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Fixated behavior and its alteration by psychotropic agents.

Vincent Paul Houser

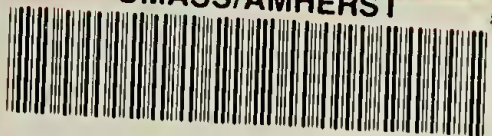
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FIXATED BEHAVIOR AND ITS ALTERATION
BY PSYCHOTROPIC AGENTS

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B. A., Boston College, 1965

Thesis

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INTRODUCTION

In the past five years, the psychological literature has become awakened to the importance of chemical coding in certain brain structures. Largely due to the work of Grossman and others, it has now become generally acceptable to talk about certain modes of behavior as being controlled by neural systems that are chemically distinct (i.e., systems that contain the same specific neural transmitter substance).

Specifically, two types of neurochemical systems have been investigated principally because these systems are known to function in the peripheral nervous system. The chemical substances which act to mediate these two systems are acetylcholine (ACH) and the catecholamines. The role of acetylcholine in the transmission of nervous impulses in the peripheral nervous system has been extensively documented. Likewise, pharmacologists have studied the role of the various catecholamines in depth and have left little doubt that these chemicals also act as chemical transmitters at the terminals of the peripheral sympathetic nervous system (Schildkraut and Kety, 1967).

Whether or not the above two chemicals act in a similar manner in the central nervous system is still in doubt. No conclusive neurophysiological evidence has yet been produced that points to any single chemical substance

as being a central transmitter. There is some fragmentary evidence that suggests that several chemical substances (including acetylcholine and the catecholamines) may act as central transmitters. These data are not as yet conclusive and until specific evidence (e.g., discovery of naturally occurring stores of ACH or norepinephrine in presynaptic endings, etc.) is obtained on the existence of central transmitters, caution must be exercised in proposing such systems.

With the above consideration in mind, psychologists and pharmacologists have nevertheless found it advantageous to assume that there are naturally occurring chemical transmitters in the central nervous system. These chemicals are amenable to change by the introduction of certain drugs with known pharmacological properties and thus the levels of certain brain amines thought to be central transmitters are open to experimental manipulation. These manipulations can then be correlated with observed behavioral changes in an attempt to infer what kind of systems in the CNS control specific behavioral changes. In other words, psychologists use drugs with known properties as tools in the study of processes that may control the behavior of the normal animal. This type of inferential analysis necessarily has its drawbacks when one is dealing with the varied and complex processes that must go on in the CNS. These drawbacks, however, are somewhat offset by the relatively precise and controlled behavioral measures

that the psychologist can devise to test behavioral deficits that are correlated with the introduction of certain drugs. The psychologist, therefore, is able to add certain inferential data that are helpful to other disciplines in their search for more direct evidence on the role of chemical modulation in the CNS.

With these basic considerations in mind, the evidence for cholinergic and adrenergic mediation of behavior will be presented.

Carlton (1963) proposed a mechanism for the control of behavior which assumed that behavioral responses were a result of the interplay of two functionally independent neurochemical systems in the brain. One system was assumed to be cholinergic and to function to inhibit unrewarded responses. The other system, according to Carlton, was adrenergic and increased activity to all responses. According to this mechanism, learning could be considered a function of cholinergic inhibition of unrewarded response systems and the ensuing dominance of the uninhibited adrenergic excitatory control system that is rewarded. In other words, all those responses that are unrewarded are inhibited by a cholinergic system thus allowing the one adrenergic system (rewarded response) that is not inhibited to become dominant.

The evidence that Carlton (1963) cites to support his thesis covers a wide range of behavioral situations. The

first assumption of this mechanism - that there are two functionally opposed chemical systems present in the CNS, one which increases behavioral responses and the other which inhibits them - has been tested. Elevations of cholinergic activity with eserine have been shown to produce a marked inhibition of avoidance responding similar to that produced by reserpine or chlorpromazine (Pfeiffer and Jenney, 1957). Pfeiffer and Jenney also obtained such results with pilocarpine and arecoline, drugs known to mimic the effects of ACH (Goodman and Gilman, 1955). This evidence thus lends support to Carlton's mechanism by showing decreased behavioral responding to either an increase in cholinergic activity or a decrease in adrenergic activity. This would be expected if the two systems were antagonistic. Furthermore, Pfeiffer and Jenney (1957) have provided data that strongly suggest that these effects were due to an action on the central, rather than the peripheral nervous system.

The excitatory effects of increased adrenergic activity has been documented by Scheckel and Boff (1966). They reported increased rates of responding on Sidman avoidance schedules to injections of tetrabenazine and iproniazid. Tetrabenazine releases the bound stores of norepinephrine within the cell which then diffuse out of the cell and apparently increase nervous activity via their role as central transmitters. The norepinephrine itself is not metabolized by MAO due to the introduction of iproniazid

which is a MAO inhibitor. In their paper, Scheckel and Boff (1966) report several other experiments which vary the level of brain norepinephrine in the rat with the same results. If norepinephrine is released externally (i.e., not allowed to be metabolized by MAO) behavioral measures (i.e., Sidman) increase while if levels of norepinephrine are decreased by drugs such as reserpine, behavioral measures show a decline in response rate.

Other investigators have noted a relationship between excitatory adrenergic activity and certain behavioral situations which give rise to emotional states. Mason, Mangan, Brady, Conrad, and Rioch (1961) have found, in the rhesus monkey, that increases in blood levels of epinephrine occurred in situations which combined uncertainty or unpredictability with the threat of noxious stimuli and anticipation of the need for coping behavior. Release of norepinephrine without concurrent elevation of the epinephrine level occurred when the conditions associated with administration of the noxious stimuli were familiar, unambiguous, and predictable. In other words, adrenergic activity seems not only to cause more behavioral response activity but, in turn, seems to be correlated with fear-like emotional states.

Returning to Carlton's (1963) hypothesis concerning a cholinergic inhibitory system, it will be remembered that this system effects non-reinforced responses only.

Pfeiffer and Jenney's (1957) work pointed to the existence of a cholinergic system which antagonized an adrenergic system leading to fewer behavioral responses. Going one step further, Hearst (1959) also has reported evidence that indicates that this cholinergic system acts to inhibit non-reinforced responses. In this study, animals were trained to "wait", not respond, for a given period, after which one of two auditory stimuli was presented. Reinforcement was delivered to the animal only if it pressed a particular lever of the two available when one stimulus was on and pressed the other when the other stimulus was on.

The animals normally responded appropriately to the levers during stimulus periods and emitted few responses between them. When given scopolamine (an anticholinergic drug), however, they emitted many responses between periods and tended to perseverate in their responding to one lever, regardless of which stimulus was on. The animals were subsequently given a series of extinction sessions, during which responding declined. The animals were continued on extinction but were then given injections of scopolamine before each session. Hearst found that (a) levels of responding returned to those obtained under the drug before extinction, (b) this behavior was also characterized by a tendency to perseverate and to respond between stimulus periods, and (c) continued extinction under scopolamine (for thousands of non-reinforced responses)

failed to result in a decline in performance. He also reported that when the scopolamine injections were discontinued, performance dropped to the low levels that had been obtained before scopolamine injections were begun. Thus, it would seem that attenuation of cholinergic activation does, indeed, release responses that are normally inhibited due to non-reinforcement.

Other studies bear on the relationship between non-reward and cholinergic activity. Carlton (1961) showed that amphetamine (a drug which mimics the effects of norepinephrine), scopolamine, and atropine increased the number of errors made during the acquisition of an alternating two bar instrumental situation. These effects can be related to the increased probability of intrusion of incorrect responses due to an increase in activation with amphetamine, on the one hand, and to an attenuation of the usual effects of non-reinforcement with the anticholinergics on the other.

Rather similar effects to those cited above were also reported by Whitehouse (1959) who used the traditional T maze. It is reasonable to suppose that learning to make a correct "choice" in a T maze involves, to some extent, the extinction of the tendency to make the wrong one. In the study by Whitehouse, it was found that reduction in cholinergic activity with atropine significantly decreased the rate at which rats learned discrimination problems in the maze. Furthermore, Whitehouse (1967) has also reported

that atropine produces a significant decrement in acquisition over and above the decrement produced by the addition of irrelevant cues in a T maze. Additionally, the decrement produced by atropine was dose related. Whitehouse thus concludes that this experiment lends support to Carlton's (1963) view that a cholinergic system in the brain is involved with the extinction of non-reinforced responses, since it can be assumed that responses to irrelevant cues required extinction and that the increase in number of cue alternatives of which only one set was relevant placed greater demands on the cholinergic system.

Krech, Rosenzweig and Bennett (1960) have added more interesting data that tend to support Carlton's (1963) mechanism of an inhibitory cholinergic system that mediates unrewarded responses. They report that animals exposed to more complex environments show a different cortical-subcortical cholinesterase (ChE) ratio than animals who have not been so exposed. Specifically, they note that the more complex the environment, the lower the cortical-subcortical ratio of cholinesterase activity. Controls for body weight, strain and nutritional factors were used as well as controls for change due to handling and locomotor activity. These authors concluded that this evidence demonstrates a measurable and consistent change in the patterning of ChE in the rat brain as a function of environmental stimulation.

To clarify how this data lends support to Carlton's thesis one can refer to an earlier study by Krech, Rosenzweig and Bennett (1956). In this study, hooded rats were tested in the Krech Hypothesis Apparatus under the progressively soluble training procedure. After testing, the animals were sacrificed and determinations were made of their level of cholinesterase activity in the visual and somesthetic areas of the cerebral cortex. An analysis of the behavioral and chemical data suggested that the behavioral differences between animals high and low in ChE activity level indicate differential ability to shift the dimension of discrimination, such that a high ChE level is associated with an ability to maintain a probabilistic response pattern, while a low ChE level is associated with a more thorough commitment to the dominant stimulus (Krech et al., 1956). These two studies supply data that suggest that brain levels of ChE are related to environmental stimulation. Consequently, stimuli are able to modify chemical concentrations in the brain which, in turn, can modify electrical transmission. Thus, the link between external experience and brain modification is made. Furthermore, this change in chemical concentrations seems to be related to behavioral response patterns in that the more ChE available the more able an animal is to inhibit a response to the dominant stimulus in favor of a more probabilistic pattern. Therefore, as we will see below, higher concentrations of ChE lead to more activity in cholinergic systems which

allows the animal to inhibit responses to dominant stimuli, thus allowing for shifts in the dimension of discrimination which leads finally to a more probabilistic response pattern based on reward. In summary, high ChE levels insure an active cholinergic system which inhibits unrewarded responses, thus prohibiting any dominant stimulus to determine behavior. Behavior is then determined solely by the reward contingencies.

More conclusive evidence for the above statements was provided by Russel, Watson and Frankenhaeuser (1961). They reported that reduced brain ChE activity was associated with differential effects on the behavior (i.e., speed of conditioning was not altered significantly, whereas speed of extinction was so effected). Specifically, high ChE levels were associated with fast extinction and vice versa. In discussing their findings, Russel et al. (1961) noted that ChE activity level provides a measure of the readiness of nerve impulse transmission in the CNS and that the relative ease of nerve impulse transmission requires the extinction of old behavior patterns and the formation of new ones. Under such circumstances, speed of extinction might well be the pacemaker step in the series of adaptive behavior changes. The above experiment tends to support the conclusion that this pacemaker step, at least under certain circumstances, is related to brain ChE activity in such a way that high

ChE activity is associated with more rapid extinction. This finding has much in common with the suggestions of Krech et al. (1956) mentioned above. Specifically, high cholinergic activity leads to faster extinction and extinction is simply the inhibition of an unrewarded response. Therefore, the above series of studies suggest that ChE levels can be modified by experience and that higher levels tend to allow the animal to inhibit responses that are unrewarded even if they are responses to dominant stimuli. High levels of ChE thus lead to faster extinction which is the first step in the behavioral change implied in learning.

Let us now briefly review the essential concepts outlined thus far in this presentation. Carlton (1963) has suggested that there are two mutually antagonistic neurochemical systems in the brain. One is excitatory, adrenergic in nature, and coupled to reward. The other is inhibitory, cholinergic, and controls responses that are unrewarded. Evidence has been cited showing that response levels can be manipulated using this model as a reference. Decreased cholinergic or increased adrenergic activity leads to more response activity (Hearst, 1959; Scheckel and Boff, 1966). Increases in cholinergic activity or decreases in adrenergic activity leads to less behavioral activity (Pfeiffer and Jenney, 1957; Scheckel and Boff, 1966). Furthermore, adrenergic

activity can be increased by exposure to emotional states that can be described as fear or conflict situations (Mason et al., 1961).

Finally, evidence was reviewed that supported Carlton's hypothesis that the cholinergic system acts to inhibit unrewarded responses. Hearst (1959) reported that a reduction in cholinergic activity (via the introduction of scopolamine) blocked extinction. Carlton (1961) showed that amphetamine, scopolamine, and atropine increased the number of errors made during the acquisition of an instrumental response. Krech et al. (1960) showed that increased cholinergic activity via increased ChE level led to inhibition of responses to dominant stimuli leading to a more varied response pattern. Finally, Russel et al. (1961) demonstrated that decreased ChE levels lead to slower extinction and thus less inhibition to unrewarded responses. In summary, then, there is considerable support for the idea that there are two mutually antagonistic systems, one which adrenergically mediates responses followed by reward, and one which cholinergically inhibits responses followed by nonreward.

Since the publication of Carlton's paper in 1963, there has been reported in the literature several instances where anticholinergic drugs have failed to affect performance. If an active cholinergic inhibitory system were located in the brain, the introduction of such drugs would be expected to adversely effect the performance of

a learned response. Addressing himself to these inconsistent findings, Gerbrandt (1965) has proposed a modification of Carlton's original hypothesis. Specifically, Gerbrandt (1965) proposes a descriptive model which assumes that control of behavioral responses is a function of discrete brain systems, mutually inhibitory in their effects, which function to release highly stable responses or to increase the stability of a behavioral response by inhibiting competing responses of higher stability. The author further proposes that these systems can be biased by cholinergic stimulation and adrenergic blockage and vice versa. This model thus assumes that such stable responses as active avoidance are controlled by a system that releases this stable response. Unstable responses such as passive avoidance are acquired by active inhibition of more stable competing responses by another system. Furthermore, when one system is acting (the releasing system analagous to Carlton's adrenergic system), the other (inhibitory system analagous to Carlton's cholinergic system) is inactive. Under this model learning is a function of inhibiting competing responses (by a cholinergic system) in the early phase of learning (acquisition) and the later release of a stable response by the other adrenergic system during the performance phase. Somewhere during the latter stages of acquisition the inhibitory system phases out and the releasing system phases in.

Evidence for this hypothesis is extensive and varied.

It has been reported that crystalline implants of cholinergic, but not adrenergic, stimulants will interfere with performance on a CAR when these implants are placed in the medial septal area (Grossman, 1964). Also, Meyers, Roberts, Riciputi, and Domino (1964) have found that cholinergic blocking drugs (scopolamine and atropine) disrupt only the acquisition and not the retention of a CAR. On the other hand, chlorpromazine (an adrenergic blocker) blocked performance of a CAR (Chalmers and Erickson, 1964). Longo (1966) reported that atropine and scopolamine when administered during the period of formation of the avoidance reflex caused notable alterations in the response, while they were inactive in fully trained animals. Finally, Meyers (1965) reported that scopolamine disrupted the acquisition but not the performance of an active avoidance task while it adversely effected both the acquisition and the performance of a passive avoidance task. This would be expected if Gerbrandt is correct in postulating an inhibitory cholinergic system that phases out after acquisition of a stable response (active avoidance) but does not phase out in the acquisition of an unstable response (passive avoidance). The general implication of the above studies is that there is a phasing out of a cholinergic system during acquisition and a phasing in of an adrenergic control system during the performance of a learned response.

In summary, before the Maier paradigm is described, it seems possible to combine the two above mechanisms proposed by Carlton (1963) and Gerbrandt (1965) into a single model that will prove useful in explaining a wide range of behavior. One can assume, as Carlton did, that each response has an excitatory adrenergic system related to it. The strength of this system in relation to the strength (or stability) of other competing response systems determines the probability of this response occurring. Furthermore, every response has a cholinergic inhibitory system associated with it which is activated when the response is punished. Therefore, the learning of any response is a function of the level of the excitatory adrenergic system associated with the rewarded response and the consequent reduction of excitatory systems related with unrewarded or punished responses. As in Gerbrandt's (1965) model, one would have to postulate two phases. First, during the early phases of acquisition many responses are in the animal's "habit hierarchy". In testing the new situation, the animal makes many varied responses. Usually only one or two responses are rewarded and the others are either punished or unrewarded. The rewarded response systems would be enhanced (due to feedback from the reward) and thus these systems would become more excited. The non-rewarded systems would still be rather active and so to insure that the rewarded systems became dominant and reward is obtained, the

cholinergic inhibitory systems would become active as a consequence of non-reward. They would lower the excitatory level of the unrewarded systems and so only the rewarded response would become dominant. Once this dominance is established, Gerbrandt's second phase would come into being. The inhibitory cholinergic systems would phase out and the dominant excitatory system is "released" to control behavior.

The Maier Paradigm

The Maier paradigm used in behavior fixations is based on the two-choice discrimination procedure using the Lashley jumping stand. The animal is placed on an electrified grid and allowed to jump to either of two closed doors (one is dark and the other is illuminated by a 25 watt bulb). The animal must make a jumping response within 30 seconds of being placed on the grid or else a shock comes on and forces a response. In the first phase the two-choice problem is insoluble - half the responses to the dark and bright windows are punished by locking the windows and allowing the animal to drop four feet into a net, and the other half of the responses to either window are rewarded. The reward is applied to each window in a random sequence. One other motivational aspect is present in the Maier paradigm in that the rats are 23 hours food deprived and food is available behind the doors on a platform. Whenever the animals choose

an unlocked door, they are allowed to eat. This first insoluble phase goes on for 160 trials - 10 trials a day. The behavioral result is usually a stereotyped response to a position (i.e., the animal always jumps to the left or right window). In the second phase, the problem is made soluble. A position-stereotyped animal in this stage is usually given a non-spatial cue (dark) as the correct response. Therefore, whenever the animal jumps to the dark it is rewarded, and the dark window is randomly switched from left to right for 200 trials - 10 trials a day. In a typical experiment, 15 to 20% of the animals solve in this 200 trial period while the rest maintain their position stereotype (fixation), always jumping to the right or left. Increasing the testing period over 200 trials rarely leads to any more solutions. There is, however, ample evidence that fixated animals do discriminate between the rewarding and punishing aspects of the soluble problem, in that abortive jumps are fewer and latencies are typically shorter to the correct stimulus than to the incorrect. In other words, at the end of the soluble problem, the fixated rats typically are jumping more quickly when the dark (rewarded) window appears on their fixated side than when the bright (punished) window appears. It can therefore be assumed that the animal has made the association between reward and punishment and the two stimuli presented (Feldman and Green, 1967).

The question that readily comes to mind is why the

animal persists in making a response (i.e., position fixation) that to the experimenter is less than desirable. The animal can receive 100% reward and no punishment if the correct response is made. In spite of this, the animal continues his fixated response pattern even after his latencies of jumping show that the rat expects punishment to the bright and reward to the dark window.

With this question in mind, let us now present a model based on the previously reviewed literature above that will attempt to clarify the results obtained in experiments using the Maier paradigm.

Statement of the Model

First of all, the assumptions of the model are taken directly from the evidence presented by Carlton (1963) and Gerbrandt (1965) reviewed above. They are briefly: 1) that all responses are controlled by two mutually antagonistic neurochemical systems, 2) that one system is cholinergic and tends to inhibit unrewarded responses while the other is adrenergic and tends to increase the probability of occurrence of rewarded responses, 3) that the adrenergic control system can be activated by fear or conflict situations and finally, 4) the two systems operate in phases, during acquisition the inhibitory system is dominant, while during performance the adrenergic system is in control of behavior.

The model itself is a direct application of the

combined Carlton-Gerbrandt model outlined above to behavior fixations. Now, one can examine the Maier paradigm to see if the above assumptions can explain the development of a fixation. During training the animal has built up equal excitation to all four stimuli in both directions (spatial - right versus left; light cue - bright versus dark) due to the fact that all stimuli were rewarded equally. Therefore, the animal comes into the initial task relatively unbiased and can make responses to each stimulus.

Then the animal is put into the insoluble problem stage. A new dimension enters the situation at this point in that negative incentives are operative. If the animal jumps to the incorrect window, he falls four feet and if he delays jumping for over 30 seconds, he receives a painful shock. Negative incentives create two types of activity according to our assumptions. First, whenever the animal jumps to the incorrect window, the inhibitory (I) system for that response becomes more active and inhibits all excitation for that response pattern. Concurrently, the fear that is aroused by the fall and shocks received by the animal increases the adrenergic excitatory activity in all response systems. This increased adrenergic activity, however, affects activity only in the non-punished response systems for, although norepinephrine is released in the response system that controlled the punished response, it does not lead to more

activity due to the active inhibition of the I system. Therefore, on the next jump, the animal is less likely to make the previous punished response. If punished to the right bright the animal might now jump to left bright because the I system to right might be high and the adrenergic system (E system) to left has been increased by fear. In a normal soluble situation, the animal would thus alternate his responses depending on the contingencies of reward and punishment. A punished response would be inhibited by I system while unpunished responses would benefit from more adrenergic activity due to fear and the increased activity from reward. Thus, eventually the animal would build up excitation to the correct response. Further, when the I system phased out later in acquisition, the total excitation for the correct response would be much higher than competing responses; the correct response would be "released" on every trial and the animal would solve. Finally, it is proposed that these events occur with one dimension at a time (spatial or non-spatial). After one dimension is equally punished and inhibited, the animal switches to the other dimension. This dimension is then under the control of the I and E systems and the correct response is thus strengthened differentially. This is the process that leads to solutions in the soluble problem.

In the insoluble problem, however, there is no correct response since all the responses are punished randomly, and

ultimately, inhibition and excitation build up evenly for all responses. Therefore, the animal during acquisition may alternate its responses trying to improve its situation. Somewhere during acquisition, the organism must find an equilibrium for all these systems since both E and I cannot build up indefinitely. Therefore, the built-in safety factor labeled by Gerbrandt (1965) as the I system "phase-out" occurs to stop this buildup. (The animal now has high E and I systems depending on what response was punished least.) At any given time one system is more dominant than any of the others (i.e., the system that was rewarded most). When the I system phases out it does so quickly within one or two trials thus leaving one response in one dimension (remember only one dimension is handled at a time) dominant. The systems are now "set" and an equilibrium is reached where negative incentives no longer effect the buildup of these systems. The I system is phased out and thus not excited. The fear associated with falling and shock merely maintains excitation at these "set" levels thus offsetting any decay over time that might occur. Under this mechanism the animal has reached a type of physiological equilibrium which in psychological terms might be termed "a reduction of conflict". The animal will remain fixated in this response pattern until the external stimuli change significantly to allow the animal to recognize a change in reward contingencies and thus cause the I system to

phase in again to begin the process of extinction which always precedes the acquisition of a new learned response. In essence, the animal has to some extent treated the insoluble problem as soluble, phasing out his I system, so that he can settle down to one response pattern. The only difference is that the response he chooses is not rewarded 100% of the time.

In the soluble problem, the animal soon learns that a new problem is present. Typically the animals show a distinct latency curve separation to the correct and incorrect stimuli, jumping faster to the correct than to the incorrect window (Feldman and Green, 1967). This information (i.e., the discrimination) is relayed to the performance systems and the I system becomes active again. In 15 to 20% of the animals tested the I system actually is strong enough to overcome the excitation of the dominant response and extinction takes place. The fixated response is inhibited and excitation quickly builds up to the rewarded response and allows the animal to solve. In regard to solutions, it is suspected that this small percentage of animals are those that Krech et al. (1956) noted had higher levels of ChE and thus more active I systems. These are the animals, it may be recalled, who were able to shift dimensions more readily and were less under the control of the dominant stimulus. These are the animals who can inhibit a response to the dominant stimulus and act in a more probabilistic manner to obtain reward.

In regard to the ability of an animal to show quick solutions after the initial "breaking" jump (i.e., the animals do not show typical learning in the Maier paradigm; after the first correct jump to the non-fixated side they usually continue to solve with few errors [Feldman and Green, 1967]), the following must be stressed. The I and E systems so far discussed are considered performance systems and can control behavior in the above manner only when other centers make the association between reward contingencies and stimuli. Therefore, an animal that does not show latency differences to bright and dark in the soluble problem cannot act according to the model and solve. In this case, all stimuli are equally punishing so no consistent pattern of inhibition can occur. Thus, reward contingencies must be evaluated before the performance systems can play an important role in controlling behavior.

Now that the model has been applied to solvers what about the other 85% of the animals who do show latency differences (i.e., do appreciate the reward contingencies) but who do not solve? In these cases, either the E system has become so dominant due to fear that the inhibitory system is unable to suppress it; or what is more likely, these animals because of genetic and/or environmental deficiencies have less ChE levels in these systems thus reducing the activity in their I system. These animals are unable to inhibit the response to the dominant stimulus

and continue their fixated behavior patterns.

In summary, fixation takes place when no solution can be found by the animal to stabilize the upward trend of excitation in the response systems. When no clearly dominant response (i.e., reward response) can be found, the animal makes one by the normal "phasing out" of the I system. This "phasing out" sets the excitation levels of the response so that one is dominant. Therefore, one response becomes fixated even if it is not "correct", in order to stabilize the response systems involved.

Before predictions from the above model are made, one point requires clarification. The only known method of breaking behavior fixations is to guide the animal to the correct window, thus "forcing" the animal to make the correct choice for several trials. After this treatment, the animals when given a free choice will solve (Maier, 1949). The above model explains this data in the following manner. Animals forced to go to the correct window (dark) on the non-fixated side undergo two basic changes. First the E system to this window is built up because this response is rewarded (i.e., by food). Secondly, and more importantly, the behavioral conditions are radically altered from that of the normal condition. The animal becomes aware that the problem has changed in that the stimuli are different (a plexiglas screen is used) and the reward contingencies are different (100 vs 50% reward). This realization causes the I system to be triggered into

activity rapidly and more forcefully than in the normal transition from insoluble to soluble problem in the Maier paradigm where the reward contingencies become strengthened only gradually. Therefore, increased I activity causes extinction of the fixated response to take place and with the increased activity of the E system on the non-fixated side, the animal is able to solve.

The predictions offered in this paper will stem from a simple 2 x 2 design where fixated animals are given 10 trials of guidance on the first day and 10 free or non-guided trials on the second day. For each drug tested there will be four groups: (1) No Drug, No Drug (ND-ND); (2) Drug, Drug (D-D); (3) No Drug, Drug (ND-D); and (4) Drug, No Drug (D-ND). The drugs used are scopolamine hydrobromide (an anticholinergic), pilocarpine nitrate (a cholinomimetic), scopolamine methylbromide and chlordiazepoxide (CDP). Although the pharmacological properties of CDP with respect to the neural transmitters are relatively unknown, there is some evidence to suggest that it interferes with adrenergic activity in such a way as to reduce it. Scheckel and Boff (1966) reported that diazepam (similar in structure to CDP) can block the behavioral stimulation usually recorded with increases in adrenergic activity caused by injections of tetrabenazine and oproniazid. Therefore, for our purposes, CDP's action will be assumed to reduce central adrenergic activity.

The predictions based on the above hypotheses are

as follows:

(1) CDP when given to fixated animals in the above 2 x 2 design will generally have a detrimental effect on solutions. This is because the E system associated with the response to the non-fixated side will not build up as fast as normally expected under guidance due to the presumed anti-adrenergic effects of CDP. Specifically, since the free day is the time when this adrenergic system is needed most (i.e., fear to the negative incentives builds up E system to the non-fixated response), the D-D and ND-D groups will perform the worst when compared to the control. The D-ND group should show a slight decrement when compared to the ND-ND control since adrenergic feedback from reward on the guided day will be reduced.

(2) Pilocarpine, since it is a cholinomimetic, will generally enhance the ability of animals to solve. Since it increases the I system, and since this system is most active on the free day, the D-D and ND-D groups will perform the best when compared to the control. The D-ND group should not be significantly different from the control.

(3) Scopolamine, since it is an anticholinergic drug, will generally be detrimental to solutions. Specifically, since the I system is needed most on

the free day, the D-D and ND-D groups will perform the worst. The D-ND group should not be significantly different from the control.

METHOD

Subjects

Ss were 78 male albino rats from the colony maintained by the University of Massachusetts Psychology Department (descendants of Charles River CD stock). Ss ranged in ages from 4 months to 1 year at the beginning of the study. All rats were fed approximately 40 gm per day of moist Purina Lab Chow and were allowed free access to water in their living cages. 27 rats were trained by E to produce fixations by the method described below. 51 rats were trained by other experimenters in the same way and came from other experiments which made use of insoluble-soluble problem sequences and resulted in behavior fixations. Of these 51 animals, 30 were distributed in the chlordiazepoxide (CDP) procedures, and the other 21 were distributed in the scopolamine and pilocarpine procedures. The 27 rats trained by E were distributed in the pilocarpine and scopolamine series only. The use in this experiment of fixated animals from other experiments assumes that all fixated animals are basically constant with respect to this variable. Feldman and Lewis (1962) have shown that fixated rats tested over 121 days (1210 trials) under a variety of conditions never deviated from their fixated response. This supports the assumption of the equivalence and the stable characteristics of fixated animals.

Apparatus

The apparatus used was a modified semi-automatically controlled Lashley jumping stand similar to that described by Feldman (1948). This stand essentially consisted of a platform from which a rat could jump to one of two windows. One window was dark and the other was illuminated (bright) by a 25 watt bulb which was situated behind one of the two opaque plexiglas windows. The position of the bright or dark window, and the selection of which window was to be locked was controlled automatically via a switching apparatus described by Feldman (1948). A correct response through an unlocked window led to food reward, and an incorrect response to a locked window led to a bump and a fall into a net 39 inches below. Response latency in seconds was measured by starting an electric timer when the rat was placed on the jumping platform and stopping it when the rat responded. The platform consisted of a metal grid through which a shock of .40 ma (120 v) was delivered to each animal 30 seconds after it had been placed on the stand if the S had not yet jumped. A dish of food was available on the platform behind the windows as reward for correct responses.

Procedure

27 Ss were trained to jump by a method of approximation. At first the Ss were placed on the feeding platform with their daily food ration. After three or four days of

familiarization with the apparatus, Ss were given individual training trials. During this period the jumping platform was placed close to the stimulus windows which were held in an open position, and the rats were required to step through them to the platform behind the windows where food was available. In order to prevent position habits, each S was manually guided on even-numbered trials to the window opposite the one it had chosen on the previous trial. Each rat received 10 trials a day, 5 jumps to each window. Every day the jumping platform was moved back about one inch from the windows until the rats were jumping 8 1/2 inches. Then, the windows were gradually closed. At first the rats had to brush past them, but eventually they had to push them open in order to reach the food reward on the back of the platform. One of the windows was illuminated, thus presenting the rat with a bright-dark stimulus pattern. The bright and dark windows were switched after every even-numbered trial. The guidance on even-numbered trials continued throughout this training period. The rats were fed during jumping trials and were allowed to finish their daily ration in a 1/2 hour period immediately following their jumping trials.

After preliminary training, each S was given the insoluble problem situation for 160 trials at 10 trials per day. In the insoluble problem situation, the windows were locked in random order so that there was no response

which permitted consistent escape from punishment (i.e., each animal was punished 50% of the time in a random order). The rats soon showed increased resistance to jumping and the grid shock was necessary to force a response 30 seconds after the trial began. After about 40 or 50 trials the animals showed a consistent response pattern, always jumping to the right, left, bright, or dark window. The position stereotype was the dominant mode of response and most animals jumped either to the right or left consistently. Sixteen days were set as the limit for this phase since Maier and Feldman (1948) found that the optimum number of fixations and the optimum strength of fixations could be obtained with about 160 trials.

Following the insoluble problem phase, all the rats were given a 20-day test, 10 trials per day, for the stability of their responses. A 20 day test period was chosen because Maier, Glaser, and Klee (1940) have shown that if the rat changes its stereotyped response for a new one, it will probably do so within 200 trials. The soluble discrimination situation used in this phase consisted of requiring each rat to abandon its stereotyped response for a learned bright-dark discrimination. Animals that had developed left or right position responses, or consistent response to the bright window, were now required to go to the dark window, while those that had developed responses to the dark window in the insoluble stage were required to go to the bright

window. Animals that solved the discrimination within the 200 trial test period were dropped from further experimentation. The criterion of solution was no more than one error in three successive days (i.e., one mistake in 30 consecutive trials).

All animals whose stereotyped responses persisted after the 20 day test for fixation, and the 51 animals that came from other experiments, 78 animals in all, were divided into 11 groups. These groups fell into three categories as follows: (1) the chlordiazepoxide (CDP) groups which consisted of 30 animals from other experiments; (2) the pilocarpine groups which consisted of 13 Ss trained by the E and 7 Ss from other experiments, and, (3) the scopolamine groups which consisted of 14 Ss trained by E and 14 Ss from other experiments.

All fixated animals were given the following treatment. On the first day each animal was given 10 guided trials to the correct window of a soluble problem. Guidance was given by placing a plexiglas screen between the platform and the incorrect window, thus forcing the animal to make a correct response. On the next, or even, day the plexiglas screen was removed and the animals were given 10 "free" trials during which they could jump to either window. The third day repeated the sequence with 10 guided trials and so on. In other words, the animals were guided on odd days and non-guided on all even days. This procedure was continued for all animals until they

solved the discrimination problem on even days or had been given 340 trials in all, whichever came first. The criterion for solution was the same as in the soluble problem; namely, 29 out of 30 correct responses on three consecutive non-guided days. The motivational factors were also constant, food being available behind the correct window, and shock was used if the animal failed to jump 30 seconds after a trial began.

As part of this above treatment, the effects of three drugs upon problem solutions were tested. Drugs were administered by intraperitoneal injection. There were four groups in the CDP series. The first group (ND-ND) consisted of 9 animals and underwent the above behavioral test with no drug on either day. The second group (D-D, N=6) received 15 mg/kg of CDP 30 minutes before the first trial on both the guided and non-guided days. The third group (D-ND, N=9) received the drug only on the guided day and the fourth group (ND-D, N=6) received drug only on the non-guided day.

In the scopolamine series, Ss received 1.0 mg/kg of scopolamine hydrobromide 30 minutes before the first trial on drug days. The first group (D-D, N=7) received this drug on both days. The second group (D-ND, N=7) received the drug only on the guided day and the third group (ND-D, N=7) received the drug only on the non-guided day. To test for the possible peripheral effects of this drug, scopolamine methobromide (1.0 mg/kg given 30 minutes

before the first trial) was given to a fourth group (N=7). This drug was given in a manner similar to whichever scopolamine hydrobromide group differed the most from the ND-ND control group described above in the CDP series. This group turned out to be the D-ND group and so the scopolamine methobromide (Methyl-scopolamine) group received the drug only on the guided day.

Finally, the pilocarpine nitrate series consisted of three groups who received 5.0 mg/kg of the drug 30 minutes before the first trial on drug days. The first group (D-D, N=7) received the drug on both days. The second group (D-ND, N=7) received the drug only on the guided day, while the third group (ND-D, N=6) received the drug only on the non-guided day.

All animals were run 23 hours food deprived as during the soluble test described above, and were fed 40 grams of wet Purina Lab Chow each day after the 10 trials were completed.

RESULTS

The results will be reported in three sections, each dealing with a specific drug. Before analyzing the data, however, the overall design and statistical methodology will be reported. The analysis was a completely randomized one factor design in which the 11 groups were the between factor. Table 1 gives the values for the Bartlett tests for homogeneity of variance that were carried out. As can be seen from these values, there can be no assumption of homogeneity of variance within drug groups as well as for tests between them. Therefore, a nonparametric analysis was called for that could be applied to the above completely randomized design. The Kruskal-Wallis one way analysis of variance by ranks was chosen as the overall test for group effects. It proved to be highly significant ($H = 32.80$, $p < .001$) on 10 df. Once an overall group effect had been established, Mann Wilney U tests were used to determine specific differences among groups.

CDP

Figure 1 presents the percent correct responses as a function of the number of non-guided days for the three CDP groups and the ND-ND control group. As can be readily seen, CDP, in general, had a detrimental effect upon solutions. Table 2 presents the Mann Wilney U values

TABLE I

Hartley's Test for Homogeneity of Variance

Comparison	F Max Value	Degrees of Freedom	Probability Value
Overall test consisting of all 11 groups	87.42	11, 6	$p < .01$
CDP Groups	24.85	4, 6	$p < .01$
Pilocarpine Groups	77.87	4, 6	$p < .01$
Scopolamine Groups	29.97	5, 6	$p < .01$

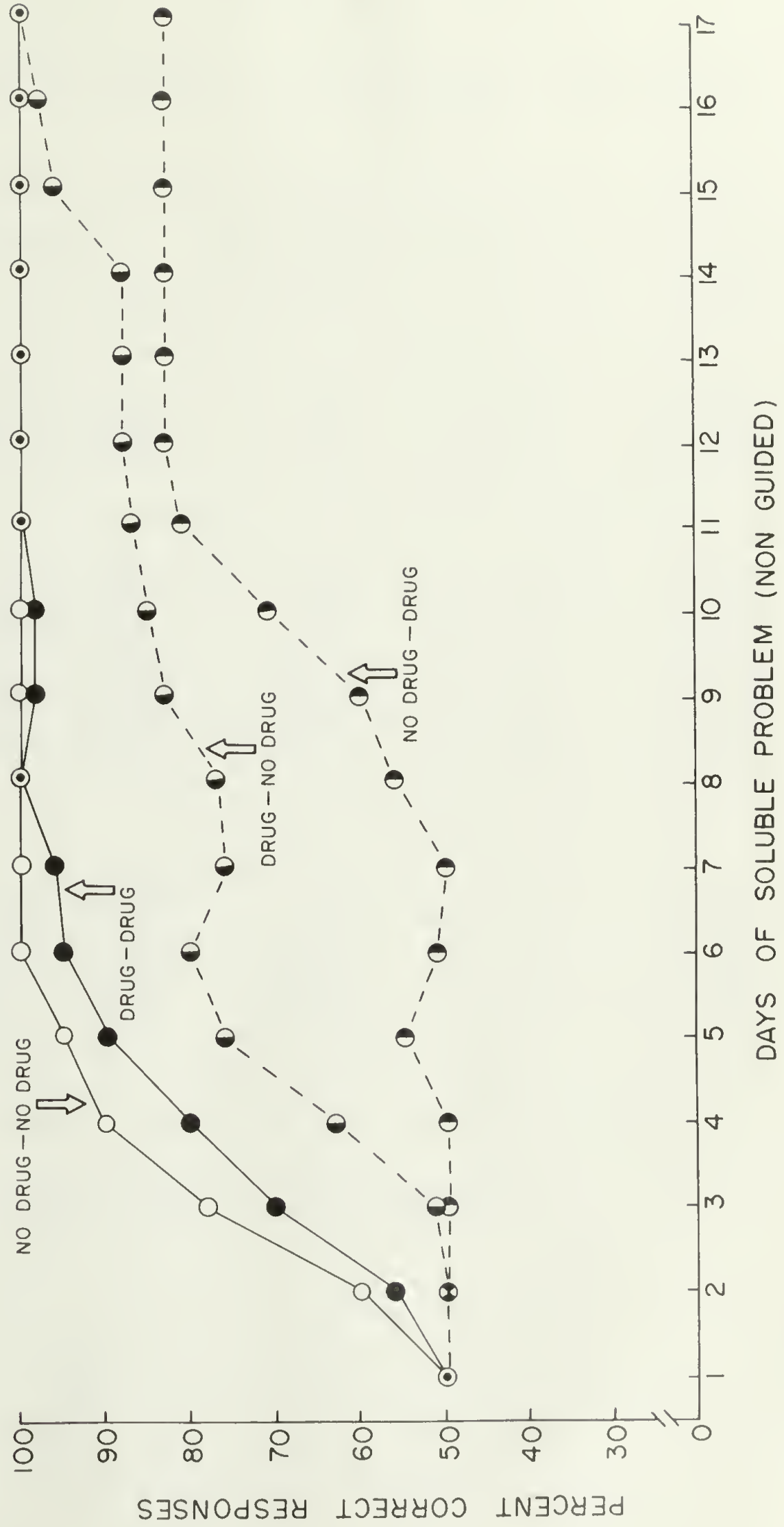


Figure 1. The Percent Correct Responses as a Function of the Number of Non-Guided Days for the Three CDP Groups and the ND-ND Control Group.

TABLE II

Mann Witney U Values for the Multiple Comparisons

Drug	Comparison	Mann Witney U Value	N ₂	N ₁	Probability Level	
CDP						
	ND-ND vs D-D	19	9	6	p > .05	ns*
	D-ND vs D-D	12	9	6	p < .05	s*
	D-ND vs ND-D	13	9	7	p > .05	ns
Scopolamine						
	ND-ND vs D-D	20	9	7	p > .05	ns
	ND-D vs D-D	18	7	7	p > .05	ns
	ND-ND vs ND-D	13.5	9	7	p < .05	s
	ND-D vs D-ND	17.5	7	7	p > .05	ns
	ND-ND vs Methyl-S	28.5	9	7	p > .05	ns
	D-D vs D-ND	11.5	7	7	p > .05	ns
	ND-ND vs D-ND	5.0	9	7	p < .01	s
Pilocarpine						
	ND-ND vs D-ND	.5	9	7	p < .001	s
	ND-ND vs D-D	7.0	9	7	p < .01	s
	ND-ND vs ND-D	20.5	9	6	p > .05	ns
	ND-D vs D-ND	6.5	7	6	p < .026	s
	D-D vs ND-D	18.5	7	6	p > .05	ns

* ns = not significant; s = significant

for the specific comparison among groups for the three types of drugs. As can be seen from the table, there was a significant difference between the D-ND and the D-D groups in the CDP tests, and a comparison between the D-ND and ND-D groups showed there was a strong trend toward a difference. If the U value had been one point less, the difference would have reached the .05 confidence level. To summarize, the only significant difference in Figure 1 occurred between the D-D and the D-ND groups, and there was a strong suggestion that there was a difference between the D-ND and the ND-D groups.

Scopolamine

Figure 2 presents the percent correct responses as a function of the number of non-guided days for the three scopolamine groups, a Methyl-scopolamine D-ND group, and the ND-ND control. In general, the scopolamine groups showed a decrement in performance as compared to the ND-ND control. Table 2 also presents the Mann Whitney U values for the specific comparison among the scopolamine groups. As can be seen, the only significant differences were between the ND-ND and ND-D groups and between the ND-ND and D-ND groups. All other comparisons were not significant. Both the Methyl-scopolamine and D-D groups were not significant from the ND-ND control. Furthermore, the ND-D and the D-ND groups were not significantly

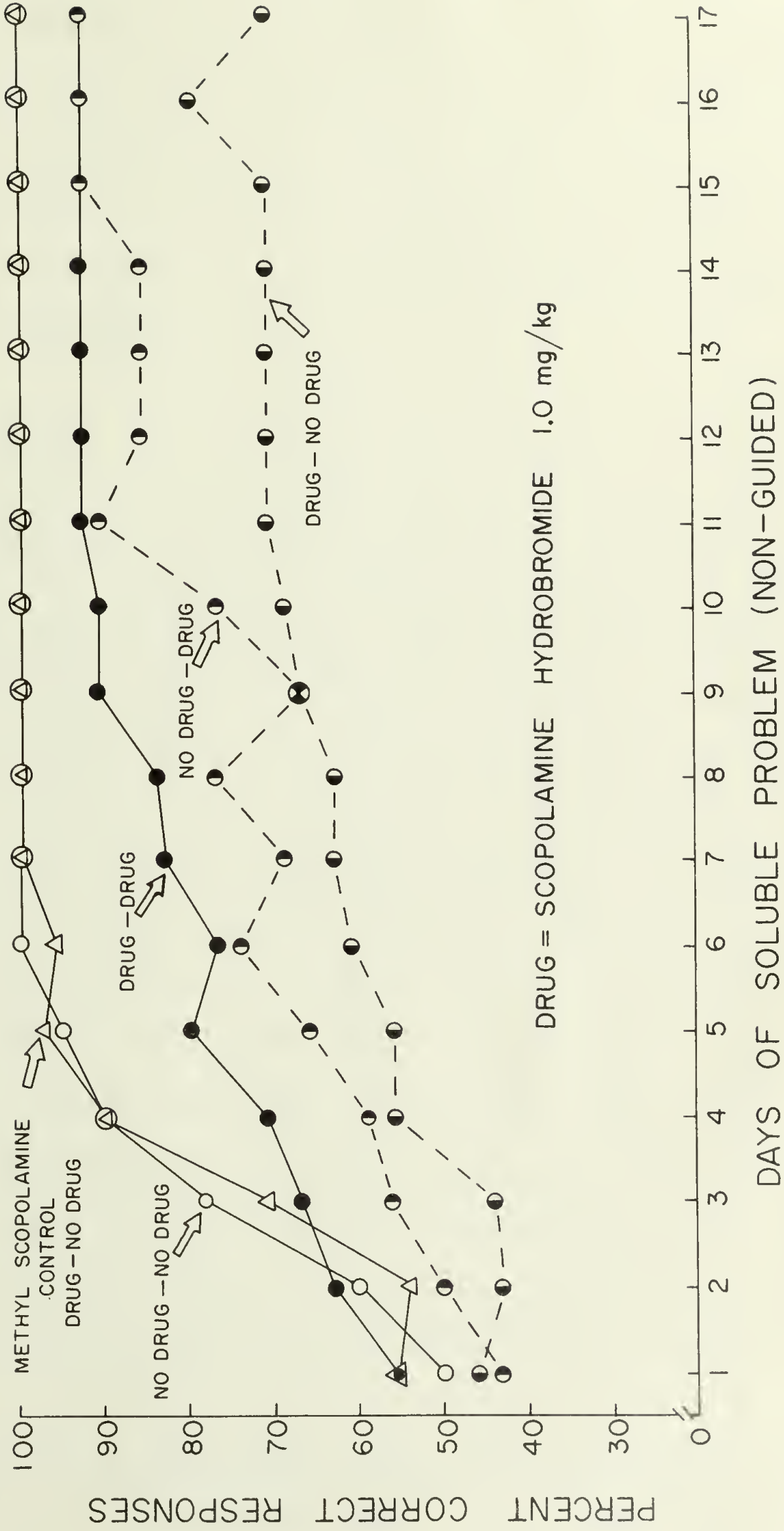


Figure 2. The Percent Correct Responses as a Function of the Number of Non-Guided Days for the Three Scopolamine Hydrobromide Groups, a Methyl-Scopolamine Group, and the ND-ND Control Group.

different. Finally, the other comparisons in Table 2 show that the D-D group was somewhere between the ND-ND control and the two alternating drug groups (ND-D, D-ND) and was not significantly different from any of them. In summary, the only significant difference in Figure 2 was between the ND-ND control and the two alternating drug groups (D-ND, ND-D).

Pilocarpine

Figure 3 presents the percent correct responses as a function of the non-guided days for the three pilocarpine groups and the ND-ND control. This data shows a mixed effect with some groups doing better than the control and some worse. Table 2, again, presents the Mann Whitney U values for the specific comparisons. This analysis showed that both the D-D and D-ND groups in Figure 3 differed significantly from the ND-ND control. Furthermore, the ND-D group seemed to lie between the D-D and ND-ND groups and did not differ significantly from either of them. Finally, the two alternating drug groups (ND-D, D-ND) differed significantly from each other. In summary, both the D-D and D-ND groups differed significantly from the ND-ND control in Figure 3. The ND-D group did not differ from the control but it was different from the D-ND group.

Comparisons were made, using the Mann Whitney U test, between those animals trained by the E (younger Ss) and

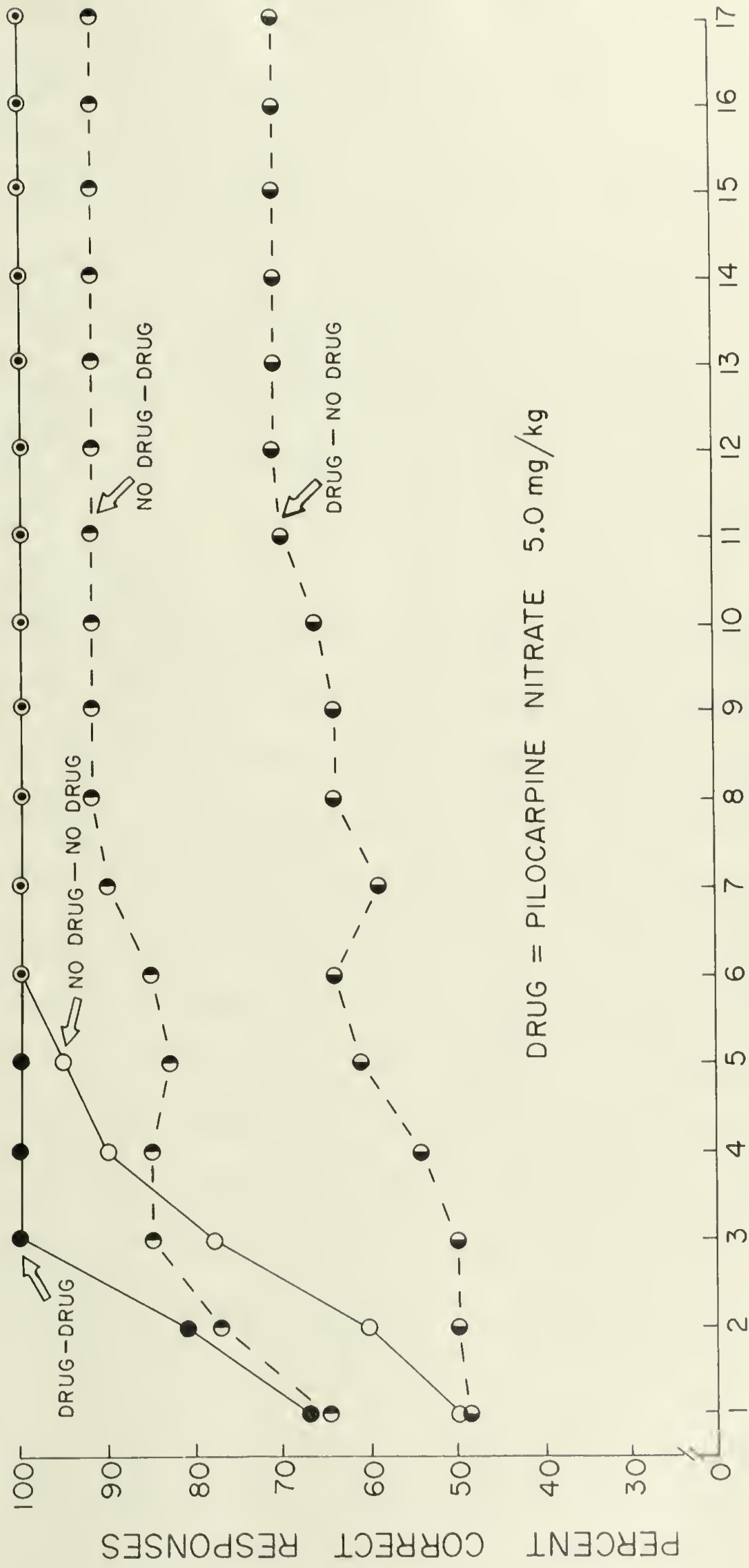


Figure 3. The Percent Correct Responses as a Function of the Number of Non-Guided Days for the Three Pilocarpine Groups and the ND-ND Control Group.

those that came from other experiments (older Ss). These comparisons were made within a specific group and therefore only those groups consisting of both types of Ss could be used in this analysis. Table 3 presents the Mann Whitney U values for these comparisons. As can be seen, none of the differences reached a probability level of .05 and, therefore, the null hypothesis was not rejected. All Ss performed consistently within a group, no matter how old they were or by whom they were trained.

Response Latency

The latency data for all 11 groups was examined throughout the experiment for non-guided days only. The data, since many Ss solved, represented a decreasing N. In some instances, the group latency data consisted of measures from only one or two animals. For this reason our curves could only be suggestive and are not presented here. Table 4 presents the mean latencies for the first non-guided day for the six alternating drug condition groups. These latencies gave the impression the CDP lowered mean latency while scopolamine and pilocarpine raised them. Therefore, in this context, pilocarpine and scopolamine would seem to have the same behavioral effect.

TABLE III

Mann Witney U Values for Groups with
Differentially Trained Ss

Drug	Comparison	Mann Witney U Value	N ₂	N ₁	Probability Level
Pilocarpine					
	D-D	4.5	5	2	p = .571
	ND-D	1.0	3	3	p = .10
	D-ND	3	5	2	p = .286
Scopolamine					
	D-D	5	5	2	p = .571
	ND-D	3	5	2	p = .286
	D-ND	5	4	3	p = .429

TABLE IV

Latency Data for the First Non-Guided Day
for the Partial Drug Groups

Groups	Latency	Difference Between Groups
CDP ND-D	15.08 sec	
CDP D-ND	18.11 sec	-3.03 sec
Scopolamine ND-D	26.58 sec	
Scopolamine D-ND	14.24 sec	+12.34 sec
Pilocarpine ND-D	26.10 sec	
Pilocarpine D-ND	12.63 sec	+13.47 sec

DISCUSSION

It was predicted that the drugs used would have their effects, either detrimental or enhancing, on the non-guided day in particular, and so the groups that would differ significantly from the control would be the D-D and ND-D groups. In almost all cases, however, the two alternated drug groups (D-ND and ND-D) performed worse than either the ND-ND control or the D-D group given the same type of drug on both days.

An explanation of the separation of performance curves between the alternated drug groups and the constant groups (D-D, ND-ND) might be the following. In the ND-ND and D-D groups transfer from one condition, guided, to the other, non-guided, was not hindered by a change in stimulus conditions. That is to say, that the drug or no drug stimuli were identical on both days. In the alternated drug groups (D-ND, ND-D), however, these conditions were not constant. In one case the drug was absent on the non-guided day and in the other it was present only on this day.

If this drug-induced decrement was a general effect, it accounts for some of the discrepancy between our former predictions and the data. Specifically, correct responses were effected by two contributing factors. These factors were (1) a general drug induced decrement that separates the two constant stimuli groups (ND-ND, D-D) and the two

alternated stimulus groups (ND-D, D-ND) and (2) a specific drug effect which may have been detrimental or enhancing. These two factors now allow us to more fully understand some of the data.

The CDP data (Figure 1) showed that there was a difference between the alternated condition groups (D-ND, ND-D) and the constant condition groups (D-D, ND-ND). This difference probably was due to a drug-induced decrement like the one proposed above. All other differences in Figure 1 are not significant although the comparison between the D-ND and ND-D groups did show a strong trend. The meaning of this trend is in doubt, however, for if it is interpreted to mean that CDP has a detrimental effect on the non-guided day (as predicted earlier) then one would expect that the D-D group would also show a decrement when compared to the ND-ND control. Since this was not the case, it seems more parsimonious to assume that this trend was only due to chance variation or some uncontrolled variable rather than a specific drug decrement on the non-guided day. In summary, then, the major finding of the CDP series was a general drug induced decrement between the constant condition groups (ND-ND, D-D) and the alternated drug groups (ND-D, D-ND). No specific drug effects seemed to be present and thus the predictions given in the introduction concerning CDP were not borne out.

Turning to the scopolamine data in Figure 2, one can

see that scopolamine, in general, had a detrimental effect upon performance. Again, the decrement between the two constant condition groups (ND-ND, D-D) and the two alternated drug groups (ND-D, D-ND) can be accounted for by a general drug-induced decrement. This, as in the CDP series, was the major finding. It accounts for the only statistical difference in the data. This data, however, was not very clear cut in that the D-D group seemed to lie between two groups (ND-ND, ND-D) that were significantly different from each other. Therefore, the D-D group could belong to either population. If the D-D group, in reality, was more closely related to the ND-D group, then one could argue that scopolamine has a decremental effect when given on the non-guided day. Furthermore, if this hypothesis were correct, one would expect that the ND-D group would perform at a significantly poorer rate than the D-ND group. This was not so, as Figure 2 readily points out, and the difference between the D-D and ND-ND groups was not significant. Therefore, there was little or no data to support the prediction that scopolamine would have a specific detrimental effect if given on the non-guided day.

There was some evidence that the general drug induced decrement described above was a central effect. The Methyl-scopolamine control and the ND-ND control did not differ from each other significantly. This fact argues

for the central mediation of the behavioral effects of scopolamine hydrobromide, since Methyl-scopolamine mimics the peripheral effects of this drug but does not readily pass the blood brain barrier (Carlton, 1963).

In summary, the scopolamine series was not clear cut in its effects. There was a definite general drug induced decrement as in the CDP series. There was also some suggestion that there might be a slight specific decremental drug effect, but this conclusion was rather tenuous due to the absence of statistical verification.

The pilocarpine data, on the other hand, was much more clear cut than the other two drug tests. This data seemed to embody two effects. First, there was some evidence for a general drug induced decrement in that the D-ND group differed from the ND-ND control. The fact that the ND-D group did not differ from the control either argues against a general drug induced decrement or suggests that another antagonistic (i.e., enhancing) effect was connected with this particular group. Since the first two drug series showed the generalized drug induced decrement, it would seem that the latter explanation has more empirical support. If, then, one accepted the hypothesis that pilocarpine had a specific enhancing effect when given on the non-guided day, one would expect that the D-D group would show better performance than the control. This indeed was the case as seen in Table 2. Therefore, in this case, specific drug effects were clearly shown

by the performance of the D-D group. Also, this effect was enhancing in that it seemed to aid performance and even counteracted the normal drug induced decrement that usually occurs between the ND-ND control and the ND-D group. Furthermore, one can assume that this enhancing effect was produced only when the drug was given on the non-guided day. This hypothesis was supported by the poor performance of the D-ND group.

Therefore, the original hypothesis concerning the effects of pilocarpine was partially borne out. The specific effect of the drug was enhancing and was effective on the non-guided day. The prediction, however, did not account for the poor performance of the D-ND group. Furthermore, whether this specific drug effect was due to pilocarpine's cholinomimetic properties is still in doubt due to the inconclusive scopolamine data. If the cholinergic properties of these drugs was crucial one would expect that scopolamine would have opposite effects to those seen under pilocarpine. Specifically, the D-D and ND-D scopolamine groups should show a decrement when compared to the ND-ND control. This was not the case. Furthermore, the ND-D scopolamine group should show a decrement when compared to the D-ND group. Again, this was not borne out in the data. Therefore, one can only conclude that the enhancing effects of pilocarpine may be due to some other properties of this drug and that its cholinomimetic characteristics did not seem to be

crucial to the behavioral changes it affected.

In summary, it can be said that the major finding of this study was the general drug-induced decrement noted with all three drugs. The secondary finding was the enhancement effect shown with pilocarpine when it was administered on the free day. An explanation of this finding is difficult at the present time due to the scopolamine data which argues against a cholinergic mechanism. In the future behavioral measures should be devised that would reduce the variability that occurred in this data. The group mean differences in the scopolamine and CDP series were obscured statistically by the large variances within groups (i.e., as shown in Table 1). Therefore, any small specific effects that occurred in either the CDP or scopolamine series were lost. These variances might be reduced if a simpler behavioral test was used (i.e., simple active avoidance) or if other designs using the Lashley jumping stand were used. Specifically, the drugs could be given during the insoluble problem to see if they effect the number of solutions in the soluble problem. In this design, the data would consist of a number of solutions and the variances within a group would no longer be a problem, as it was in the above design.

SUMMARY

A group of male albino rats from the colony maintained by the University of Massachusetts Psychology Department were used in this study. The apparatus consisted of an adaptation of the Lashley jumping stand which contained an electrified jumping platform. All animals used in this study were trained and then subjected to an insoluble, followed by a soluble problem. 78 of these animals who failed to solve the soluble problem were then used in the following 2 x 2 design. Animals were guided to the correct window on the first day and non-guided on the second. This procedure continued until the animals reached a criterion of 29 out of 30 correct responses on three consecutive non-guided days or a total of 340 trials in all, whichever came first. There were 11 groups in all and four different drugs were tested. They were pilocarpine nitrate (5.0 mg/kg), scopolamine hydrobromide (1.0 mg/kg), scopolamine methobromide (1.0 mg/kg) and chlorodiazepoxide (CDP) (15.0 mg/kg). The four CDP groups received the drug in the following order: ND-ND, D-D, ND-D, and D-ND. The three pilocarpine nitrate groups received the drug in the following order: D-D, ND-D, D-ND. Furthermore, the three scopolamine hydrobromide groups received the drug in an identical order to that of pilocarpine. Finally, the scopolamine methobromide control received the drug only on the guided day. The results showed that both

CDP and scopolamine hydrobromide had detrimental effects while the pilocarpine nitrate had mixed effects.

The data supported a general drug induced decrement hypothesis. Furthermore, pilocarpine seemed to have a specific enhancing effect along with a generalized decrement. The cause of this specific effect was unknown, although its cholinomimetic properties seemed not to be crucial.

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