in size, color and shape. Each medicated tablet contained 4 mg. of perphenazine. Each patient received a total of 12 tablets a day. Group HD received four 4 mg. tablets of perphenazine, t.i.d.; Group LD, one 4 mg. tablet of perphenazine and three 4 mg. perphenazine placebo tablets, t.i.d.; and Group P, four 4 mg. perphenazine placebo tablets, t.i.d.

All patients included in the study were withdrawn from all previous medication for a period of at least three full days. Experimental medication, following one of the three schedules adopted for



this investigation, continued for three consecutive days. Tests were conducted on the day following completion of the medication schedule. The subjects were examined in a randomized order with the sequence of the two tasks reversed with successive subjects. The conduct of the investigation, relative to all the randomization aspects, was controlled and supervised by a colleague.

The double-blind condition was present throughout the study, i.e., neither this investigator nor the patient was aware of the group to which she was assigned nor the medication she had received. The meaning of the tasks to the subject was not investigated in the present instance to the extent of obtaining quantitative and objective data. All evidence however, including spontaneous comments of the patients and ward and medical personnel, indicated that the patients viewed the tasks as tests of speed, mental alertness and of intelligence of some kind. As such, it is considered highly likely that each patient was set to participate and respond optimally. Each patient was told that she was being asked to perform a number of tasks which would provide the medical staff with information useful in its efforts to help her. All observations were made individually in the same room under relatively constant conditions of illumination and room temperature. Furnishings and equipment in the room were not moved or changed during the period of study. This included the 4' x 4' x 30" table which provided the surface on which the test materials were placed. The subject and examiner sat at adjacent sides of the table with the subject seated to the left of the examiner always in the same position in the room. A 200 watt bulb suspended directly above the table was used to illuminate the test materials. No shadows were cast in any



instance. The physical conditions are thus considered to have been relatively identical for all patients.

RESULTS

Experiment I (Narrowed Attention Task)

Table 3 summarizes the performance scores (to the nearest whole second) for each subject according to the experimental conditions. The experiment provided each subject with two opportunities to respond to one of two simultaneously presented stimuli each of which was an inherant aspect of the same symbol, a colored geometric figure. In the first instance, the subject was to name shapes while ignoring colors; in the second, name colors while ignoring shapes. Difference scores between times taken to name one stimulus alone and time to name that same stimulus in the presence of the second interfering stimulus served as the basic data for this experiment. The algebraic addition of a constant eliminated minus values and rendered the data more manageable without violating any aspect of the statistical analyses and allowable interpretations. The two sets of difference scores were plotted separately. Since each distribution of scores was approximately bell-shaped, no transformation was necessary. A Pearson product-moment coefficient of correlation, $r = .146$, between the two sets of difference scores for all sixty patients indicated that separate analyses should be made. Table 4 summarizes the mean performance scores, in seconds, of the three groups of subjects according to the experimental conditions. Separate t tests were made between the mean performance scores of the high-drug group and the low-drug and placebo groups in naming geometric figures in the presence of interfering colors. (Table 5.) The resulting t ratios of 1.57 and 1.35 for 38 degrees of

Table 3

SUMMARY OF PERFORMANCE OF RESEARCH POPULATION ON MODIFICATION OF "STROOP" TEST (TIME IN SECONDS)

Low Drug Group (N = 20)						High Drug Group (N = 20)						Placebo Group (N = 20)					
Task*						Task*						Task*					
I	II	III	IV	III-I + 100	IV-II + 100	I	II	III	IV	III-I + 100	IV-II + 100	I	II	III	IV	III-I + 100	IV-II + 100
87	46	85	47	98	101	126	90	105	73	79	83	85	68	67	68	82	100
107	87	92	73	85	86	133	95	134	124	101	129	102	79	94	74	92	95
155	127	175	137	120	110	103	66	96	81	93	115	121	105	127	100	106	95
138	111	110	124	72	113	288	221	244	290	56	169	79	56	73	54	94	98
100	72	102	82	102	110	140	112	133	123	93	111	75	60	76	59	101	99
134	87	103	88	69	101	87	68	99	76	112	108	135	115	189	123	154	108
164	90	155	94	91	104	77	58	78	59	101	101	91	76	95	76	104	100
100	84	97	83	97	99	135	73	151	79	116	106	88	49	80	49	92	100
102	89	99	125	97	136	71	54	75	53	104	99	82	64	74	70	92	106
73	63	73	66	100	103	90	76	103	88	113	112	172	92	138	94	66	102
73	51	73	59	100	108	117	88	119	98	102	110	137	100	102	101	65	101
67	60	80	57	113	97	91	60	85	66	94	106	157	90	152	98	95	108
107	76	89	72	82	96	126	100	143	91	117	91	122	80	101	70	79	90
99	81	108	94	109	113	104	67	84	71	80	104	230	73	219	69	89	96
135	79	130	94	95	115	136	91	154	92	118	101	304	271	319	289	115	118
104	74	102	69	98	95	78	68	73	61	95	93	83	69	81	70	98	101
81	56	71	60	90	104	100	93	108	90	108	97	142	79	88	60	46	81
172	133	139	104	67	71	77	63	87	63	110	100	84	61	78	62	94	101
71	53	61	47	90	94	207	102	223	103	116	101	95	60	100	53	105	93
221	113	187	93	66	80	105	81	98	70	93	89	193	161	151	144	58	83

* I - Naming Geometric Figures when presented alone.

II - Naming Colors when presented alone.

III - Naming Geometric Figures in presence of interfering Colors.

IV - Naming Colors in presence of interfering Geometric Figures.

Table 4

PERFORMANCE SCORES ON A MODIFICATION OF THE "STROOP" TEST OF THREE GROUPS OF PATIENTS TESTED UNDER DIFFERENT TREATMENT CONDITIONS

Treatment Group	N	Mean Time in Seconds Task*				Changes in Performance Due to Interference	
		I	II	III	IV	III - I + 100	IV - II + 100
Low Drug	20	114.30	81.60	106.55	83.40	92.05	101.80
High Drug	20	119.55	86.30	119.60	92.55	100.05	106.25
Placebo	20	128.85	90.40	120.20	89.15	91.35	98.75

* I = Naming Geometric Figures when presented alone.

II = Naming Colors when presented alone.

III = Naming Geometirc Figures in presence of interfering Colors.

IV = Naming Colors in presence of interfering Geometric Figures.

Table 5

COMPARISON OF PERFORMANCE CHANGES ON MODIFICATIONM OF STROOP TEST DUE TO INTERFERENCE
(Naming Geometric Figures in presence of interfering Colors)

Treatment Group	N	Mean Score*	Difference	t
Low Drug	20	92.05	8.00	1.57
High Drug	20	100.05	8.70	1.35
Placebo	20	91.35		

* Time in seconds for naming Geometric Figures in presence of interfering Colors - time in seconds for naming Geometric Figures alone + 100.

freedom were found not significant. High-drug dosage may therefore be considered statistically indistinguishable in its effects as compared separately with low-drug and placebo medication and the null hypothesis of no effect is tenable.

Similarly, a comparison of mean performance scores of the high-drug group and the low-drug and placebo groups in naming colors in the presence of interfering geometric figures resulted in *t* ratios of .88 and 1.69 (Table 6). For 38 degrees of freedom neither of these is significant and the null hypothesis of no effect with regard to high-drug medication is tenable. In summary, high-drug medication may be considered as having no significant effect on performance of the kind called for in this experiment when the two performances are considered separately. Since the differences shown in the last two columns of Table 4 are parallel, an analysis of the combination of the two might prove fruitful (Table 7). A comparison of the mean combined performance scores of the high-drug group and the low-drug group resulted in a *t* ratio of 1.77. For 38 degrees of freedom, this is not significant and is in agreement with the results of the separate analyses. A comparison of the high-drug group and the placebo group resulted in a *t* ratio of 2.14 which for 38 degrees of freedom is significant at better than the .05 level of confidence. It may be concluded that combining the two performance scores results in a more sensitive measure which barely reaches the conventional level of confidence. The direction of this effect is opposite to that predicted. The first of the major hypotheses of this investigation is thus considered not confirmed according to the experimental conditions and statistical analyses employed.

Table 6

COMPARISON OF PERFORMANCE CHANGES ON MODIFICATION OF STROOP TEST DUE TO INTERFERENCE
(Naming Colors in presence of interfering Geometric Figures)

Treatment Group	N	Mean Score*	Difference	t
Low Drug	20	101.80	4.45	.88
High Drug	20	106.25	7.50	1.69
Placebo	20	98.75		

* Time in seconds for naming Colors in presence of interfering Geometric Figures - time in seconds for naming Colors alone + 100.

Table 7

COMPARISON OF COMBINED PERFORMANCE CHANGES ON MODIFICATION OF STROOP TEST DUE TO INTERFERENCE

Treatment Group	N	Mean Score	Difference	t
Low Drug	20	194.40		
			11.90	1.77
High Drug	20	206.30		
			15.80	2.14
Placebo	20	190.60		

Experiment II (Broadened Attention Task)

The performance scores for all sixty subjects are summarized in Table 8 according to the experimental conditions. Mean performance scores for each group for each trial are presented in Table 9.

Figure 5 is a graphic representation of the group data in Table 9. The number of guesses for the "less likely" event over the last eight trials served as the basic data for this experiment. This decision was based on an inspection of the performance curves in Figure 5 which illustrates graphically the systematic tendency of the low-drug group to make less guesses for the less likely event than the other two groups over trials. Accordingly the data were subjected to an analysis of variance involving repeated measurements of subjects in independent groups (16). In the analysis between the low-drug and high-drug groups, Table 10, the main effect of treatment method is significant ($F = 4.41$; d.f. = 1 and 38; $p < .05$); the main effect of trials is also significant ($F = 3.70$; d.f. = 7 and 266; p.001). The significant interaction variance, treatments x trials, ($F = 6.54$; d.f. = 7 and 266; $p < .001$) is interpreted as meaning that the obtained difference in trend among the two groups cannot be reasonably attributed to chance. As a product of the joint effect of method and trial, the interaction variance tells us that one of the treatment schedules (low drug in this instance) is more effective over trials.

The analysis between the low-drug and placebo groups (Table 11) further strengthens the suggestion that low-drug patients are provided with an advantage in performing the task presented over trials. The main effects of treatment ($F = 10.33$, d.f. = 1 and 38; $p < .01$) and trial ($F = 4.45$; d.f. = 7 and 266; p .001) are both significant. The interaction variance, treatments x trials, is also significant ($F = 3.23$; d.f. = 7 and 266; $p < .01$).

Table 8

SUMMARY OF GUESS FREQUENCIES FOR UNLIKELY COLOR (BLUE) OF PATIENTS ON EACH OF THIRTEEN TRIALS

Low Drug (N = 20)													High Drug (N = 20)												Placebo (N = 20)											
Trials*													Trials*												Trials*											
1	2	3	4	5	6	7	8	9	10	11	12	13	1	2	3	4	5	6	7	8	9	10	11	12	13	1	2	3	4	5	6	7	8	9	10	11	12	13
4	6	5	6	6	6	5	4	5	2	2	3	3	4	5	4	5	5	4	3	1	1	0	0	1	2	5	6	3	5	3	2	3	4	2	3	0	1	1
5	5	5	2	1	1	0	1	3	1	4	1	0	6	5	5	5	4	4	4	4	3	4	4	4	4	5	6	5	3	4	5	5	3	3	6	5	4	5
3	4	5	4	7	0	0	1	1	0	0	1	1	6	6	6	7	8	7	8	6	6	6	5	5	4	4	4	6	4	4	3	4	1	2	2	2	2	2
6	5	6	5	6	7	5	3	2	4	7	3	2	6	7	6	10	10	10	10	5	7	9	9	8	9	5	7	6	5	4	3	3	3	2	2	1	1	2
6	5	6	5	5	2	1	3	2	3	1	4	2	5	4	5	4	4	6	5	6	4	4	3	2	2	8	5	6	8	7	7	1	1	1	0	0	0	2
6	5	5	7	2	1	1	2	1	2	5	5	1	5	5	5	6	6	5	5	5	5	5	5	6	5	4	6	6	4	3	8	5	3	4	5	6	8	4
6	5	6	7	7	3	2	2	4	1	3	7	0	4	6	3	5	5	3	3	2	0	0	0	0	0	8	7	3	6	0	2	2	2	4	4	5	2	2
4	5	5	7	6	4	6	4	3	2	0	2	2	7	6	5	6	3	4	0	1	0	0	3	1	2	6	8	7	4	0	2	2	0	2	0	1	3	3
6	5	6	7	6	3	2	1	1	1	2	2	0	4	3	10	7	1	3	2	4	2	3	1	0	6	5	6	5	6	6	2	7	2	2	0	0	2	1
6	5	5	5	6	2	2	1	0	1	3	1	0	3	5	4	5	3	2	0	0	0	1	0	0	0	6	5	5	7	5	5	5	5	4	3	4	2	4
4	4	3	4	3	1	1	4	2	0	1	0	3	6	6	5	4	7	6	5	5	3	6	6	4	5	6	5	4	5	6	5	5	6	5	6	6	5	5
7	4	5	6	0	0	3	2	1	0	1	2	3	3	5	2	2	2	5	2	2	4	1	0	0	0	7	5	4	4	4	4	4	4	4	5	5	5	5
5	5	2	5	7	5	2	3	1	2	1	1	3	5	6	6	6	6	5	5	5	5	5	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5
5	5	4	5	3	1	1	0	1	0	0	0	0	3	5	7	4	3	1	0	1	2	2	0	3	1	6	6	5	7	7	5	5	4	7	4	5	4	3
4	5	6	4	3	4	3	4	3	2	4	2	4	5	4	5	6	6	1	3	2	1	1	2	3	1	5	5	5	5	5	10	5	5	5	2	5	0	5
5	6	4	6	4	4	4	1	2	4	2	4	2	1	7	6	6	6	1	3	4	3	2	3	3	2	2	7	6	4	6	5	4	5	3	6	4	5	4	6
8	4	3	10	3	2	4	4	2	0	2	0	2	1	4	6	4	6	6	1	1	1	0	0	0	1	1	5	6	5	4	5	5	3	2	3	2	3	2	3
4	4	6	3	3	3	3	3	3	4	2	4	2	2	5	5	6	4	2	1	6	3	3	1	2	1	2	5	5	5	5	6	4	2	1	4	0	0	2	0
5	4	6	5	3	2	1	0	2	2	2	2	0	5	5	4	5	5	5	5	4	0	10	5	5	5	5	5	4	5	5	7	4	3	3	3	3	3	1	2
5	3	5	5	3	0	1	0	2	1	1	0	2	5	4	5	5	4	3	5	4	5	3	3	3	3	5	5	5	6	6	2	3	3	2	2	2	0	1	2

* Actual ratio of colors for first 3 trials, $\frac{5 \text{ Blue}}{5 \text{ Red}}$; for last 10 trials, $\frac{2 \text{ Blue}}{8 \text{ Red}}$.

Table 9

PERFORMANCE SCORES ON A "GUESSING" TASK OF THREE GROUPS OF PATIENTS TESTED UNDER DIFFERENT TREATMENT CONDITIONS

Treatment Group	N	Mean Number of Guesses for Unlikely Color (Blue)* Trials												
		1	2	3	4	5	6	7	8	9	10	11	12	13
Low Drug	20	5.20	4.70	4.90	5.40	4.20	2.55	2.35	2.20	1.90	1.50	2.25	2.10	1.50
High Drug	20	4.80	5.20	5.15	5.40	4.55	3.95	3.75	2.95	3.15	2.95	2.75	2.65	3.00
Placebo	20	5.55	5.55	5.05	5.35	4.20	4.35	3.90	2.90	3.50	2.90	3.00	2.75	3.10

* Ratio of colors for first three trials, 5 Blue/5 Red; for last ten trials, 2 Blue/8 Red.

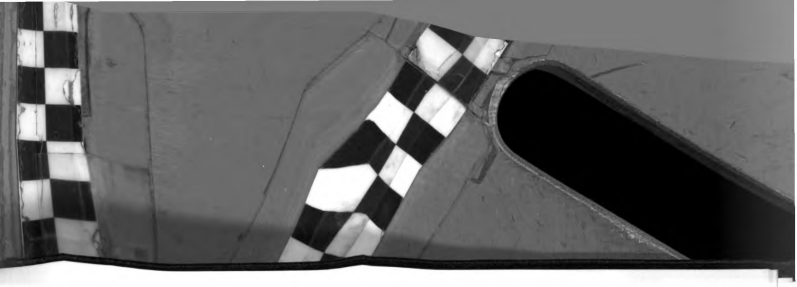


Table 10

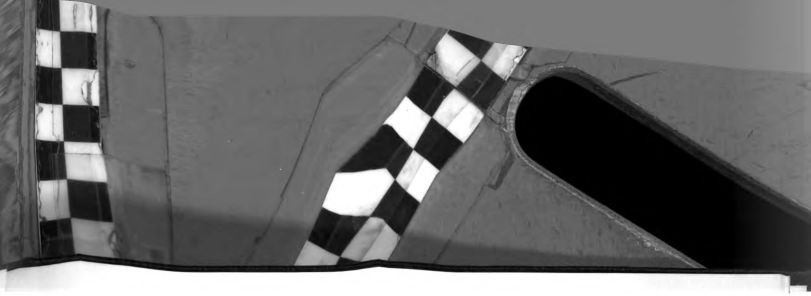
ANALYSIS OF VARIANCE OF PERFORMANCE SCORES OF TWO GROUPS OF PATIENTS TESTED UNDER DIFFERENT TREATMENT CONDITIONS (LOW-DOSE AND HIGH-DOSE DRUG) WITH EIGHT TRIALS FOR EACH GROUP

Source of Variation	Sum of Squares	d.f.	Mn. Square	F
Between Treatments	95.71	1	95.71	4.41
Between patients in same group	824.29	38	21.69	
Total between patients	920.00	39		
Between Trials	38.08	7	5.44	3.70
Interaction: Trials x treatments	67.32	7	9.62	6.54
Interaction: pooled patients x trials	391.60	266	1.47	
Total within patients	497.00	280		
Total	1417.00	319		

Table 11

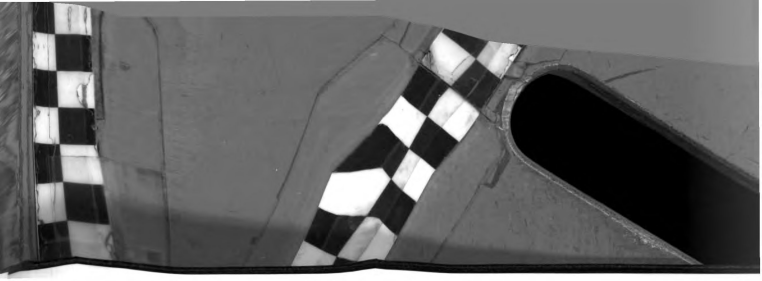
ANALYSIS OF VARIANCE OF PERFORMANCE SCORES OF A GROUP OF PATIENTS TESTED UNDER DIFFERENT TREATMENT CONDITIONS (LOW-DOSE DRUG AND IDENTICAL PLACEBO) WITH EIGHT TRIALS FOR EACH GROUP

Source of Variation	Sum of Squares	d.f.	Mn. Square	F
Between Treatments	125.00	1	125.00	10.33
Between patients in same group	464.20	38	12.22	
Total between patients	589.20	39		
Between Trials	50.10	7	7.16	4.45
Interaction: Trials x treatments	36.40	7	5.20	3.23
Interaction: pooled patients x trials	428.50	266	1.61	
Total within patients	515.00	280		
Total	1104.20	319		



Reference to Tables 10 and 11 will reveal that one error term was used for the test of significance for treatments and a second error term for the tests of significance for trials and interaction. It is to be noted that the test of significance for treatments is based on independent, randomly assigned groups of patients, whereas the tests of significance for trials and interaction between trials and treatments is based upon the same patients involving possibly the presence and effect of correlation. Because of these considerations, two different error terms are advisable; one for the possibly correlated data obtained from the same patients and one for the data obtained from independent groups of randomly assigned patients.

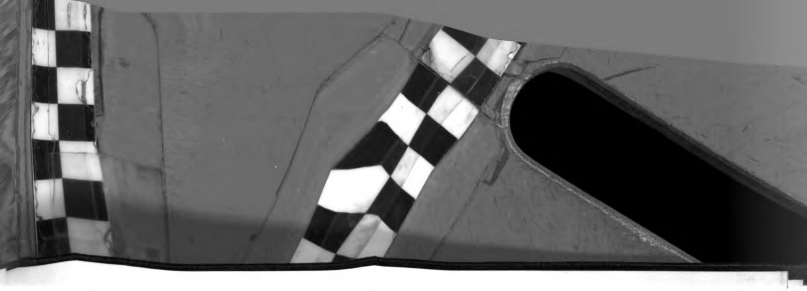
In summary, low-drug medication may be considered as having a significant effect on performance of the kind called for in this experiment. The second of the major hypotheses of this investigation is thus considered confirmed according to the experimental conditions and statistical analyses employed.



DISCUSSION

The results of the two experiments of this investigation may be viewed as failing to support the hypothesis that "patients treated with perphenazine in dosage amounts presumed to stimulate the brain-stem reticular system will perform better on a task requiring narrow attention than will patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block brain-stem reticular system activity" and supporting the hypothesis that "patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block the brain-stem reticular system will perform better on a task requiring broad attention than will patients treated with perphenazine in dosage amounts presumed to stimulate brain-stem reticular system activity." In view of the above, a re-examination of the experimental conditions seems warranted.

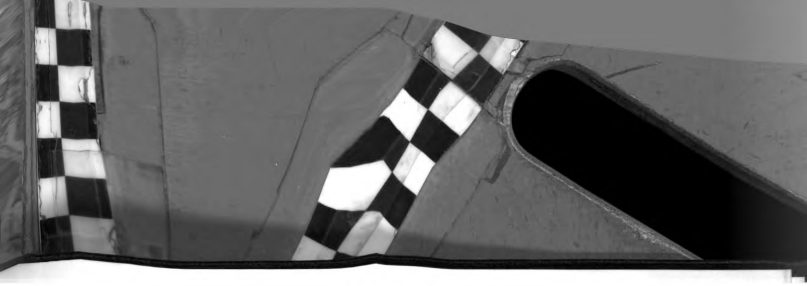
A re-examination of the materials used in both the experiments of this investigation serves to reaffirm the original assumption that the three essential experimental requirements for the observation of the focus of attention as conceptualized in this study are fulfilled. Since introspective reports of the extent to which a person ignores or utilized peripheral factors are unreliable, information about the focus of attention must come from inferences based on observed behavior (10). If factors lying outside the central focus of attention easily influence behavior, we may infer that the process of withdrawing from or ignoring peripheral factors is minimal and the focus of attention is broad. If peripheral factors are effectively ignored such that the process of withdrawing



from them is maximal leading to little or no effect on behavior, then it can be assumed that the focus of attention is narrow. These observations, translated into experimental form relative to behavior, have three requirements which are presumed inherent in the experimental materials of this investigation:

1. Both tasks present situations in which the subject's attention is directed towards some aspect of the current environmental situation.
2. Both tasks present stimuli which are removed from the central focus of the subject's attention.
3. Both tasks provide a measure of the subject's behavior which reflects responsiveness to peripheral stimuli.

The adoption of daily dosages of 12 and 48 mg. of perphenazine as medication levels which would presumably depress and activate, respectively, the mid-brain reticular system, though based on the corroborative advice and approval of a number of physician-psychiatrists, must be considered a somewhat arbitrary decision based on clinical experience and information which at the time was admittedly meager. Evidence for presuming, by means other than task performance, that 48 mg., in effect, does stimulate the mid-brain reticular system is provided by Rinaldi and Himwich (52) and Magoun (40) who show that the overactivity of this system is responsible for the production of Parkinsonism. In the present study nine of the twenty high-drug patients showed, when tested, the characteristic tremor and behavioral restlessness of Parkinsonism as compared to none in the low-drug or placebo groups. In addition, of the patients dropped from the study for various reasons, Parkinsonism was given as the cause only in those patients who had been started on high-drug medication



but had to be withdrawn because of extreme reactions making continued participation in the study clinically contraindicated.

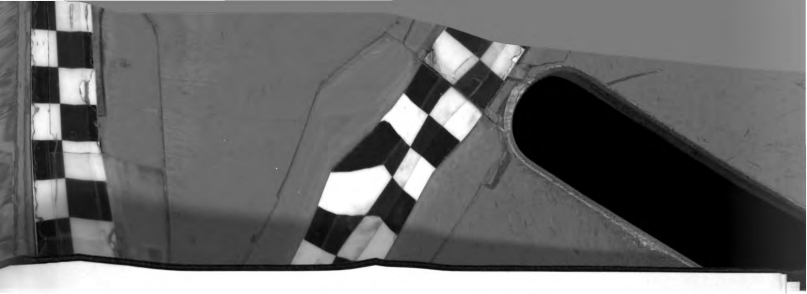
Assuming, then, on the basis of the production of Parkinsonism in high-drug patients that the brain-stem reticular system is, in effect, stimulated and activated by 48 mg. of perphenazine daily in divided doses for three consecutive days, the apparently negative results are indeed surprising and perplexing.

Drugs and procedures which seem to narrow attention include amyl nitrite, a vasodilator; methamphetamine, a sympathomimetic; an anti-cholinesterase nerve gas, which is parasympathomimetic; and the vasoconstricting cold pressor procedure. This rather heterogeneous group of agents have at least one thing in common; they all seem to have a stimulating effect on the mid-brain reticular system as shown by an alert EEG. In common with the above group of agents, high-dose perphenazine also stimulates the mid-brain reticular system but unlike them, at least within the present experimental framework, it does not narrow attention. In fact, as previously indicated, reference to Table 4 suggests that the high-drug group was the most penalized of the three groups in performing the narrowed attention task. This greater difficulty in ignoring or filtering out intrusive stimuli is oppositional to expectations in the presence of an experimentally alerted mid-brain reticular system. A possible explanation which might be put forward is suggested by the incidence of Parkinsonism within this group which suggests that the level of stimulation was too high. Broadbent (5) invokes an activation theory of attention, among others, which appears to be useful in the present instance. His concern is with the effect on behavioral efficiency as a function of level of stimulation and activation of the

nervous system. Since Parkinsonism is indicative of a disruption of the integrity of the nervous system which renders it less efficient in its functions, the activation theory seems to be in harmony with these results. Further support can be obtained from Hebb (22) who suggests that too high a level of activation is detrimental to efficiency because of its disruptive and disorganizing effects.

On intuitive grounds, the above explanation seems reasonable. But it is not the only or even the best explanation that can be offered. There is evidence that increased activity in the mid-brain reticular system may result in a decrease in sensory input (56). This squares with Hebb (23) who looks upon attention as the process that produces the selectivity of a response to a stimulus and describes it as "a central facilitation of a perceptual activity." This process, we infer, can be rendered inefficient by too intense stimulation. He refers to EEG findings indicating that all parts of the brain are continually active so that any incoming excitation must be superimposed upon an already existing excitation (23). This aspect of the problem is also discussed by Broadbent (5) who invokes a filter theory of attention which is concerned with the selection of a stimulus which may be delayed or blocked due to a high level of activity thus leading to behavioral inefficiency.

A third possible effect of excessive neurophysiological arousal is an influence on central integrative mechanisms (18). No clear explanation is as yet available, as is true with most if not all neurophysiological theories of behavior, but it has been shown that stimulating the mid-brain reticular system can somehow interfere with the central processes necessary for the assimilation of an experience (18).



The above neurophysiological evidence is presented to emphasize the possibility that over-activation of the mid-brain reticular system can lead to a functional disruption of the central nervous system which may often make inferences about behavior following experimental application or presentation of stimulating agents somewhat dubious. In view of this, the negative results obtained in Experiment I (Narrowed Attention Task) must be considered as, at least, equivocal in terms of the stated hypothesis. The first part of this hypothesis states that "Patients treated with perphenazine in dosage amounts presumed to stimulate the brain-stem reticular system will....." Based on the opinions of the psychiatrist-physicians who served as medical advisors and consultants throughout the study, it is presumed that the experimental provocation of the mid-brain reticular system with high-dose perphenazine did, in effect, produce neurophysiological arousal. That a behavioral counterpart, narrowed attention, was not concomitantly produced is explainable on the basis of possible neurophysiological effects of overstimulation of this neural sub-system.

The results of this study are seen to agree with those of Calloway (10) and Calloway and Band (11) with respect to drug effects on broadened attention. Important differences in the experimental conditions used in these studies and those used in the present investigation warrant a cautious approach, however, in assuming the operation of identical processes. Atropine, amytal, alcohol, and low-dose perphenazine, are all accompanied by behavior characteristic of broadened attention presumably due to a neurophysiological dampening of the mid-brain reticular system (10, 11). But here the major similarity ends. A drowsy atropine EEG is not accompanied by behavioral drowsiness. Amytal and alcohol, on

the other hand, produce drowsy behavior as well as a drowsy EEG. Low-dose perphenazine also produces both a drowsy EEG and drowsy behavior but unlike the other three agents, the drowsy reactions are immediately reversed by internal or external stimulation. As Calloway (10) suggests something underlying neurophysiological arousal would be the most parsimonious generalization about the drugs studied, and the most parsimonious explanation for the behavior observed would be in terms of focus of attention. But parsimony alone, as is well agreed upon, does not necessarily establish laws. In addition to the drugs, differences in research subjects contribute to difficulty in accounting for apparently expected results. Although no physiological or psychological measures of anxiety were included in the present study, a population of hospitalized female schizophrenic patients is presumed to bring to an experimental situation affective response tendencies unlike those of volunteer Johns Hopkins undergraduate and first- and second-year medical students motivated by the offer of four dollars for approximately two hours' time.

Differences in task procedures are indeed marked. Important in this respect, are the possible common and uncommon factors in the procedure used by Calloway and his associates and that used in the present investigation. Many of these factors may have important implications of behavior other than focus of attention.

In general, the results of this investigation appear to be in harmony with a growing body of literature which is intent on detailing and specifying much that is implicated in this study. Malmo (41), White (62), Samuels (56), Easterbrook (15) and others have separately directed themselves to a consideration of the relationship between activation and

performance. Though attacking the problem from somewhat different viewpoints and theoretical positions, each gives convincing support for a lawful relationship between level of activation and performance described by an inverted U curve.

The inverted U shaped curve has been shown to hold in numerous learning and performance situations when responses are plotted against activation level (15, 41).

On the basis of these recent attempts to integrate the facts of the relationship between performance and activation, Malmo (41) presents an experimental paradigm (Figure 6) which schematically formulates performance-activation relationships.

Figure 6

PERFORMANCE ACTIVATION RELATIONSHIPS
CORRESPONDING TO INVERTED U SHAPED CURVE

Activation Level	Expected Performance Level
Low	Low
Moderate	Optimal
High	Low

The paradigm is intended to show that from low activation up to a point that is optimal for a given task, level of performance rises monotonically with increasing activation level. Beyond this optimal point the relation becomes nonmonotonic. Further increases in activation produces a fall in performance.

The paradigm appears to provide a neat description of what occurred in the first experiment of this investigation. Apparently 12 mg. of perphenazine was not enough to improve behavior and 48 mg. was too much.

Crucial to the present discussion is the problem, unanswered here, of the extent to which the two tasks used in this investigation differ in complexity and the precise level of activation which is optimal for each.

An extension of the present design might well incorporate approaches that would handle the problem of weighting for task complexity. It could also include an increased number of drug-treated groups each of which would be administered the drug in graduated fixed amounts. This would permit the observation of performances with drug dosage extending in fixed amounts over a wide range.

Further efforts might well consider drugs other than perphenazine. Since the effect of activation on psychological functioning is much in need of explanation and understanding, efforts need not be limited to studies on attention.

SUMMARY

The present investigation was designed to explore a physiological activity that is widely held to be involved in attentive behavior and to test the hypothesis that experimental provocation of this activity by the drug perphenazine will be reflected in measurable behavior.

Three groups of patients were medicated orally over a period of three consecutive days. The two experimental groups respectively received low-dose perphenazine (12 mg. in divided doses t.i.d.) and high-dose perphenazine (48 mg. in divided doses t.i.d.), whereas the control group received an inactive placebo. The double-blind technique was employed.

Ss were presented with two tasks designed to measure focus of attention.

In the first task, Ss were required to respond to one of two simultaneously presented stimuli each of which was an inherent aspect of the same symbol, a colored geometric figure. Difference scores between time (in seconds) taken to name one stimulus when presented alone and time taken to name that same stimulus in the presence of the second interfering stimulus served as the basic data for this experiment.

Statistical analyses failed to differentiate between groups on the two separate parts of this task. Analyses of the combined performance scores differentiated between high-drug and placebo groups in the direction opposite to that expected.

High-dose medication is considered as having failed to affect performance of the kind called for in this experiment in the predicted

direction. The first of the major hypotheses is not confirmed. This hypothesis was stated as follows: Patients treated with perphenazine in dosage amounts presumed to stimulate the brain-stem reticular system will perform better on a task requiring "narrowed attention" (modified Stroop test) than will patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block brain-stem reticular system activity.

The incidence of Parkinsonism in the high drug group is taken as clinical evidence of activation and stimulation rendering the behavioral data and allowable interpretations somewhat equivocal.

In the second task, Ss were required to guess which of two events (one less likely than the other) would occur. The number of guesses for the "less likely" event served as the basic data for this experiment. Each trial consisted of ten events in which the ratio of less likely to more likely events was 2 to 8.

Statistical analyses significantly differentiated behavioral effects of low-dose perphenazine. These effects were in the direction of greater utilization in the use of peripheral cues required for successful performance.

The second of the major hypotheses is confirmed. This hypothesis was stated as follows: Patients treated with perphenazine in dosage amounts presumed to inhibit, depress, or block the brain-stem reticular system will perform better on a task requiring "broadened attention" (guessing game) than will patients treated with perphenazine in dosage amounts presumed to stimulate brain-stem reticular system activity.

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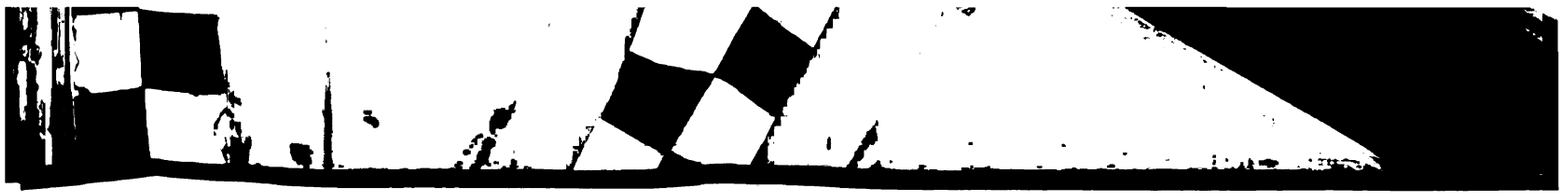

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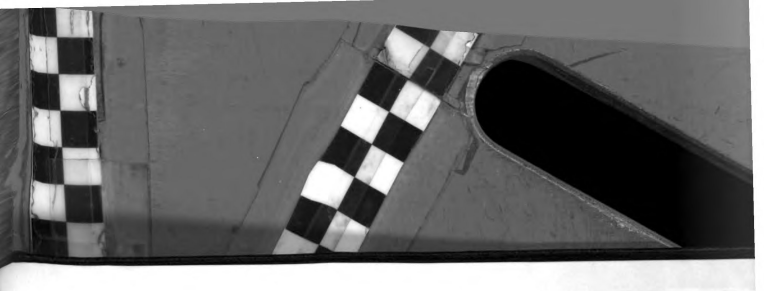

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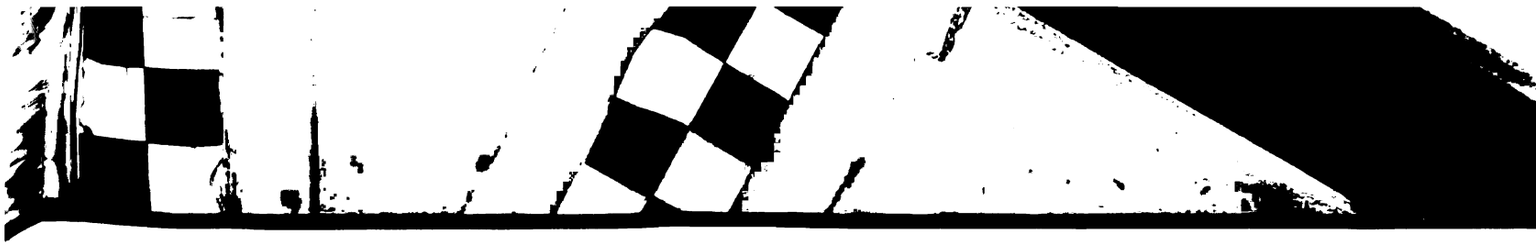

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