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The discriminative stimulus value of chlordiazepoxide

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THE DISCRIMINATIVE STIMULUS VALUE OF CHLORDIAZEPOXIDE

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It is a commonly observed phenomenon that the stimuli present when a response is reinforced become the occasion for this response upon subsequent presentation of these stimuli. Alteration of the stimuli is usually followed by a decrement in the probability of the occurrence of the response, the amount of decrement being directly proportional to the amount of alteration. Furthermore, it has been observed that stimuli can be made to control responses, in the sense that emission of mutually exclusive responses can become dependent upon the presence of differential, or discriminative, stimuli.

That internal states of the organism, as well as external cues, can become discriminative stimuli has been amply demonstrated.[1] For example, both different drive states and different levels of intensity of a single drive state have been shown to be capable of controlling mutually exclusive responses. The use of chemical agents injected into the body likewise provides a source of internal conditions which can function as discriminative stimuli, for a change in the injected chemical agent may

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1. See Appendix A for a complete survey of the literature.

produce a response decrement and injection of different agents can provide a basis for the formation of mutually exclusive responses. That both of these phenomena have been produced with a wide variety of chemical agents having an assortment of physiological effects tends to indicate that specific properties of the drugs employed cannot completely account for the obtained results; the operation of changing the stimulus conditions is at least in part involved.

Other studies, however, have interpreted an obtained response decrement following a change in the chemical state of the subject as a manifestation of some specific property of the drug producing the chemical state. These studies propose that certain drugs produce "state dependent" or "dissociated" learning, in which large response decrements, sometimes complete abolition of the response, are correlated with a change in the chemical state of the subjects. The hypothesized reason for this involves reciprocal amnesia; experiences when in the drug state theoretically have no relevance for experiences when not under drug, and conversely, experiences of a normal animal are forgotten when the animal is submitted to the drug.

The dissociation phenomenon is allegedly distinct from discrimination using internal stimuli resulting from the effects of the drug. According to Bindra, Nyman, and Wise (1965), the criterion for dissociation, as opposed to discrimination, is complete lack of transfer

of learning from one chemical state to another. However, this criterion does not stand up as a means of distinguishing dissociated from discriminative behavior. On one hand, transfer of learning does occur with smaller doses of the same drugs which produce dissociation, and on the other hand, complete lack of transfer has been shown with external stimuli as discriminative cues. Furthermore, to assume that a lack-of-transfer result indicates that learning is dissociated is to assume that the null hypothesis can be accepted when a significant difference is not obtained; this is a dubious assumption.

In the present study, it is claimed that nothing is gained by considering dissociation and discrimination as separate classes of learning processes, and that the assertion that dissociation is a phenomenon distinct from discrimination is confusing and in many cases tenuous. The observed behavior attributed to one or the other of the two phenomena cannot be differentiated, expect, perhaps, in terms of degree; it is the neural mechanisms by which the behavior is mediated that apparently form the basis of the distinction. The definition of dissociation is unclear, but seems to be concerned with different neural pathways being functional under different chemical conditions. It is very possible, however, that discriminative behavior using external cues as well as internal ones invokes in some way different neural pathways, at the periphery and/or

within the central nervous system. It would seem to be highly speculative to distinguish phenomena on the basis of mediation by different pathways at different levels of the nervous system.

The concept that experience under one state has no relevance for experience under another violates the requirements for parsimonious explanations of data--one does not know what the animal remembers or forgets.

Therefore, while it must be admitted that at least some drugs have extremely potent discriminative stimulus value, with the ability to control differential responding in situations in which other forms of stimulation are less effective, it is held that the differential responding shown under drug and no drug is not qualitatively different from the differential responding shown with any other kind of stimulus change. It is not denied that drugs may have other effects as well, such as abrogation of attention or reduction of motivation, which may affect performance in a learning situation; it is simply maintained that the evidence indicates that the stimulus value of drugs must be taken into account and considered as part of the conditioned stimulus.

The purpose of the present study was to determine if chlordiazepoxide, a recently developed tranquillizer, has stimulus properties, and if transfer appears to occur between drugged and nondrugged states. This drug has been

shown to prevent the development of fixations in rats given an insoluble problem-soluble problem paradigm in a Lashley jumping stand (Feldman, 1962); if CDP can be shown to have significant stimulus properties perhaps this phenomenon can be at least partially accounted for by a change in stimulus conditions.

Feldman's (1962) study showed that 73% (11 out of 15) of the rats given an insoluble problem while drugged solved the soluble problem given while not drugged. If both problems were experienced undrugged about 15% of the animals solved the soluble problem, and if both problems were experienced drugged about 40% of the animals solved it.

If CDP has stimulus value, there are two possible ways in which its attenuation of the development of fixations can be explained. The change in the stimulus, effectively the conditioned stimulus, may have produced a decrement in the stereotyped response developed during the insoluble problem. This stereotyped response, which is considered a response to the conflict produced by the insoluble problem, typically prevails through the soluble problem, and it has been shown (Maier and Klee, 1945) that if this mode of responding is prevented during the soluble problem the animals will subsequently solve this problem. A response decrement in the stereotyped response, produced by a change in the stimulus conditions, might have the same effect.

A stimulus change might also alter the conflict elicited by the cues from the apparatus. It has been shown (Miller and Kraeling, 1952; Murray and Miller, 1952)

that approach performance in a conflict will be increased when the situation is changed by altering features of the external stimulus, indicating greater generalization of approach than of avoidance, i.e. a steeper generalization gradient for avoidance. Perhaps this is manifested in the Lashley jumping stand situation, which may considered a complex approach-avoidance conflict, by a strengthening of the approach tendency.

The mechanism by which chlordiazepoxide produces a change in the internal stimulus conditions might be surmised from the physiological effects of the drug. A member of the benzodiazepine series, CDP is used in both humans and animals for relief of anxiety and for its muscle-relaxant, anti-convulsant and taming properties. Evidence indicates that it acts within the central nervous system, producing depressant effects upon the septum, amygdala and hippocampus (Schallek and Kuehn, 1960; Schallek, Keuhn and Jew, 1962), and on the lateral nucleus of the thalamus (Schallek and Kuehn, 1963). CDP has also been shown to raise the after-discharge threshold of the thalamus, to attenuate psychomotor seizures in response to stimulation of the amygdala and hippocampus, to raise the threshold of after-discharges in the amygdala but not the hippocampus (Schallek, Zabransky, and Kuehn, 1964), and to produce an increase in frequency of the spontaneous EEG (Schallek and Kuehn, 1965). Morillo, Revzin, and

Knauss (1962) found that following CDP injections a depression of the hippocampal response to stimulation of the lateral nucleus of the amygdala occurred in animals with a lesion in the reticular formation at the level of the superior colliculus; the diffuse thalamocortical system was not affected. Morillo (1962) found that valium and La-1, benzodiazepines related to chlordiazepoxide, produced a strong inhibitory action in the hippocampus to stimulation of the amygdala but the inter-hippocampal response was either facilitated (60% of the cases) or unaffected (40% of the cases). These results have been interpreted to indicate that the primary site of action of chlordiazepoxide is at the amygdaloid-hippocampal level, and, if generalization from other benzodiazepines to CDP is allowed, possibly involves depression of the amygdala.

METHOD

Subjects

The subjects were male Sprague-Dawley albino rats between three to five months of age at the beginning of the experiment.

Apparatus

The apparatus was a modified Lashley jumping stand having an electrified grid 8½ inches from the two 6 in. x 6 in. doors, both of which led to a 20 in. x 24 in.

platform containing a dish of food. One door was lighted by a 25 watt bulb behind it and the other was dark; which door was lighted could be shifted from side to side. During an experiment, one of the doors was locked; which door this was could also be shifted from side to side. A net hanging 32 in. below the platform and doors caught a rat who jumped to a locked door.

Pre-training procedure

The 23-hour food-deprived rats were trained to jump from the grid to closed doors which would swing open and allow access to the platform and dish of food. This was accomplished by a method of successive approximations. First the doors were tacked open and the grid was moved up to the platform, then the grid was gradually moved back, about 1 in. per day, to 8½ in. from the platform. Finally the doors were gradually closed. During this this training, the lighted side was switched every second trial, and position preferences were minimized by gently forcing a rat to respond on even-numbered trials to the side opposite the one he responded to on the previous odd-numbered trial. Eight pre-training trials per day were given to each rat.

After the animals learned to jump to closed doors, they were given 40 trials, 10 trials per day, of preference testing. During this phase of training, both

doors were unlocked, and the rats were allowed to jump to either side unless they made three consecutive consistent responses, when they were forced to jump to the opposite door.

EXPERIMENT 1

The first experiment was designed to determine if mutually exclusive responses could be learned with chlordiazepoxide, at 15 mg/kg, as the only discriminative stimulus. An alternation procedure was used, with the animals required to jump to one door when drugged and the other door when not drugged. Two control groups, one which never received CDP and one which received CDP randomly, were employed to determine if the alternation problem could be solved without a discriminative stimulus or if some property of the drug such as its anxiety-reducing ability could enable the animals to solve the alternation problem.

Procedure

The procedure in this experiment involved having one door (bright or dark) reinforced, i.e. unlocked allowing access to food, and the other punished, i.e. locked so the rat bumped against it and fell into the net. The reinforced door alternated from one day to the next, but on a given day one door was consistently reinforced. For half the animals in each group the bright door was correct on odd-numbered days and the dark one correct on even-numbered

days; for half the animals this was reversed. The situation on odd-numbered days was designated Problem A, that present on even-numbered days, Problem B.

Ten trials were given per day, and if S did not respond within 30 seconds grid shock of 0.5 ma was applied, thereby forcing a response. The animals were run for 30 consecutive days, 300 trials.

The subjects, 60 rats, were divided into three groups, 20 rats per group, which were approximately balanced for preferences and for age. Group I received chlordiazepoxide (15 mg/kg injected intraperitoneally) 30 minutes before testing on odd-numbered days and an equal volume of .9% saline solution 30 minutes before testing on even-numbered days. Group II received CDP on a random half of the days and saline on the other half; Group III received a saline injection every day. Otherwise, the three groups were treated identically.

This experiment was carried out in two successive replications, 30 rats, half of each group, being run at a time.

Results[2]

In Group I, 12 of the 20 subjects learned to jump 100% of the time to the correct door for both Problem A

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2. For detailed tables of the results, see Appendix B.

(the no-drug problem) and Problem B (the problem with drug); 6 attained the 100% correct level for Problem A but jumped to one side only (50% correct) on Problem B. The other two rats performed stereotyped responses, i.e. the same response on both problems; one rat jumped to the dark door every day (100% correct on Problem A and 0% on Problem B) and one jumped to the left side (50% correct) on both problems. In Group II all rats performed stereotyped responses, 18 of the 20 jumping to one side only every day and 2 jumping to the bright door every day. Likewise in Group III all rats performed stereotyped responses, 19 jumping to one side and 1 jumping to bright. These results are given in more detail in Table 1.

The learning curves of the three groups are shown in Figure 1. The asymptotic level of performance of Groups II and III, averaged over Problems A and B, was exactly 50%, indicating no learning whatsoever, whereas in Group I performance levelled off at 97% correct for Problem A and 73% correct for Problem B. The difference between Group I and Groups II and III is clearly significant ($p < .001$). Also, the difference between the performance of the subjects in Group I on Problem A and Problem B is significant ($p < .05$, Mann-Whitney U test).

Besides the fact that more rats solved Problem A than Problem B (18 as opposed to 12), those who solved Problem A took an average of 84 trials[3] to reach a

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3. Not including the criterion trials

TABLE 1

Performance on Conditional Discrimination (Experiment 1)

	number achieving 100% correct	number achieving 50% correct	number achieving 0% correct
Group I			
Problem A (no drug)			
with dark correct (n = 10)	9	1	0
with bright correct (n = 10)	10	0	0
Problem B (drug)			
with dark correct (n = 10)	4	6	0
with bright correct (n = 10)	8	1	1
	total = 31 percentage = 77.5%	total = 8 percentage = 20%	total = 1 percentage = 2.5%
Group II			
Problem A (drug randomly)			
with dark correct (n = 10)	0	10	0
with bright correct (n = 10)	2	8	0
Problem B (drug randomly)			
with dark correct (n = 10)	0	8	2
with bright correct (n = 10)	0	10	0
	total = 2 percentage = 5%	total = 36 percentage = 90%	total = 2 percentage = 5%
Group III			
Problam A (no drug)			
with dark correct (n = 10)	0	10	0
with bright correct (n = 10)	1	9	0
Problem B (no drug)			
with dark correct (n = 10)	0	9	1
with bright correct (n = 10)	0	10	0
	total = 1 percentage = 2.5%	total = 38 percentage = 95%	total = 1 percentage = 2.5%

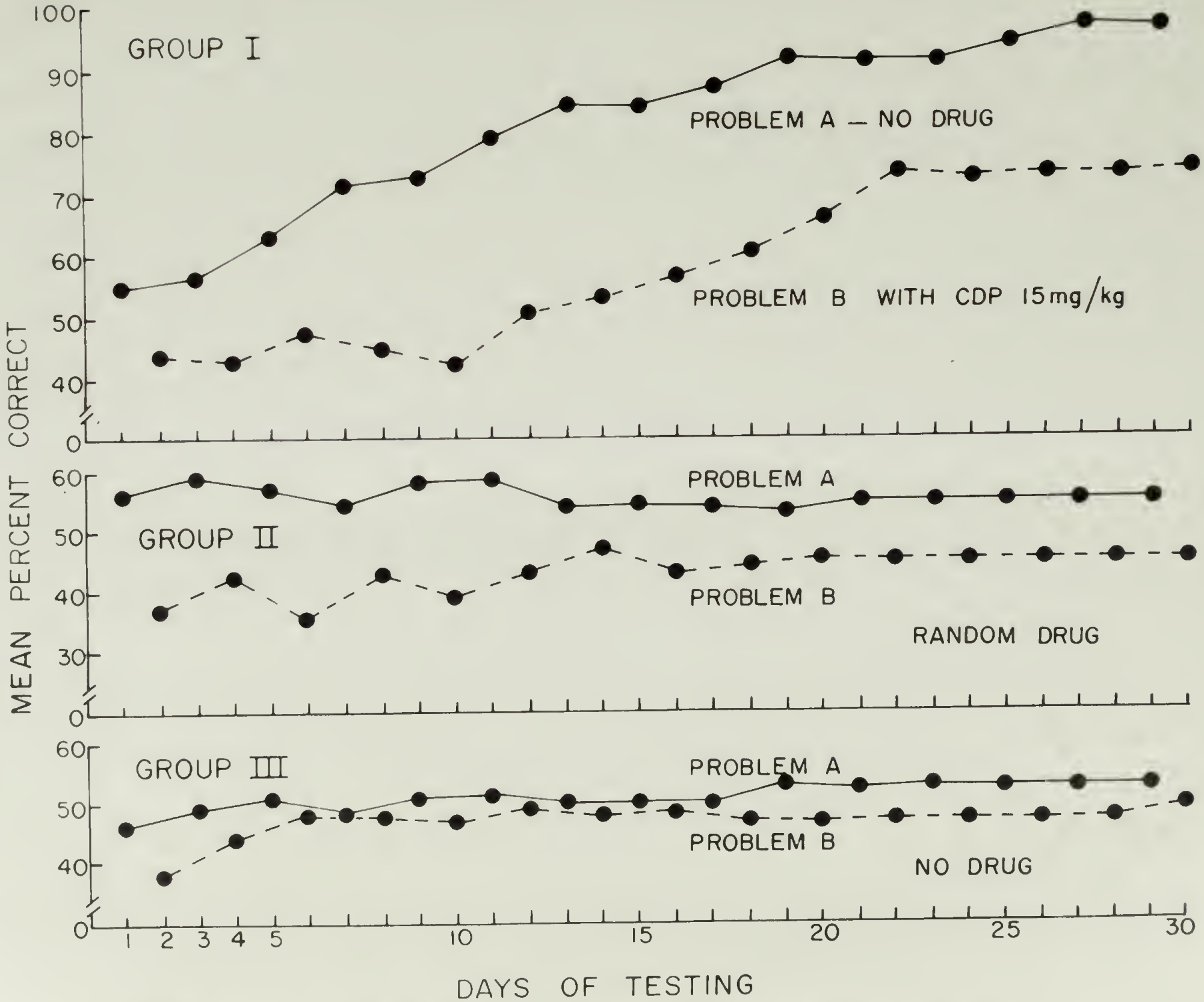

Figure 1. Experiment 1: A comparison of performance among groups I, II, and III on the conditional discrimination.

criterion of 29/30 correct responses while those who solved Problem B took an average of 108 trials to reach the same criterion. The difference between the number of trials to criterion on Problem A and Problem B is significant ($p < .05$).

After the first few sessions with drug, the mean latency for responding when drugged was consistently lower than that when not drugged. This was true for rats in both Group I and Group II, is shown in Figure 2, and is statistically significant ($p < .001$, Mann-Whitney U test).

EXPERIMENT 2

Experiment 1 showed that rats could learn to make mutually exclusive responses based upon the absence vs. the presence of 15 mg/kg of chlordiazepoxide. These results could be interpreted as indicating that CDP at this dose has stimulus value, with the ability to serve as a discriminative stimulus. They also could be interpreted as evidence that CDP produces dissociation, i.e. that there was no transfer of training between the drug state and the no-drug state, and this enabled the animals to learn mutually exclusive responses in the two states.

To determine whether transfer occurred between training in the drug state and nondrug state, groups were trained in one state only and their rate of acquisition

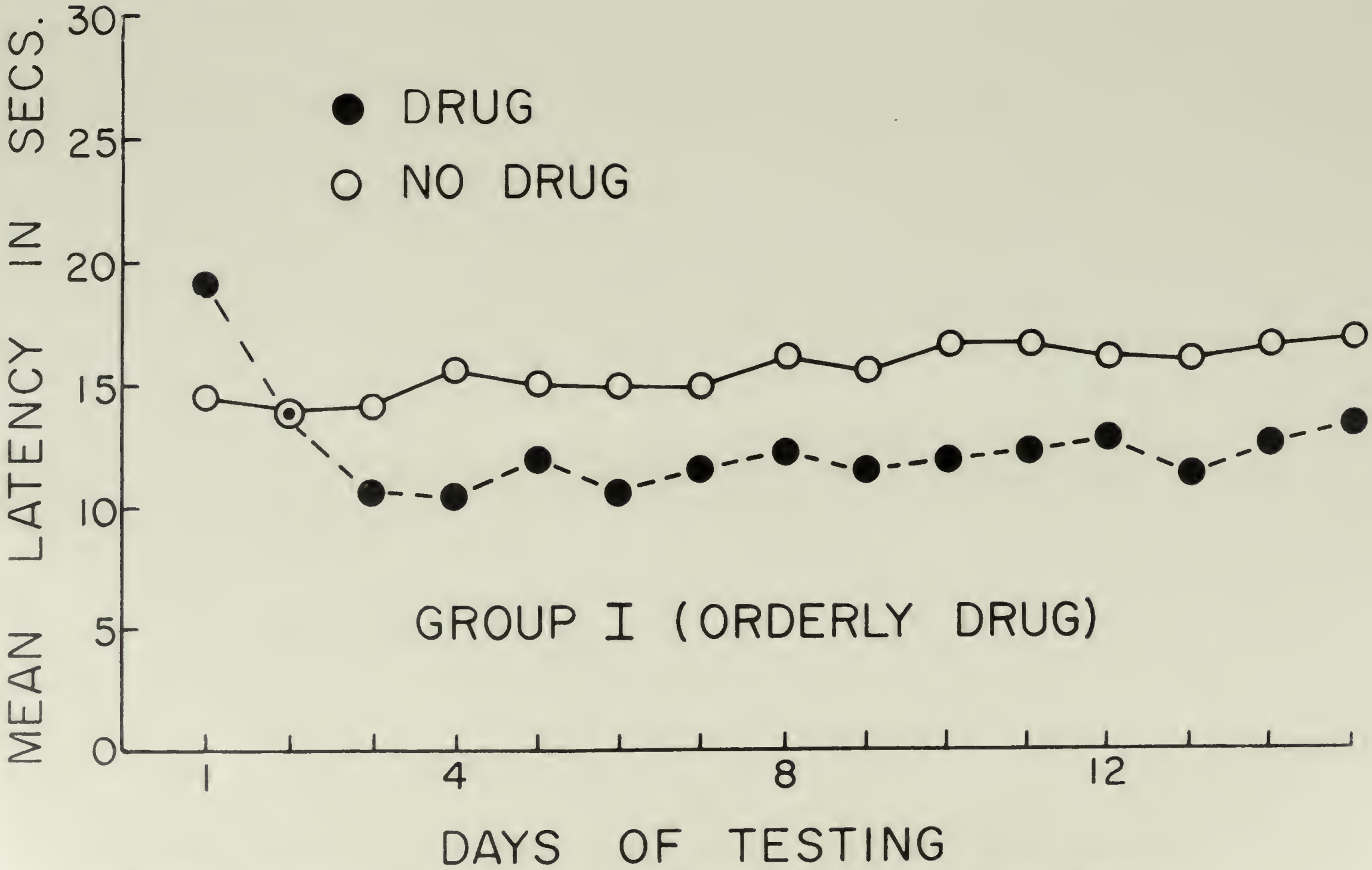

Figure 2a. Experiment 1: A comparison of response latencies between drugged and undrugged animals in Group I.

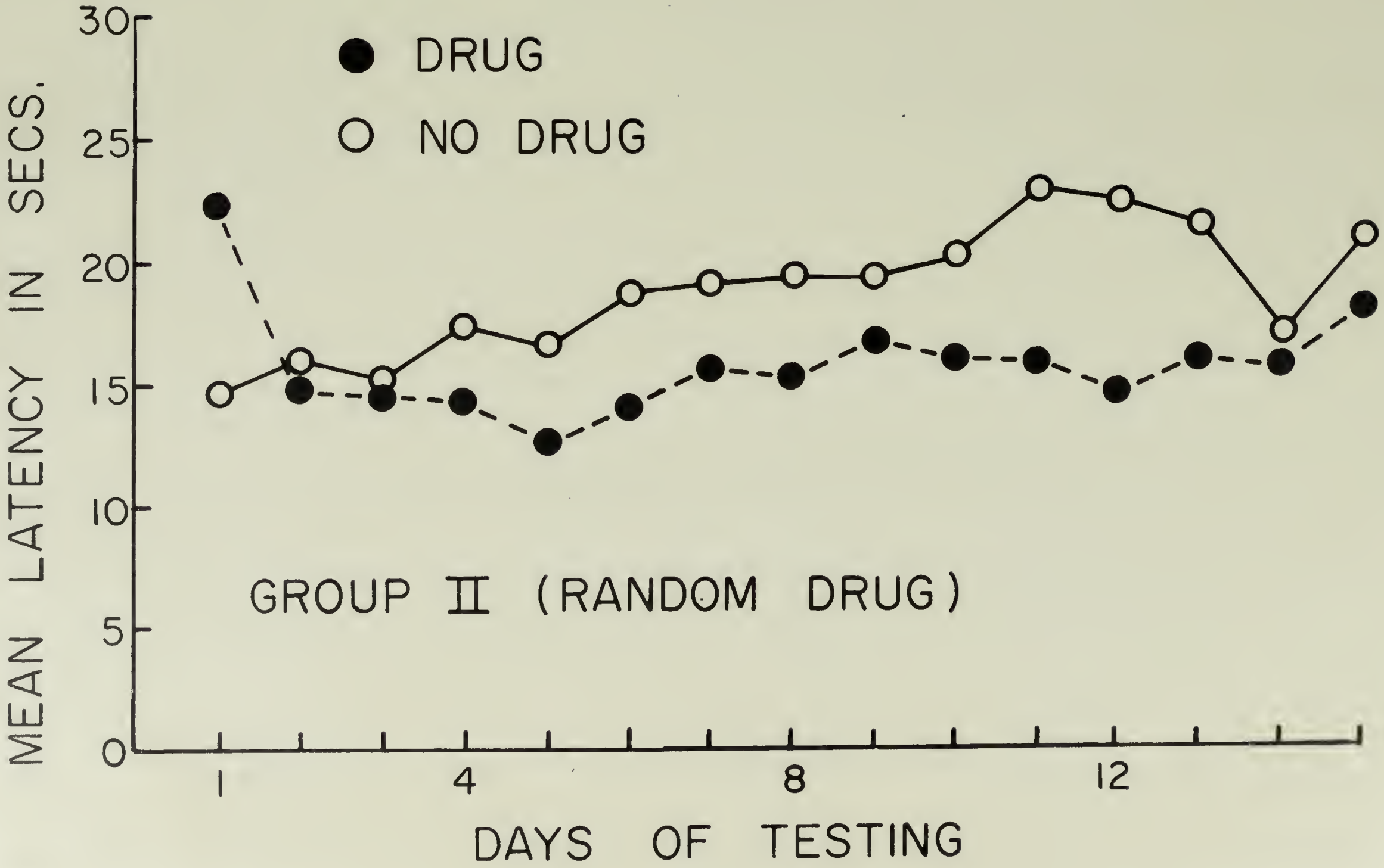

Figure 2b. Experiment 1: A comparison of response latencies between drugged and undrugged animals in Group II.

compared with the rate of acquisition of Problem A and of Problem B for Group I of Experiment 1. If there were no transfer between drug states, the rates of acquisition would be the same, but if there were transfer, the animals of Experiment 1, having two problems to learn, would take longer to learn each problem.

Procedure

Twenty-four male Sprague-Dawley albino rats were given the pre-training procedure described above and then divided into two groups. Group A was given a problem comparable to Problem A of Experiment 1: half the animals were required to jump to the bright door and half to the dark door, under conditions of no drug. Similarly, Group B was given a problem comparable to Problem B of Experiment 1: half the animals were required to jump to the bright door and half to the dark door, when they were drugged with chlordiazepoxide, 15 mg/kg. Training sessions of 10 trials occurred every other day for either 15 days (equivalent to each problem of Experiment 1) or until the rats had reached a criterion of 39/40 correct responses.

Results[4]

In Group A, which was given the no-drug problem, 11 of the 12 rats learned to jump 100% of the time to the

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4. For detailed tables of the results, see Appendix B.

correct door; 1 rat jumped to one side only, getting 50% correct. All of the rats in Group B, given drug, solved their problem, 100% correct. These results are shown in Table 2 and Figure 3.

Table 3 gives the number of trials to a criterion of 29/30 correct responses for the animals in this experiment and in Group I of Experiment 1. The difference between Group A and Group B of this experiment, i.e. between drugged and nondrugged animals, is significant by a one-tailed Mann-Whitney U test, $p < .05$.

When compared with the performance of rats in Group I of Experiment 1, the rats of Experiment 2 solved their respective problems significantly faster than the rats of Experiment 1 solved that problem. The rats of Experiment 1 took a mean of 108 trials to reach criterion under drug, while the rats of Experiment 2, with only one problem to solve, took a mean of 62 trials to reach the same criterion; and the rats of Experiment 1 took a mean of 84 trials to solve the problem given undrugged, while the undrugged animals of Experiment 2 took a mean of 50 trials to reach criterion. Both of these differences are significant at well under the .001 level.

The mean latency of drugged animals was consistently lower than the latency of undrugged animals; this is shown in Figure 4 and is significant at the .001 level.

TABLE 2

Performance on Simple Discrimination (Experiment 2)

	number achieving 100% correct	number achieving 50% correct	number achieving 0% correct
Group A (no drug) with dark correct (n = 6) with bright correct (n = 6)	6 5 total = 11 percentage = 91.7%	0 1 total = 1 percentage = 8.3%	0 0 total = 0 percentage = 0%
Group B (drug) with dark correct (n = 6) with bright correct (n = 6)	6 6 total = 12 percentage = 100%	0 0 total = 0 percentage = 0%	0 0 total = 0 percentage = 0%

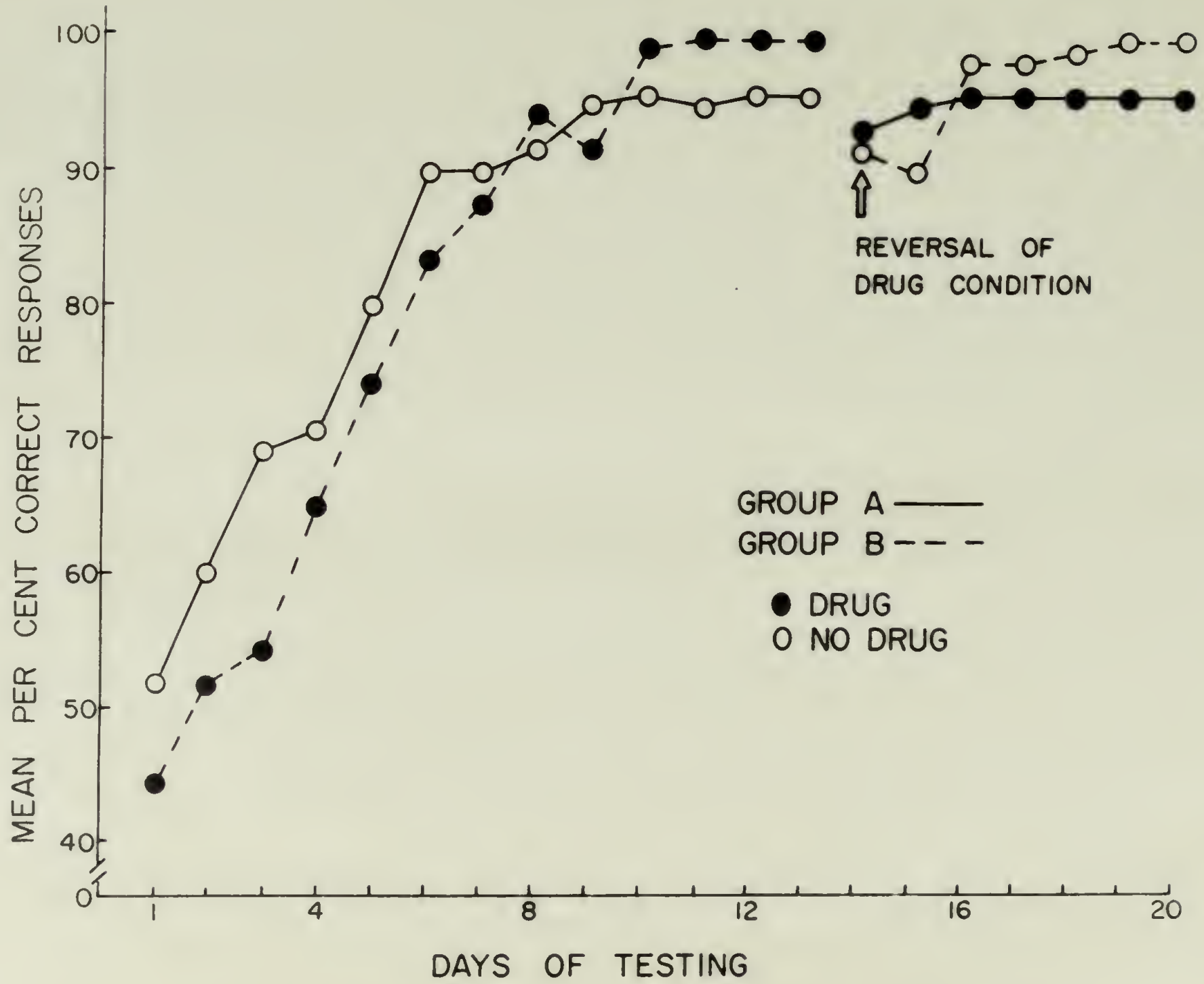

Figure 3. Experiments 2 and 3: A comparison of the performance of Groups A and B on the simple discrimination before and after drug-state reversal.

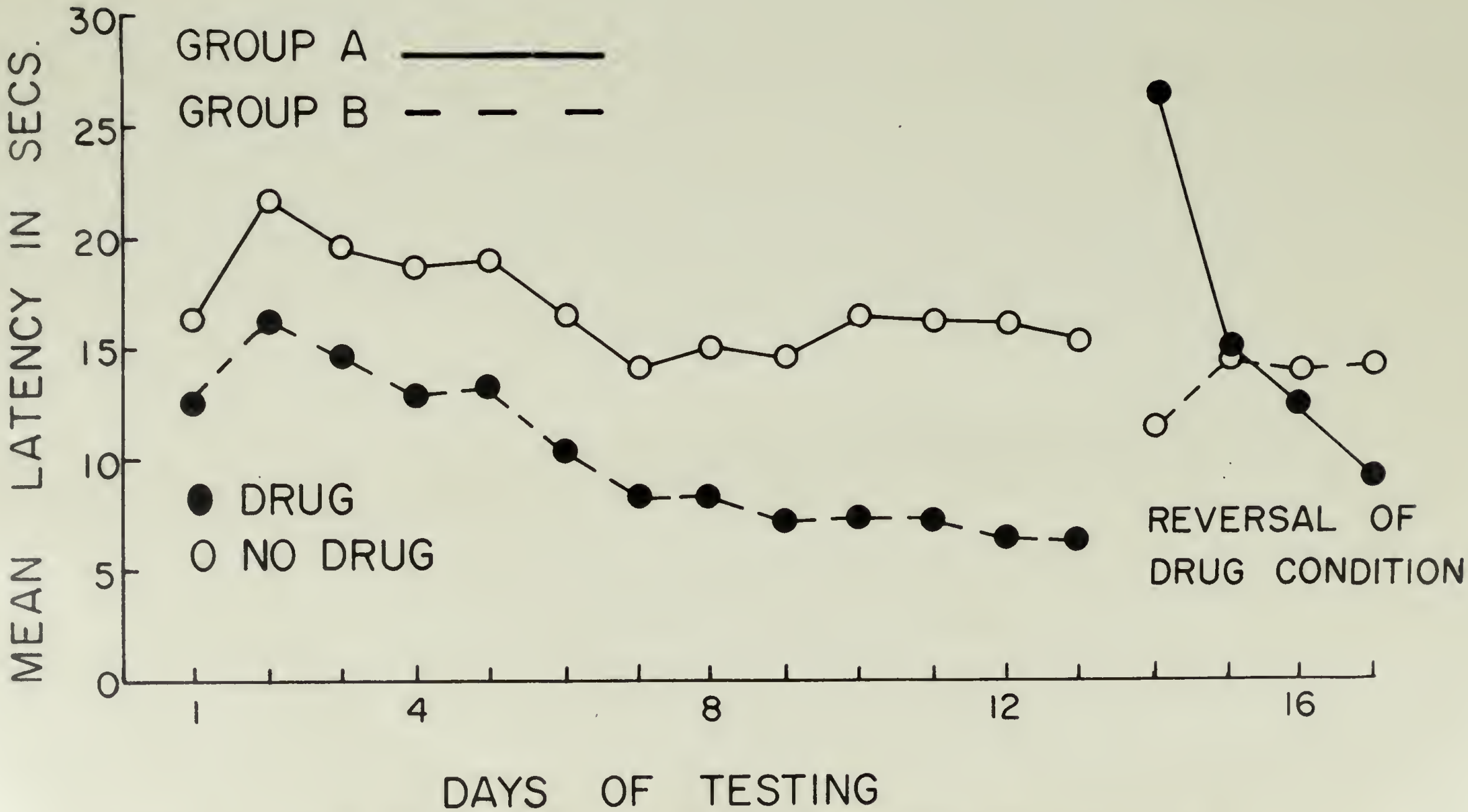

Figure 4. Experiments 2 and 3: A comparison of response latencies of Groups A and B before and after the drug-state reversal.

TABLE 3

Conditional Discrimination: Number of Trials to Criterion*			
	Problem A (no drug)	Problem B (drug)	
with dark correct	88	107	mean = 97.5
with bright correct	81	109	mean = 95.0
	mean = 85.5	mean = 108	

Simple Discrimination: Number of Trials to Criterion*			
	Group A (no drug)	Group B (drug)	
with dark correct	48	65	mean = 56.5
with bright correct	42	60	mean = 51.0
	mean = 50	mean = 62.5	

Reversal of Drug Condition: Number of Trials to Criterion*			
	Group B (no drug)	Group A (drug)	
with dark correct	12	0	mean = 6.0
with bright correct	7	2	mean = 4.5
	mean = 9.5	mean = 1	

*Mean number of trials to the criterion of 29/30 correct responses, not including the criterion trials, for animals solving the given problem.

EXPERIMENT 3

The results of Experiment 2 indicated that transfer did occur between the drug state produced by 15 mg/kg of chlordiazepoxide and the no-drug state, for animals given two problems, each in a different drug state, took significantly longer to solve each problem than did animals given only one problem. A further and more direct test of the degree of transfer between drug states would be to train animals in one state to maximal level of performance and then test the effect of changing the drug state. This was tested in Experiment 3, in order to determine the amount of response decrement occurring when the drug state is changed. Complete lack of transfer of training between drug states, maximal response decrement, would be indicated by random, i.e. 50%, responding.

Procedure

All animals in Experiment 2 who solved the discrimination, i.e. 11 rats that learned in the undrugged condition and 12 that learned in the drugged condition, were tested under the condition opposite to that existing during the acquisition procedures: the animals previously under drug were tested under no drug, and the undrugged animals were switched to drug (note that the latter animals had never experienced being drugged before). This switch occurred after 130 acquisition trials, when all animals had performed at least 39/40 correct responses. Again, 10

trials per day, on alternate days, were given until the animals again reached the criterion of 39/40 correct responses.

Results[5]

The data from the first session after the switch indicated that of the 11 animals switched from no drug to drug, 9 performed 100% correctly, 1 rat performed 90% correctly and 1 80% correctly. Of the 12 rats switched from drug to no drug, 6 rats responded with 100% correct during the first session, 4 rats with 90%, 1 with 80% and 1 with 70% correct.

Table 3 gives the results in terms of number of trials to reach a criterion of 29/30 responses correct. The deficit in performance of rats switched from drug to no drug was significantly ($p < .05$) greater than that of rats switched from no drug to drug.

If no transfer occurred between the two drug states, one would expect that the rate of acquisition of animals tested under drug after a shift in drug state would be about the same as the rate of acquisition of animals originally trained under drug, and that the rates of acquisition of undrugged animals before and after a shift in drug state would be about the same. However, these

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5. For detailed tables of the results, see Appendix B.

rates of acquisition were not the same; the difference between the number of trials to criterion of drugged animals in Experiment 2 (before a shift in drug state) and Experiment 3 (after a shift in drug state), as well as of undrugged animals in the two experiments, was significant at well under the .001 level. In terms of percent correct, there was definite transfer of training between a drugged and a nondrugged state.

Mean latencies for the two groups are shown in Figure 4. When the drug condition was changed, in either direction, latency showed a significant increase. Thus in terms of response latency, there was a response decrement occurring with a change in drug state.

DISCUSSION

First and most important, the results of Experiment 1 unequivocally demonstrated that chlordiazepoxide, at 15 mg/kg, can serve as a discriminative stimulus controlling mutually exclusive responses: 18 of the 20 animals receiving the drug correlated with the required response showed evidence of learning, while of the 40 rats not receiving the drug in this orderly fashion, 0 showed evidence of learning. Furthermore, these results cannot be attributed to some effect of the drug such as tranquillizing action, reduction of fear to allow comprehension of relevant cues, etc., for Group II received the drug as often as Group I but showed no sign of learning. Finally, since

the rats in Groups II and III behaved in a highly stereotyped manner, identical to the behavior of rats given an insoluble problem in a Lashley jumping stand, an alternation problem of this type appears to be insoluble to rats.

The results of Experiments 2 and 3 demonstrated fairly conclusively that transfer does occur between the drug state and no-drug state. This was indicated both by the significantly faster rate of acquisition when the animal had only one problem to solve instead of two problems under different drug states, and by the lack of a significant decrement, or a reversion toward random responding, when the drug condition was changed. That there was transfer of learning between the drug and no-drug state implies that the results of Experiment 1 cannot be explained in terms of dissociation of learning, amnesic effects produced by a change in drug state, etc.

There seemed to less transfer of training, more response decrement, when animals were switched from drug to no-drug than when the switch was in the opposite direction. In Experiment 3, the animals tested under no drug after being trained under drug performed significantly poorer than those tested under drug after being trained under no drug, although 6 of the 12 animals switched from drug to no drug did perform with 100% correct in the first session and no one did worse than 70%. Between the no-drug

and the drug state, there seemed to be almost complete transfer of training, almost no response decrement, for 9 out of 11 animals performed with 100% correct in the first session after the change in drug states. Between the drug and no-drug states, on the other hand, there was an intermediate amount of transfer of training, or of response decrement, neither complete lack of transfer nor complete transfer.

A fourth overall result from this study was that performance, in terms of rate of acquisition of a bright-dark discrimination, is significantly poorer when training occurs in the drug state produced by 15 mg/kg of chlordiazepoxide than when it occurs in the no-drug state. This was found in both Experiments 1 and 2, i.e. in both a conditional discrimination and a simple discrimination.

Finally, a consistent pattern appeared in the latency data. During the first few sessions given under drug, latency was high, but it decreased progressively until it was significantly lower than the latency of responding of undrugged animals. Since pre-training was always given under no drug, this initial high latency could be interpreted as supporting Bindra, Nyman and Wise's (1965) and Bindra and Reichert's (1966) contention that a change in drug state produces a deficit in the ability of the CS to initiate the response. The results of Experiment 3, showing that a change in drug state in

either direction produces an increase in response latency, further supports this notion. However, in no case did the mean latency exceed, or even come close to, 30 seconds, indicating that forcing a response with onset of grid shock was not necessary, the conditioned stimuli from the apparatus were capable of eliciting the response.

Thus at the behavioral level this drug at this dose can serve as a discriminative stimulus, and a certain amount of response decrement results from changing the stimulus conditions. It should be noted that in Experiments 2 and 3 the drug was not a relevant stimulus, it did not form a part of the stimulus complex composing the discriminative stimulus. The response decrement resulting from changing the drug state of animals trained in a situation with the drug state being part of the discriminative stimulus might be greater than was the response decrement resulting from changing the drug state of animals trained in a situation in which the drug condition at hand is irrelevant to solution of the problem. For example, the response decrement resulting from a reversal of conditions of Experiment 1 might be larger than was the one obtained in Experiment 3.

While the drug can serve as a discriminative stimulus, the mechanism by which this effect is obtained is another question; two possibilities exist. One explanation would be to consider the process to be similar or identical to

the one by which external stimuli come to control responses, by modification of afferent input. The action of the drug might produce a change in the pattern of neural propagation somewhere along the line, appearing at the level of the neural substrate of learning (whatever that may be) as differential patterns of input in the drug state and the nondrug state. The conventional mechanisms of reinforcement would function as usual to produce differential responding. And the degree to which this afferent input is important in learning the discrimination would determine the degree of response decrement resulting from modification of it.

It is possible that the drug in some way changes the level of motivation, and this is the change which is discriminated. There is evidence, for example, that chlordiazepoxide increases hunger (i.e. that rats eat more when drugged) and that it decreases fear. Thus the mechanism allowing for drive discrimination might also permit drug discrimination. This hypothesis is no more than an extension of the above, for relative to the "neural substrate of learning" all that is different in the two states (drugged and undrugged) is patterning of neural impulses.

The other possible way in which chlordiazepoxide might have come to serve as a discriminative stimulus is by affecting the learning process directly. Some of the prevalent theories of the neural basis of learning

hypothesize that the essential neural changes which occur as learning takes place involve increased efficiency of synaptic action so that new or rearranged neural circuits appear. It is well established that the functional capacity of a neuron is dependent upon the nature of the chemical milieu surrounding it. Therefore, if learning involves establishment of reverberating circuits in some manner, and if the change in chemical milieu produced by the drug changes the transfer characteristics so that certain circuits become disfunctional under drugged conditions, then the obtained results, establishment of mutually exclusive responses in different drug states, might be expected. This would be true dissociation of learning; responses learned under one set of chemical conditions would be inaccessible in another.

Besides having difficulty explaining the fact that transfer occurs between drug states, this second hypothesis appears to add a superfluous assumption to those underlying the other hypothesis, for it depends upon the validity of reverberating circuits being the basis of learning, or at least selective synaptic transmission between certain neurons being involved in the learning process itself, not just in performance. Other theories of the neural basis of learning postulate that the essential changes are changes in the molecular structure of nucleic acids following from a particular pattern of neural impulses.

If this is the process involved in learning, to produce dissociation a drug would have to affect directly the molecular structure of the nucleic acids. While changes in the chemical milieu may well produce facilitation or inhibition of already-established neural circuits, either by affecting the threshold of the neuron or by affecting the processes involved in synaptic transmission, and thereby produce differential patterns of neural impulses, afferent and/or efferent, that drugs affect the molecular structure of nucleic acids by a means other than producing differential patterns of neural impulses (modification of afferent input) is unknown.

Thus there are two possible mechanisms by which CDP could have produced differential responding; one assumes that CDP has stimulus value and affects the learning mechanism in the same manner as any other stimulus, and the other assumes that CDP affects the learning mechanism directly. The learning mechanism, whatever it may be, then functions to allow the learning of different responses in the different drug states. Since the second hypothesis involves an additional assumption, that the learning mechanism is susceptible to direct modification by drug action, the first hypothesis is considered to be more parsimonious.

The distinction must be made between learning and performance, and whatever the mechanism may have been by which

the rats learned to jump to one door when drugged and the other when not, there may have been another factor operating to affect the level of performance under the drugged and nondrugged states, for there was a tendency for the problem submitted to drugged animals to be solved both less often and slower than the problem submitted to undrugged animals and for latency to be lower when the animals were under drug. Possibly these results could be accounted for by a decrease in fear (of hitting a locked door) or an increase in hunger (approach toward the platform with its dish of food); there is evidence that CDP produces both of these effects. They also could be accounted for by postulation of impairment of some mechanism involved with the maintenance of attention, or of a mechanism involved in assessment of the effects of lack-of-positive or of negative reinforcement.

Sachs, Weingarten, and Klein (1966) proposed that chlordiazepoxide, among other drugs, interferes with attention responses, and therefore "in complex learning tasks which require close attention (e.g. delay or discrimination), ...(these) agents disrupt performance." (p. 27). This is supported, according to Sachs et al, by the finding that chlordiazepoxide abolishes the hippocampal theta rhythm, which is frequently taken as an index of attention, orienting, etc.

If it can be assumed that responding in the Lashley jumping stand situation is at least partially under control

of aversive factors, then perhaps the decrease in latency seen in drugged animals could be accounted for by abrogation of attention paid to these aversive aspects. However, that latency was lower in animals who had solved the bright-dark discrimination, as well as those who had not, implies that fear of a locked window could not be a very important part of the aversive aspects controlling responding.

Another possible explanation of the poorer performance of drugged animals would be by postulation of impairment of some mechanism involved in the assessment of reinforcement contingencies. Several mechanisms for mediation of the effects of reinforcement have been proposed. Carlton (1963), for example, cites evidence for the involvement of a cholinergic system as a mechanism acting selectively to inhibit responses which are not reinforced. The level of activation is viewed as the mechanism controlling the tendency for all responses to occur; the inhibitory cholinergic system antagonizes this action on nonreinforced responses. Gerbrandt (1965) proposes a similar mechanism with the hypothesis that discrete and reciprocally inhibitory systems determine the release and control of stabilized responses. One neural system, biased by cholinergic stimulation and adrenergic blockade, functions to control behavior competing with a response to be learned, while another, which is biased by adrenergic stimulation and cholinergic blockade, is implicated in the release of learned responses.

The amygdala as a structure has also been implicated in the mediation of the effects of reinforcement. After reviewing the literature concerning the amygdala, Gloor (1960) concluded that its function involves motivational reinforcement of behavioral patterns; Goddard (1964) concluded that it involves suppression of motivated approach behavior. The amygdala has also been included in a system involved in drive inhibition, i.e. suppression of nonrewarded conditioned responses (Brutkowski, 1965).

Therefore, if a primary action of chlordiazepoxide were to depress the amygdala, Carlton's cholinergic system and/or Gerbrandt's control system, the poorer performance under drug would be acoounted for by attenuation of the inhibitory effect produced by nonreinforcement or punishment, and the decrease in latency would be accounted for if depression of the control system facilitated the release system. That chlordiazepoxide might have the effect of attenuating the inhibition of responses controlled by nonreinforcement and punishment is supported by results reported by Cook (1964). These results indicated that response rates which are normally held back by a VI or DRL schedule of positive reinforcement, or which are normally suppressed by punishment (response-contingent shock), are enhanced by administration of chlordiazepoxide. This could be interpreted to support the concept that CDP produces

impairment of the mechanisms involved in the control of responding by the reinforcement contingencies of the situation.

However, while CDP has apparently been shown to depress the amygdala, both Carlton's (1963) and Gerbrandt's (1965) hypothesized mechanisms for the control of responding were cholinergic systems and there is no direct evidence that chlordiazepoxide exerts an anticholinergic effect. Perhaps on the contrary, CDP has been shown to block the depressant effects of DOPA injection and to reduce the ability of iproniazid to antagonize tetrabenazine depression (Sternbach, Randall, and Gustafson, 1964). These results are inconclusive, but they could be interpreted as indicating that chlordiazepoxide produced inhibition of an adrenergic, rather than a cholinergic, type of system.

At any rate, the effects of non-positive reinforcement, or the processes involved in attention, were not completely suppressed; 12/20 animals in Experiment 1 and 12/12 animals in Experiment 2 did eventually achieve the 100% correct level of performance under drug. Furthermore, 2 animals, one in Experiment 1 and one in Experiment 2, failed to solve the given problem even though they were undrugged.

In conclusion, it may be pointed out that the effects of chlordiazepoxide, or of any drug, may be multiple. Thus CDP may produce a modification of the total afferent input which serves as the conditioned stimulus, providing

a basis for the establishment of differential responding, and at the same time may produce impairment of some mechanism involved with control of competing responses extraneous to the conditions of reinforcement.

Both of these effects have direct relevance for the usefulness of chlordiazepoxide as a tranquillizer, of course. That the drug has stimulus value implies that any learning taking place under drug will show a decrement when the drug is withdrawn. Furthermore, if the drug produces some kind of impairment of performance abilities through abrogation of attention or reduction of motivation, or by any other means, its usefulness as a therapeutic agent is diminished. It has been suggested (Heistad, 1957; Miller, 1966) that gradual withdrawal from drug therapy might attenuate the stimulus-generalization decrement; perhaps this would also ameliorate the performance decrements produced by direct effects of the drug.

APPENDIX A

SURVEY OF THE LITERATURE

That internal states of the organism, as well as external cues, can serve as discriminative stimuli has been amply demonstrated. For example, in the classical "drive discrimination" studies of Hull (1933) and Leeper (1935), rats learned to make different responses based, presumably, on different internal stimuli arising from food deprivation as opposed to water deprivation: when all other elements in the stimulus complex were the same they would take one of two paths to a goal box when hungry and the other when thirsty. Brown (1940) also produced evidence that rats could acquire differential responses based on the conditions of hunger and thirst. Heron (1949) eliminated the spatial element in the discrimination by requiring the animals to go to the bright side of an apparatus for food and to the dark for water, with the bright and dark sides interchanged randomly. Bailey and Porter (1955) demonstrated that cats can use the cues specific to hunger and thirst to learn a discrimination, and Bailey (1955) showed that drive cues are as effective as a brief tone sounded just before the response and more effective than a tone present for long before the response.

Miller (1961) reported an experiment in which approach responses were punished when motivated by one

drive but not when motivated by another; rats were given shocks for running down an alley to a goal when they were under one drive, either hunger or thirst, but not when they were under the other. Half the animals received dry food in the goal box when they were hungry and water when thirsty; half received sugar water all the time, thus controlling for the effects of anticipatory goal responses. All groups learned not to run when motivated by the punished drive, although the group which had no cues from anticipatory goal responses took longer to learn. Miller concluded that fear and conflict can be conditioned specifically to the internal cues of a given drive. And, as he points out,

> it should be noted that this experiment is superior to most others which have demonstrated reasonably rapid learning of a good discrimination between drives, in that the learning to respond to the cues from the drive is not confounded with learning to go to different places or to get different goal objects which elicit different anticipatory goal responses. (Miller, 1961, p. 21)

Amsel (1949) and Levine (1953) showed that rats could learn a discrimination on the basis of differential irrelevant drive stimuli (from food or water deprivation) when the motivation involved escape from noxious stimulation; Winnich (1950) showed the same thing with differential cues based on food deprivation opposed to satiation. Furthermore, it has been shown that rats can learn mutually exclusive responses with only different levels of intensity of a

single drive as discriminative cues (Jenkins and Hanratty, 1949; Bloomberg and Webb, 1949).

Drive states do not provide the only source of internal conditions which may function as discriminative stimuli; the use of chemical agents injected into the body provides a direct and relatively rapid means of altering internal stimuli. Conger (1951) and Barry, Koepfer and Lutch (1965) showed that rats could learn a discrimination based upon the presence or absence of alcohol in their system. Cook, Davidson, Davis, and Kelleher (1960) have shown that the physiological changes produced by injection of several substances can come to serve as conditioned stimuli for an avoidance response, while injection of saline never produced the response.

Stewart (1962) produced a differential escape response based on the presence or absence of either chlorpromazine or imipramine, showing that rats could differentiate between saline and a pharmacological agent. However, this study did not employ no-drug controls to eliminate the possibility that the rats discriminated on the basis of the alternation procedure or the time of day. Stewart also showed that the chlorpromazine-trained response transferred to other doses of chlorpromazine and to certain other drugs (acepromazine, perphenazine and prothipendyl, but not prochlorperazine or imipramine), while the imipramine-trained response did not transfer to either chlorpromazine or acepromazine.

This selective transfer may reflect some kind of similarity in the physiological effects of the drugs.

That the internal state induced by injection of chlorpromazine may function as a stimulus was also shown by Otis (1964). The probability of occurrence of a conditioned avoidance pole-jumping response decreased significantly when the internal condition of the animal was changed from that present during training. Again, a change in stimulus conditions produced a response decrement.

Using morphine and dl-amphetamine, Belleville (1964) found that a response acquired in the presence of drug-induced internal stimuli showed greater resistance to extinction when these stimuli were present during extinction than when they were replaced by a placebo injection; and conversely, when drug-induced stimuli were not present during acquisition the resistance to extinction was greater if this condition was duplicated during the extinction period. Thus a change in the chemical state of the animal was always correlated with a response decrement. Furthermore, when acquisition conditions were reinstated a rebound of increased responding occurred. That this was true regardless of the nature of the drug used led Belleville to conclude that specific properties of the drugs employed could not account for the obtained results; the decrement in responding must have resulted from changing the stimulus conditions.

Other studies have reported the occurrence of response decrements following a change between a nondrug state and a drug state. These include drug states produced by systemic injection of benactyzine (Jacobson and Sonne, 1955, 1956), chlorpromazine (Hunt, 1956), thioridazine (Heistad and Terres, 1959), atropine (Paskal, 1962), and pentobarbital (Holmgren, 1964). Sachs (1962) reported that when conditioning cats to avoid shock after intraventricular injection of saline, calcium or potassium, response decrements occurred whenever an animal was tested following an injection of something other than what was administered during training.

Bindra and Mendelson (1962) found that the decrement in performance produced by injection of a drug was greater with higher levels of training. This was interpreted to indicate a negative multiplicative interaction effect between change in drug state and amount of training.

Bloch and Silva (1959) found that of three groups of rats trained in a maze with a latent learning technique, those who were given the exploratory period under sodium pentobarbital and then trained under deprivation-reward conditions without drug did not show the typical latent learning effect. This was considered as "no retention," although no comparison was made between the learning curve of this group and that of animals trained without previous experience in the maze. Nevertheless, rats given

Nembutal during the exploratory period were definetely inferior to rats given the exploratory period undrugged in the test when all animals were undrugged; animals given the exploratory period under meprobamate showed "good retention" although there seems to have been some decrement.

Bloch and Silva interpreted their results in terms of fear and curiosity evoked to the novel situation. Nembutal theoretically diminished fear but diminished curiosity as well, therefore the animals were "not receptive to the maze cues" (Bloch and Silva, 1959, p. 553); meprobamate reduced fear but left curiosity intact. The fact that the animals under Nembutal showed a progressive decrease in number of culs de sac entries and in time scores was considered to be "the result of an automatic activity not leading to any real learning of the maze pathway" (p. 553). Why automatic and stereotyped activity should lead to a decrease in blind alley entries and time scores, thereby producing "pseudo-learning" curves, is unclear. It would seem that the results of this experiment could be explained more simply by the concept of a generalization decrement.

Carlton and Vogel (1965) found that administration of scopolamine before pre-exposure to a stimulus produced attenuation of the habituation of that stimulus when the animal was re-exposed withoug drug.

This too can be interpreted in terms of stimulus change--the stimulus-without-drug had never before been experienced.

Several studies have investigated the effects of drugs on approach-avoidance conflicts, approaching the problem of a response decrement occurring with a change from a drug state to a nondrug state from the viewpoint of the therapeutic value of the drug. Barry, Etheredge, and Miller (1965), for example, tested whether therapeutic learning facilitated by the fear-reducing effect of amobarbital sodium would transfer from the drugged to the normal state. Rats were trained to press a bar for food, then were shocked at unpredictable times when pressing the bar until they stopped pressing. The shock was then eliminated, and the hungry rats were given trials in an attempt to get them to relearn pressing the bar. During the retraining "therapy session," rats given sodium amytal performed better than those given placebo, but this therapeutic effect failed to transfer to subsequent trials with no drug, for removal of the drug produced a large response decrement. The greater the dose given, the greater was the decrement produced.

Miller (1961) reported that in the same situation, chlorpromazine also had a therapeutic effect, and the superiority of the drug group in the post-drug test

did transfer, although with some decrement. Miller emphasized the importance of analyzing the exact stimulus conditions under which fear was originally established, because a change in stimulus conditions, however the change occurs, produces a reduction in fear.

Barry, Wagner and Miller (1962) tested the effects of alcohol and amobarbital on the frustration produced when hungry rats who had learned to run down an alley for food were given trials with no food in the goal box. They found that while the drugs attenuated extinction, thus supposedly reducing frustration, there was no appreciable carry-over to tests given without the drug.

Krieckhaus (1965) found that the "therapeutic" effect of d-amphetamine on avoidance performance of rats who had been trained without drug in a shuttle box failed to transfer from the drugged to the nondrugged condition. Krieckhaus, Zimmerman and Miller (1965), who gave d-amphetamine from the beginning of the training to avoid shock, also found that the drugged animals showed greatly improved learning. Again, when the drug was withdrawn the benefit was largely lost. Withdrawal from progressively higher doses of the drug produced progressively greater decrements in performance.

All of these results were interpreted in terms of generalization decrements in response. For example:

> It is well known that many drugs produce novel sensations and other changes in the stimulus situation. Therefore, learning which has occurred in the drugged state may be expected to suffer a stimulus-generalization decrement in transferring to the nondrug state. (Barry, Etheredge, and Miller, 1965, p. 151)

Miller (1966) suggested that since the withdrawal from stronger doses of drugs produces greater decrements in adaptive behavior while smaller changes in a stimulus complex produce smaller stimulus-generalization decrements in the response, perhaps it would be worthwhile to test the effects of gradual withdrawal from drug therapy.

Studies which specifically controlled for the effects of stimulus change have found that this variable does contribute to the results. Thus Grossman and Miller (1961) found that while rats ran farther and faster toward a desired goal in an approach-avoidance conflict situation when tested under either alcohol or chlorpromazine, regardless of the drug state during establishment of the conflict, animals whose condition was changed showed an additional increase over animals whose drug state was the same. Therefore the effects of stimulus change cannot be completely neglected in studies of drug effects.

Barry, Miller, and Tidd (1962) noted that animals

inhibited from approaching a goal from fear of shock show an increase in approach performance when tested under amobarbital. While drug increased approach performance whether prior training in the conflict had been under drug or not, approach performance was further increased by a shift to a new condition, regardless of whether the shift was from drug to placebo or from placebo to drug. Again, the operation of changing the conditions had an effect of its own.

Heistad (1957) took a somewhat different approach to the question of the stimulus value of the internal environment and the therapeutic effect of changing the internal environment. He noted that

> <u>every</u> aspect of the environment which is regularly associated with a response during the learning process may become a part of the total stimulus complex which acquired the capacity to elicit that response on subsequent occasions...Maximum (response)...requires exact reproduction of the stimulus conditions which prevailed during learning. (Heistad, 1957.p. 540)

Emotional response is typically accompanied by complex changes in the internal as well as the external environment, and since all of these changes occur in temporal contiguity with the emotional response, they all become part of the CS eliciting the response. Therefore, it is possible to interfere with performance of previously learned emotional behavior by any treatment procedure which changes those aspects of the internal environment, usually mediated by the hypothalamus

and autonomic nervous system which were associated with the learning of that behavior. However, learned emotional response which have been weakened by stimulus changes will recover if the stimulus conditions which prevailed during the learning process are reinstated. Furthermore, a change in the original stimulus conditions sufficient to interfere with retention of a conditioned emotional response will also interfere with the extinction of the response, for if the response does not occur it can not occur unrewarded.

Heistad (1958) tested the hypothesis that changes in those aspects of the internal environment which are correlated with conditions of emotion constitute changes in the CS and therefore interfere with retention of a conditioned emotional response along a gradient of stimulus generalization. He pitted electroconvulsive shock and chlorpromazine against each other, for according to Heistad, since ECS results in sympathetic dominance and chlorpromazine produces parasympathetic dominance their combination should tend to cancel each other out and restore the hypothalamic balance prevalent during the original learning. Retention of a learned CER was tested after each was administered separately and in combination. In accord with the predictions, both

interfered with retention of the CER when administered separately, indicating a generalization decrement effect, but when chlorpromazine and ECS were administered together partial restoration of the CER occurred.

Heistad concluded that the state of hypothalamic-autonomic activity at the time of emotional conditioning should be included among the stimulus conditions which acquire the properties of a CS. Any sufficiently great change in hypothalamic-autonomic status, and consequent status of the internal environment, constitutes a change in the CS and may interfere with retention of emotional learning along a gradient of stimulus generalization.

Thus evidence indicates that the use of chemical agents injected into the body provides a source of internal conditions which can function as stimuli, for responses acquired under one set of stimulus conditions and tested under another may show a response decrement and injection of different agents may provide a basis for the formation of mutually exclusive responses. That both of these phenomena have been produced with a variety of chemical agents having an assortment of physiological effects tends to indicate that specific properties of the drugs employed cannot completely account for the obtained results; the operation of changing the stimulus conditions produced by the

drug is at least in part involved.

Other studies, however, have interpreted an obtained response decrement following a change in the chemical state of the subject as a manifestation of some specific property of the drug producing the chemical state. These studies propose that certain drugs produce "state dependent" or "dissociated" learning in which large response decrements, sometimes complete abolition of the response, are correlated with a change in the chemical state of the subjects. The hypothesized reason for this involves reciprocal amnesia; experiences when in the drug state theoretically have no relevance for experiences when not under drug, and conversely, experiences of a normal animal are forgotten when the animal is submitted to the drug. Other concepts attributed to dissociation are "dual personality" and the concept of an "experimental scission of [the subject] into two distinct behavior-systems by selective action [of the drug]." (Culler, Coakley, Shurrager, and Ades, 1939, p. 273.)

The dissociation phenomenon is allegedly distinct from discrimination using the internal stimuli which result from the effects of the drug. According to Bindra, Nyman, and Wise (1965), the criterion for dissociation, as opposed to discrimination, is complete lack of transfer of learning from one chemical state

to another.

The first demonstration of what was called dissociation was by Girden and Culler (1937), who found that a conditioned response (contraction of the semitendinosus muscle to avoid shock) established under curare vanished upon recovery to the normal state and reappeared spontaneously and in full strength upon recurarization, while a conditioned response established in a normal dog disappeared under curare but reappeared upon recovery.

Girden and his co-workers accounted for this phenomenon by hypothesizing that curare renders the animal functionally decorticate, and therefore conditioning occurs at sub-cortical levels.

> It is...conceivable that under curare the normal cortical dominance is inhibited, and that conditioning therefore occurs at subcortical levels (thalamus). When the animal revives the cortex again functions normally and the (conditioned) thalamic activities are inhibited. Likewise the CR established in the normal animal (with participation of the cortex) is inhibited under curare (due to general inhibition of the cortex). (Girden and Culler, 1937, p.272)

Thus curare was thought to produce some kind of a block or cleavage between the drug-state and normal experiences. The animal was

> independently conditioned on separate levels or by disparate patterns of the central nervous system to the same stimulus at the same time. It may well be called an experimental form of <u>dual personality</u>: the animal replies by two independent behavior systems to the same stimulus, one in one state and one in the other. Normal learning proceeds at cortical levels, curarized learning at other (presumably sub-cortical) levels. (Culler, Coakley, Shurrager, and Ades, 1939, pp. 266-267)

The dissociation or "plane of cleavage" hypothesis, that a conditioned response is confined to the drug state in which it was produced because learning in the drug state involves completely different pathways from learning in the normal state, the pathways of one state being disfunctional in the other, was supported by two neurophysiological studies. Culler, Coakley, Shurrager, and Ades (1939) demonstrated that under curare both rheobase and chronaxie of the cortex, but not of the motor roots, were elevated, indicating that the quanta of electrical energy required to stimulate the cortex in the motor area and produce a muscle twitch was greater when the animal was under curare than when he was not--i.e. that curare depressed cortical function. In addition, Girden (1940) showed that in animals with bilateral extirpation of cortical auditory areas no dissociation occurred under curare with an auditory CS, presumably because all conditioning took place at sub-cortical levels, the block between the normal and curare states being disrupted.

Several responses have been shown to manifest the dissociation phenomenon under curare, including contraction of the semitendinosus muscle (Girden and Culler, 1937; Girden, 1947), a generalized struggle response (Girden, 1942a), increase in blood pressure (Girden, 1942b) and a pupillary conditioned response (Girden, 1942c). The phenomenon has been produced

with both curare and erythroidine hydro-bromide (Girden, 1942a), and Girden (1947) used monkeys to confirm the data on dogs showing a reciprocal amnesic effect produced when vascillating between drug state and normal state.

Case and Funderbunk (1947) reported that a response learned in a curare state would be performed when the animal was drugged with physostigmine even though it was not performed when the animal was undrugged. This was interpreted to indicate that physostigmine mimics the dissociative properties of curare.

In contrast to the results of Girden and his co-workers, Harlow (1940) found that with mild doses of curare a conditioned response did transfer from drug to normal states. Also, it should be noted that d-tubocurarine, a compound closely related to curare, does not produce dissociation (Solomon and Turner, 1962). Gardner and McCullough (1962) replicated both the dissociative effect produced by erythroidine and the failure of d-tubocurarine to produce dissociation.

Overton (1964) ran a series of experiments demonstrating state-dependent or dissociated behavior with sodium pentobarbital, a drug which has extensive depressent effects on the central nervous system. Rats were trained to escape from foot-shock in a T-maze by making the correct choice. Two groups were trained to run to a specified goal box while in one drug state

(produced by either pentobarbital or saline) and then tested in the other; two other groups were required to run to one goal box when in one drug state and to the opposite goal box when in the other. Results indicated that learning was state-dependent: the first two groups showed random performance on trials when their drug condition was changed; the second two groups showed differential responses controlled by drug state, which was interpreted as dissociation.

In a second experiment, the method of savings was used in an attempt to evaluate the degree of state dependence; subjects were trained to perform a response in the drug state, then training was continued in the nondrug state. The absence of a significant difference between the number of errors produced after these animals were taken off the drug and a control group receiving training only in the nondrug state indicated no transfer of training between drug and nondrug states.

Overton also demonstrated that two responses could be established concurrently by alternating training trials under the two drug conditions. When the rate of learning in each drug state was compared with that of a control group trained in one state only, the learning curves were "similar". Therefore Overton concluded that training while nondrugged had no significant effect upon concurrent learning and performance while drugged, i.e. learning in the two states was dissociated.

In order to determine the relation between dose of pentobarbital and degree of dissociation, Overton trained subjects concurrently to run to one goal box when not drugged and to the other when drugged with one of five doses of pentobarbital (25, 20, 15, 10, or 0 mg/kg). All groups except the control (0 mg/kg dose) learned to respond differentially at close to the 100% level of performance, but the rate at which the various groups acquired differential responses differed significantly. The amount of transfer of training between the nondrug state and the drug state, as indicated by a decrement in rate of learning to respond differentially, increased regularly as the dose establishing the drug state was decreased. This indicates that dissociation is only an extreme form of a continuous phenomenon.

Finally, Overton investigated the effectiveness of the pentobarbital drug state as an agent controlling differential responses with the effectiveness of various other stimuli, including both exteroceptive and interoceptive stimuli. Eight groups were employed, each subject being required to run to one goal box when under one condition and to the other when under another condition. The conditions used as discriminative stimuli were the following: (a.) pentobarbital vs. saline injection, (b.) multiple external stimuli consisting of a light, a tone, and increased shock level, vs. no light, no tone, and reduced shock level, (c) single external stimulus of

100-watt light vs. 7-watt light, (d) gallamine triethiodide (Flaxedil), a curareform drug which produced a decrement in running speed about equal to that produced by pentobarbital but which presumably had few effects on the central nervous system, vs. saline, (e) tetraethylammonium chloride, which produced blockade of the autonomic nervous system, vs. saline, (f) 23-hour food deprivation vs. 23-hour water deprivation, and (g) no discriminative stimuli other than the cues from the alternation procedure. Results showed that the difference between pentobarbital and saline rapidly established control over differential responding; multiple external stimulus changes acquired control over differential responding more slowly; and none of the other six groups learned the discrimination in 400 trials. Why the latter result was obtained is questionable, for previous studies have demonstrated the ability of these stimulus conditions to produce differential responding. It may reflect an insensitivity of Overton's procedure to the production of discriminated responding by demanding escape from unavoidable shock.

Overton interpreted his results as evidence for the ability of drug state changes to produce performance decrements being based on neither exteroceptive nor interoceptive sensory cue changes. He concludes that

> as pentobarbital acquired control of responses much more rapidly than any of the sensory cues selected, a parsimonious explanation might be to suggest a mechanism of control different from the one that allows discriminative cues to control responses. (Overton, 1964, p. 10)

By this Overton apparently means that modification of afferent neural input is not responsible for the state-dependent learning produced by pentobarbital. He hypothesized that one possible mechanism for the phenomenon involves mediating processes. "We can predict," he claims,

> that learning should be state-dependent in any brain in which learning involves the establishment of complex mediating processes (MPs) which are re-entrant or self-exciting. In any such brain a change in drug state sufficient to produce even a small change in the transfer characteristics of the individual cells which make up previously learned MPs would modify the timing and routing of nerve impulses within those MPs enough to disrupt them. This disruption might occur while still leaving brain function sufficiently intact so that new MPs could be learned; these would be specific to the new drug state, just as the previous learning was specific to the nondrug state. (p. 11)

Overton does not, however, account for the fact that transfer of training does occur with smaller doses of the drug:

> partial dissociation of learning (partial transfer of training occurs between drug states not sufficiently different from each other to produce total dissociation. The more similar two drug states are, the more complete the transfer of training which occurs between them. (p. 11)

This latter feature of the phenomenon of dissociation is one of the primary attributes of stimulus discrimination.

Bindra, Nyman, and Wise (1965) produced evidence that the dissociation phenomenon is specific to the response required, for acquisition of an immobility response and extinction of an escape response transferred

between a phenobarbital-induced and a normal state, but extinction of the immobility and acquisition of the escape response, as indicated by increased latency, did not transfer. They interpreted this to mean that at least these instances of dissociation involved impairment of processes concerned with initiation of movement but not processes involved in response selection. As Bindra et al point out, however, chemical specificity cannot be restricted to connections between the CS and the movement-initiating mechanism, for Overton's (1964) study indicated the existence of chemical specificity for connections between the CS and the response-selection mechanism when his animals failed to select the correct response under changed chemical states. That Overton used stronger barbiturate doses than Bindra et al might imply that connections between the CS and the movement-initiating mechanism are more susceptible to changes in chemical state than are the connections between the CS and the response-selection mechanism.

Bindra an Reichert (1966) produced further evidence supporting the hypothesis that processes involved in response choice and in movement initiation are not identical, with the movement-initiation processes being more susceptible to changes in the chemical state of the organism. In a T-maze situation, with avoidance of shock as the motivation, changing the drug state produced no effect upon response selection (proportion

of correct choices) or upon response execution (running time), but produced a marked increase in latency (the rats were given prompting shocks until they responded, thereby forcing a response). This occurred regardless of whether the shift was from no drug to drug (pentobarbital) or from drug to no drug. Thus the discrimination transferred; the ability of the CS to initiate the response did not transfer.

Although it is possible that drugs produce changed chemical states which alter (either facilitate or inhibit) neural transmission in certain parts of the nervous system, the above results cannot be interpreted as drug-produced impairment of some neural mechanism involved in movement-initiation, for the impairment occurred whenever the chemical state was changed, not just when phenobarbital was present. Perhaps an explanation should involve a generalization decrement: the total CS (including internal cues) conditioned to making the response was changed sufficiently by alteration of the chemical state to produce a response decrement; once the response was forced, the cues of making the response restored the initial situation sufficiently to allow correct responding. It would be interesting to know if the response decrement produced by change in the external CS is specific to initiation of movement.

Overton (unpublished) has reported a series of experiments in which rats were required to discriminate

drug states in order to escape from shock in a T-maze. The establishment of mutually exclusive responses in different drug states was considered to indicate dissociation of learning, the speed with which a pair of drug states acquire control of differential responding giving a measure of the degree of dissociation between the two drug states. The research was designed to compare the dissociative effects of various centrally acting drugs, and involved 21 different sets of drug conditions.

Several depressant drugs, including pentobarbital, phenobarbital, alcohol, urethane, and meprobamate produced a state in which learning was "partially dissociated" from learning occurring in the nondrug state. These drugs were approximately equivalent (i.e. could not be discriminated from each other) and were interchangeable. Transfer tests with chloral hydrate, paraldehyde, secobarbital, chloralose, or subanesthetic doses of ether indicated that these drugs were interchangeable with the other depressant drugs, while transfer tests with d-amphetamine, bemegride sulphate, gallamine, LSD, and physostigmine indicated that these drugs did not mimic the depressant drugs.

Bemegride sulphate was found to antagonize the effects of pentobarbital, for when the two were administered together the animal tended to make the

response appropriate to the nondrug state, and increasing the doses of bemegride progressively reduced the effects of pentobarbital. Bemegride given by itself was not discriminated from no drug.

Atropine produced a drug state in which learning was partially dissociated from learning in the nondrug state and from learning which occurred under pentobarbital. The rats could both discriminate atropine from pentobarbital and discriminate a combination of atropine and pentobarbital from saline indicating that the effects of atropine neither mimicked nor antagonized those of pentobarbital. Overton interpreted this to be evidence that atropine-like drugs produce dissociation by a mechanism different from that by which depressant drugs produce it; therefore all dissociation phenomena cannot be attributed to a unidimensional process.

Several anticholinergic drugs, including scopolamine, homatropine HBr, and cyclopentolate HCl were found to be equivalent to atropine, indicating that perhaps atropine produced dissociation via its anticholinergic action. Transfer tests with two quaternary atropine derivatives which do not produce the central nervous system actions characteristic of atropine but do mimic its peripheral actions, consistently resulted in nondrug responses. This indicated to Overton that the CNS actions of atropine, rather than its peripheral

actions, are responsible for dissociation of learning.

Overton failed to find dissociative effects of several drugs which have been shown by other investigators to be agents producing what he calls dissociation. These drugs include chlopromazine and imipamine; physostigmine showed very weak dissociative effects on T-maze learning. Overton concluded that this reflected a lack of sensitivity of the T-maze task to the dissociative effects of drugs.

Chlordiazepoxide, at 30 mg/kg, produced response control rapidly. In transfer tests, pentobarbital-trained rats gave drug responses when tested with chlordiazepoxide, but the reverse was not dependably true. In a group of six rats trained to discriminate pentobarbital from chlordiazepoxide, two did acquire differential responses, four did not. Overton concluded that chlordiazepoxide does dissociate learning in the T-maze and shares some properties with the depressant drugs.

To account for the production of dissociation of learning by drug action, Overton proposed two theoretical models. The first assumes that the process is not qualitatively different from that by which external stimuli control responses.

> Suppose that a drug acts primarily on some system in the brain...which projects to those systems where the structural changes accompanying learning occur. Drug actions on such a receptor system (perhaps restricted to a particular region

> of the brain) will result in changes in the propagation from this system; these will appear as changes in the afferent neural input to the region where learning occurs. The control of differential responses can thus develop via the same mechanisms whether this control is exerted by centrally acting drugs or by discriminative stimuli acting through the sensory systems. With drugs, however, the dissociation between two states can be much more extreme because of the very strong influence which some systems of the brain are able to exercis on others due to their structural connections. (Overton, pp. 27-28)

What is meant by "the strong influence which some systems exercise on others due to their structural connections" is unclear; it is also unclear what kind of "system" Overton has in mind. Furthermore, if this is acceptable as a model accounting for the effects of drug action, and Overton admits that it explains "the many similarities between control of differential responses by stimuli and by drug states," (p. 28), it is unclear why a different term, "dissociation," is given to the effects of drug action, implying a difference between drug action and stimulus action, and why the effects of the drugs are repeatedly referred to as "amnesic effects."

Overton's second proposed model assumes

> that the drug acts diffusely and changes the characteristics of cells within those regions of brain where the structural modifications resulting in learning take place. Many theories of learning suggest that the acquisition of a response involves rather subtle changes in the transfer functions of a large number of cells (or synapses) such that these cells participate in a patterned activity appropriate to produce the behavioral response. Because of the many interactions between the different units in such a complex reentrant

> system, a change in the characteristics of its' constituent units may greatly modify system behavior. (p. 28)

Overton elaborates upon this model, implying that the dissociation phenomenon occurs because a change in drug state disorganizes either partially or completely any neural response which has been established in another drug state. He apparently considers this disorganization to be in some way qualitatively different from the state of affairs produced by a change in afferent neural propagation. He definately does not consider the "amnesic effects produced by drug state changes" to be related to stimulus discrimination, for he feels that it is unlikely they are "normally significant in determining behavior," and claims that "the fact that dissociation can occur reflects an interesting and previously unknown property of the learning mechanism." (p. 31)

Another adamant proponent of the concept of dissociation as a phenomenon qualitatively distinct from stimulus discrimination is Eugene Sachs. Sachs, Weingarten, and Klein (1966) trained rats in a hurdle jump conditioned avoidance response, and then tested their behavior under various drug conditions. Five groups were employed: Group L_1 (n = 5) was trained under chlordiazepoxide (15 mg/kg) to a criterion of 20/20 correct responses in three successive sessions, then given a schedule of saline injections for a

period of about the same duration as the training period, then tested under various conditions. L_2 rats (n = 7) were trained under CDP to a criterion of 18/20 correct responses in two successive sessions, and tested directly. The control group was trained under saline to a criterion of 20/20 correct responses in three successive sessions, then split into three groups, in which LC (n = 4) was given a schedule of CDP injections equivalent in spacing and number to that required by a weight-matched animal in the L_1 group, TC (n = 6) was given a fixed course of nine chlorpromazine (CPZ) injections comparable to the average of the LC group, and the CC group (n = 5) was tested directly. Test data was based on sessions of 20 extinction trials, blocks of 5 trials being followed by 2 "reminder trials." Each novel-condition test was bracketed by two tests in the training condition; the data for the new condition were evaluated against the pooled mean value of these two surrounding tests. In the test sessions, failure to respond within 20 seconds was considered a "failure,", indicating no retention of the response (the ISI during training was 10 seconds).

Rats trained with chlordiazepoxide acquired the CAR significantly faster than controls trained with saline. When tested in the undrugged state, CDP-trained animals showed a 9.7 second increase in mean

latency, with 63% of the animals showing "failures"; the deficit was greater in the L_1 group than in the L_2 group. CDP-trained animals also performed poorly in tests under CPZ, with a 14 second increase in latency.

Saline-trained rats showed a decrement whenever their internal condition was changed, although the decrement was not as great as that shown by CDP-trained animals. The mean decrement shown by the pooled control groups tested under CDP was about 4.5 seconds. Animals who had been given the series of injections between training and testing, either of CDP or CPZ, typically showed less of a decrement when tested under either drug than animals tested directly after training.

Successive tests under novel conditions showed a progressive decrease in the amount of latency increase over that performed in the training condition. Sachs et al interpret this to indicate that tolerance is acquired by experience with, and training, by the "reminder" trials, under the drug, i.e. "an accommodation to performance under drug" (p. 23). They also claim that their evidence indicates that no difference exists between drug-produced cues resulting from administration of CPZ and CDP; their basis for this is that animals given the habituation session with one of these drugs show less of a decrement when given the other than do the controls given no habituation session,

supposedly indicating cross-tolerance between the drugs. Based on the equivalence of CDP and CPZ, Sachs et al assert that

> an explanation in terms of drug-produced-cues could hardly be applicable to the results obtained with CDP-trained animals, since CPZ produces an even greater deficit than saline, and both effects are far more dramatic and show less evidence of accomodation than comparable control group comparisons. (p. 23)

Sachs et al feel that while the results of other studies, e.g. that of Otis (1964), may have been determined by the stimulus effects of drugs,

> the reliance on these as a general explanation of dissociation is another matter. In the present experiment it is shown that in highly overtrained rats...a phenomenon can be obtained in which the failure in transfer is uniform and virtually dichotomous. (p. 25)

However, it is questionable whether Sachs et al's experiment showed a "dichotomous nature" of the effect of changing conditions. Their response measured was latency, and even a marked increase in latency can hardly be considered qualitatively different from lower latency. The delegation of a failure to jump within 20 seconds as complete loss of retention seems unjustified in view of Bindra, Nyman and Wise's (1965) and Bindra and Reichert's (1966) results.

Sachs et al base their argument for the qualitative difference between dissociation and discrimination on Bindra's (1959) demonstration that the performance decrement ensuing from a change in stimulus conditions

is a function of the novelty of the stimulus alterations, with the competing responses which occur to interfere with the learned response being elicited to novelty. Introduction of stimuli which have been previously habituated theoretically do not result in a response decrement, even though they were not part of the original training situation.

The magnitude of the effects attributable to stimulus alterations resulting from drug injection was assessed by use of the three control groups. According to Sachs et al, the direction of the differences between the control groups (those given "habituation" injections of drug showing less of a decrement on transfer tests than those experiencing the drug condition for the first time), "is incompatible with an explanation of the dichotomous response of the CDP trained animals in terms of drug-produced-stimuli" (p. 26). However, this would seem to be contrary to, rather than in accord with, Bindra's interpretation of the production of response decrements produced by stimulus change, for if the differences between the control groups can be considered significant, the direction of these differences seems to indicate that the drug does have cue properties. The fact that the effect of drug ommission on the behavior of drug-trained animals was more potent than the effect of its addition to normally trained rats, on

the other hand, is difficult to explain in terms of Bindra's concept of generalization decrement, for as Sachs et al point out, all animals were thoroughly accustomed to being undrugged.

Sachs et al conclude that

> it seems most likely that the instances of complete dissociation are attributable to changes in the state of the brain, rather than the sensorium...Drugs are usually thought to exert a selective action, affecting some regions of the brain more than others. Therefore, it may be that a clear dissociative effect is dependent on change in state in particular regions, and is not a simple consequence of change per se. (pp. 26-27)

The cause of dissociation is attributed to abrogation of attention and consequent interference with habituation. According to Sachs et al, attention is normally compelled by novelty, and as a result of paying attention, stimuli lose their novelty and gain familiarity. The insensitivity to novelty, theoretically produced by drugs which produce dissociation, allows for rapid learning of simple approach and avoidance responses by reduction of competing responses to the novelty of the situation, although this same impairment of attention reputedly disrupts performance in complex learning tasks. When the drug is withdrawn the situation suddenly becomes novel, and the responses trained under drug are replaced by responses to novelty, thus accounting for the response decrement.

While this explanation explains the response decrement produced by a change from drug to no drug,

it would seem to predict facilitation of performance, or at least no change in performance, with a shift from no drug to drug. This is not what occurs.

Sachs et al demonstrated clearly that a large response decrement (i.e. latency increase) occurs with a change in conditions. It is not clear, however, why this decrement must be considered entirely in terms other than a generalization decrement, admittedly a large one, but one not qualitatively different from that occurring with any other kind of change in conditions. There may well be an effect of chlordiazepoxide upon attention, but surely the effects of stimulus change produced by administration of the drug cannot be denied.

REFERENCES

Amsel, A. Selective association and the anticipatory response mechanism as explanatory concepts in learning. J. exp. Psychol., 1949, 39, 785-799.

Bailey, C.J. The effectiveness of drives as cues. J. comp. physiol. Psychol., 1955, 48, 183-187.

Bailey, C.J. and Porter, L.W. Relevant cues in drive discrimination in cats. J. comp. physiol. Psychol., 1955, 48, 180-182.

Barry, H., Etheredge, E.E., and Miller, N.E. Counterconditioning and extinction of fear fail to transfer from amobarbital to nondrug state. Psychopharmacologia, 1965, 8, 150-156.

Barry, H., Koepfer, E., and Lutch, J. Learning to discriminate between alcohol and nondrug condition. Psychol. Rep., 1965, 16, 1072.

Barry, H., Miller, N.E., and Tedd, Gail E. Control for stimulus change while testing effects of amobarbital on conflict. J. comp. physiol. Psychol., 1962, 55, 1071-1074.

Barry, H., Wagner, A.R., and Miller, N.E. Effects of alcohol and amobarbital on performance inhibited by experimental extinction. J. comp. physiol. Psychol., 1962, 55, 464-468.

Belleville, R.E. Control of behavior by drug-produced internal stimuli. Psychopharmocol., 1964, 5, 95-105.

Bindra, D. and Mendelson Interaction of habit strength and drug effects. J. comp. physiol. Psychol., 1962, 55, 217-219.

Bindra, D., Nyman, K., and Wise, J. Barbiturate-induced dissociation of acquisition and extinction: Role of movement-initiating processes. J. comp. physiol. Psychol., 1965, 60, 223-228.

Bindra, D. and Reichert, H. Dissociation of movement initiation without dissociation of response choice. Psychon. Sci., 1966, 4, 95-96.

Bloch, S. and Silva, A. Factors involved in the acquisition of a maze habit, analyzed by means of tranquillizing and sedative drugs. J. comp. physiol. Psychol., 1959, 52, 550-554.

Bloomberg, R. and Webb, W.B. Various degrees within a single drive as cues for spatial response learning in the white rat. J. exp. Psychol., 1949, 39, 628-636.

Brown, W.L. A study of changes in orientation resulting from intra-organic motivation in learning. J. comp. Psychol, 1940, 30, 111-127.

Carlton, P.L. Cholinergic mechanisms in the control of behavior by the brain. Psychol. Rev., 1963, 70, 19-39.

Carlton, P.L. and Vogel, J.R. Studies of the amnesic properties of scopolamine. Psychon. Sci., 1965, 3, 261-262.

Case, T.J. and Funderbank, W.H. An effect of curare on the central nervous system. Trans. Am. Neurol. Ass., 1947, 72, 195-196. (cited in Overton, unpublished).

Conger, J.J. The effects of alcohol on conflict behavior in the albino rat. Quart. J. Stud. Alcohol, 1951, 12, 1-29.

Cook, L. Effects of drugs on operant conditioning. In H. Steinberg (Ed.), Animal behavior and drug action. London: J. & A. Churchill, Ltd., 1964.

Cook, L., Davidson, A., Davis, D.J., and Kelleher, R.T. Epinephrine, norepinephrine, and acetylcholine as conditioned stimuli for avoidance behavior. Science, 1960, 131, 990.

Culler, E., Coakley, J.D., Shurrager, P.S., and Ades, H.W. Differential effects of curare upon higher and lower levels of the central nervous system. Amer. J. Psychol., 1939, 52, 266-273.

Feldman, R.S. The prevention of fixations with chlordiazepoxide. J. Neuropsychiat., 1962, 3, 254-259.

Gardner, L. and McCullough, C. A reinvestigation of the dissociative effect of curareform drugs. Amer. Psychol., 1962, 17, 398. (abstract).

Gerbrandt, L.K. Neural systems of response release and control. Psychol.Bull., 1965, 64, 113-123.

Girden, E. Cerebral mechanisms in conditioning under curare. Amer. J. Psychol., 1940, 53, 397-407.

Girden, E. The dissociation of blood pressure conditioned responses under erythroidine. J. exp. Psychol., 1942, 31, 219-231. (b)

Girden, E. The dissociation of pupillary conditioned reflexes under erythroidine and curare. J. exp. Psychol., 1942, 31, 322-332. (c)

Girden, E. Generalized conditioned responses under curare and erythroidine. J. exp. Psychol., 1942, 31, 105-119. (a)

Girden, E. Conditioned responses in curarized monkeys. Amer. J. Psychol., 1947, 60, 571-587.

Girden, E., and Culler, E.A. Conditioned responses in curarized striate muscle in dogs. J. comp. Psychol., 1937, 23, 261-274.

Gloor, P. Amygdala. In J. Field, H.W. Magoun, and V.E. Hall (Eds), Neurophysiology, Vol. II. Washington: Amer. Physiol. Soc., 1960.

Goddard, G.V. Functions of the amygdala. Psychol. Bull., 1964, 62, 89-109.

Grossman, S.P. and Miller, N.W. Control for stimulus-change in the evaluation of alcohol and chlorpromazine as fear-reducing drugs. Psychopharmacologia, 1961, 2, 342-351.

Harlow, H.F. The effects of incomplete curare paralysis upon formation and elicitation of conditioned responses in cats. J. genet. Psychol., 1940, 56, 273-282.

Heistad, G.T. A bio-psychological approach to somatic treatments in psychology. Amer. J. Psychiat., 1957, 114, 540-545.

Heistad, G.T. Effects of chlorpromazine and electro-convulsive shock on a conditioned emotional response. J. comp. physiol. Psychol., 1958, 51, 209-212.

Heistad, G.T. and Torres, A.A. A mechanism for the effect of a tranquillizing drug on learned emotional responses. Univ. Minnesota med. Bull., 1959, 30, 518-527.

Heron, W.T. Internal stimuli and learning. J. comp. physiol. Psychol., 1949, 42, 486-492.

Hull, C.L. Differential habituation to internal stimuli in the white rat. J. comp. Psychol., 1933, 16, 255-273.

Hunt, H.F. Effects of drugs on emotional responses and abnormal behavior in animals. In Conference on drugs and psychiatry. Washington: National Research Council, 1956.

Jacobson and Sonne. The effect of benactyzine on the conditioned responses in the rat. Acta pharmacol. (Kbh), 1956, 12, 310-320.

Jacobson and Sonne. The effect of benzilic acid diethylaminolhylester, HCl (benactyzine) on stress-induced behavior in the rat. Acta pharmacol. (kbh), 1955, 11, 135-147.

Jenkins, J.J. and Hanratty, J.A. Drive intensity discrimination in the albino rat. J. comp. physiol. Psychol., 1949, 42, 228-232.

Krieckhaus, E.E. Decrements in avoidance behavior following mammillothalamic tractotomy in rats and subsequent recovery with dexedrine. J. comp. physiol. Psychol., 1965, 60, 31-35.

Krieckhaus, E.E., Zimmerman, Patricia, and Miller, N.E. D-amphetamine reduces freezing and improves shock avoidance behavior. J. comp. physiol. Psychol., 1965, 60, 36-40.

Leeper, R. The role of motivation in learning: A study of the phenomenon of differential motivational control of the utilization of habits. J. genet. Psychol., 1935, 46, 3-40.

Levine, S. The role of irrelevant drive stimuli in learning. J. exp. Psychol., 1953, 45, 410-416.

Maier, N.R.F. and Klee, J.B. Studies of abnormal behavior in the rat: XVII. Guidance versus trial and error in the alteration of habits and fixations. J. Psychol., 1945, 19, 133-163.

Miller, N.E. Some recent studies of conflict behavior and drugs. Amer. Psychol., 1961, 16, 12-24.

Miller, N.E. Some animal experiments pertinent to the problem of combining psychotherapy with drug therapy. Comprehensive Psychiatry, 1966, 7, 1-12.

Miller, N.E. and Kraeling, D. Displacement: Greater generalization of approach than avoidance in a generalized approach-avoidance conflict. J. exp. Psychol., 1952, 43, 217-221.

Morillo, A. Effects of benzodiazepines upon amygdala and hippocampus of the cat. Int. J. Neuropharmacol., 1962, 1, 353-359.

Morillo, A., Revzin, A.M., and Knauss, T. Physiological mechanism of action of chlordiazepoxide in cats. Psychopharmacol., 1962, 3, 386-394.

Murray, E. and Miller, N.E. Displacement: Steeper gradient of generalization of avoidance than of approach with age of habit controlled. J. exp. Psychol., 1952, 43, 222-226.

Otis, L.S. Dissociation and recovery of a response learned under the influence of chlorpromazine or saline. Science, 1964, 143, 1347-1348.

Overton, D.A. Discriminative behavior based on the presence or absence of drug effects. Amer. Psychol., 1961, 16, 453-454. (abstract)

Overton, D.A. State-dependent learning produced by depressant and atropine-like drugs. Unpublished manuscript.

Overton, D.A. State-dependent or "dissociated" learning produced with pentobarbital. J. comp. physiol. Psychol., 1964, 57, 3-12.

Paskal, V. Dissociative effects of atropine on a simple learned task in the rat. (Cited in Overton, unpublished)

Sachs, E. The role of brain electrolytes in learning and retention. Unpublished doctoral dissertation, Univ. Rochester, 1962. (Cited in Overton, unpublished)

Sachs, E., Weingarten, M., and Klein, N.W. Effects of chlordiazepoxide on the acquisition of avoidance learning and its transfer to the normal state and other drug conditions. Psychopharmacologia, 1966, 9, 17-30.

Schallek, W. and Kuehn, A. Effects of benzodiazepines on spontaneous EEG and arousal responses of cats. In K Akert, C. Bally, and J.P. Schadi (Eds), Progress in brain research, Vol. 18. Amsterdam: Elsevier Publishing Co., 1965.

Schallek, W. and Kuehn, A. Effects of psychotropic drugs on limbic system of cat. Proc. soc. exp. biol. Med., 1960, 105, 115-117.

Schallek, W. and Kuehn, A. Effects of trimethadione, diphenylhydrantion, and chlordiazepoxide on after-discharges in brain of cat. Proc. soc. exp. biol. Med., 1963, 112, 813-817.

Schallek, W., Kuehn, A., and Jew, N. Effects of chlordiazepoxide (Librium) and other psychotropic agents on the limbic system of the brain. Ann. N. Y. Acad. Sci., 1962, 96, 303-314.

Schallek, W., Zabransky, F., and Kuehn, A. Effects of benzodiazepines on central nervous system of cat. Arch. Int. Pharmacoalyn., 1964, 149, 467-483.

Solomon, R.L. and Turner, L.H. Discriminative classical conditioning in dogs paralyzed by curare can later control discriminative avoidance responses in the normal state. Psychol. Rev., 1962, 69, 202-219.

Sternbach, L.H., Randall, L.O., and Gustafson, Sarah R. 1,4-Benzodiazepines (chlordiazepoxide and related compounds). In M. Gordon, (Ed.), Psychopharmacological agents, Vol. I. New York: Academic Press, 1964.

Stewart, J. Differential responses based on the physiological consequences of pharmacological agents. Psychopharmacologia, 1962, 3, 132-138.

Terrace, H.S. Discrimination learning with and without errors. J. exp. analysis Beh., 1963, 6, 1-28.

Winnich, W. The discriminative function of drive stimuli independent of the action of drive as motivation. Amer. J. Psychol., 1950, 63, 196-205.

Appendix B

TABLE 4

Experiment 1: Percent Correct

Days of Testing	Group I Problem A	Problem B
1		
2	54.5%	
3		43.5%
4	56.0%	
5		42.5%
6	63.0%	
7		47.0%
8	71.5%	
9		44.5%
10	72.5%	
11		42.0%
12	79.0%	
13		50.5%
14	84.5%	
15		53.0%
16	85.0%	
17		56.5%
18	87.0%	
19		60.5%
20	92.0%	
21		66.0%
22	91.5%	
23		73.5%
24	91.5%	
25		72.5%
26	94.5%	
27		73.5%
28	97.5%	
29		73.0%
30	97.0%	
		74.0%

The difference between performance on Problem A and Problem B is significant by the Mann-Whitney Test, $p < .001$, $U = 32$.

TABLE 4, continued

Days of Testing	Group II Problem A	Problem B
1		
2	56.0%	
3		37.0%
4	59.0%	
5		42.5%
6	57.0%	
7		35.5%
8	54.5%	
9		43.0%
10	58.0%	
11		39.5%
12	58.5%	
13		43.0%
14	54.0%	
15		47.0%
16	54.5%	
17		43.0%
18	54.0%	
19		44.5%
20	53.0%	
21		45.5%
22	55.0%	
23		45.0%
24	55.0%	
25		45.0%
26	55.0%	
27		45.0%
28	55.0%	
29		45.0%
30		45.0%

During the last 10 days of testing, all of the difference between performance on Problem A and B is due to two rats who jumped to the bright window every day, getting 100% correct on Problem A and 0% correct on Problem B; the other 18 rats received exactly 50% correct.

TABLE 4, continued

Days of Testing	Group III Problem A	Problem B
1	46.5%	
2		38.0%
3	49.5%	
4		44.5%
5	51.0%	
6		48.5%
7	48.5%	
8		48.0%
9	51.0%	
10		47.0%
11	51.5%	
12		49.5%
13	50.5%	
14		48.0%
15	50.0%	
16		49.0%
17	50.0%	
18		47.0%
19	53.0%	
20		47.0%
21	52.5%	
22		47.5%
23	53.0%	
24		47.5%
25	52.5%	
26		47.5%
27	52.5%	
28		47.5%
29	50.0%	
30		49.5%

TABLE 5

Experiment 1: Response Latency

Group I

Days of Testing	Problem A	Problem B
1	14.5 sec	
2		19.2 sec
3	14.0 sec	
4		13.8 sec
5	14.3 sec	
6		10.6 sec
7	15.7 sec	
8		10.4 sec
9	15.0 sec	
10		12.0 sec
11	15.0 sec	
12		10.6 sec
13	15.0 sec	
14		11.5 sec
15	16.2 sec	
16		12.3 sec
17	15.7 sec	
18		11.5 sec
19	16.8 sec	
20		12.0 sec
21	16.8 sec	
22		12.3 sec
23	16.2 sec	
24		12.9 sec
25	16.1 sec	
26		11.4 sec
27	16.7 sec	
28		12.6 sec
29	17.0 sec	
30		13.4 sec

TABLE 5, continued

Experiment 1: Response Latency

Group III

Days of Testing	Problem A	Problem B
1	13.6 sec	
2		17.7 sec
3	14.5 sec	
4		14.9 sec
5	15.4 sec	
6		16.0 sec
7	17.6 sec	
8		17.0 sec
9	17.9 sec	
10		16.8 sec
11	18.2 sec	
12		18.9 sec
13	17.9 sec	
14		20.9 sec
15	19.1 sec	
16		19.1 sec
17	19.4 sec	
18		20.3 sec
19	20.4 sec	
20		21.1 sec
21	18.4 sec	
22		20.3 sec
23	18.9 sec	
24		19.7 sec
25	19.2 sec	
26		18.6 sec
27	20.8 sec	
28		20.6 sec
29	20.2 sec	
30		20.4 sec

TABLE 5, continued

Experiment 1: Response Latency

Groups I and II

Days of Testing	not drugged	drugged
1	14.6 sec	20.8 sec
2	15.0 sec	14.3 sec
3	14.8 sec	12.6 sec
4	16.6 sec	11.4 sec
5	15.8 sec	12.4 sec
6	16.9 sec	12.4 sec
7	17.1 sec	13.6 sec
8	17.8 sec	13.9 sec
9	17.5 sec	14.2 sec
10	18.5 sec	14.0 sec
11	19.9 sec	14.1 sec
12	19.4 sec	13.8 sec
13	18.9 sec	13.8 sec
14	17.0 sec	14.2 sec
15	19.0 sec	15.8 sec

The difference between response latency of drugged and undrugged animals is significant by a Mann-Whitney Test, $p < .001$, $U = 19$.

TABLE 6

Experiment 2: Percent Correct

Days of Testing	Group A	Group B
1	51.7%	44.2 %
2	60.0%	51.7%
3	69.2%	54.2%
4	70.8%	65.0%
5	80.0%	74.2%
6	90.0%	83.3%
7	90.0%	87.5%
8	91.7%	94.2%
9	95.0%	91.7%
10	95.8%	99.2%
11	95.0%	100.0%
12	95.8%	100.0%
13	95.8%	100.0%

Group A's failure to reach 100% was due to one rat who jumped to one side only, receiving 50% correct. He was tested for 2 more days after those reported above, but did not abandon this response. The other 23 rats were run in Experiment 3.

Experiment 3: Percent Correct

Days of Testing	Group A	Group B
1	93.3%	91.7%
2	95.0%	90.0%
3	95.8%	98.3%
4	95.8%	98.3%
5	95.8%	99.2%
6	95.8%	100.0%
7	95.8%	100.0%

Group A's scores are adjusted to account for the one rat who wasn't run in this experiment but was run in Experiment 2, in order to keep the perspective of the response decrement.

TABLE 7

Experiment 2: Response Latency

Days of Testing	Group A	Group B
1	16.1 sec	12.6 sec
2	21.9 sec	16.4 sec
3	19.6 sec	14.8 sec
4	18.9 sec	13.0 sec
5	19.9 sec	13.4 sec
6	16.7 sec	10.5 sec
7	14.2 sec	8.4 sec
8	15.2 sec	8.4 sec
9	14.6 sec	7.3 sec
10	16.6 sec	7.4 sec
11	16.4 sec	77.3 sec
12	16.3 sec	6.4 sec
13	15.4 sec	6.3 sec

The difference between Group A and Group B is significant by a Mann-Whitney U Test, $p < .001$, $U = 9$.

Experiment 3: Response Latency

Days of Testing	Group A	Group B
1	26.7	11.5
2	15.2	14.9
3	12.5	14.0
4	9.2	14.3

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A Dissertation

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