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The effects of physostigmine sulfate on inferential learning in the rat

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THE EFFECTS OF PHYSOSTIGMINE SULFATE ON INFERENTIAL LEARNING IN THE RAT

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The following study has arisen out of an interest in the recent work done on the chemistry of neural transmission. Since experimentation has indicated that certain chemicals affect some lower level learning performance of animals such as maze performance, this experiment is an attempt to find out whether the same effects hold for such a chemical on higher order learning processes, as indicated by Maier's three-table-test.

In work dealing with brain chemistry and adaptive behavior, Rosenzweig, Krech, & Bennett (1960) treated several hypotheses dealing with cholinesterase (ChE) levels. Their first hypothesis dealt with behavior preference and ChE activity in defined cortical areas. They tried to produce defined spatial preference behavior by introducing lesions in the appropriate cortical regions. The hypothesis that ChE activity in any cortical region was an index of the transmission efficiency of that region was found unsatisfactory and abandoned. The second hypothesis was that animals with spatial preferences were generally superior in adaptive behavior to animals with visual preferences. Different strains of animals bred for high and low ChE levels were examined. A negative correlation was expected between high ChE level and the number of errors the animal made. Instead, a positive correlation was found which led to the third hypothesis. The third hypothesis operated under the assumption that acetylcholine (ACh) and

ChE were under relatively separate genetic controls, and therefore ChE activity would not be a good index to ACh functioning. Also, the assumption was retained that learning was intimately related to the ACh transmission system and therefore ChE. They hypothesized that "learning capacity is related to the levels of both ACh and ChE, such that, within limits, the greater the amount of ACh functioning at the synapse, the greater the efficiency of transmission and, consequently, the greater the learning ability."

It is generally accepted that ACh, as well as other chemicals, is one of the definite neurochemical transmitters in the central nervous system (Crossland, 1960). Several experiments have been reported which are related to Rosenzweig, Kretch, & Bennett's third hypothesis. McGaugh (1959) reported that strychnine--which acts by inhibiting ChE and reducing the graded synaptic resistance--if administered in small doses, increases learning (measured in terms of number of errors) in the Lashley III Alley maze. In an unpublished doctoral thesis, Platt (1950) found that another ChE inhibitor, di-isopropyl flourophosphate (DFP), facilitated discriminative learning in rats.

Kishimoto, Nakurshi, & Nisho (1957) reported that

stimulation of the autonomic nervous system with adrenalin and ACh shortened the latent times in linear maze learning of mice. Kishimoto, et al. (1958) also found that the running time itself was not affected by injections of adrenalin or ACh. Nakanishi & Tanaka (1958) confirmed the fact that running times alone were not affected by adrenalin and ACh injections when their rats ran straight mazes under various intensities of hunger.

Tolman (1937) distinguished between seven different levels of learning. The work which has been discussed so far has dealt with lower level learning tasks (largely trial and error as described in Tolman's third level of learning). Tolman described an inferential type of learning which he assigns to the sixth level. One of the tasks which demonstrated this sixth level of learning was described in Maier's "reasoning" experiments. Maier (1929) found that rats were able to apparently combine two separate experiences to produce a response. He would expose the animal to Experience I of gaining familiarity with the runway patterns of an apparatus and then to Experience II which was finding food in one area of the apparatus. If the animal could combine Experience I and Experience II, Maier considered reasoning to be involved. The animal was considered to have combined Experience I and Experience II if after being removed from the food area of the apparatus and being placed in another area it could return to the

food area without any errors (thus implying the animal had a knowledge of the layout of the apparatus). Later, he formally defined reasoning as "the ability to combine spontaneously two or more separate or isolated experiences to form a new experience which is effective for obtaining a desired end." (Maier, 1934, p. 212). This is the definition of reasoning as it is used in this paper (included under Tolman's sixth level of learning). Maier (1938) also claimed that a rat could combine as many as four experiences to solve a problem. He felt that the reasoning exhibited by rats in his tests was not explainable by trial and error (Maier, 1929) and qualitatively different from learning (Maier, 1931). Maier (1937, 1938) supported his thesis that learning was a different process from reasoning when, through the production of cortical lesions, reasoning performance would be affected whereas learning performance would not. It will be noted that Tolman (1937) would agree with Maier's results but would disagree upon the terminology used. What Maier calls reasoning in this case is merely Tolman's sixth or inferential level of learning.

Hamilton & Harned (1944) employed Maier's three-table-test and found decreased reasoning ability in the offspring of mother rats who were given sodium bromide. Mendenhall (1940) used Maier's three-table-test to conclude that sodium phenobarbital injections in rats also decreased reasoning ability.

In the present experiment, it was decided to employ Maier's three-table-test in an examination of the effects of a cholinesterase inhibitor on higher level learning in rats. In order to assess the generality of the effect, it is of interest to know whether a cholinesterase inhibitor improves higher level learning in the same way it does the lower levels of learning.

In an unpublished masters thesis, Merrill (1961) examined the effects of varying amounts of the cholinesterase inhibitor Eserine (trade name of Abbott for physostigmine sulfate) on reasoning in mice using the Maier three-table-test. He injected five gradated dosages from .050 gm. per gm. of body weight to .150 gm. per gm. of body weight into five different groups of six white mice each. The hypothesis was that performance would increase up to a certain drug dosage, and then begin to decline with the higher dosages. Hypothesized results were reported for the .125 gm. and .150 gm. concentrations of Eserine where performance was below that of the control group (injected with distilled water). Only one group (.100 gm.) showed a score (45% passing) which was above Maier's 33% minimum significant score (Maier, 1932). The animals injected with concentrations of .050 gm. and .075 gm. were considerably below 33.3% and the control group was only 25%.

There were several elements neglected by Merrill which could have contributed to his results. Since Maier's

three-table-test requires visual discriminations, it may have been advisable for Merrill to use an animal with a pigmented eye (Munn, 1950), p. 126). Also, Merrill did not note the relative humidity and temperature under which the experimentation was conducted. Farris and Griffith (1949, pp. 303-304) state that room temperature is of paramount importance when working with drugs and atmospheric conditions could also be influential. Merrill did not exercise a closely controlled deprivation schedule for his animals and some were undoubtedly at different deprivation levels than others during the trials. Merrill suggested that the testing apparatus be periodically rotated so that an animal would not obtain an orientation based on cues within the testing room rather than within the apparatus itself, but he did not implement this suggestion. This could be an important factor because if the animal could associate a particular feature of the testing room (e.g., a chair) with the feeding position, it would be a mere delayed reaction to return to the chair position to continue feeding. This would eliminate the need for Maier's Experience I and thus destroy the process of reasoning as defined and used in this experiment. It is also desirable that the animal's vision should be blocked from one table to the next to help prevent the animal from using strictly delayed visual cues in relocating the food.

In brief, the purpose of this experiment was to

examine the effects of the ChE inhibitor physostigmine sulfate (Eserine) on the performance of hooded rats on the Maier three-table-test for reasoning. The hypothesis to be tested--stated in the null form--is that as the level of Eserine is increased the animals will exhibit no improvement of performance on the Maier three-table-test. This hypothesis will be rejected should the mean performance scores among animals injected with different drug levels differ at or beyond the .05 level of significance.

METHOD

Subjects

The subjects were 21 male and 21 female hooded rats of the Long-Evans strain, purchased from the Simenson Laboratories in California. All animals were born on the same day and were 115 days old at the beginning of the experimentation. One animal expired during the last week of experimentation because of a lethal dose of Eserine administered in error.

Apparatus

The apparatus was basically patterned after that used by Hamilton & Harned (1944). Three tables, one square with a 9 inch side, one round with a 9 inch diameter, and one triangular with a 9 inch altitude were connected by elevated pathways which were 3 feet from the ground (see Fig. 1). The square table was gray with a 1/2 inch hardware cloth surface; the round table was white with a metal surface;

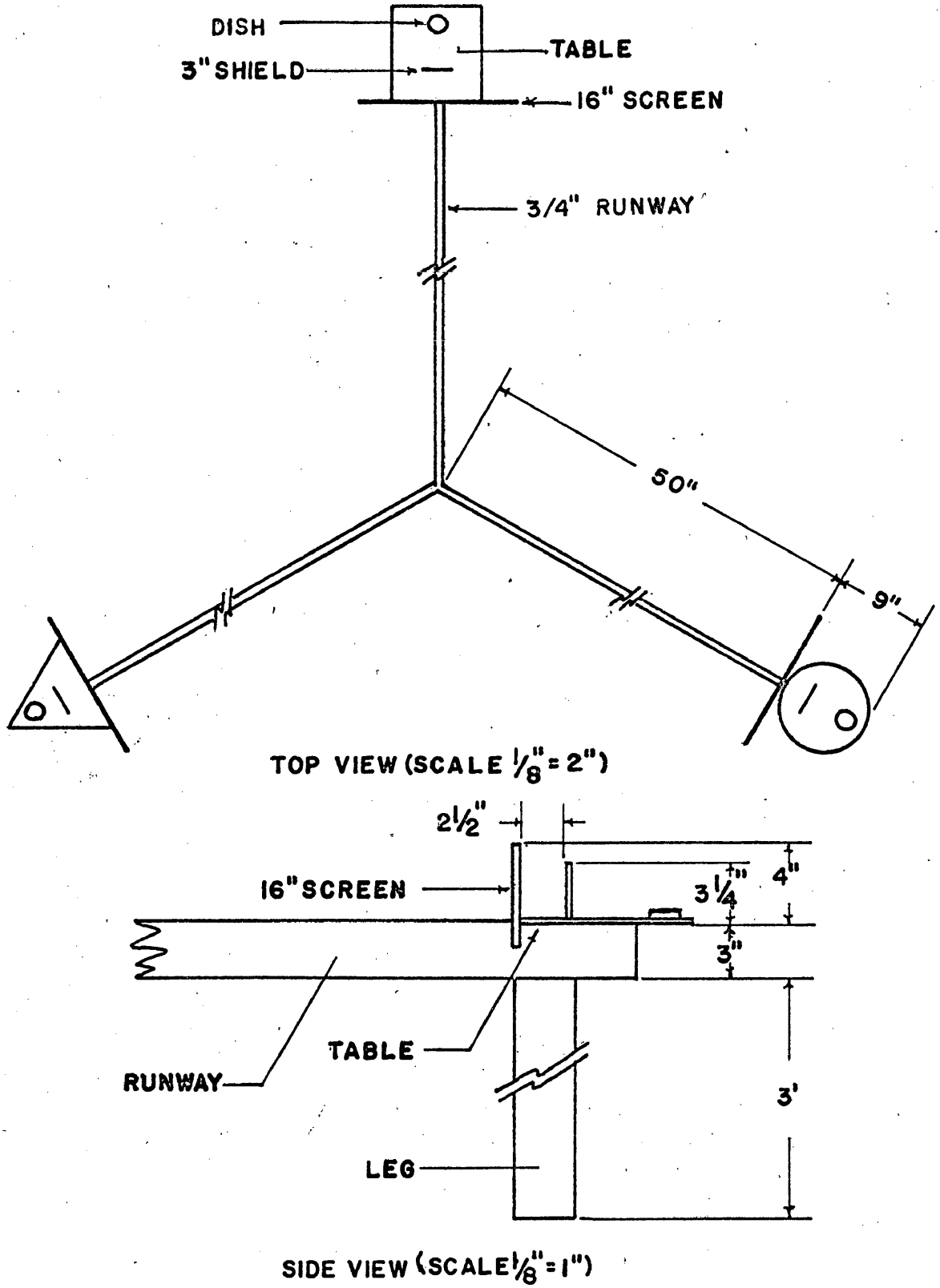

Fig. 1. Detail of three-table apparatus.

and the triangular table was black with a wood surface. Each table had an opaque screen resting at the point where it joined the runway. The screen was 16 inches long and 4 inches high. Each screen had a square hole 3 inches in diameter cut in the center to allow the animal access to the table from the runway. The screens and runways were painted flat black. Merrill (1961) and Hamilton & Harned (1944) omitted the screen while Maier (1932) included it. In order to eliminate possible visual cues from one table to another (or, from the choice point onto a table), the 3 inch square entrance hole onto the table should also be blocked to the line of vision. For this reason, on each table, 2 and 1/2 inches from the screen was a 3 inch square white shield which served to block vision from one table or a runway to another table but still allowed access to the table. See Fig. 1 for a detail of the tables. One each of 3 shallow dishes 2 inches in diameter and 1/4 inch high were placed on each table and served to contain the food.

The apparatus was located in a basement room, in which the animals were also housed. Outside noise and other undesired extraneous cues were at a minimum. Fig. 2 provides an illustration of the size and arrangement of the room. Since the position of the apparatus was rotated daily, its relationship to the room was not always the same as is pictured on the figure. Three of the walls of the experimental room were solid while the fourth was

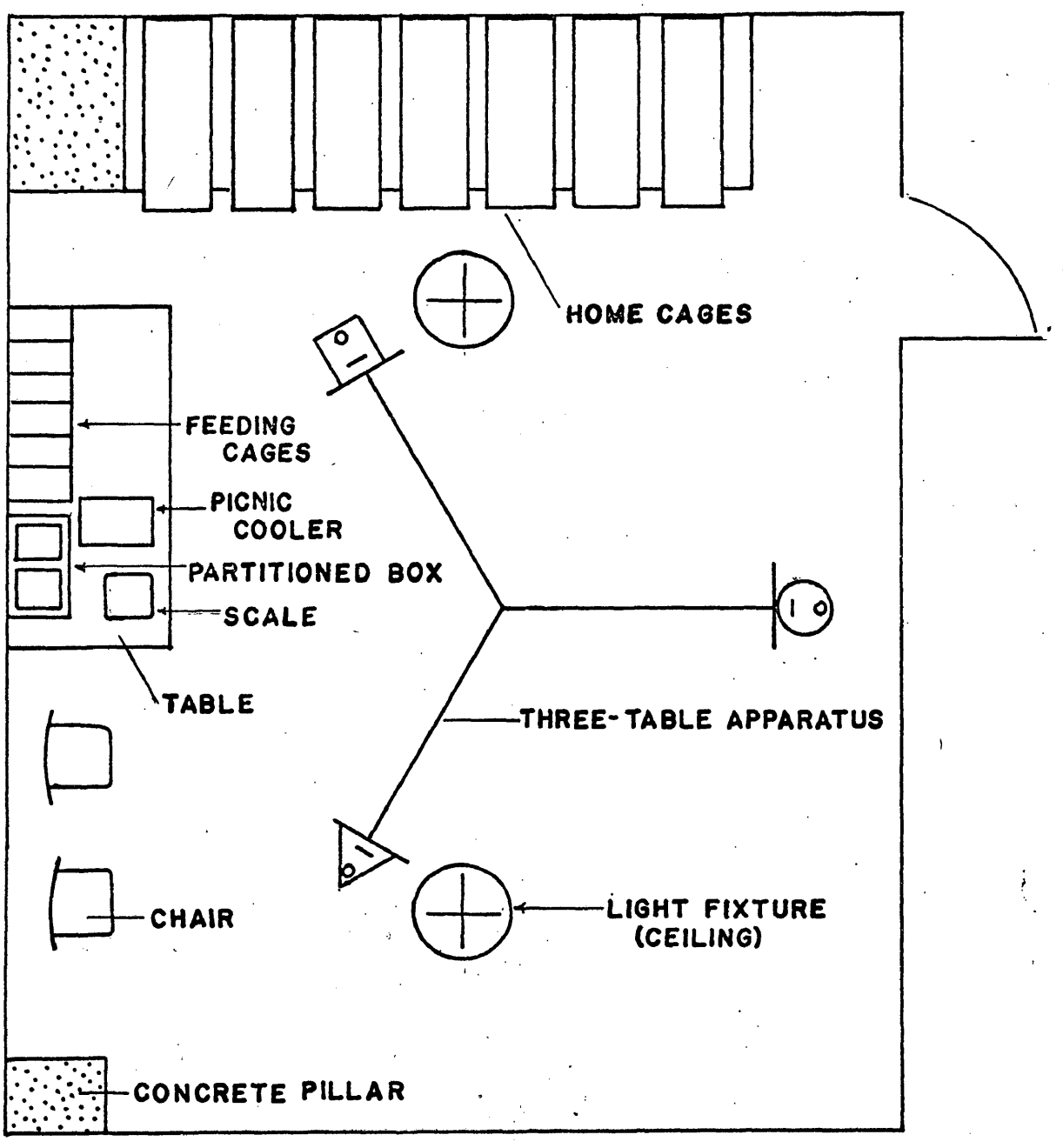

Fig. 2. Diagram of room arrangment.

constructed of 2 inch mesh wire netting, which acted as a partition to separate the experimental area from the rest of the room. Illumination was furnished by two overhead light fixtures which were fitted with 100 watt bulbs. At three different locales in the room, food was contained in open cups to help equalize olfactory cues present within the room.

Procedure

The animals were arbitrarily assigned to the groups so that there were equal representations of males and females within each group. There were 5 experimental groups and 2 control groups. They were allowed to feed ad lib. on Purina Laboratory Chow for the first week after they were received. At the beginning of the second week, each animal was weighed, placed on the apparatus, allowed to explore for 5 minutes, and then placed into a feeding cage for approximately an hour. No food was in the cups while the animals were exploring. During the exploration week and the remainder of the experiment, the animals were fed a pre-weighed amount of food which would maintain them at 80% of what their original weight had been. In all cases when the animals were being fed on schedule, the groups were trained in the same order during the same time of day as the previous day. When all of the animals of a group were in the feeding cages, the housing cage was taken from the table and as they were being placed into a feeding compartment,

the appropriate animal of the previous group was taken from that compartment and placed into the housing cage on the floor. During all trials, males and females were alternated to help eliminate any olfactory influence from animals having previously performed. After six days of exploring, the animals were given a rest day where they were fed on schedule but not placed on the apparatus.

On the eighth day the animals were begun on six days of practice trials as advised by Maier (1932). During the practice trials, each animal was placed in one partition of a two partition box for 10 minutes and then placed on the apparatus and allowed to explore for 5 minutes with the food cups empty. The animal was then taken from the apparatus and placed simultaneously with some Purina Laboratory Chow on a pre-determined table and allowed to eat for one minute. The subject was next placed on one of the other pre-determined tables and given seven minutes to locate the food again. Table 1 shows the random order of presentation on tables used by Maier (1932). Two randomized sets are given.

The first animal in a group was assigned to Series I and the second animal to Series II. This method of assignment was continued for all animals of all groups. When an animal had finished either Series I or II it was started on the opposite Series. The alternation of presentation of series was continued in the above mentioned manner throughout

the entire experimental session. After a trial, the animal was placed into a feeding cage and allowed an hour in which to eat the preweighed amount of food.

At the beginning of each day of trials the tables were revolved to a different position and fresh food was taped under the tables to equalize olfactory cues. The animal was always placed on the feeding table from the right side of the table and was taken to the starting table by the shortest route from the feeding table. When transported from one table to another, S was carried so that it would have E's body in between it and the apparatus. If the animal did not return to the feeding table within 7 minutes of being placed on the starting table, E would carry it to the feeding table and allow it to eat for approximately 30 seconds before placing it in the feeding cage.

After 6 days of practice trials, the animals were given another rest period. On the day preceding the rest period one more day of practice sessions was given. The day following the practice session, the same procedure was followed as before with the exception that after the animal was weighed, it was injected with the drug or placebo. Group VII control group was not injected at all. The syringe was loaded immediately before injecting the animal. All injections were made on the right ventral side. The animals usually offered no resistance and did not exhibit any signs of distress. To help alleviate any discomfort to

Table 1

Randomized Combinations for Presentation of the Three-Table-Test for Reasoning

Series I			Series II		
Day	Start	Food	Day	Start	Food
1	X	Y	1	Y	X
2	Z	X	2	Z	Y
3	X	Z	3	Y	Z
4	Y	X	4	X	Y
5	Y	Z	5	X	Z
6	Z	Y	6	Z	X

Table 2

Dosages of Eserine for the Various Groups of Rats

Group	Quantity of Eserine (γgm. per gm. body wt.)
I	.050
II	.075
III	.100
IV	.125
V	.150
VI	Saline only
VII	No injection

the animals, a needle was changed for a new needle after 12 injections. The groups were rotated so that every other day a group would receive injections with a needle that had been used on a previous group.

Two fresh standard solutions of drug were mixed each day. The first solution was used for Groups I, II, and III and the second standard solution was used for Groups IV and V. From the standard solution, a solution of proper dilution was mixed for each group approximately ten minutes before the first member of the group was to be injected. Table 2 gives the concentration of injection for each animal. All of the drug was dissolved in normal saline solution. All animals received the same proportional volume of injection relative to their body weight. Injections were made with a 2 c.c. syringe and 3/4 inch 25 gauge needles.

Following the injection, S was placed in the partitioned box and remained for 10 minutes to allow the drug time to take effect. After the 10 minute wait, the animal was treated as it had been the week prior to drug treatments. The days with the injections constituted the actual trials. There were 17 days of trials. After each 6 days of exposure to the apparatus, a rest day was introduced.

Two performance scores were recorded, number of correct trials, and number of errors. When the animal was placed on the starting table, a stop watch was started.

If S did not locate the correct table with the food on it within 7 minutes, it was taken to the table by E and allowed to feed for approximately 15 seconds before being placed in the feeding cage. If the animal went directly to the feeding table with no incorrect choices, the trial was counted as correct. If one or more errors were made before reaching the feeding table, the trial was counted as incorrect. An error constituted the choice of an improper runway or a U-turn leading away from the correct choice (Hamilton & Harned, 1944). An error was scored if the animal's hind feet entered onto an improper runway. An animal was considered to have reached a table if his front shoulders passed over the threshold of the table.

The temperature and relative humidity were noted each day. The temperature was maintained between 76 degrees and 84 degrees F. with no more than a 2 degree change during any single 6 day testing period. The relative humidity was maintained between 48 percent and 52 percent with no more than 2 percent relative humidity variation during any single 6 day test period.

RESULTS

The data (correct scores and errors) were subjected to an analysis of covariance according to the procedures described by Winer (1962, pp. 606-615). There were 7 treatment levels and 3 time periods. Each time period represented a block of 5 days. During the experiment, the time

periods were actually in blocks of 6 days. However, during one of the days, an accident with the handling of the drug prevented the trials from being run and so a day of trials was randomly eliminated from the other two weeks in order that equal numbers could be maintained within the cells. Since one of the animals died during the final week, the missing data for these 4 trials were estimated by the procedure recommended by Cochran & Cox (1957, p. 80). The covariate measure was the 6 day period of trials with no drug injection (with one day randomly eliminated to equal the number of the other groups). Despite random assignment of the animals to treatments, statistical tests indicated significant differences among mean scores during preliminary training. Use of pre-test scores as a covariate was introduced to compensate for this apparent initial inequality.

Bartlett's test indicated homogeneity of variance among the groups. When the criterion of number of correct trials was examined, the analysis of covariance indicated that there were no differences significant at the .05 level. Table 3 gives the summary of the analysis of covariance for correct scores. The analysis of covariance for errors (see Table 4) indicated that there was a difference between the corrected treatment levels significant at the .05 level. There were no significant differences attributable to time of testing or interaction of time and drug level.

Table 3

Analysis of Covariance for Correct Scores

Source	S.S.	d.f.	M.S.	F ratio
Drug Level	9.38	6	1.56	1.30
Subj. within Drug Level	42.11	35	1.20	
Time	.68	2	.34	
Drug X Time	12.43	12	1.04	
Residual	76.22	70	1.09	
Drug Level (adjusted)	9.34	6	1.56	1.28
Subj. within Drug Level (adj.)	41.46	34	1.22	

Table 4

Analysis of Covariance for Error Scores

Source	S.S.	d.f.	M.S.	F ratio
Drug Level	52.74	6	8.79	2.22
Subj. within Drug Level	138.56	35	3.96	
Time	7.35	2	3.68	
Drug X Time	37.21	12	3.10	
Residual	263.44	70	3.76	
Drug Level (adjusted)	52.63	6	8.77	2.53 *
Subj. within Drug Level (adj.)	117.55	34	3.46	

* $p \leq .05$

DISCUSSION

Since there were no significant differences in the correct scores, it indicated that the drug had no significant effect on the ability of the Ss to make a correct choice. In describing the sixth or inferential level of learning, Tolman says, "After having learned the general path sequences, the animal is given a reward . . . directly at some specific locus at a point distant from the entrance and is then carried back . . . to the entrance and is required 'inferentially' to expect this distant reward . . . so that he thereupon takes . . . the appropriate new path for getting to such more distant point." (Tolman, 1937, pp. 205-206). The drug levels in this experiment did not significantly affect the ability of S to take the appropriate new path for getting to the appropriate more distant point which indicates that the drug Eserine does not affect performance on Tolman's inferential level of learning as measured by Maier's three-table-test. The drug Eserine did, however, appear to affect the number of errors made. It is suggested that the errors made are not as good a measure of Tolman's inferential level of learning as are the correct scores but rather are more appropriately a measure of trial and error behavior. The reason for this conclusion is that if the animal made one error by going to an incorrect table, since he had just come from the other incorrect table, it

was merely a matter of making the only final choice thus lending the situation to trial and error performance. The correct score indicated that the animal went straight to the correct table without trial and error behavior.

The next question is why Eserine will affect performance on lower level learning tasks but not on higher level learning tasks (Tolman's inferential level as measured by Maier's three-table-test). As discussed earlier, measures were exercised in this experiment which helped limit the cues available to S to the apparatus and thus brought the task into closer agreement with Maier's definition of reasoning (and Tolman's definition of inferential learning). These measures were not considered by earlier experimenters (including Maier). It is therefore suggested that the answer to the question, why Eserine did not affect higher level learning performance, is that when Maier's three-table-test is used with proper controls, animals cannot solve the problem. In order to solve the problem, it is essential that the animals employ a lower level trial and error learning. Wolfe & Sprague (1935) hinted at this when they duplicated Maier's procedure and concluded that learning was involved but that reasoning was not. Maier (1935) replied with a criticism of the age of Wolfe & Sprague's animals. According to Maier, it is desirable and sometimes necessary to have animals up to or over 120 days old. However, Hanson (1949), after working with 100 animals of both sexes on the three-table-test concluded

that age makes no difference on performance if the animals are first accustomed to the apparatus. The animals in this experiment were accustomed to the apparatus and were 115 days old at the beginning of the experimentation.

Maier (1932) reported the performance of his rats on the three-table-test using the formula correct scores minus incorrect scores divided by the total number of scores. He considered .33 to be the minimum score of acceptable performance. He reported that in general the scores of animals were between .70 and .80. Of the animals in the current experiment, only 6 performed at .60 or better (3 animals at .60 and 3 animals at .73) and twenty of the animals were below .33. While it is possible that the drug injections interfered with the performance of the animals, Group VII (no injection group) had 3 animals with .47 and the other 3 animals were below .33. These results indicate that the animals in this experiment were performing considerably more poorly than were Maier's animals. This adds additional support to the possibility that the animals were having more difficulty solving the problem than were Maier's animals. Since, as discussed earlier, this experimenter used some additional controls which Maier did not use, it is suggested that these controls were responsible for the poor performance of the animals in the current experiment. The difficulty the Ss had in solving this problem may have affected the experimental results and

obscured any drug level differences which might have otherwise been present. If the effects of Eserine on Tolman's inferential level of learning are to be further investigated, it is suggested that a test be employed which is one other than Maier's three-table-test. Further investigation should be made of Maier's three-table-test to determine if the animals can solve it when the cues are restricted to just the apparatus.

Next, it is of interest to examine the shape of the curve which demonstrates the nature of the error performance differences found between the treatment levels. Table 5 gives the adjusted means for the treatment levels and Fig. 3 shows the graphic relationship. A test of the differences between the means using the Newman-Keuls procedure (Winer, 1962, pp. 309-310) indicates that at the .05 level of significance all groups differ from Group I but do not differ between themselves. A contradiction to expected results is that the low dosage level (Group I) produced more errors than did the two control groups (VI and VII) which involved no drug. Why should the lowest level of Eserine produce more errors than the control groups while the other groups did not produce a significantly greater number? It will be noted that Merrill (1961) obtained a curve with the same relationship between the low drug and control group (Table 6 and Fig. 4). Bennett, Diamond, Krech, & Rosenzweig (1964) point out that there are

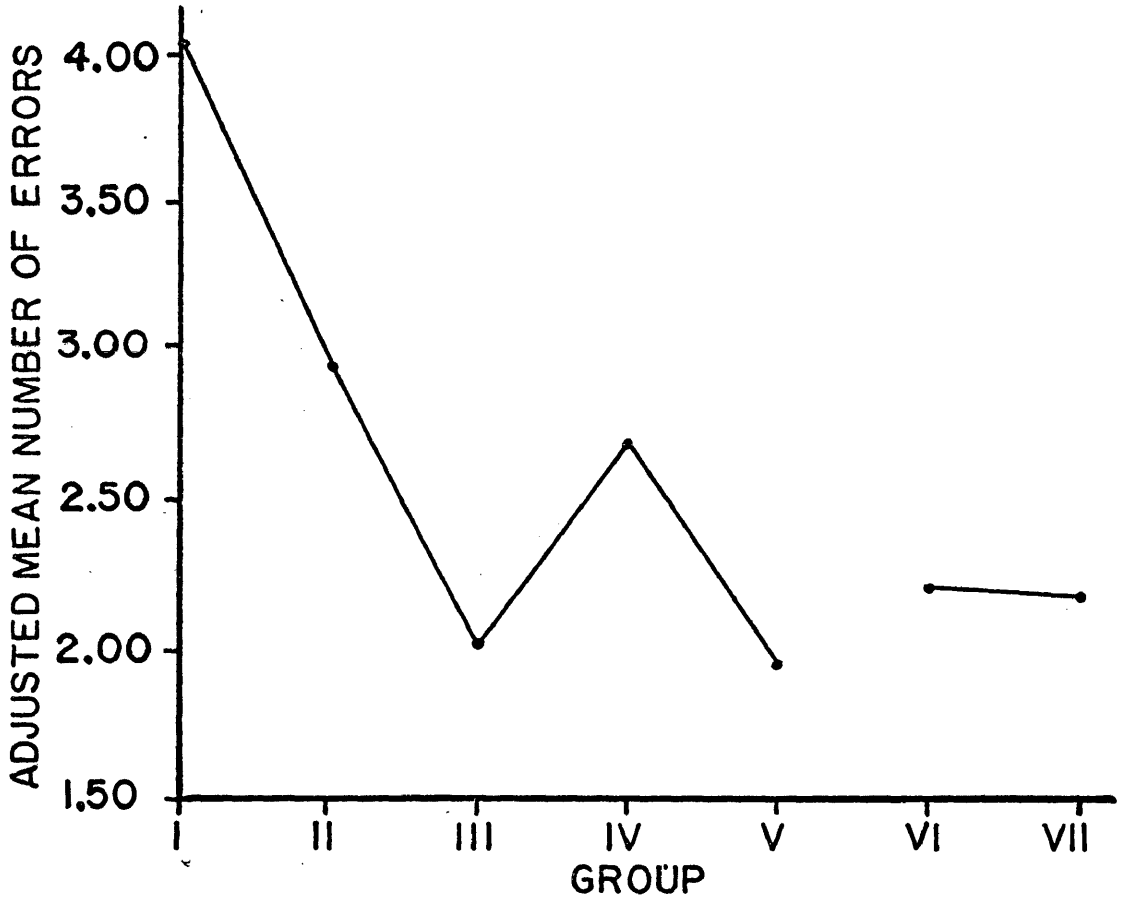

Fig. 3. Comparison of adjusted group means.

Table 5

Adjusted Mean Values for the Error Scores

Group	Adjusted Mean
I	4.02
II	2.95
III	2.05
IV	2.69
V	1.94
VI	2.31
VII	2.29

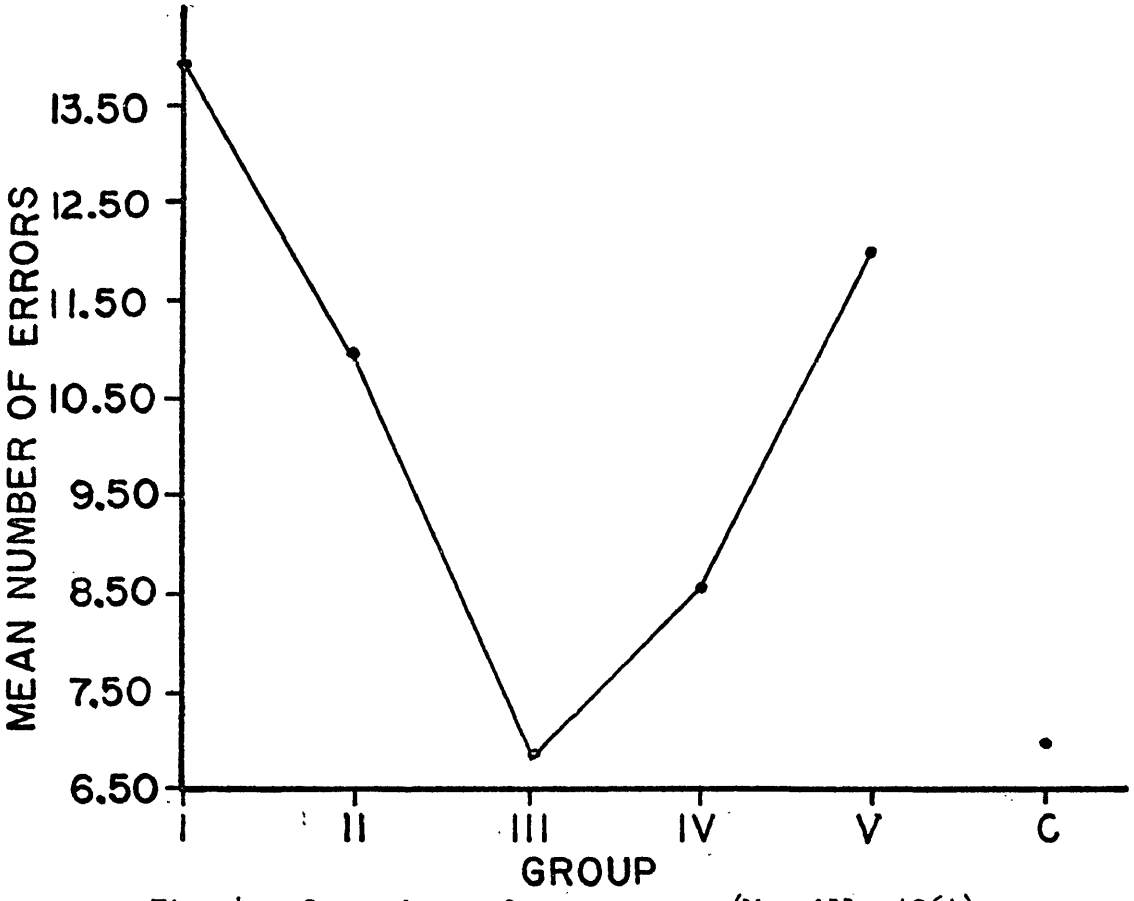

Fig. 4. Comparison of group means (Merrill, 1961).

Table 6

Mean Values for the Error Scores (Merrill, 1961).

Group	Mean
I	14.00
II	11.00
III	6.60
IV	8.50
V	12.00
Control	7.00

other chemicals involved in learning performance other than the acetylcholine-cholinesterase relationship. Therefore, another possible explanation for the unexpected relationships on the curve could be that the task which is required on Maier's three-table-test, even though involving trial and error behavior, is of a different nature chemically from the maze learning of previous experiments with ChE levels. As was suggested previously in this discussion, the animal may have been performing a delayed reaction task which, according to Tolman, is on a higher level than maze learning. The trial and error performance in a delayed reaction experiment could involve different chemical relationships from the maze learning task. The possibility of different chemical interactions for tasks of different complexity levels offers a possible explanation as to why ChE inhibitors have one effect on maze learning but a different effect on the Maier three-table-test.

More research is necessary investigating the relationship of ChE to higher level learning tasks. Also, the drug Eserine should be examined for its specific relationship to those chemicals relating to cortical activity.

SUMMARY

Several studies were cited which presented evidence that cholinesterase inhibitors facilitate performance of mice on learning tasks. No such published studies had apparently been conducted examining the effects of a cholinesterase inhibitor on higher level responses.

Maier (1929) found that rats could apparently combine two separate experiences to produce a response. He later defined this ability as reasoning. Maier's reasoning is considered to be the same as Tolman's (1937) sixth or inferential level of learning and the two terms were used interchangeably in this study. Maier (1929) designed the three-table-test to test reasoning ability in rats.

The present study used Maier's three-table-test to measure the effects of a cholinesterase inhibitor (Eserine) on the inferential level of learning of rats. Five gradated dosages of Eserine were injected into the peritoneal cavity of five different groups of rats with 6 rats in each group. Two control groups were used, one receiving saline injections and the other receiving no injections.

The scores were recorded in terms of number of errors made and number of correct first attempts. A complex analysis of covariance was conducted comparing the performance of each group with every other group and also comparing performance over time as well as drug level and time interactions.

There were no significant differences between the correct scores at the .05 level or beyond. The error scores indicated a significant difference at the .05 level between drug levels.

It was concluded that Eserine did not affect inferential learning performance on the three-table-test. However, Eserine does appear to have an effect on lower level learning and it was suggested that the three-table-test is in reality testing nothing other than Tolman's third or trial and error level of learning. The nature of the relationship of one drug level to another was not what would be expected for the simple maze learning tasks. It was suggested that the performance demanded of the animals in Maier's three-table-test involves different cortical chemical processes than does the performance on maze learning tasks. The need for further investigation is indicated.

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