The Effects of Life Cycle Therapeutic Dosage Administration of Drugs to Albino Rats

II. On Activity, Maze Learning and Relearning*†

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An earlier paper (1) has presented some of the effects of life cycle, oral therapeutic dosage administration of thirteen drugs to albino rats of the Wistar strain. Housing conditions, general care and diet, drug administration, formation of control and test groups were also discussed.

In the present study a maze was used primarily for the purpose of determining the effect of certain drugs administered daily for long periods of time on the activity of treated animals as compared to that of litter mate controls. Shirley (2) has found the revolving cage to be an excellent tool for studying the activity of the normal rat, but the writer has found it extremely inaccurate as a means of determining activity variations. The elevated *T*-maze has been found to express variations in activity drive with a high degree of accuracy. The animal is placed in a position which approaches the normal. He may run or not as he wishes.

A very simple pattern of elevated *T*-maze was used because of space limitations (Fig. 1). It was constructed of seventeen sections presenting sixteen culs-de-sac. The running strips were one inch wide and the total direct distance between starting point and goal was 35 ft.

Manually controlled drops were placed at seven points on the maze, the locations of which are shown in Fig. 1. These drops were used to prevent backtracking, a factor that must be eliminated if travel time and total time on the maze are to have any significance. The drops were constructed of light tin plates which were cushioned with rubber to insure a minimum of noise. They were operated individually by strings.

The same maze procedure was followed for all test and control groups run on the maze during the study. Experiments were started at 8 p. m., an animal from a control or test group being placed at the starting point at this time. Thereafter, the animals in the control and test groups were alternated on the maze until all had completed a run during the same evening or night. The animals were not touched after being placed on the maze. Food consisting of powdered crackers and milk was placed at the end of the maze, but the animals were not aware of its presence there until they had completed the first run. Similar dishes of food were placed at the right and left of the center of the maze in an attempt to rule out the sense of smell as a factor in maze learning.

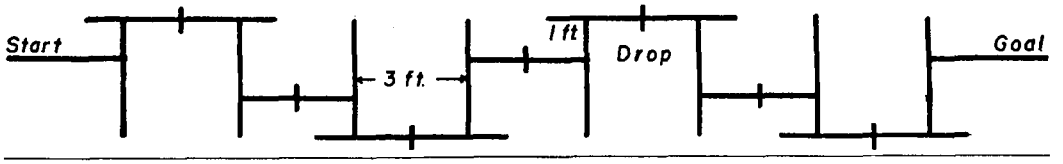

Fig. 1.—Diagram of *T*-Maze.

The maze was cleaned thoroughly each night after a group had completed a run, with a pinoleum antiseptic. Sections to which drops were not attached were reversed at this time.

Test groups to be run on the maze were deprived of the regular evening drug feeding which was given to the animals after the runs were completed. Purina Fox Chow briquets *ad libitum* were substituted for the normal cooked diet during maze learning and relearning periods. This change served to establish enough hunger to insure reasonable activity in most instances.

The animals were placed on the maze on successive nights until each rat in the test and control groups had completed three consecutive trials without error. A record of trials, errors, travel time, *i. e.*, time in motion, and total time on the maze was kept for each animal.

The drugs investigated in this manner are listed in Table I together with the dosage schedule. Summaries of results obtained, except for barbital and amytal, are presented in Tables II to VI, inclusive. The values listed are average values in each instance and represent the average for the group in completing three successive runs without error. The age of all groups, the number of rats per group and the length of drug feeding periods are included in the tables.

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Relearning trials were executed in the same manner as the learning trials, with the exception that the caffeine animals and their controls were given only six trials during relearning. The rats in these groups were considerably younger than those in other groups, and the interval between learning and relearning was only about half as long.

TABLE I.—DRUGS AND DRUG DOSAGE PER KG. OF RAT

Drug	70–200 Days, Mg.	200–300 Days, Mg.	300 Days to End of Period, Mg.	Average Human Dose, Gm.
Caffeine	3.0	6.0	9.0	0.20
Aspirin	4.3	8.6	12.9	0.30
Aminopyrine	4.3	8.6	12.9	0.30
Antipyrine	4.3	8.6	12.9	0.30
Barbital (Na)	7.1	14.2	14.2	0.50
Amytal (Na)	2.0	4.0	6.0	0.15
Phenobarbital (Na)	0.9	1.8	2.7	0.03
Alurate (Na)	2.0	4.0	6.0	0.15
Allonal				
Alurate	1.7	3.4	5.1	0.12
Aminopyrine	3.0	6.0	9.0	0.20

CAFFEINE (TABLE II)

Cheney (3) has studied the effect of caffeine on reaction time in humans. Doses below 3.0 mg./Kg. body weight had no effect, while doses between 3.0 and 4.0 mg./Kg. produced variable effects. However, doses above 5.0 mg./Kg. always produced a decrease in reaction time over at least a 3-hr. period.

Horst and Jenkins (4) obtained similar results with doses as low as 2.0 mg./Kg., the effect frequently being observed for 24 hrs. after administration. The doses used by these experimenters for humans compare favorably with the doses used by the writer for albino rats.

Lashley (5) has given caffeine to albino rats 10 min. before placing the animals on the maze, in doses corresponding by weight to 4- and 8-grain doses for man. He states that caffeine retards learning in rats in direct proportion to the size of the dose, and that large doses of the drug result in increased activity and reduced accuracy of performance.

Macht (6) has given caffeine to trained adult rats in doses varying from 10 to 50 mg./Kg. Excitement was produced in 71% of the experiments, while depression resulted in 24%. No effect was observed in 5%.

From the results presented in Table II, it would seem that caffeine as administered during this study stimulated all phases of maze behavior in female rats. A marked increase in activity was especially noticeable while these animals were on the maze. The normal animal, or an animal not motivated by some type of drive such as thirst or hunger, will frequently loiter at the starting position for long periods, and will usually feel his way rather carefully as he progresses. The caffeine females, however, started forward almost at once and actually appeared to be running at full speed even before the maze was learned. They would frequently run into a cul-de-sac so rapidly that they would be unable to stop. Although they would often run over the end, they were invariably able to pull themselves back to the top of the running strip. This excessive activity was not observed in any other group placed on the maze.

As has been stated in an earlier paper (1), the caffeine females evidenced an increased activity in the cage. They also appeared to have increased appetites, although there was no evidence of an increase in food consumption. The caffeine females were also considerably below their controls in weight at this period. This weight and apparent appetite difference may have been responsible, in part at least, for the marked increase in activity in the caffeine females. A lack of hunger drive was evidenced, however, by the fact that the animals infrequently ate the food when finally reaching goal.

Relearning trials for females produced about the same activity and error variations as did learning.

Horst and Willson (7) have reported a sex variation in humans in the effects of caffeine, the dosage ratio for men and women being about 2:1.

The results presented in Table II suggest a similar sex variation for albino rats, for, while caffeine stimulated all phases of maze behavior in females, this effect is very slight or completely lacking for males. The per cent of errors is observed to have been increased for caffeine males during both learning and relearning. During the six trials of relearning the six caffeine males made, respectively, five, seven, eight, two, four and three errors while the

TABLE II.—MAZE LEARNING AND RELEARNING OF CAFFEINE GROUPS, MALE AND FEMALE

	Males[a]			Females[b]		
	Test Group, 6	Controls, 5	Variation from Controls, %	Test Group, 7	Controls, 5	Variation from Controls, %
LEARNING						
Av. trials	15	17	−13	18.4	24.4	−24
Av. errors	60	49	+22	55.0	78.0	−29
Travel time	9.7 min.	11 min.	−12	9.7 min.	15.4 min.	−37
Total time	48.0 min.	51 min.	− 6	29.3 min.	71.0 min.	−59
RELEARNING[c]						
Av. errors	4.8	1.8	+17	13.0	16.6	−22
Travel time	146 sec.	156 sec.	− 6	144 sec.	208 sec.	−30
Total time	10.2 min.	7.3 min.	+38	9.9 min.	16.7 min.	−40

[a] Initial age 38 weeks, 28 weeks on drug.
[b] Initial age 39 weeks, 29 weeks on drug.
[c] Six trials for all groups: males, 6 weeks after learning; females, 11½ weeks after learning.

five controls made one, five, one, one and one errors. The six caffeine males made sixteen perfect runs during relearning, an average of 2.7. The five controls made twenty-three perfect runs, an average of 4.6.

ANTIPYRETIC DRUGS

There is little evidence in the literature of antipyretic drug effects as a result of continued administration, upon activity or learning. Jones (8) has attempted to determine the effect of aspirin upon learning in human beings and states that the drug seems to have a neutral effect.

Macht and Bloom (9) have studied the effect of single doses of quinine sulfate, salol, sodium salicylate, acetanilid, phenacetin, antipyrine and aminopyrine on the behavior of rats in the circular maze. Relatively small doses of 10 mg. or less were used, the performance of the animals being determined before, 1/2 hr. after and 3 hrs. after administration. They conclude that all of the antipyretics depress the behavior and memory habits of rats. Antipyrine and aminopyrine were the most effective in this respect, according to these authors.

The effects of three antipyretic drugs on maze activity and maze learning and relearning have been studied during this investigation. Two of these, antipyrine and aminopyrine, are included in the reference presented above. The third antipyretic, aspirin, is similar in its actions to the salicylates two of which were studied by Macht and Bloom (9).

Aspirin effects (Table III) on maze performance during learning are rather varied although the tendency is toward depression. Total time on the maze was increased significantly for both test groups, as was travel time for males. The relearning data for females reveal further evidence of depression, although a negative variation for total time has replaced a rather high positive variation obtained during learning. This change is even more marked for males, from +62% during learning to −16% during relearning. Trials and errors for males reveal no effect. The same data for females, while significantly higher than for the controls in three instances, show a slight decrease in average errors during learning.

Aminopyrine (Table IV) may be said to have had no depressant effect on maze behavior during learning. There is, in fact, a significant decrease in total time as compared to controls. Antipyrine, however, has caused some depression, especially in activity on the maze.

There can be little question as to the depressant effect of these two antipyretics during the relearning period. Large positive variations, coupled with the fact that the animals appeared completely lost during much of the relearning process, lead the writer to concur with Macht and Bloom (9) in their state-

TABLE III.—MAZE LEARNING AND RELEARNING OF ASPIRIN GROUPS, MALE AND FEMALE

	Males[a]			Females[b]		
	Test Group, 7	Controls, 6	Variation from Controls, %	Test Group, 6	Controls, 6	Variation from Controls, %
LEARNING						
Av. trials	21	19.7	+ 7	17	15	+13
Av. errors	106	105.0	+ 1	68	70	− 3
Travel time	16 min.	12.4 min.	+29	8.5 min.	8.1 min.	+ 5
Total time	118 min.	72.6 min.	+62	68 min.	54 min.	+26
RELEARNING[c]						
Av. trials	11.8	11.7	+ 1	10.0	8.7	+15
Av. errors	23.0	23.5	− 2	18.7	16.3	+15
Travel time	5.6 min.	4.0 min.	+40	5.3 min.	3.9 min.	+36
Total time	20.7 min.	24.4 min.	−16	17.6 min.	18.5 min.	− 5

[a] Initial age 70 weeks, 60 weeks on drug.
[b] Initial age 62 weeks, 52 weeks on drug.
[c] Males, 10 1/2 weeks after learning; females, 12 1/2 weeks after learning.

TABLE IV.—MAZE LEARNING AND RELEARNING OF AMINOPYRINE AND ANTIPYRINE GROUPS, FEMALE

	Aminopyrine			Antipyrine	
	Test Group, 8	Variation from Controls, %	Controls, 7	Test Group, 7	Variation from Controls, %
LEARNING[a]					
Av. trials	17.3	+ 2	16.9	18.0	+ 6
Av. errors	79.0	− 1	79.4	86.4	+ 9
Travel time	7.5 min.	+ 3	7.3 min.	8.7 min.	+19
Total time	53.4 min.	−17	64.6 min.	74.3 min.	+15
RELEARNING[b]					
Av. trials	14.9	+26	11.8	16.0	+36
Av. errors	43.1	+75	24.6	55.0	+124
Travel time	7.3 min.	+30	5.6 min.	7.9 min.	+41
Total time	46.2 min.	+113	21.7 min.	43.0 min.	+98

[a] Initial age 59 weeks, 49 weeks on drug.
[b] Twelve weeks after learning.

ment that aminopyrine and antipyrine are powerful depressants when judged by their effects on maze behavior.

BARBITURIC ACID DERIVATIVES

Omwake (10) has given 100 mg./Kg. doses of barbital to male and female rats on alternate days for 4 1/2 months, reporting only a slight decrease in activity. The ability to locate a reward in a maze in 30 min. showed no significant differences between treated and control animals, but the percentage of barbital rats successful in 5 min. was definitely lower, according to this author.

Fields (11) has found that the daily administration of 1/8-grain doses of phenobarbital to rats for 18 days did not interfere with learning or retention of maze patterns. The phenobarbital animals were more active but made more errors.

Russell and Hunter (12) have completely anesthetized rats with sodium amytal following five trials on the maze. Results obtained from five trials following anesthesia failed to show a significant difference between the retest records of normal animals and the retest records of anesthetized animals.

Williams (13), Williams and O'Brien (14) and Mendenhall (15) have determined the effects of sodium phenobarbital on maze performance and all report a marked inferiority in the drugged animals as measured by errors and time, in both learning and relearning. A similar inferiority was observed by Mendenhall (15) in two reasoning problems.

The maze behavior effects of five barbituric acid derivatives, including allonal, were studied during this investigation and the results bear out the findings of Williams (13), Williams and O'Brien (14) and Mendenhall (15).

Five barbital males were placed on the maze after 69 weeks of continuous drug feeding, at 79 weeks of age. None of the five animals showed more than a suggestion of activity during the first seven trials. One hour before the eighth trial was to begin, the group was given 5 mg. of caffeine per rat orally. When placed on the maze following this dose of caffeine, three of the five climbed down immediately, one left the maze at the eighth intersection, and the fifth animal completed the run after 10 min. and 16 sec., making sixteen errors. In ten trials for each of the five barbital animals, only four completed runs were made, two by each of two animals.

Five amytal males, litter mates of the barbital males, were continued on the maze for twelve trials with ten litter mate controls. The amytal animals were sluggish as compared to the controls but they were much more active than the barbital animals. During these twelve trials the amytal rats made 26% more errors than the controls, the travel time was 41% greater and the total time 44% greater. The

TABLE V.—MAZE LEARNING AND RELEARNING OF SODIUM PHENOBARBITAL GROUPS, MALE AND FEMALE

	Males[a]			Females[b]		
	Test Group, 6	Controls, 6	Variation from Controls, %	Test Group, 6	Controls, 6	Variation from Controls, %
LEARNING						
Av. trials	21	19.6	+ 8	19.4	15	+29
Av. errors	126	104.7	+20	93.5	70	+37
Travel time	15.4 min.	12.7 min.	+24	9.7 min.	8.1 min.	+20
Total time	93.7 min.	72.6 min.	+28	64.0 min.	54.0 min.	+19
RELEARNING[c]						
Av. trials	16	11.7	+37	13.0	8.7	+59
Av. errors	36	23.5	+53	32.0	16.3	+106
Travel time	6.7 min.	4.0 mm.	+67	6.0 min.	3.9 min.	+37
Total time	63.3 min.	24.4 min.	+155	65.4 min.	18.5 min.	+250

[a] Initial age 70 weeks, 60 weeks on drug.
[b] Initial age 62 weeks, 52 weeks on drug.
[c] Males, 10 1/2 weeks after learning; females, 12 1/2 weeks after learning.

TABLE VI.—MAZE LEARNING AND RELEARNING OF ALLONAL AND SODIUM ALURATE GROUPS, FEMALE

	Allonal			Alurate	
	Test Group, 8	Variation from Controls, %	Controls, 7	Test Group, 7	Variation from Controls, %
LEARNING[a]					
Av. trials	19.6	+13	17.3	18.7	+ 8
Av. errors	107.0	+32	81.0	97.0	+20
Travel time	11.0 min.	+30	8.5 min.	9.6 min.	+13
Total time	69.3 min.	+26	55.1 min.	58.8 min.	+ 6
RELEARNING[b]					
Av. trials	17.3	+66	10.4	14.9	+43
Av. errors	59.0	+124	26.2	51.2	+96
Travel time	9.2 min.	+84	5.0 min.	8.3 min.	+66
Total time	48.0 min.	+95	24.6 min.	42.0 min.	+70

[a] Initial age 50 weeks, 40 weeks on drug.
[b] Eleven weeks after learning.

ten controls made sixteen perfect runs during the period as compared to five for the five amytal rats. Three of the ten controls failed to make a perfect run in twelve trials as compared to three of five amytal rats.

Maze behavior effects of sodium phenobarbital on male and female rats, and of allonal and sodium alurate on females, are presented in Tables V and VI. Sluggishness was observed during learning in both phenobarbital groups and allonal. It was very evident for all test groups during the relearning period. Attention is called to the fact that the phenobarbital females required $3^1/_2$ times as much total time during relearning as did their litter mate controls, while the phenobarbital males required $2^3/_5$ times as much as their controls. Travel time for all groups shows a less marked but consistent positive variation for all test groups.

All test groups were inferior in learning to the controls and this inferiority was even more marked during relearning.

Allonal seems to have exerted a stronger depressant effect than alurate, the barbituric acid derivative contained therein. This is undoubtedly due to the presence of aminopyrine in the compound since this drug has been shown to exert a powerful depressant effect upon maze performance during the relearning period.

SUMMARY

The effects of continuous daily oral administration of nine commonly used drugs on maze performance in albino rats have been presented. The drugs were administered in doses approximating, on a weight basis, the average daily therapeutic dose for adult humans. Test groups and litter mate controls were subjected to maze learning after drug feeding periods varying with the group, from 28 to 69 weeks. All groups, with the exception of sodium barbital and sodium amytal, were allowed to relearn the maze after rest periods varying from 6 to $12^1/_2$ weeks.

Caffeine has stimulated all phases of maze performance in female rats during both learning and relearning. Activity was affected most noticeably. Caffeine males failed to show a similar stimulation. There were, in fact, some evidences of depression during relearning in these animals.

Of three antipyretic drugs investigated, aspirin had the least effect. There is, however, some evidence of depression during learning in males and during relearning in females.

Aminopyrine exerted no depressant effect during learning. The total time on the maze was significantly less than for controls. Antipyrine animals exhibited some depression during learning and both drug groups were markedly depressed in all phases of maze performance during relearning.

All five barbituric acid derivatives were found to exert a powerful depressant effect, more especially on activity as judged by travel time and total time records. While it is difficult to draw comparisons because of differences in age and length of feeding periods for the barbiturate groups, the author would list the five barbituric acid derivatives tested, in order of increasing depressant effect, as follows; sodium alurate, allonal, sodium phenobarbital, sodium amytal, sodium barbital.

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