THE EFFECTS OF DIPHENYLHYDANTOIN ON
MAZE PERFORMANCE

APPROVED:

Earl W. Hooker
Major Professor

Minor Professor

Dean of the School of Education

Dean of the Graduate School
THE EFFECTS OF DIPHENYLHYDANTOIN ON
MAZE PERFORMANCE

THESIS

Presented to the Graduate Council of the
North Texas State University in Partial
Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

Harold Kenneth Dudley, Jr., B. S.
Denton, Texas
June, 1968
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF ILLUSTRATIONS</td>
<td>v</td>
</tr>
<tr>
<td>Chapter</td>
<td></td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>II. METHOD</td>
<td>22</td>
</tr>
<tr>
<td>Subjects</td>
<td></td>
</tr>
<tr>
<td>Apparatus</td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
</tr>
<tr>
<td>III. RESULTS</td>
<td>28</td>
</tr>
<tr>
<td>IV. DISCUSSION</td>
<td>32</td>
</tr>
<tr>
<td>V. SUMMARY AND RECOMMENDATIONS</td>
<td>37</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
</tr>
<tr>
<td>Recommendations</td>
<td></td>
</tr>
<tr>
<td>APPENDIX I</td>
<td>40</td>
</tr>
<tr>
<td>APPENDIX II</td>
<td>41</td>
</tr>
<tr>
<td>APPENDIX III</td>
<td>43</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>44</td>
</tr>
</tbody>
</table>
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>28</td>
</tr>
<tr>
<td>II.</td>
<td>30</td>
</tr>
<tr>
<td>III.</td>
<td>31</td>
</tr>
<tr>
<td>IV.</td>
<td>41</td>
</tr>
<tr>
<td>V.</td>
<td>43</td>
</tr>
</tbody>
</table>

I. Amount of Drug Given to Each Subject in the Experimental Group

II. Results of $t$ Test on Time Scores for Two Randomized Groups

III. Results of $t$ Test on Error Scores for Two Randomized Groups

IV. Computation of $t$ for Error Scores of Two-Randomized-Group Design

V. Computation of $t$ on Time Scores for Two Randomized Groups
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mean Running Times of All Subjects on Each Trial During the Training Trials</td>
<td>29</td>
</tr>
</tbody>
</table>
CHAPTER I

INTRODUCTION

Life would be simple indeed if people's needs were immediately and automatically satisfied. There are many obstacles, both environmental and internal, which interfere with need gratification and complicate efforts to maintain one's self and to become self-actualizing. These obstacles place stress on the organism. They require extra effort and a change in ongoing activity if the organism is to cope with them and meet its needs. When the stress is excessive, it overtaxes an organism's resources and leads to a breakdown of integrated functioning. The factors usually crucial in determining the severity of stress are the individual's evaluation of the stress and the individual's resources for withstanding the stress. Coleman has stated that "... an individual always reacts not simply to the situations, but to the situations as he evaluates it—especially in relation to his feelings about his own ability to cope with it" (6, p. 39).

Stress and its effects on behavior is a subject of which both clinicians and experimentalists have become increasingly
aware within the last two or three decades. In human beings it has been observed mainly under naturally occurring conditions, as reported by Davis (10) and Archibald (1) on psychiatric war casualties. Bowlby (3) has found that prolonged separation from the mother, in the case of infants, has marked pathological effects on development. In animals, stress has been studied chiefly in the laboratory, where a variety of techniques have been evolved to disrupt existing adaptation patterns and to replace these by certain forms of non-adjustive behavior. Probably the fullest and most systematic set of data derives from those studies which have been grouped together under the title of experimental neurosis. In such studies as those discussed by Liddell (26), the animal is faced with a problem situation in which he is forced to act, but for which his adjustive capacities are limited. This produces stress.

A stressful situation may be regarded as essentially one in which a major disruption of the relationship between an organism and its environment has taken place. Under non-stressful conditions this relationship tends to be relatively harmonious; the environment, on the one hand, will gratify the needs and expectations of the individual, while the organism, on the other, can adequately meet the demands made
upon it by external stimulation. The relationship will suffer some disruption when the organism meets a novel situation for which it has no adjustive response readily available and in which it cannot find such a response until a period of trial-and-error behavior has taken place. Even in such circumstances, the disruption will generally be a minor one and adjustment will eventually occur. It is only when the difficulty of the task confronting the organism is so increased as to approach a no-solution situation that one may speak of a stress situation.

The relation between the complexity of a problem and the capacities of the individual to solve it is only one factor defining the organism-environment relationship. Another is the degree of motivation which impels the organism to face the problem, and which thus restrains it within the situation. Only when a drive has been activated can a psychological relationship between the individual and his environment be talked about, and only when this drive is sufficiently strong to persist is it possible for a major disruption in this relationship to occur. Thus, as Lazarus, Deese, and Osler (25) have pointed out, stress cannot be defined in terms of the environment alone; the motives and capacities of the organism and their interaction with the environment must also be taken
into account. Fuller's (15) definition of a stressful situation, as one in which adjustment is difficult or impossible, but which motivation is very strong, satisfactorily complies with this demand. Disruption of the organism-environment relationship can be brought about in several ways: Traumatic situations, frustrations, and conflict situations.

Schaffer (33) has indicated that the behavioral symptoms which emerge under stress refer, first, to changes in general activity and, second, to changes in the learning process. Changes in general activity can be classified under two dimensions of behavior: the rate and the range of activity. The former refers to the excitatory-inhibitory classification which Pavlov (30) proposed and which entails the shift of activity toward either one of the two extremes of this dimension when stress is applied. In the excitatory type, which tends to be more common, behavior is greatly speeded up and disorganized, and the fine adjustment of reaction to stimuli found under normal circumstances is lost. As Duffy (12) has stated, action needs to be inhibited until relevant factors in a problem situation have been taken into account. In the inhibitory type, on the other hand, disorganization of behavior assumes a different form, for here the shift of activity is toward the other extreme.
Numerous physical changes take place under these forms of stress. Strong unexpected stimuli, injuries, and situations evaluated as threatening lead to marked physiological changes designated by Cannon (5) as emergency emotional reaction, for they represent the total mobilization of body resources to deal with the stress situation. These changes are effected largely through the autonomic nervous system and include increased muscle tonus, the dumping of stored sugar into the blood stream, the speeding up or deepening of breathing, faster beating of the heart, increased neural activity, and the secretion of adrenalin. Gellhom (16) had shown that when emotion reached a high level of intensity or continued over a sustained period, there is a disturbance in coordination between sympathetic and parasympathetic nervous systems resulting in autonomic disorganization. This would indicate that there is an electrical imbalance or disturbance between the systems. Selye (34) found that all organs of the body except the adrenal cortex showed involutive or degenerative changes in stressful situations.

Constantinides and Carey (7) have shown that rats repeatedly subjected to stress developed many signs of pathology. Blood vessels are thickened and adrenal glands became large and brown. Other changes included a wasted thymus and stomach
ulcers. The elevation of the blood pressure under stress has been known for a long time because of the work of Hickam, Cargill and Golden (23).

The second dimension of behavior refers to the general constriction of functioning which occurs in a stress situation. Maier (27), Selye (34), and Brumer and Postman (4) have all demonstrated the wide range of activity in a problem solving situation. Hamilton and Krechevsky (20) have shown experimentally that behavior tended to lose its plasticity and instead assumed a marked stereotypy.

Turning to the learning process under stress, it has been found that there are certain respects in which this process differs from the kind of learning found in nonstressful situations. These differences manifest themselves (a) in the increased rate of acquisition of certain responses, (b) in their persistence in a stereotyped form for long periods without reinforcement, and (c) in their unadaptive character. In fact, all three of these characteristics may be said to be aspects of the same feature, namely, the greatly increased sensitivity of the learning mechanism operative under stress, which fixates whatever response is dominant at the time and prevents its being extinguished even when it is followed by nothing but unfavorable consequences.
When seeking an explanation for all these characteristics of behavior under stress, it is found not only that few attempts have been made in this direction, but that none of the proposals put forward so far has attempted to explain both the changes in general activity and those in the learning process. Pavlov (30) sought to account for the former by his theory of the respective dominance of excitatory or inhibitory cortical processes, but in the absence of empirical confirmation this theory has now been abandoned. More detailed attention has been given to the learning process and the problem of abnormal fixations; in particular, Mowrer's (29) anxiety reduction theory has been applied to these phenomena by several authors. It is an attempt to force specific learning under normal conditions. Eglash (13) has effectively criticized this attempt; briefly, such a theory has yet to explain why, in the first place, the dominant rather than the most effective response is adopted under stress, often without a preliminary trial-and-error period; and secondly why this response, unlike other drive-reducing responses, assumes such a rigidly stereotyped, unvarying form, which will not even be altered when the animal perceives that the original stress situation is losing its noxious quality. Maier (27) on the other hand, made no attempt to apply the
same laws of learning to "frustration-instigated" responses as to problem-solving behavior; but he did not go beyond stating the distinction, and thus failed to point out a mechanism to account for the peculiarities of learning under stress.

In view of the inadequacy of existing theories, Schaffer (33) began looking for an alternative explanation by turning to the neurophysiological background of the phenomena. He made particular reference to the functional relationship of the cortex to the lower cerebral centers. It is generally agreed that in the mature animal under nonstressful conditions this relationship is mainly one of dominance of the cortex over the more primitive centers, so that the activity of the organism is on the whole cortically influenced and modified. Under conditions calling forth emotional behavior, however, mechanisms known to be subcortically situated become activated, and it appears that then the relationship changes and a shift in emphasis occurs from cortex to subcortical centers; or, as Darrow (?) has put it, whenever the cortex is no longer able to deal with different excitation, a process of relative functional decortication takes place. Thus, in a stressful situation, an electrical imbalance takes place. It may be that the physiological activity of the cortex then becomes inhibited by disruptive discharges from subcortical areas,
with the result that the cortex can no longer exert its controlling influence over lower centers. Now this notion, when systematically extended to the whole area of behavior under stress, may well serve as an explanatory scheme for the peculiarities characterizing such behavior. The neurophysiological explanation of stress proposed by Schaffer (33) will receive the most consideration in this paper. The above writings are only a sample of the literature on the effects and causes of stress, and because of the interest of the public and scientists, even more research is being done in order to solve the problems of stress.

In all the areas of research dealing with the neurophysiological aspects of stress, the most promising method of reducing stress is with the use of drugs. This research has brought about the growing interest and experimentation of many drugs. In recent years a great deal of public and scientific attention has been focused on the use of so-called tranquilizers and other tension reducing drugs. In most cases tranquilizers seem to have the effect of reducing anxiety and tension and improving psychological integration and stress tolerance, but they cannot correct the faulty attitudes and response patterns which are often at the root of mental disturbance. The remarkable success of the tranquilizing
drugs in treating mental disorders has tended to obscure the fact that they cure symptoms rather than eliminate causes. Thus as Wortis (42) has stated, many people have turned to tranquilizers as a means of reducing the tension and stress of everyday living. Some have found that the drugs make them feel much better and more capable of dealing efficiently with their problems; others have been able to detect no appreciable results; and still others have suffered undesirable side effects which seem to outweigh any benefits. A great deal of research is being done to evaluate the drugs more fully and to improve them. The work by Ross and Cole (32) is an excellent review of the literature on psychopharmacology.

The most common forms of psychoactive drugs used today may be considered under four main headings: (1) sedatives, (2) tranquilizers, (3) activators, and (4) psychomimetic drugs. The forms of drugs mentioned above have had the spotlight in the area of research with reducing anxiety, and improving psychological integration and stress tolerance.

Only recently have the anticonvulsant drugs been used in this area of research. Although the anticonvulsant drugs are usually associated with the treatment of epilepsy, with further research, it may be discovered that they have a place in the treatment and handling of anxiety, stress and other personality disorders.
The anticonvulsant drug used in the research reported in this paper is Diphenylhydantoin Sodium. The trade name for this drug is Dilantin. Diphenylhydantoin was introduced into medicine for the symptomatic treatment of epilepsy by Merritt and Putnam (28) in 1938. Whereas the usefulness of bromide and phenobarbital in convulsive disorders was discovered more or less by chance, diphenylhydantoin was developed as the result of an extensive experimental study of potentially anticonvulsant chemicals, with the technique of electroshock convulsions in laboratory animals. The discovery of diphenylhydantoin as an antiepileptic agent represents a signal advance in therapeutics for three reasons. First, the drug is not a sedative, and thus for the first time it was clearly demonstrated that chemicals effective in epilepsy need not necessarily be hypnotics. Second, the efficacy of diphenylhydantoin in psychomotor seizures has given impetus to studies on the basic metabolic, neurophysiologic, and electroencephalographic differences between the various types of epilepsy and has indicated that anticonvulsants discovered in the laboratory might show therapeutic specificity for particular categories for clinical seizures. Finally, diphenylhydantoin and its congeners, as well as anticonvulsants from other chemical classes, have proved to be valuable laboratory tools for the study of experimental seizures with the
dual objective of obtaining a better understanding of the nature of the convulsive process and elucidating the relationship between chemical structure and anticonvulsant action.

Diphenylhydantoin sodium is a white, odorless, microcrystalline powder with a slightly bitter taste. It is marketed for oral administration in sealed capsules, containing either thirty or hundred mgm of the drug, and in scored flavored tablets containing 0.05 grams; diphenylhydantoin in oil is also available in capsules containing 100 mgm of the drug. Diphenylhydantoin sodium is freely soluble in water, but its aqueous solutions are strongly alkaline, which makes parenteral administration impracticable because of tissue irritation. The chemistry of diphenylhydantoin was surveyed in the review by Ware (40).

Diphenylhydantoin exerts antiepileptic activity without causing general depression of the central nervous system. Indeed, even after toxic doses, depression is not observed, but rather excitatory effects are manifested. Diphenylhydantoin is not a general anticonvulsant; therefore, it is not useful for the emergency treatment of poisoning by convulsant drugs, or for tetanus, or status epileptics. Even in the preventive treatment of clinical seizures, the salutary effect of diphenylhydantoin is specific and confined to grand mal and psychomotor epilepsy.
When diphenylhydantoin was introduced, it was on the basis of its ability to inhibit electrically induced convulsions in cats by elevation of seizure threshold. Closer analysis of the phenomenon by Goodman and Gilmer (18) and Ziskind, Sjaardema, and Bercel (43) has indicated that the drug, in contrast to other anticonvulsants neither raises the threshold for minimal electroshock seizures in normal animals nor prevents such convulsions, as demonstrated in a variety of laboratory animals by the occurrence of EEG seizure discharges, overt convulsions, and postictal depression.

The action of diphenylhydantoin on the peripheral nerve is such as to stabilize the neuronal membrane against the lowering of threshold and the high frequency discharge of impulses induced by repetitive supramaximal stimulation or reduction in calcium ions. Indeed, wherever the finer mechanism of action of diphenylhydantoin has been explored, the drug appears to stabilize rather than raise normal threshold, and to prevent spread of seizure activity rather than to abolish the primary focus of seizure discharge. These results were stated by Toman and Davis (36) and Toman and Goodman (37).

Controversy has arisen in connection with the effects of diphenylhydantoin on electroshock seizure threshold in man. Hemphill and Walter (22), Gruber, Faury, and Drake (19) and Fingl, Olsen, Harding, and Cockett (14) have reported
that diphenylhydantoin, in repeated injections, increased threshold in patients undergoing electroshock therapy, while Toman, Swinyard, and Goodman (39) and Swinyard and Toman (35) have interpreted similar observations as representing a change in seizure pattern rather than threshold.

Another problem which has received attention is the effect of diphenylhydantoin on the pattern of seizures. Hamphill and Walter (22) observed that atypical seizures were frequent among patients treated with diphenylhydantoin prior to receiving electroshock therapy. Barany and Stein-Jensen (2) have observed that anticonvulsant drugs in general and diphenylhydantoin in particular modified electroshock seizures by reducing or abolishing the tonic phase in animals and in man. It was noted that with diphenylhydantoin, in contrast to many other drugs, the modified clonic seizures in animals were quite prolonged.

Barany and Stein-Jensen (2) interpreted the change in pattern as representing a greater action of diphenylhydantoin upon subcortical mechanisms responsible for the tonic phase of seizures than upon cerebral cortex. Since the medulla in particular had been shown to have a high seizure threshold, a selective vulnerability to anticonvulsant drug action might be expected. However, Gley (17) had observed that larger
doses of diphenylhydantoin are required to modify or prevent seizures in the decerebrate than in the intact animal, while Knoefel and Lehmann (24) failed to find any effect of diphenylhydantoin on seizures in decerebrate preparations. The more rapid post-seizures recovery of animals pretreated with diphenylhydantoin has been shown by Barany and Stein-Jensen (2) to occur to an equal degree for responses at all levels of integration from medulla to cerebral cortex. This finding suggests the possibility that diphenylhydantoin may reduce seizure activity at all levels of the brain, in which case the modification of seizure pattern need not be interpreted on a specific anatomical basis.

Woodbury (41) has shown with radiosodium that diphenylhydantoin accelerates the active process controlling sodium movement across brain cell membranes, so as to decrease the intracellular content of this cation; decreased intracellular and increased extracellular sodium in brain tissue appears to favor diminished susceptibility to experimentally induced seizures.

In the past decade, or so, diphenylhydantoin has been found to be useful in other areas besides in the treatment of epilepsy. Diphenylhydantoin has been employed for the treatment of disturbed nonepileptic psychotic patients. It
has been reported that excitability and irritability are diminished in an impressive number of cases, irrespective of the type of psychosis; but the best responses are obtained in catatonic excitement states. It has been both affirmed and denied that diphenylhydantoin improves the behavior of problem children who are not epileptic, but who have abnormal electroencephalograms.

During the past few years the use of diphenylhydantoin has taken many new forms. It has been used to treat drug addicts, skin diseases, severe pain, asthma, migraine headaches, heart disorders, and hypertension. Harris and Kokernot (21) have suggested that since diphenylhydantoin causes a suppressing discharge of "ectopic impulses in acute myocardial necrosis," it should be tested for use in cardiac preparations.

The most recent research on diphenylhydantoin has been by Toman and Gordon (38). Their animal experiments reinforced the feasibility of Dreyfus' (11) theories that (a) electrical activity in the body can make a mind less able to concentrate, and (b) diphenylhydantoin, by lowering or canceling the excess electricity, can clear the mind. Toman and Gordon pointed out that in young, healthy people, when a brain cell is stimulated by a thought, by a sensory impression, or by an electrical stimulus, the cell fires, then
subsides once more. In abnormal conditions, the stimulated nerve cell keeps on firing. They have stated "that if a drug like diphenylhydantoin could normalize the cells' firing, by cutting out the static, perhaps the mind might clear and learning ability improve." Raines (31) has also indicated that diphenylhydantoin depresses repetitive discharges. Since stressful situations bring about excessive brain stimulation, and thus electrical activity is increased, diphenylhydantoin may be a useful drug in alleviating this condition.

Making the assumption that diphenylhydantoin has a lowering or canceling effect on excess electricity in the brain, it is the purpose of this study to determine the effects of diphenylhydantoin in a stressful learning situation. The following hypothesis was proposed:

If the anticonvulsant drug diphenylhydantoin does have calming effects upon subjects, then subjects that have had diphenylhydantoin before a stressful learning situation should have better performance than a group of subjects that have not had diphenylhydantoin treatments.
CHAPTER BIBLIOGRAPHY


34. Selye, H., Physiology and Pathology of Exposure to Stress, Montreal, Acta Incorporation, 1950.


CHAPTER II

METHOD

Subjects

In this experiment 24 naive, white rats were used. All subjects were between forty-five and sixty-five days of age at the time of testing. Six females and 18 males were divided evenly to make up the control and experimental groups. The subjects were maintained on ad libitum food and water before the experiment. The weight of the subjects ranged from 138 to 233 grams.

Apparatus

The apparatus used in this experiment was a simple T-maze. The whole maze was placed on a single piece of plywood. The starting box and the goal boxes were made of heavy wire, and the alley ways were made of clear plastic. The dimensions were as follows: the starting box and the two goal boxes were 6 inches high, 10 inches wide, and 8 inches long. The alley from the sliding door of the start box to the far end of the alley was 36 inches long. The length of the alley from goal box door to goal box door was also 36
inches. The dimensions of the alleys were 6 inches wide and 5 inches high. The starting box and the two goal boxes each had a sliding door in front of them to allow for closing and opening of the boxes. The entire bottom of the maze was covered by ½ inch copper strips. A transformer allowing for 1.2 milliamps of current was attached to the maze to provide shock in order to provide a stressful situation. A diagram of the apparatus is shown in Appendix I.

Procedure

In the preliminary training, the subjects were familiarized with the routine of the maze. The right or left turning preference was determined for each subject during this procedure. Each rat was allowed to explore the maze for 10 minutes each day for 2 days.

In the training phase all rats were trained to proceed to the goal box opposite the one preferred during the familiarizing period. The subjects were on a twenty-four hour food deprivation schedule which served as the motivation for action. Each subject received a .5 gram food reward in the goal box. Each animal was given a total of 20 trials. This criterion was established in a study by Loken (2).

During the training phase of the experiment, each subject in the Control Group was given a saline solution injection
three hours before the experiment was begun. Each subject in the Experimental Group was also given 40 mg/kgm per body weight of diphenylhydantoin. The criteria for the amount of drug used in this study was taken from a study done by Fingl, Olsen, Harding, Cockett, and Goodman (1).

During the training procedure, all subjects were injected, 3 hours before the running of the maze, with $\frac{1}{2}$ cc. of the required solution. Three hours were allowed between the time the injections were made and the training, because Fingl (1) made the observation that diphenylhydantoin has its most pronounced effects 3 hours after its injection. The Control Group received $\frac{1}{2}$ cc. of the saline solution, while the Experimental Group received 40 mg/kgm of diphenylhydantoin. Distilled water was added to the diphenylhydantoin in order for the total amount of the injection to equal $\frac{1}{2}$ cc. All injections were administered intraperitoneally with a one cubic centimeter tuberculin syringe and needle. This method of administration was chosen for three reasons: (a) the drug administered was non-irritating; (b) the peritoneum of the abdominal cavity presented a large absorption area; and (c) the technique was simple and could be performed by one person.

Three hours after the injections, each subject was placed in the start box. The subject was then shocked for 5 seconds
and then the start box was opened. The time was recorded from the time the start box door was opened until the subject reached one of the goal boxes. Whether the response was correct or incorrect was also recorded.

The testing trials were also begun after 24 hour food deprivation. Three hours before the testing, each subject in both groups was given an injection of \( \frac{1}{2} \) cc. of a saline solution (distilled water).

During the testing procedures, each subject was placed in the start box, shocked for 5 seconds, and then let out of the start box. During the testing trials, the time was recorded from the time the start box door was opened, until the subject reached the correct goal box. Whether the subject made an error during the running of the maze was also recorded. An error was recorded each time a subject made a turn into a wrong alleyway. Each subject was given 10 test trials.

Extraneous variables such as time, temperature, and place were held constant, and every effort was made to keep the interexperimental intervals as identical for all animals as possible. A one day interval was allowed between the training trials and the testing trials.

A t test for randomized groups was used on the average time scores for the ten test trials to determine if there
was a significant difference between the two groups means at the .05 level of significance. A t test was also employed on the number of errors of each subject during the test trials. The .05 level of significance was used for this test also.
CHAPTER BIBLIOGRAPHY


CHAPTER III

RESULTS

Endeavoring to measure the effects which a specific drug had on learning ability, 12 white and naive rats were administered diphenylhydantoin and 12 were administered 1/2 cc. of distilled water. Table I represents the amount of drug given to each subject in the experimental group.

TABLE I

AMOUNT OF DRUG GIVEN TO EACH SUBJECT IN THE EXPERIMENTAL GROUP

<table>
<thead>
<tr>
<th>Subjects in Experimental Group</th>
<th>Amount of Drug Given to Each Subject in Experimental Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.28</td>
</tr>
<tr>
<td>2</td>
<td>10.30</td>
</tr>
<tr>
<td>3</td>
<td>8.48</td>
</tr>
<tr>
<td>4</td>
<td>7.80</td>
</tr>
<tr>
<td>5</td>
<td>10.80</td>
</tr>
<tr>
<td>6</td>
<td>5.52</td>
</tr>
<tr>
<td>7</td>
<td>7.47</td>
</tr>
<tr>
<td>8</td>
<td>6.40</td>
</tr>
<tr>
<td>9</td>
<td>9.92</td>
</tr>
<tr>
<td>10</td>
<td>6.28</td>
</tr>
<tr>
<td>11</td>
<td>5.96</td>
</tr>
<tr>
<td>12</td>
<td>6.55</td>
</tr>
</tbody>
</table>

Each subject in the experimental group was given 40 mgm/kgm per body weight of diphenylhydantoin with the amount of
drug given in milligrams. Each subject was then given 20 training trials in order to learn the appropriate maze response. Figure I represents the mean running time of all subjects on each trial during the training procedures. This represents a learning curve for each group.

Fig. 1—Mean running times on each trial during the training trials with times measured in seconds.

As Figure 1 shows the learning curves of the experimental group and the control group were very homogeneous. The mean
running time for all of the experimental group was 13.24 for the twenty trials, while the mean running time of the control group was 12.91.

The 10 test trials were given one day after the training procedures. Each subject was allowed to run the maze until the correct response had been made. The time was recorded from the time the subject left the start box until the correct goal box was reached. The number of errors was also recorded for each subject on each trial. After each subject ran the 10 test trials, the average running speed was calculated for each subject. A $t$ test for randomized groups was used to determine if there was a significant difference between the two group means at the .05 level of significance. Table II represents the results of the $t$ test on the mean running times of the experimental and control groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Means</th>
<th>Standard Deviation</th>
<th>$t$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>7.6108</td>
<td>3.44</td>
<td>1.47</td>
<td>.2 (N.S.)</td>
</tr>
<tr>
<td>Control</td>
<td>11.0925</td>
<td>7.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The \( t \) value was not found to be significant at the .05 level. The difference between the two groups means was not large enough to accept the experimental hypothesis.

During the testing procedure, the number of errors was also recorded for each subject as the maze was run. A \( t \) test for randomized groups was used on the error scores of each subject on the 10 test trials to determine if there was a significant difference between the two group means at the .05 level of significance. Table III presents the results of the \( t \) test on the mean error scores of the experimental and control groups.

**TABLE III**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Means</th>
<th>Standard Deviation</th>
<th>( t )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.083</td>
<td>1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>1.4166</td>
<td>1.416</td>
<td>1.31</td>
<td>.2 (N.S.)</td>
</tr>
</tbody>
</table>

Although the experimental group had 48 per cent fewer errors than the control group, this difference was not significant at the .05 level of significance.
CHAPTER IV

DISCUSSION

It was proposed in this paper, that if diphenylhydantoin does have calming effects upon subjects, then subjects that have had diphenylhydantoin before a stressful learning situation should have better performance than a group of subjects that have not had diphenylhydantoin treatments. If one accepts the maze as a stressful learning situation, then the results of this study indicate that diphenylhydantoin injections do not significantly improve the learning ability of rats in a stressful learning situation. Any conclusion which might be drawn from this study at the present stage must be hasty and premature. To say at this point that diphenylhydantoin injections cause learning impairment or improvement in stressful conditions would be to go beyond the data.

Although the theories explaining the phenomena associated with stressful situations are varied and inadequate, it is usually agreed that animals under nonstressful conditions are dominated by the cortex. Under conditions of stress, however, mechanisms known to be subcortically situated become activated, and it appears that then the relationship changes and a shift
in emphasis occurs from cortex to subcortical centers. Culler and Mettler (1) have come to this conclusion in their research. These results were also confirmed by the experiments on conditioning under curare and erythoidine by Girden (3). These drugs have been said to suppress cortical activity and thus enable subcortical processes to function independently. Whenever the cortex is no longer able to deal with afferent excitation, a process of relative decortication takes place. Thus, the cortex is unable to influence the lower centers.

If the cortex control theory is true, then there are a number of reasons that would account for the nonsignificant results obtained in this study. First, it must be remembered that in a stressful learning situation there is (a) an increased rate of acquisition of certain responses, (b) a persistence in a stereotyped form for long periods without reinforcement, and (c) a formation of unadaptive responses. This presents a greatly increased sensitivity of the learning mechanisms operative under stress. Thus, the stressful situation in this study may not have been stressful enough to cause a disruption of the organisms functioning and learning may have been facilitated in each group. Second, if the physiological activity of the cortex becomes inhibited by disruptive discharges from subcortical areas during a stressful
learning situation, and if diphenylhydantoin does not seem to have the ability to alter the cortex's stability after one injection, the results of this study are in agreement with Fingl (2) and Woodbury (5). One administration of diphenylhydantoin does not have any significant effects on the stability of the cortex or other electrical activity of the brain and thus again both groups would be affected equally. The results of the studies done by Woman and Gordon (4) have shown that repeated injections of diphenylhydantoin could increase the ability of subjects in a learning situation. Although the results of the present study do not agree with the results of the work of Toman and Gordon, repeated dosage given to each subject might have resulted in similar results. Third, the type of learning task employed in this study may not have been appropriate for testing the effects of a drug on subjects in a stressful learning situation.

It is also possible that there may have been some intra-individual reactions that affected the results of this study. Since the drug is easily absorbed, safe, and does not depend on the body for its metabolism, this is unlikely.

Although the learning ability of the subjects in the experimental group in this experiment did not have significantly better performance in the maze than the control
group, it must be noted that the observed behavior of the experimental group was noticeably different. The experimental subjects were much more docile and relaxed than the control group during the training procedures. The experimental subjects were easier to handle and ran the maze with greater ease and with fewer errors than the control group. Each subject in the control group urinated and left stools in the maze during the training and testing procedures, while none of the experimental subjects defecated during the training procedures, and only 2 subjects left any form of defecation during the testing procedures. These behavioral differences may indicate that the drug did affect the animals, but not in ways which were reflected in the type of measures employed in this study.
CHAPTER BIBLIOGRAPHY


CHAPTER V

SUMMARY AND RECOMMENDATIONS

Summary

This study was an attempt to test the theory that diphenylhydantoin, when administered before a stressful learning situation, could improve the performance in that stressful situation. Six female and eighteen male, naive, white rats were used in this study. All subjects were trained to run a simple T-maze. The experimental group was given injections of diphenylhydantoin and the control group was given injections of a saline solution before the training procedures were begun. All subjects were placed on 24 hour food deprivation before the training and testing trials were begun.

The hypothesis that subjects receiving an injection of diphenylhydantoin before a stressful learning situation would do better than subjects that had only received a saline solution was tested. A significant difference was not found to exist between the time scores or the error scores, and the experimental hypothesis was rejected.

Statistical analysis of the data revealed that although the means of the two groups were different, they were not
different enough to lead to rejection of the null hypothesis. This indicates that the dosage of diphenylhydantoin used in this study does not increase the learning ability of a subject during the simple choice task employed in this study.

**Recommendations**

Based on the results and conclusion of this investigation, several additional related conditions require further experimentation and exploration.

1. The experiment should be repeated with each subject in the experimental group receiving enough diphenylhydantoin to build up an effective level of the drug. Additional research should also be done concerning the correct concentration and volume of diphenylhydantoin to be injected.

2. Future investigation might be done with the use of this drug in other areas besides learning. Because of the behavioral changes observed in the subjects in this experiment, behavioral changes in stressful conditions with the use of diphenylhydantoin would be an important area of research.

3. Future investigation might be carried out in order to see what mechanisms diphenylhydantoin acts upon to affect the electrical activity in the brain.

4. Future investigation might be carried out in other kinds of learning tasks with the same criteria, or even different criteria.
5. Future investigations might select a different species, one which would manifest the desired behavioral and physiological changes without any confounding effects.

6. Future investigations might be carried out in which another control group would be added which did not receive any injections or shock. This would enable the experimenter to see if the stress merely accentuated learning in both groups.
APPENDIX I

DIAGRAM OF T-MAZE

Copper strips

Goal Boxes

Start Box
APPENDIX II

TABLE IV
COMPUTATION OF \( t \) FOR ERROR SCORES OF TWO-RANDOMIZED GROUP DESIGN

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Errors</th>
<th>Errors</th>
<th>Subjects</th>
<th>Errors</th>
<th>Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( X_1 )</td>
<td>( X_2 )</td>
<td></td>
<td>( X_1 )</td>
<td>( X_2 )</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>16</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>16</td>
<td>8</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>9</td>
<td>11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>9</td>
<td>12</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

\[ n = 12 \] \[ \sum X_1 = 25 \] \[ \sum X_1^2 = 75 \] \[ n = 12 \] \[ \sum X_2^2 = 17 \] \[ \sum X_2 = 35 \]

\[ \bar{X}_1 = 2.083 \] \[ \bar{X}_2 = 1.4166 \]

\[ SD = 1.44 \] \[ SD = .99 \]

\[ t = \frac{X_1 - X_2}{\sqrt{\frac{\sum X_1^2/n_1 - (X_1)^2}{n_1-1} + \frac{\sum X_2^2/n_2 - (X_2)^2}{n_2-1}}} \]
\[
t = \frac{0.6664}{\sqrt{\frac{1.911}{11} + \frac{0.909}{11}}}
\]

t = 1.31 \\
\text{df} = 22 \\
P = 0.2
APPENDIX III

TABLE V

COMPUTATION OF \( t \) ON TIME SCORES FOR
TWO RANDOMIZED GROUPS

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>CONTROL GROUP</th>
<th>EXPERIMENTAL GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN Scores</td>
<td>( X_1^2 )</td>
</tr>
<tr>
<td>1</td>
<td>6.05</td>
<td>36.602</td>
</tr>
<tr>
<td>2</td>
<td>30.79</td>
<td>948.024</td>
</tr>
<tr>
<td>3</td>
<td>2.98</td>
<td>8.880</td>
</tr>
<tr>
<td>4</td>
<td>11.80</td>
<td>139.240</td>
</tr>
<tr>
<td>5</td>
<td>8.54</td>
<td>72.931</td>
</tr>
<tr>
<td>6</td>
<td>17.39</td>
<td>302.412</td>
</tr>
<tr>
<td>7</td>
<td>10.52</td>
<td>110.670</td>
</tr>
<tr>
<td>8</td>
<td>11.98</td>
<td>143.520</td>
</tr>
<tr>
<td>9</td>
<td>4.22</td>
<td>17.808</td>
</tr>
<tr>
<td>10</td>
<td>7.29</td>
<td>53.144</td>
</tr>
<tr>
<td>11</td>
<td>12.28</td>
<td>150.552</td>
</tr>
<tr>
<td>12</td>
<td>9.28</td>
<td>86.118</td>
</tr>
</tbody>
</table>

\( n=12 \) \( X_1=133.11 \) \( \sum X_1^2=2069.905 \)
\( n=12 \) \( \sum X_2^2=91.33 \)

\( X=11.0925 \)
\( SD=7.34 \)
\( X=7.6108 \)
\( SD=3.44 \)

\[
t = \frac{11.0925 - 7.6108}{\sqrt{\frac{2069.905/12 - 122.988}{11} - \frac{91.33/12 - 57.9121}{11}}}
\]

\[
t = \frac{3.4817}{\sqrt{4.5 - 1.9767}}
\]

\( t=1.4739 \) \( df=22 \) \( P=.2 \) (NS)
BIBLIOGRAPHY

Books


Selye, H., Physiology and Pathology of Exposure to Stress, Montreal, Acta Incorporation, 1950.

Articles


Reports

Unpublished Materials
