

STATE-DEPENDENT LEARNING WITH CENTRALLY
AND NON-CENTRALLY ACTIVE DRUGS

by

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ABSTRACT

State-dependent learning has been studied in cases where differential responses are required under varying drug conditions and where some unitary response must be performed under varying conditions of drug and non-drug. In the former case, response dissociation is considered to be a result of the cue properties of drugs while in the latter case it is believed to be a consequence of CNS modification of neural circuits representing coded responses. The present study was designed to determine if the stimulus properties of a drug without direct CNS activity could produce state-dependent dissociation. Results indicated that only with the centrally active agents pentobarbital and chlorpromazine could any appreciable dissociation be obtained, while the ANS stimulant, l-epinephrine, could not produce dissociation. It is argued that responses are coded under specific CNS conditions; and that, in order to reproduce a response, those or similar conditions must be reinstated.

INTRODUCTION

State-dependent learning constitutes a procedure whereby the effects of drugs on a previously learned response may be assessed in two ways: 1) effects resulting from direct action of drugs on learned responses and 2) effects resulting from state-change (drug to non-drug, or vice versa). It is this latter class of effects with which the field of state-dependent learning is most concerned. The inability to transfer response performance from one state to another is termed the "dissociation" of learning and this dissociation is generally taken to represent the result of changed chemical environments within the organism, when fatigue, motivational changes, retention, and so forth can be ruled out.

Two procedures have commonly been used to assess the state-dependent properties of drugs. In the first case, subjects are required to make spatial discriminations in order to escape shock, with discriminative cues for the correct response being internal, state- (drug-) produced stimuli. One particular advantage in using this approach is that it makes possible the classification of related pharmacological compounds by use of yet another behavioral procedure. For example, the experimenter using an electrified

T-maze may require the subject to make a right turn escape response while drugged with phenobarbital and a left turn response while undrugged. Following these initial procedures, various other depressant drugs, related to phenobarbital structurally and pharmacologically, may be administered and the similarity of their behavioral effects (in this case, response control) assessed.

A more satisfactory method for obtaining state-dependency is to systematically alter central states in successive testing phases. The most efficient design with this approach is a simple switchback, transfer-of-training paradigm in which two groups are trained on a particular task in acquisition, one under drug conditions and the other under non-drug conditions. During testing, both groups are split with half performing under conditions identical to those during acquisition (no state-change groups) and half performing in the condition not present during acquisition (state-change groups). This design thus yields four basic groups (drug-drug; non-drug-non-drug; drug-non-drug; and non-drug-drug) which allows for the simultaneous measurement of simple drug effects on behavior as well as state-change effects. It is necessary to understand that state-dependent learning, as typically defined, involves a dissociative effect; and, thus, performance during testing must be dramatically reduced or, ideally, completely abolished. Such dissociation is necessary regardless of whether a stimulant

or depressant drug is used and whether drug effects on acquisition are facilitative or disruptive.

Although a wide variety of drugs have been used in the study of state-dependent learning, a larger number of studies have been concerned with the barbiturates and phenothiazine tranquilizers. Results with the barbiturates have been very consistent, indicating that state-dependent learning is a stable and reliable effect and that, for most members of the barbiturate class, this dissociation represents a very large and often total inability to transfer responses. Overton (1964) reports response control of learning with sodium pentobarbital (25 mg/kg) in avoidance learning in the T-maze. These effects were shown to be directly proportional to the size of the drug dosage and would seem to indicate that any degree of dissociation desired could be experimentally produced.

Barry, Etheredge, and Miller (1965) using a barpress task to produce conditioned suppression have also reported large response decrements after state-change with amobarbital in doses of 20 and 30 mg/kg. In subsequent research, Overton (1966) demonstrated that phenobarbital (80 mg/kg), pentobarbital (20 mg/kg), ethanol (2.4 mg/kg) and a host of other depressant drugs could all be discriminated sufficiently from saline states as to provide for efficient and rapid acquisition of differential escape responses. Moreover, no differential response control could be obtained

with states based on phenobarbital vs. pentobarbital or in cases where doses of the same pharmacological agent were not sufficiently different (e.g., 5 vs. 7.5 mg/kg of pentobarbital).

That state-dependent learning is not, at least in the case of the barbiturates, a result in changes in sensory apparatus or their processing abilities has been supported by research by Overton (1964, 1968). In the first experiment, subjects were trained to perform differential escape responses in a T-maze based on pentobarbital (20 mg/kg) vs. saline, gallamine (a curare-form drug causing muscle flaccidity) vs. saline, tetraethylammonium (an ANS blocker) vs. saline, and using a single external stimulus vs. no signal stimulus or multiple external stimuli vs. no signal stimulus. Only in the cases of pentobarbital administration and use of multiple stimuli could the subjects efficiently learn the discrimination, indicating that the formation of the response-controlled discrimination was not dependent on the role of external cues or changes in their nature or autonomic responses which might serve as cues. In the latter research, after differential responding had been learned between pentobarbital and saline states, subjects were blinded or subjected to wide variations in shock intensity. Such manipulations did not affect the learned discrimination, indicating that it was relatively independent of tactile

and visual stimuli. Moreover, subjects blinded prior to acquisition were able to learn the differential responses and others given a discrimination based on shock levels as cues for responding were not --- again indicating that drug effects on vision or shock sensitivity could not be responsible for the state-dependent effect.

In an attempt to discover the nature of barbiturate-induced dissociation, Bindra and his associates have conducted a series of experiments which employ a variety of tasks. In the first experiment, Bindra, Nyman and Wise (1965) tested for state-dependent dissociation in transfer from acquisition to extinction and extinction to recovery using escape and immobility responses. They found dissociative effects during extinction of the escape response and during recovery of the immobility response. Subsequent investigations (Bindra and Reichert, 1966, 1967), again using phenobarbital, demonstrated dissociative effects on an avoidance response only when the measure used was start-time latency and dissociation of an habituation response. Taken together, Bindra and his co-workers consider the foregoing results which indicate that dissociation occurs only in instances where responses must be initiated or in instances where a measure like latency is used to indicate that dissociation may consist more of an inability to transfer response initiation than of response choice.

Of the experiments on state-dependent learning carried out with tranquilizers, most have been concerned with the phenothiazine, chlorpromazine (CPZ). Results with this drug however have been equivocal, making any final conclusions impossible. Stewart (1962) has demonstrated that subjects can acquire a differential spatial escape response when the discriminative stimuli were drug-produced cues with 4, 5, or 6 mg/kg CPZ for one response and saline-produced stimuli for the other. Later, testing with other tranquilizers of the phenothiazine class indicated that administration of acepromazine (4-8 mg/kg), perphenazine (4-6 mg/kg), and prothipendyl (12 mg/kg) produced internal stimuli sufficiently similar to CPZ so as to produce transfer of the escape response.

Otis (1964) using a pole-climbing conditioned avoidance response (CAR) and 1.25 mg/kg and Lal (1969) using a shuttlebox CAR and 3 mg/kg CPZ have both obtained evidence for state-dependent dissociation. In the experiment by Otis, the dissociation decrements amounted to from 20-50 percent in the condition change from drug to non-drug. However, testing was conducted three weeks after acquisition, thereby confounding retention with state-change effects and making evaluation of the results difficult. The study by Lal on the other hand is straightforward and dissociation in this case amounts to a 6-28 percent decrement in responding. The results of both of these studies are in contrast

to the above reviewed experiments with barbiturates where response decrement estimates after state-change range from 80-90 percent to several hundred percent depending on the measure used.

Contrary to the above evidence for state-dependent learning with CPZ are a number of investigations which have failed to produce the effect. Miller (1961) has attempted to obtain state-dependent dissociation with 2 mg/kg CPZ on the conditioned suppression of a lever-press response. His results indicated that on the first day of testing after state-change (drug to non-drug) a non-significant decrement of 12 percent of animals suppressing responding occurred which was followed by performances identical or nearly identical to pre-change performance for the remaining seven test days. Grossman and Miller (1961) likewise have demonstrated that CPZ in doses of 2 mg/kg does not produce state-dependent dissociation in fear tests without shock or in fear-plus-pain tests with shock.

Other investigations with CPZ have attempted to obtain state-dependent learning while testing during response extinction. Denenberg, Ross, and Ellsworth (1959) using mice and the extinction of a shuttlebox CAR found that CPZ in doses of 1.5 and 4.5 mg/kg did not produce dissociation as evidenced by greater resistance to extinction in state-change groups. Similarly, Ader and Clink (1957) have shown

that doses of 1.5 mg/kg CPZ in rats does not produce state-dependent effects during the extinction of a shuttlebox CAR.

This occasional inability to obtain state-dependent dissociation does not always occur in experiments with other types of tranquilizers. Using the benzodiazepine, chlor-diazepoxide (CDP), Brown, Feldman, and Moore (1968) have discovered that doses of 15 mg/kg produce states sufficiently different from saline to make possible a brightness discrimination based on the cue properties of the two central states. Sachs, Weingarten and Klein (1966) have further demonstrated state-dependent learning with 15 mg/kg CDP which dissociates with changes to .25 and .5 mg/kg CPZ and to injections of amphetamine. In addition to these studies with CDP, there are reported observations of dissociation with the phenothiazine, thioridazine (Heistad and Torres, 1959) and the propanediol, meprobamate (Bloch and Silva, 1959).

Although no general theory regarding the neural requirements for the acquisition of learned responses has evolved from the many studies in the field of state-dependent learning, a number of theoretical models have been proposed to explain dissociative effects. These models may be divided into two general groups: 1) discriminative stimulus or drug-cue hypotheses and 2) central state or "chemical milieu" hypotheses.

The drug-cue hypothesis was born of those studies which required subjects to demonstrate the learning of differential responses based on the presence or absence of internal, drug-produced stimuli. In this case, the assumption is made that subjects can utilize the peripheral effects of pharmacological agents such as dilation of the pupils and changes in blood pressure and heart rate as discriminative cues. These cues are information bearing in that they "tell" the subject what response is correct for that testing session or what reinforcement contingencies are in operation.

If one considers the training procedures used for the differential responding paradigm, the drug-cue hypothesis is quite tenable. In the situation where a subject must make a right turn escape response when drugged with a barbiturate versus a left turn response when drugged with a stimulant, the only possible cues for making the correct response are autonomic, physiological stimuli. The requirement for producing the effect is that ability to make these differential responses must be specifically trained to two discriminable drug states. Thus, the drug-cue hypothesis is a by-product of the way in which the environment is experimentally structured; that is, one forces the subject perhaps to take advantage of the cue properties of drugs in order to learn the effective behaviors.

Some investigators such as Belleville (1964) and Otis (1964) have attempted to apply the drug-cue hypothesis to cases in which state-dependent dissociation occurs but in which differential responding is not required. In other words, these authors believe that the inability to transfer something like a CAR is also a result of changes in internal cues. The application of the drug-cue hypothesis in such cases is perhaps inappropriate and, since the same response is always required, seems to be born of speculation rather than experimental evidence.

In experiments where no differential responding is required, the discriminative stimuli which cue the response are external stimuli which do not change from training to testing sessions (e.g., bell or buzzer CS in signaled active avoidance). For the drug-cue hypothesis to hold then, it is essential that the states in question modify the reception or processing of external sensory stimuli (the CS or S^D) or that the theorist propose that the seemingly unimportant autonomic stimuli really do cue the response.

In opposition to this point of view, the central state or "chemical milieu" hypothesis has been proposed which considers state-dependent dissociation to be the effect of the action of drugs principally on the central as distinguished from the peripheral nervous system. The assumption is that the CNS coding of a learned response, whatever it may constitute, depends on the physiological

condition of the brain at the time at which it is laid down. Thus, any change in the central conditions will modify or disrupt the coded nervous system representation of the response and make its evocation less probable.

The nature of the "chemical milieu" hypothesis has taken two major forms to date. Bindra and Reichert (1967) propose that state-dependency is a result of the breakdown of neural connections between the sensory consequences of environmental stimuli and the motivational mechanisms of response performance. This presumably would entail disruption of the neural coding mechanisms responsible for transfer between affector and effector systems. This form of the "chemical milieu" hypothesis is proposed by Bindra and Reichert as part of a previously mentioned theory that dissociation with the barbiturates is a result of changes in response initiation and not in response choice mechanisms. Thus, it may be a fairly specific hypothesis and may only apply to the mechanism of dissociation of the barbiturate drugs.

The model proposed by Overton (1964), from whence the designation "chemical milieu" was borrowed, is a more general hypothesis and it attributes state-dependent learning to an interference with complex mediational processes which normally route and modify neural impulses in such a way that a previously learned response may be "reselected." This would mean that dissociation involves disruption of

the transfer capabilities of the brain linking sensory events to motor responses.

Attention should be directed to two important aspects of the Overton model. First, in a given neural circuit which is the central representation of an S-R connection, the theory only states that some disruption of the circuit need occur to produce dissociation. There is no requirement that the transfer of cell A to B or of cells C to D and D to E be totally abolished, for in this case the response could never be reproduced and perhaps some phenomenon such as forgetting would be more appropriate as an explanation. What the theory does require is that these transfer capabilities be in some way actively disrupted or unable to be actualized in the changed chemical state. Secondly, one should note that the model is very general with respect to the exact process affected by the state-change. Thus, the dissociation may result from disruption of sensory processing ability, attention mechanisms, associative processing, response initiation mechanisms, or any other central nervous system components which are involved in the selection of a response. The particular level at which drug effects providing for dissociation would be found would be specific to the individual drug being considered.

In order to determine if the drug-cue hypothesis is sufficient to explain state-dependent dissociation it is necessary to obtain such dissociation in a task which does

not involve differential responding and using a drug which maximizes peripheral nervous system activity alone. The present study employs the sympathetic stimulant l-epinephrine and a conditioned avoidance response. If the peripheral effects of a drug which serve as discriminative cues are important in the production of the dissociation phenomenon, then state-dependent learning should be obtained. However, if central state modification by direct drug action on the CNS is necessary for dissociation, then no dissociation should be observed with epinephrine since it does not cross the blood brain barrier to any appreciable extent (Weil-Malherbe, Axelrod, and Tomchick, 1959). In addition to the sympathetic stimulant, the present study utilizes two centrally active nervous system depressants, pentobarbital and chlorpromazine, because of their known production of dissociation and as references against which to compare the effects of l-epinephrine.

METHOD

Subjects

Sixty male rats (Holtzman strain) weighing from 350 to 400 grams throughout the experiment were used as subjects. The animals were housed in wire mesh cages, two subjects per cage, prior to the beginning of training. During training and testing, subjects were housed singly in individual wire cages. Food and water were available ad libitum throughout the entire experiment.

Apparatus

A two-compartment shuttlebox measuring approximately 62 x 25 x 17.5 mm. was used in the present study. The frame of the apparatus was constructed out of dark grey wood with the two end sides composed of wood and the back facing of brown reinforced fiberboard. The top and front panels of the shuttlebox were clear plexiglass in composition, with the grid floor being composed of .5 mm. in diameter copper rods placed approximately 2 mm. apart. The two compartments of the apparatus were separated by a 7.5 mm. high wooden hurdle on which two copper rods had been placed in order to provide shock to the hurdle and to prevent subjects from sitting on the hurdle to avoid shock.

Shock as the UCS was provided by a scrambler-shock generator which contained variable voltage controls so that the experimenter could adjust shock levels during training for individual subjects. The location of the shock was regulated by an automatically programmed microswitch apparatus which was attached to the grid floors of the compartments. The only illumination provided during the experiment was via a 25 watt cylindrical light bulb located approximately 37.5 mm. above the top of the apparatus.

Intertrial intervals as well as shock and CS durations were regulated by two Hunter Decade Interval counters (Model 111-C), while latency data was recorded automatically by a Multi-Activity Printout Counter (Layfayette Instrument Co., Model 5711). Data was recorded as time in seconds between 1) CS onset and UCS onset or between CS onset and the response, and 2) between UCS onset and the occurrence of the response.

Procedure

Subjects were randomly assigned to one of 12 groups, 5 subjects per group. The experimental design involved use of a simple switchback, transfer-of-training paradigm in which all four possible combinations of drug (D) and non-drug (ND) states were represented. This yielded a total of four groups (ND-ND, D-D, ND-D, D-ND) for each of three drugs, for a total of 12 experimental groups. Drug states were

produced by injection of chlorpromazine hydrochloride (CPZ, 2 mg/kg), sodium pentobarbital (SPe, 20 mg/kg), or 1-epinephrine (Epi, .125 mg/kg), while non-drug states were provided by injections of normal saline (0.9% NaCl) in amounts equal to those of drug volumes for each individual subject. Saline, CPZ and SPe were obtained as commercially prepared liquid injectibles and were administered intraperitoneally (i.p.) in injection volumes of .25 - .35 cc. Epi was obtained as the granular catecholamine and was suspended in peanut oil and injected into the nape of the neck sub-cutaneously in volumes of .05 - .15 cc.

The particular dosage levels for each drug were chosen on the basis of past research which has shown them to be effective in altering the course of CAR acquisition, while at the same time allowing sufficient learning to observe possible experimental effects. In addition, the dose levels were chosen because of their demonstrated ability to produce dissociation to some extent. In the case of epinephrine, subjects were tested 1.5 hours after injection while for CPZ and SPe testing was conducted 45 minutes after injection of the drug. In the latter case, it was necessary to wait for the animal to recover sufficiently from the ataxic motor effects of the drug before any training or testing was initiated. This took from 30 to 45 minutes depending on the particular subjects. When saline injections were given, the delay between injection and training or

testing was the same as that on drug days for the particular subject.

Phase I (training) for all subjects consisted of six daily sessions, 20 trials per day, one session per day, on consecutive days. A trial was defined as either a single avoidance or escape response and consisted of CS (damped house buzzer) presentation for 7 seconds, followed by UCS (.6 mA foot shock) with the CS terminating prior to UCS onset in all cases. If the response was made prior to UCS onset, the CS was terminated and the UCS eliminated for that trial. The intertrial interval was 15 seconds in length and responses during this interval were neither effective in delaying onset of the next CS presentation nor were they punished.

In Phase II (testing), subjects were given a chance to perform the CAR under the same procedures described above for Phase I, except that appropriate-change or no state-change were now in operation. The test phase consisted of 20 trials per session, for two sessions on two consecutive days, one session per day. Thus, for subjects performing under conditions identical to those of training (no state-change groups) or for subjects not demonstrating the dissociation effect, Phase II should serve as additional training time. On the other hand, for subjects in state-change groups demonstrating state-dependent dissociation in

testing, Phase II performance should decrease and testing phases should act as a period of "reacquisition."

The data from both training and testing phases were collected in a number of ways, the following two measures being used: percentage of avoidance responses in each 20 trial session and the latency of responding in each session.

RESULTS

Figures 1 and 2 show a clear difference in avoidance acquisition between experimental groups and over periods of acquisition for percentage CAR and latency data respectively. Since the thirty saline-injected subjects were run in groups of ten and since there were no differences between the acquisition performance of these groups of subjects, only the first ten saline subjects were included in analyses of acquisition performance. Analyses of variance (4 groups x 6 days of training, mixed design) revealed a significant effect of days of acquisition, groups, and the interaction using both response measures.

Using percentage CAR as a measure, group differences were found to be significant ($F = 13.39$, $df = 3, 16$, $p < .001$) as were the days effect ($F = 110.08$, $df = 5, 180$, $p < .001$) and their interaction ($F = 1.94$, $df = 5, 180$, $p < .025$). For both main effects, multiple t-tests were performed. In the case of group effects, these tests revealed that the CPZ group differed significantly from both saline and Epi groups ($p < .025$ for each), with the comparison between CPZ and SPe groups barely missing statistical significance at the .05 level. The saline, SPe and Epi groups did not differ among themselves. Post-hoc testing with the trials effect revealed significant differences between days

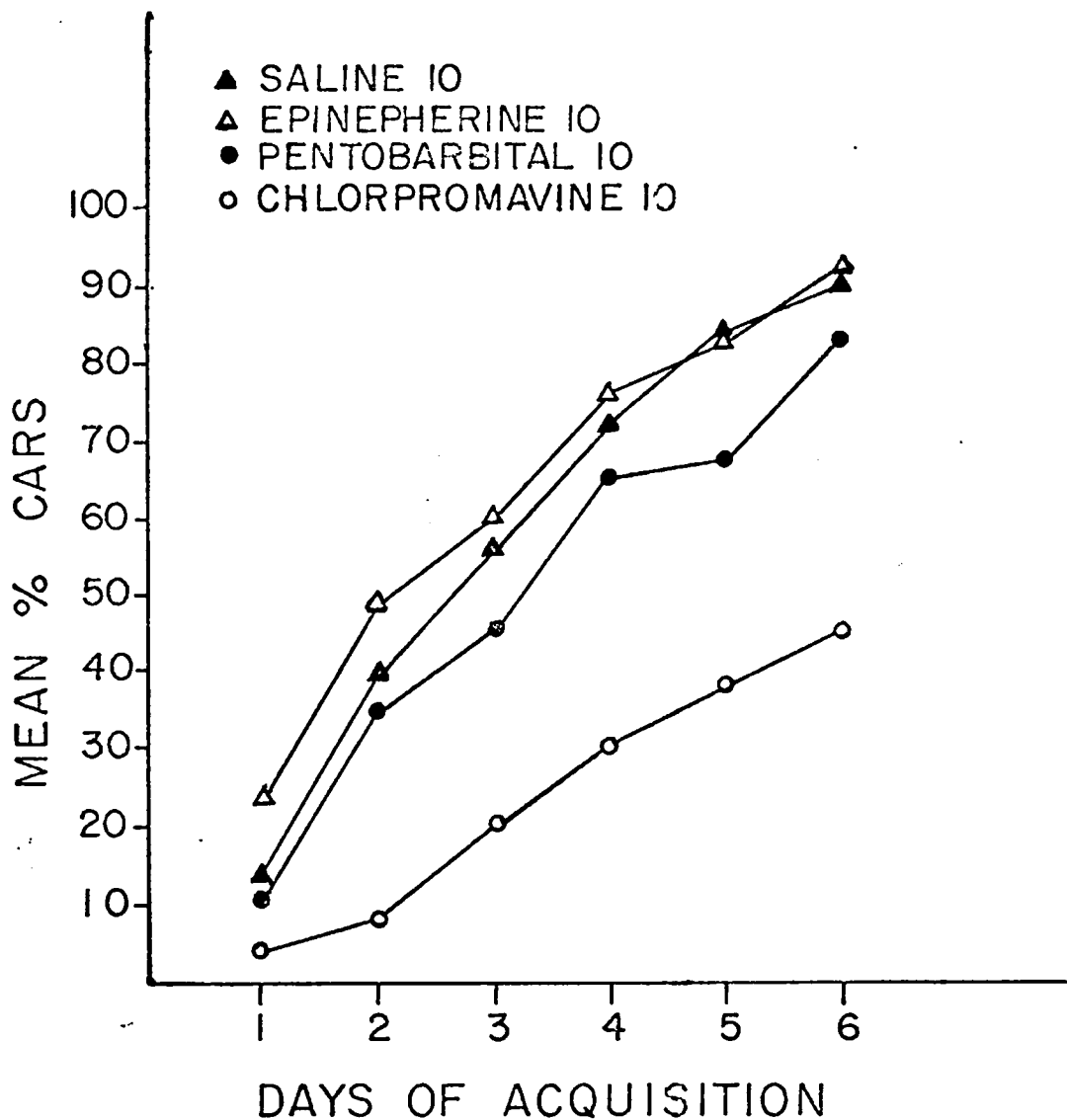


Figure 1. Acquisition curves for drug and saline control subjects showing the relatively poorer performance of CPZ subjects and the slightly better performance for epinephrine subjects. -- Note: numbers in the legend refer to number of subjects on which the acquisition curves are based for each group.

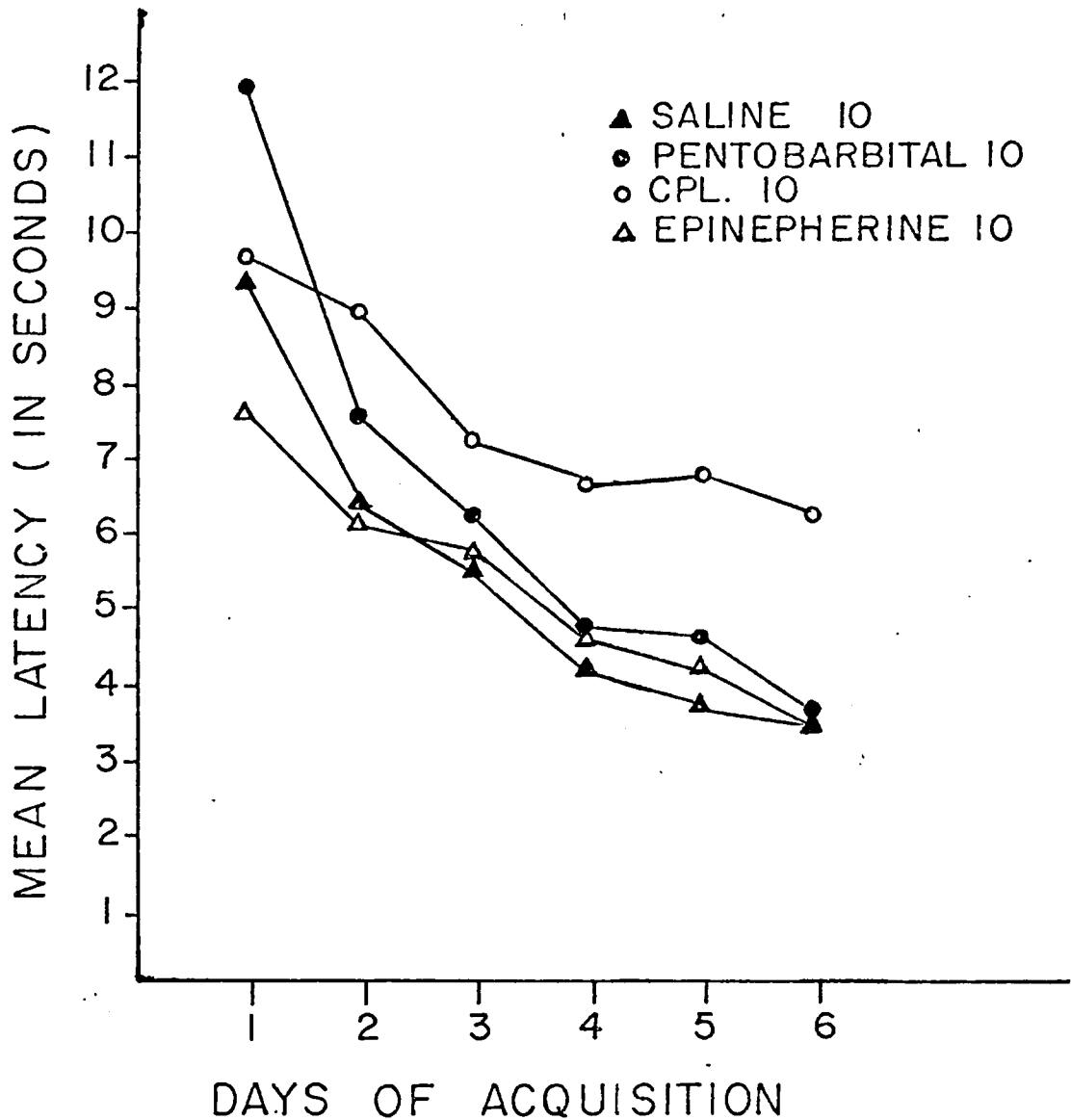


Figure 2. Acquisition curves for drug and saline control subjects showing the relative decrement in performance for CPZ subjects and close correspondence in scores for the other groups. -- Note: numbers in the legend refer to number of subjects on which the acquisition curves are based for each group.

1 and 2 ($p < .005$), 2 and 3 ($p < .05$) and 3 and 4 ($p < .01$) only. The interaction effect was analyzed by use of the Cochran and Cox test with comparisons being made between each drug group and saline controls at each day of acquisition. These tests revealed no differences between SPe or Epi groups when compared with controls at any of the acquisition days. However, differences were observed between CPZ subjects and controls of days 2 (mean of 8 and 39.5% respectively) and 3 (20% and 56% respectively) with $p < .05$ and on days 4 (29.5% and 73%), 5 (37.5% and 84%) and 6 (44.5% and 90%) with $p < .01$.

The results presented above for percentage CAR data are almost exactly paralleled by the latency data. As above, analysis of variance revealed a significant groups effect ($F = 6.62$, $df = 3, 36$, $p < .005$), days effect ($F = 103.64$, $df = 5, 180$, $p < .001$) and the interaction ($F = 7.88$, $df = 5, 180$, $p < .001$). T-tests demonstrated that CPZ group differed significantly from saline and Epi groups ($p < .05$ for each) but not when compared to SPe subjects. As above, SPe, Epi, and saline subjects did not differ among themselves. Analysis of the days effect showed significant improvement between days 1 and 2 ($p < .005$) and days 2 and 3 and 3 and 4 ($p < .05$ for each) only. Interactions were again analyzed by comparing each drug group to controls at each day of acquisition. No differences were obtained between Epi and saline controls or between SPe and control subjects on days

2 through 6; however, SPE subjects were significantly higher than controls on day 1 (means are 11.86 and 9.28 seconds respectively; $p < .05$). Comparisons between CPZ and saline subjects demonstrated significantly lower latencies for controls only on days 2 (8.89 and 6.35 seconds respectively), 5 (6.70 and 3.70 seconds) and 6 (6.20 and 3.41 seconds) with $p < .05$ for each.

The state-dependent learning effect is assessed by using a 2 x 2 analysis of variance (drug or non-drug in training vs. state-change or no-state-change in testing) with significant effects on the latter factor suggesting dissociation. In order to conclusively demonstrate state-dependency, post-hoc comparisons should be made between ND-D and D-ND groups and their respective controls (ND-ND and D-D respectively). This should reveal to what extent the state-dependent effect relies on the contribution of each state-change group. For example, post-hoc tests may reveal the change to ND in testing does not depress performance below that of subjects trained and tested with D. Thus, the change ND-D must be contributing the majority of the effect. In this case, the result may be interpreted as a simple drug effect. However, it may be revealed that change from ND to D does not depress performance below that of subjects trained and tested with ND. Thus, the change D-ND must be contributing maximally to the dissociation effect. This has been termed "asymmetrical" dissociation, the

significance of which is not clear (Overton, 1971a). In the present study, this type of analysis was carried out singly for each of the drugs and on each day of testing and is presented below in that manner.

Figure 3 depicts the behavior of SPe subjects and shows that on state-change days groups ND-D and D-ND show large decrements in responding (indicating dissociation), while groups D-D and ND-ND both show small increments in responding. Tables 1 and 2 yield further evidence by showing the amount of response decrements for each individual subject in the two state-change groups, there being an 82 percent average decrease in the ND-D group and a 48 percent average decrease in the D-ND group for day one of testing. Analysis of variance of the data showing percentage CAR on day one indicates significant state-change effects ($F = 47.38$, $df = 1, 16$, $p < .001$) and post-hoc testing indicates that both state-change conditions contribute to the overall effects (D-ND vs. D-D comparison significant with $p < .01$ and ND-D vs. ND-ND comparison with $p < .001$). Analysis of day one latency data indicates a significant state-change effect ($F = 33.23$, $df = 1, 16$, $p < .001$) and post-hoc comparisons indicate again that both conditions contribute to the dissociative effect.

With inspection of Figure 3, one may note that in both the ND-D and D-ND groups, there is improvement in performance on the second day of testing. In these cases,

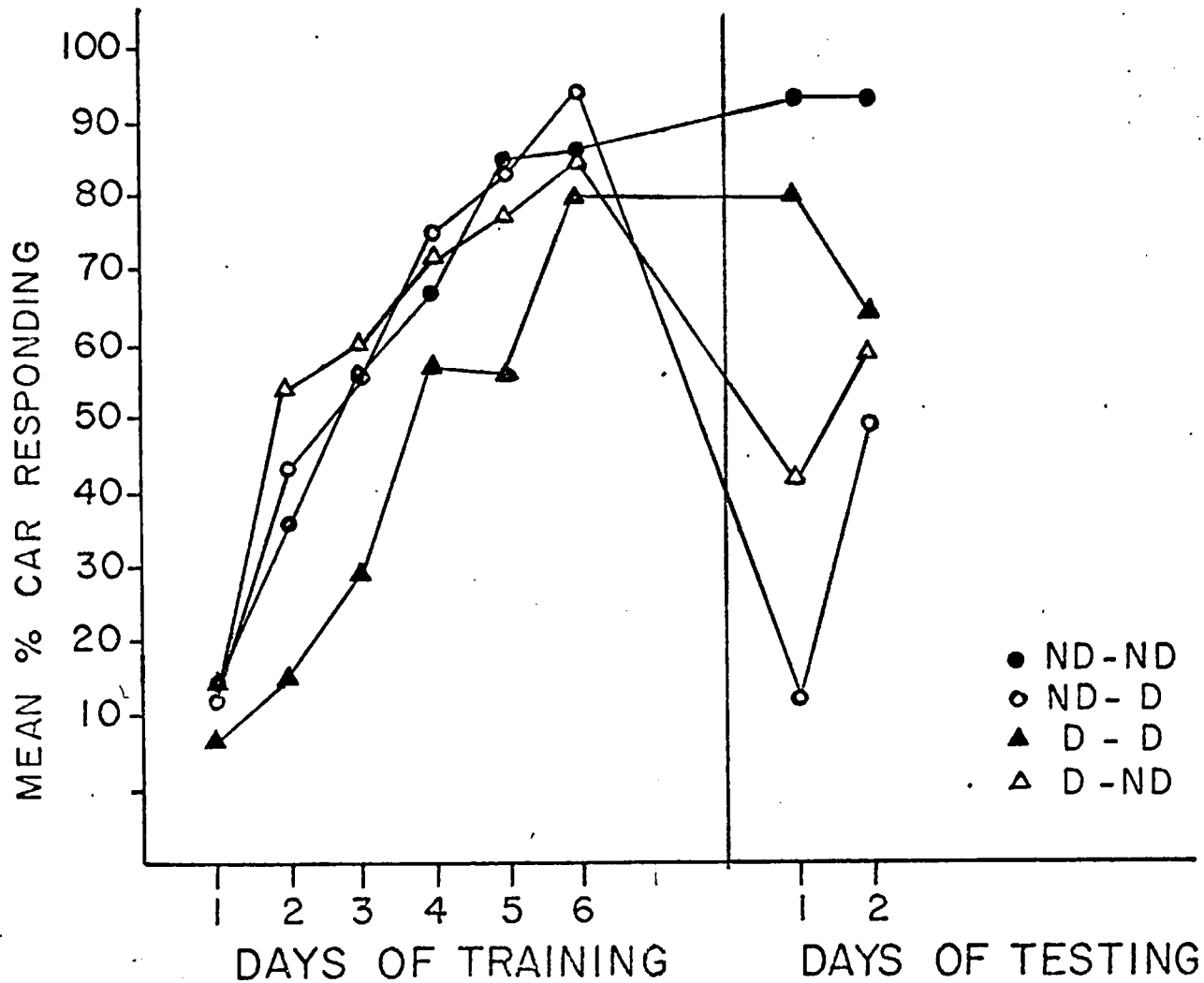


Figure 3. Responding of pentobarbital subjects in each of the four conditions is depicted for acquisition and testing phases. -- Note especially the decrements in responding in the state change groups in the first testing session and the large improvements for the second test session in those same groups.

average percentage decrements are reduced to 45 percent for the ND-D group and 24 percent in the D-ND group; that is, almost a 50 percent reduction in both cases. Analysis of variance using percentage CAR data for day two demonstrates no significant differences for the state-change effect ($F = 3.13$, $df = 1, 16$, $p < .10$), nor is the analysis of latency data indicative of state-change effects ($F = 4.03$, $df = 1, 16$, $p < .10$). The lack of statistical significance is probably due to the decrements on day two of testing in the D-D group which made comparisons between state-change and no change groups smaller.

Figure 4 presents the data for all CPZ-treated groups in the experiment using percentage CAR data, demonstrating rather large differences in the rate and final performance level between CPZ and saline subjects and that no state-change groups show little change in responding, while both state-change groups demonstrate decrements. Inspection of Tables 1 and 2 indicates that this dissociative effect amounts to an average percentage change of 37 percent in the ND-D group and an 11 percent change in the D-ND group. Analysis of variance shows a significant state-change effect for the percentage CAR data ($F = 7.93$, $df = 1, 16$, $p < .025$) as well as for the day one latency data ($F = 9.98$, $df = 1, 16$, $p < .01$). In both cases, however, post-hoc tests indicate that the ND-ND vs. ND-D comparisons are significant ($p < .01$) whereas the D-D vs. D-ND comparisons are

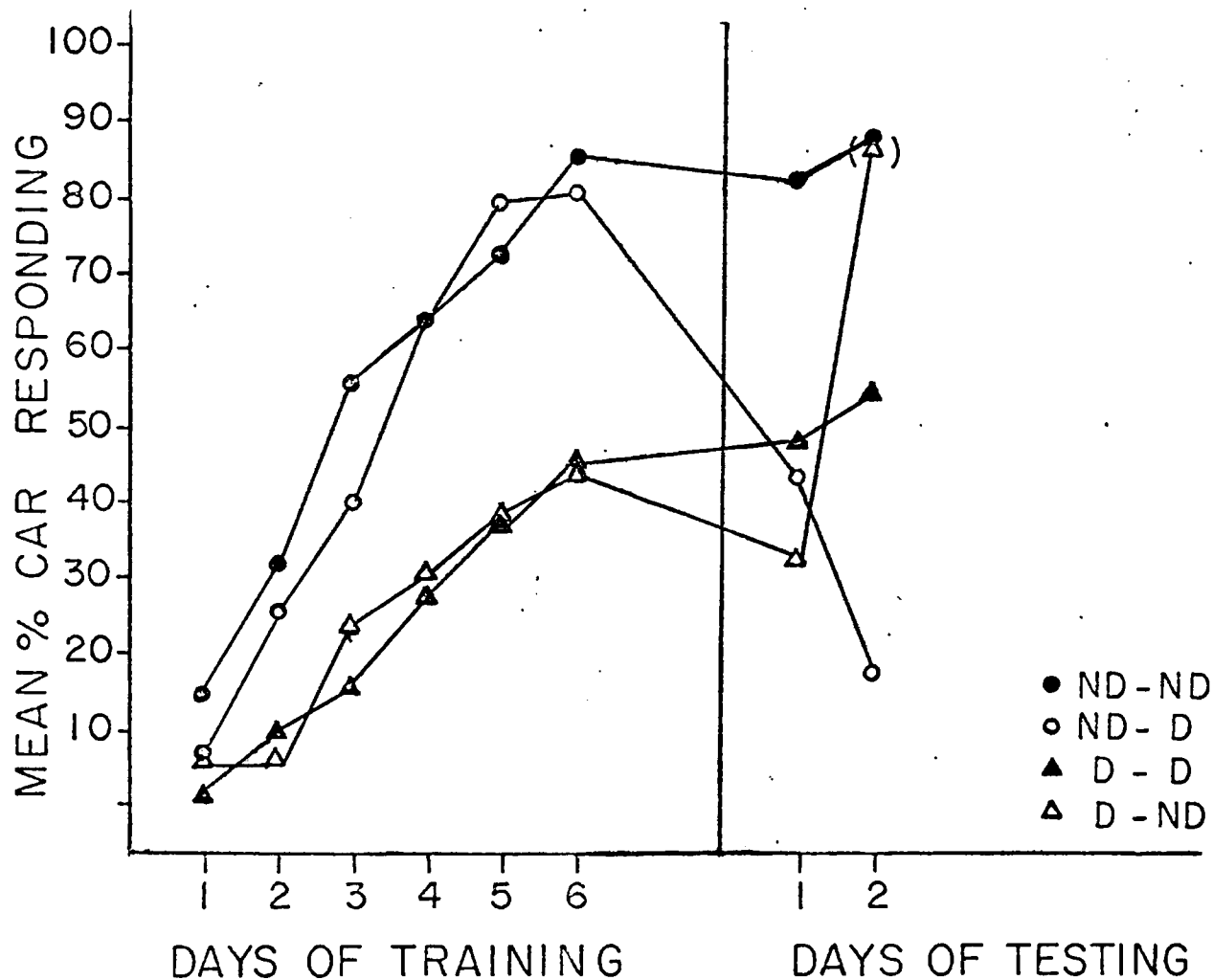


Figure 4. Responding of chlorpromazine subjects in each of the four conditions is depicted for acquisition and testing phases. -- Note especially the decrements in responding in state change groups in test session one (large in the ND-D group and rather small in the D-ND group) and the differential performance in these two groups in the second test session.

not. Thus, the majority of the state-dependent effect is due to the dissociation of the ND-D group and may reflect for the most part a simple drug effect.

Inspection of Figure 4 indicates that on day two of testing while no state-change groups continue to improve, the ND-D group shows increasingly greater decrements whereas the D-ND group shows a dramatic increase in performance. Tables 1 and 2 indicate that the decrement in the ND-D group is 63 percent (26 percent greater than on day 1) and the increment in the D-ND group is 44 percent above that of maximal responding in that group during acquisition. Analyses of variance demonstrate significant state-change effects for both percentage CAR data ($F = 10.74$, $df = 1, 16$, $p < .005$) and latency data ($F = 21.05$, $df = 1, 16$, $p < .001$); however, once again, post-hoc testing indicates that the D-D vs. D-ND comparison is not significant in both cases. Therefore, the state-change represented by the ND-D group is most influential in producing the statistical result.

As can be seen from Figure 5, there is little difference between state-change and no state-change groups on either day of testing. Tables 1 and 2 indicate that with percentage CAR data the ND-D group had 3 percent and 0 percent average decrements on days 1 and 2 of testing while the D-ND group had 6 percent and 3 percent average decrements on testing days. Analyses of variance using CAR and

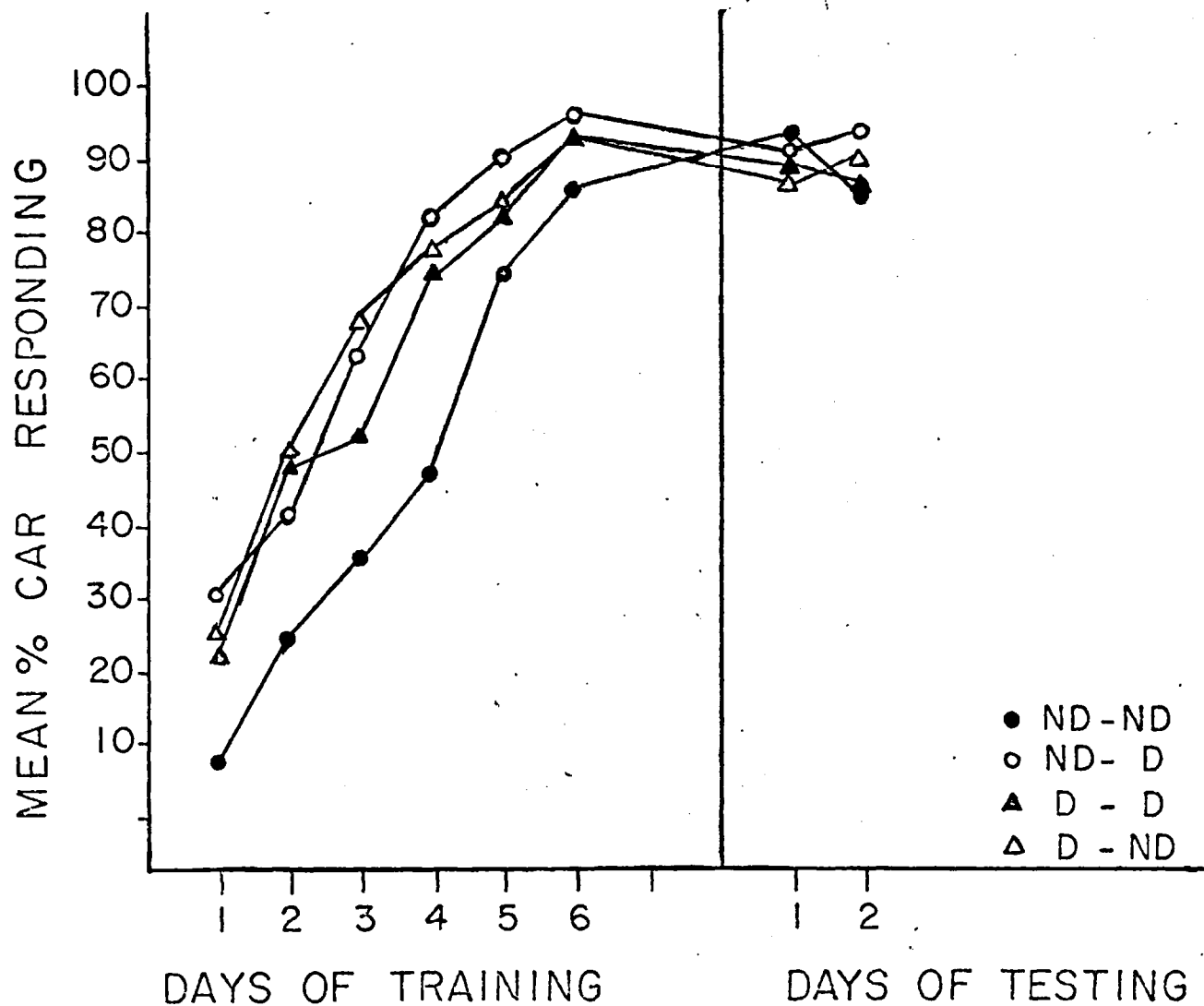


Figure 5. Responding of epinephrine subjects in each of the four conditions is depicted for acquisition and testing phases. -- Note the lack of differences in testing between state change and no state change groups.

TABLE 1

Percentage CAR change in drug grouped subjects in state change from drug to non-drug (D-ND) -- Minus sign indicates decrements and plus sign increments in responding.

| Ss | GROUPS | | | | | |
|------|----------------------|-------|-----------------------|-------|---------------------|-------|
| | <u>Pentobarbital</u> | | <u>Chlorpromazine</u> | | <u>Epinepherine</u> | |
| | Day 1 | Day 2 | Day 1 | Day 2 | Day 1 | Day 2 |
| 1 | -45 | -40 | -10 | +70 | 0 | +5 |
| 2 | -85 | -5 | -20 | +15 | -5 | -5 |
| 3 | 0 | +5 | -30 | +45 | -10 | -5 |
| 4 | -50 | -35 | -5 | +45 | 0 | +5 |
| 5 | -60 | -45 | +10 | +45 | -15 | -15 |
| AVE. | -48 | -24 | -11 | +44 | -6 | -3 |

TABLE 2

Percentage CAR change in drug grouped subjects in state change from non-drug to drug (ND-D) -- Minus sign indicates decrements and plus sign increments in responding.

| Ss | GROUPS | | | | | |
|------|----------------------|-------|-----------------------|-------|---------------------|-------|
| | <u>Pentobarbital</u> | | <u>Chlorpromazine</u> | | <u>Epinepherine</u> | |
| | Day 1 | Day 2 | Day 1 | Day 2 | Day 1 | Day 2 |
| 1 | -95 | -10 | -95 | -90 | -15 | 0 |
| 2 | -70 | -70 | -30 | -40 | 0 | 0 |
| 3 | -85 | -90 | +5 | -35 | 0 | -5 |
| 4 | -95 | -45 | -5 | -55 | -10 | 0 |
| 5 | -65 | -10 | -60 | -95 | +10 | +5 |
| AVE. | -82 | -45 | -37 | -63 | -3 | 0 |

latency data for both days failed to evidence any significant effects. Thus, no state-dependent dissociation could be obtained with the use of the ANS stimulant.

DISCUSSION

As previously mentioned, state-dependent learning procedures allow one to assess both simple drug effects and state-change effects. In this section, results will be discussed in terms of the following categories: 1) the effects of drugs on avoidance acquisition and 2) state-dependent effects.

Figures 1 and 2 show the effects of SPe on the course of avoidance acquisition using two different response measures as being small and, as indicated in the Results section, as being not significantly different from acquisition in saline-injected groups. The inability of SPe to disrupt or cause decrements in avoidance acquisition has been shown in the past by Iwasaki, Iwahara, and Nomura (1966) using both a pole-climbing and classic shuttlebox avoidance response. These authors used a 19 mg/kg dose of SPe and reported the following effects, both of which are directly comparable to those of the present study: 1) there is no significant differences in latencies between SPe and control subjects, except on day one of acquisition, and 2) no differences were obtained when a response measure like number of CARs was used.

With a related barbiturate, amobarbital, it has been shown that CAR acquisition is facilitated while activity is increased (Powell, Martin and Kamano, 1965) and the incidence of competing responses and other emotionally-related behaviors reduced (Kamano, Martin and Powell, 1966). It was thus originally believed that barbiturates facilitate avoidance acquisition by preventing the development of antagonistic responses, presumably as a result of fear reduction and consequent increase in activity. In a more recent experiment, Martin, Kamano and Powell (1967) observed that avoidance was facilitated in drugged subjects, but without activity differences either before or after CS presentation. Because escape latencies were longer in drugged subjects at the beginning of training, these authors now suggest that avoidance is facilitated because drugged subjects receive more punishment (i.e., shock) for the ongoing competing response than do those subjects with shorter latencies. Thus, competing responses should be eliminated more rapidly in drugged subjects and acquisition accordingly facilitated.

In the present study, qualitative observations did not reveal any differences between activity levels of SPE and control subjects. Likewise, SPE neither facilitated acquisition of the response nor produced decrements in escape latencies. It is possible that facilitation only occurs in circumstances where differential punishment for

competing responses occurs, just as Powell, Martin, and Kamano (1965) suggest.

The acquisition rates for CPZ subjects are shown in Figures 1 and 2 and are significantly depressed when compared to performances of control subjects. A very large body of literature has accumulated regarding the effects of CPZ on aversively-motivated behavior and these data show relatively good agreement for the range of effective dosages despite differences in strains of subjects, techniques, environmental parameters, type of task and amount and route of drug administration. Chipman (1966), for example, using a 2 mg/kg dose of CPZ has shown that there is a decrease in the mean number of CARs during acquisition in drugged subjects and that increasing CS intensity decreases the drug's effects (although never to a level comparable to that of controls). Similarly, McMurray and Jacques (1959) have demonstrated that a dose as small as 1 mg/kg CPZ significantly reduces the percentage of avoidance responses and increases the median time of those that were made. Their subjects responded effectively to shock itself and escape responses were preserved, indicating that motor effects were not critical factors in producing the results.

Perhaps the most popular explanatory hypothesis of the decrements in avoidance with CPZ has been the one which focuses on the motivational effects of the drug. It is often observed that CPZ-treated subjects respond less

readily to the presumably aversive CS and display many new types of competing responses (e.g., immobility) even with non-ataxic doses. For example, Posluns (1962) noted that doses of CPZ that impaired the CAR did so by delaying the initiation of each component of the motor response. Likewise, Bindra (1962) found that 1 to 4 mg/kg CPZ increased inertia, or the inability of subjects to change from one activity to another in a lever-press response. Indeed, in the present study, CPZ-subjects were often observed to make fragmentary responses to the CS which fell short of the hurdle-crossing response required of the task. In such cases, they did not attempt to complete the response even when an appreciable amount of the CS-UCS interval remained. However, when shock did begin, subjects escaped quickly and effectively. Therefore, it seems as if CPZ-treated subjects were indeed learning aspects of the task, but could not complete the task requirements in response to other than primary motivators.

Data presented in Figure 1 show that the rate of acquisition of a CAR is greater in subjects given Epi than any other group, including saline controls. In the present study, however, this facilitative effect was not found to be statistically significant and this because of large between-subject variability. Previous research which has attempted to explicate the role of sympathetic release of adrenal catecholamines has yielded contradictory results.

Some authors have reported either facilitation or depression of response rates after Epi administration (Stewart and Brookshire, 1967; Sines, 1959) while others report no effects at all (Moyer and Brunnel, 1958; Sieling and Benson, 1959). In an excellent study, Latane and Schacter (1962) have reported that weak adrenalin solutions (.125 mg/kg) do facilitate avoidance acquisition when measures such as the percent of subjects reaching criterion and total number of CARs are used. These authors consider such effects to be independent of changes in activity levels and believe the drug effect to be a result of increased emotional reactivity to environmental stimuli. The reasons for the inconsistent results are as yet unclear; however, factors such as dosage, procedural variations, and phase during which drug is administered are likely candidates.

The major finding of the present study is that state-dependent learning is produced in varying degrees by centrally active drugs and that there is a lack of dissociation with the non-centrally active sympathetic stimulant, epinephrine. As previously discussed, pentobarbital produced relatively large performance decrements in both state-change conditions and on both days of testing. On day one of testing with chlorpromazine, state-dependent learning was also evidenced to some extent, amounting in the D-ND condition to an 11 percent average decrement. With epinephrine, no changes in performance as a result of

state-change was observed and thus the non-centrally active agent was incapable of inducing dissociation.

These results would argue for a "central milieu" hypothesis wherein modification of the central nervous system is considered to underlie the state-dependent effect. According to this view, drugs, such as epinephrine, which do not cross the blood brain barrier to any appreciable extent (Weil-Malherbe et al. 1959) and do not therefore have direct central activity, are incapable of producing dissociation. The discriminative cue hypothesis would lead one to believe that any internally-produced changes can be monitored by an organism and utilized during acquisition and performance of a task. However, in the present experiment, epinephrine, despite its internally-produced effects which include piloerection, increased cardiac output, changes in the tone and movement of smooth muscle, etc., did not produce the state-dependent effect. It would therefore seem that such internally-produced cues are not sufficient in specifying the response to be emitted.

Furthermore, this inability to produce dissociation does not seem to be a result of either epinephrine itself characteristically or of the dosage used in the present experiment. Cook et al. (1960) have reported that subjects can be successfully reflex conditioned when the CS was internal, peripheral stimuli produced by l-epinephrine (10 mcg/kg, i.v.), l-norepinephrine (10 mcg/kg, i.v.),

acetylcholine (20 mcg/kg, i.v.), and jejunal loop pressure (10 cm-Hg). Thus, epinephrine and other peripherally-active drugs can produce state-dependent-like effects, but only in cases where the physiological stimuli they produce are maximized for learning and are the only cues available to the subject for determining what response is necessary.

In order to rule out the possibility that pentobarbital-induced state-dependent effects are mediated by changes in muscle flaccidity or by the ANS effects of the drug, Overton (1964) attempted to obtain response control with gallamine (a skeletal muscle relaxant) and tetraethylammonium (an ANS blocking agent). In neither case could adequate response control be obtained, again a result in support of the "chemical milieu" hypothesis. Moreover, manipulations of shock levels or the visual capacity of his subjects did not affect the state-dependent response control seen with the barbiturates, thus arguing that changes in sensory reception were not involved in the state-dependent effect (Overton, 1968).

Moreover, as Overton (1971a, -b) points out, only anti-muscarinic and anti-nicotinic drugs which have both central and peripheral activity are associated with the acquisition of response control, whereas those with only peripheral effects are not associated with response control to any appreciable extent. Thus, drugs like atropine methyl nitrate (a postganglionic parasympathetic blocker)

and phenoxybenzamine (an alpha-adrenergic blocker) did not readily produce response control. All this does not mean to say that internally-produced, peripheral cues can never provide for response control, only that in tasks not maximizing the utilization of these effects, peripheral cues are relatively unimportant. For cases not involving explicit differential cue responding, the neural basis of stored, learned responses must be modified and this requires a pharmacological agent with direct CNS activity.

The models variously proposed by Overton (1964, 1966) consider state-dependent learning to occur because of state-change-induced alterations in the transfer capabilities of neurons. Presumably, the circuits in which such state-change-affected cells participate are rendered less likely to function in the changed state and consequent variations in behavior result. What has yet to be considered in the state-dependent literature is the particular effects drugs can have on nervous system structures (e.g., reticular formation) and individual components (i.e., neurons) which could reasonably produce such state-dependent transfer capabilities. Moreover, what is necessary is a more precise description of the operations which produce "response characteristic circuits" which can function only under particular types of conditions of the brain.

It is axiomatic among neurophysiologists that the nervous system works via a pulse coded system in which

participants in some neural circuit are involved as a result of their response characteristics. Pfaff (1969) has proposed that such neural coding is based on changes in the probabilities of firing of a set of neurons which results from consistent use of the circuit being established. These changes, he points out, need not be specific macromolecular alterations (as proposed by RNA-DNA theorists), but instead may result from any number of changes associated with metabolic alterations such as the supplying of neurons with metabolic substrates, synthesis of transmitter substances, and so forth. For the pulse-coded system, this might involve changes in membrane events which affect the electrical characteristics of the cells in a circuit and would include such properties as ion conductance, action potential threshold, and response of the transmitter-dependent biomolecular membrane.

In addition, in a system as complex as the brain, one should not expect these individual circuits representing learned responses to function in a vacuum. The activity of these circuits should be dependent on converging systems such as the ascending reticular system (ARAS) which provides for degrees of arousal and reactivity of the nervous system, the limbic system which would provide affective aspects of responding, and those systems of an inhibitory nature which actively delimit responses antagonistic to that represented by the circuit in question. Thus, in delineating the basis

of drug-produced disruption, one must consider two things: 1) what system is affected by the drug (ARAS, limbic, etc.) and 2) which neuronal changes are involved (ion conductance, transmitter events, etc.).

This viewpoint of neural organization has great importance for the understanding of state-dependent learning. What it contends is that responses are learned and coded under specific conditions found in the nervous system; modification of that coded circuit by some physiological manipulation, such as drug administration, will in some way disrupt the integrity of the circuit. The extent to which such disruption occurs will determine the extent of the changes observed in behavior. Regardless of the specific mechanism responsible for response coding, what is true is that all constituents of the circuit in question must be within some normal limits of functioning before the coded response can be reproduced. Thus, if CNS conditions with no drug are sufficiently different from those conditions when the response was originally coded under the influence of the drug, then state-dependent dissociation should be obtained. However, if states are not sufficiently different, then responses would not be differentially coded by the nervous system and no dissociation should be obtained.

That the centrally active drugs utilized in the present study and in other state-dependent learning researches have effects on neural systems and on cellular

events as proposed by the "differential coding" hypothesis has been demonstrated by electrophysiological, biochemical and pharmacological investigations (Root and Hofmann, 1965). However, the "differential coding" model does not require that state-dependent learning be considered a result of CNS states caused only by administration of pharmacological agents. Indeed, it should be true that any physiological manipulation which affects the chemical and electrical properties of neural circuits is capable of producing state-dependent dissociation. In support of this expectation, Sachs (1961, 1962) has demonstrated dissociation of a CAR under conditions of altered central excitability (produced by raising the K^+ or Ca^{++} concentrations of cerebrospinal fluid) and Bures has recently been reported to consider the spreading depression effect to be an example of state-dependent learning (Pribram, 1968).

In perhaps the most dramatic example of dissociation with spreading depression, Bures and Buresova (1960) showed that application of KCl to the cortical surface after acquisition of avoidance or approach responses caused large decrements in responding, with recovery not occurring until drug effects had dissipated. Next, rats were trained to make a simple spatial discrimination and then given reversal training 24 hours later with unilateral spreading depression. Animals tested with no spreading depression or with the contralateral hemisphere depressed responded as if

no reversal training had been given, whereas subjects tested with spreading depression of the previously depressed hemisphere responded in accordance with reversal training.

Although the mechanism of action of spreading depression effects are not entirely clear, it is generally considered to be a result of changes in potassium transfer of cortical neurons (Grafstein, 1956) such that liberation of relatively large quantities of potassium depolarizes neighboring neurons as part of a chain reaction. Thus, the above data, at least in part, do indicate the possibility of producing state-dependent dissociation by providing for changes in ionic events during testing phases.

In summary, the present experiment has provided evidence that state-dependent learning was produced only by centrally active drugs when a task was used which does not require differential responding. On the basis of such findings, a model of neural coding is proposed which asserts that responses coded by the CNS are specific to the conditions prevailing during the encoding process. Furthermore, it has been pointed out that drugs have both neurophysiological and biochemical effects which are consistent with this model and that other areas and types of research support a "differential response coding" viewpoint.

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