ANATOMICAL AND BEHAVIORAL EFFECTS OF 5-FLUORO-2-DEOXYURIDINE ADMINISTRATION TO RATS AT DIFFERENT PHASES OF CENTRAL NERVOUS SYSTEM DEVELOPMENT

By

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DEDICATION

This dissertation is the culmination of a quarter of a century of education; for education is but life itself. It is dedicated to those who have taught me, and shared with me, the power and passion of life.

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It is very sad, looking back, to have to thank those that you are about to leave. Words often fall short of feelings. I hope that each of you knows how much I have cared if I am unable to fully express it on this page.

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Pregnant Long Evans rats were injected subcutaneously with either 30mg/kg 5-fluro-2-deoxyuridine or water on Days 10 and 11, Days 13 and 14, or Days 16 and 17 of gestation. All groups were fostered to nontreated mothers at birth. During adulthood all animals were tested on a variety of behavioral tasks. Motor deficits were found in all three treated groups when tested for the ability to walk on parallel bars. None of the three treated groups were found to differ from controls in audiogenic seizure susceptibility. Activity decreases were seen in animals treated on Days 13 and 14 and Days 16 and 17. Although all groups learned a spatial discrimination in a T-maze with little difficulty, animals treated on Days 13 and 14 and Days 16 and 17 performed poorly on the position reversals, with the animals treated on Days 13 and 14 performing more poorly than those treated on Days 16 and 17.

INTRODUCTION

Cells of the central nervous system (CNS) are vulnerable to any agent or environmental condition which interferes with their proliferation, migration, or differentiation. All parts of the CNS do not develop simultaneously. Since each structure in the CNS has its own time table of maturation, at a given prenatal time some cell population will be especially vulnerable to factors which interfere with their development or existence. Other less active populations will be less affected. Agents interfering with cell proliferation on different days of development of the CNS will consequently result in cellular deficits and deformities in different regions of the adult brain. It would also be expected that different behavioral deficits arise as a consequence of intervention on different days of gestation because of the different cell populations affected.

The present study was an attempt to investigate this possibility by administering 5-fluoro-2-deoxyuridine (FUDR) during three different periods of pregnancy, Days 10 and 11, 13 and 14, or 16 and 17. FUDR inhibits the activity of the enzyme thymidine synthetase, thereby blocking DNA replication (Bosch, Harbers & Heidelberger, 1958; Taylor, Haut, & Tung, 1962; Reyes & Heidelberger, 1965; Conrad & Ruddle, 1972), and has been shown to inhibit cell division in the developing nervous system (Langman, Shimada, & Rodier, 1972; Andreoli, Rodier, & Langman, 1973; Webster, Shimada, & Langman, 1973).

In an attempt to find behavioral correlates of the predicted anatomical disruptions, we tested the animals using several techniques which have been shown to be sensitive indications of level of functioning of the CNS after teratological intervention. Changes related to prenatal intervention have been found in activity (Furchtgott & Echols, 1958a; Werboff, Havlena & Sikov, 1962; Petit & Isaacson, in press), audiogenic seizure susceptibility (Geller, 1973; Petit & Isaacson, in press), walking on parallel bars (Werboff, Goodman, Havlena & Sikov, 1961; Furchtgott & Echols, 1958b), and T-maze learning and reversal learning (Haddad, Rabe, Laquer, Spatz, & Valsamis, 1969; Furchtgott, Jones, Tacker & Deagle, 1970). Thus, on the basis of prior research, we selected these procedures for the study of animals born to FUDR treated mothers.

METHOD

Timing of Pregnancy

Female Long Evans hooded rats (Rattus norvegicus) were placed with males and vaginal smears were taken every morning. The day on which sperm were found in the smear was considered Day 0 of pregnancy (E0). Animals were then randomly assigned to either three experimental groups or three control groups and housed singly. Mating was continued until two mothers and two corresponding foster mothers for each experimental and control condition were obtained.

Experimental and Control Treatments

All injections were made subcutaneously. On E10 and 11, two mothers received 30mg/kg FUDR (dissolved in distilled water), while two mothers received distilled water injections as a control. On E13 and 14, another two mothers received 30 mg/kg FUDR while two mothers received distilled water injections. On E16 and 17, an additional two mothers were given 30mg/kg FUDR and two mothers received distilled water. Thus, each experimental and control mother received one injection on each of two successive days of pregnancy. Foster mothers were left undisturbed throughout pregnancy.

Fostering and Postnatal Rearing

Within 12 hrs after birth, litters from all experimental

and control mothers were culled to 12 pups and fostered to normal mothers which had delivered no more than 24 hrs earlier. All offspring were then left undisturbed until Postnatal Day 23 (PN23), when they were earmarked and separately housed. From the two litters comprising each experimental and control group, 16 animals were randomly selected for testing, one half of the animals in each group coming from each litter.

Apparatus and Testing Procedure

Beginning at PN45 the animals were handled for 5 min daily for 3 days. On PN48, 49, and 50 the animals were tested for locomotor activity in an automated activity arena for 5 min each day (see Lanier & Isaacson, 1974), for details of the apparatus.

Starting on PN51, the animals were placed on a 23-hr water deprivation schedule. Starting on PN54, the animals were allowed to explore a T-maze for 3 days in groups of eight. The alleys of the apparatus were 11 cm wide and 14 cm high with a hinged plexiglas top. The stem was 90 cm long with a 27 cm start box at the end. Each arm was 47 cm long, with a water spout at the end protruding 1 cm into the arm. Clear guillotine doors were located between the start box and the stem, and in each of the arms adjacent to the choice point. Preliminary exposure lasted 1/2 hr for each group and consisted of handling, apparatus exploration, and drinking in

the goal compartments. During preliminary exposure, water was available in both arms of the maze. On the fourth day, the animals began training on a spatial discrimination in the T-maze. The animals were trained to go to the right arm of the maze for water reinforcement; the left arm contained a spout from an empty water bottle. After entering the correct arm the plexiglas guillotine door was lowered and the animal was allowed to drink for 10 sec before being returned to the start chamber to begin the next trial. If the animal entered the incorrect arm, the guillotine door was lowered to prevent a corrective response, and the animal was left for 10 sec before being returned to the start chamber. The animals were given 10 trials per day until a criterion of no more than two errors in two successive days was reached. Upon reaching criterion, each animal was begun on reversal training, during which water was available in the left arm of the maze. During the reversal learning the animals were given 10 trials a day until reaching a criterion of no more than two errors in 1 day. When the animals reached criterion on the reversal, the position of the water was again switched to the right arm of the maze. They were run to criterion performance again. Once more a change in the location of the reward was made as the animal reached criterion, for a total of three reversals.

Following reversal learning, all animals were maintained on 23-hr water deprivation and tested for their ability to walk on two horizontal bars 36 in long, set 1.5 in apart, and connected to a supporting panel at both ends. One end had a

water tray placed against a dark surface and was designated the goal. The other end, the starting point, had a light surface. The rods were marked off in inches. The animal was first placed at a distance of 6 in from the goal end of the rods with front and rear feet in position and facing the water tray. If the animal reached the water it was placed 12 in, then 18 in, or farther from the goal end until 120 sec of time on the bars had elapsed. Animals were never allowed to drink more than 5 sec each time they reached the water tray during the practice trials. Immediately following the practice period the animal was placed in position at the starting end with front and rear feet on the rods and pointed in the direction of the water tray. The animal was then observed until it traversed the length of the rods. Time to traverse the rods was recorded, as well as complete or partial falls.

The animals were then returned to ad lib. water, and 2 days later tested for audiogenic seizure susceptibility, once that morning and once 36 hrs later (at night). The apparatus was a modified Lehigh Valley Electronics operant chamber with the feeding mechanisms removed. A noise level of 103-105 dB was produced by placing a telephone bell in the space previously occupied by the feeding mechanism. The animals were placed inside the apparatus for 15 sec, after which the sound was presented continuously for 120 sec. For scoring purposes, the 120 sec was divided into four, 30-sec segments. Behavior was scored during each 30-sec segment on seven counts: (1) quiet, (2) grooming, (3) walking, (4) running, (5) hopping, (6) clonic movements, and (7) tonic movements.

Two days following audiogenic seizure testing, all animals were sacrificed with an overdose of ether and intracardially perfused with physiological saline followed by 10 percent formalin. The brains were removed, trimmed flush to the anterior extent of the cerebral cortex and posterior extent of the cerebellum. The brains were placed in 10 percent formalin and allowed to harden for 3 days and weighed. The dimensions of the brains were measured to the nearest .001 in (.0025cm) in three planes by use of a micrometer caliper. Anterior-posterior (A-P) measurements were taken from the most anterior tip of the isocortex to the most posterior tip of the isocortex closest to the midline. The medial-lateral (M-L) brain width was evaluated at the most posterior portion of the isocortex measuring the width across the entire extent of the brain (both hemispheres). Dorsal-ventral (D-V) measurements were taken from the base of the brain to the top of the isocortex at its most posterior extent. The brains were then embedded in celloidin and cut coronally at 30 μm. Every eighth section was mounted and stained with thionin.

RESULTS

An initial analysis of variance was run on scores of the three control groups on all variables. No differences were found, so their scores were combined to form a single control group (Group C) for subsequent statistical analysis. An analysis of variance was used to analyze all data unless otherwise noted. When a significant F was found, a Dunnetts post-ANOVA test was used to compare the control group with the experimental groups (see Edwards, 1968). Only significant differences are reported.

Anatomical Results

The anatomical results of this study are summarized in Table 1.

Brain Weight

No differences were found between the brain weights of Group C, the group receiving FUDR on E10-11 (Group 10-11) or the group receiving FUDR on E13-14 (Group 13-14). The brains of animals receiving FUDR on E16-17 (Group 16-17), however, weighed less than the control group ($p < .01$).

Brain Size

No differences were found in any measurement of brain size between Group C, Group 10-11, or Group 13-14. The Group 16-17 brains were smaller than the Group C brains in the A-P

TABLE 1

Mean Values for Brain Weight and Brain Size

	Brain Weight (gm)	Brain Size (cm)		
		A-P	M-L	D-V
Group C n=48	2.45	1.63	1.66	1.03
Group 10-11 n=16	2.45	1.63	1.66	1.03
Group 13-14 n=16	2.45	1.64	1.65	1.03
Group 16-17 n=16	2.11[b]	1.49[b]	1.62[b]	1.04

b = significantly different from Group C at the .01 level.

($p < .01$) and M-L ($p < .01$) dimensions but not in the D-V dimension.

Histology

Histological examination of sample brains revealed no obvious abnormality of cellular elements or structures in any of the groups (see Figures 1, 2, 3, and 4).[1]

Behavioral Results

The results of the various behavioral tests are summarized in Table 2.

Activity

The females were more active than the males in all groups ($p < .01$). The Group 10-11 animals were less active than the Group C animals ($p < .05$), while the Group 13-14 and Group 16-17 animals were more active than the Group C animals ($p < .01$).

Spatial Discrimination Learning and Reversal

Figure 5 represents the maze performance of the various groups. No differences were found between Group C and any of the three treated groups in the number of errors made during original learning. There was no difference in the error scores of Group C and Group 10-11 on any of the three reversals

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[1]The brains of experimental and control animals were examined by Jay B. Angevine, Jr., as well as the author and Robert L. Isaacson; no one was able to find any histological differences in any of the brains.

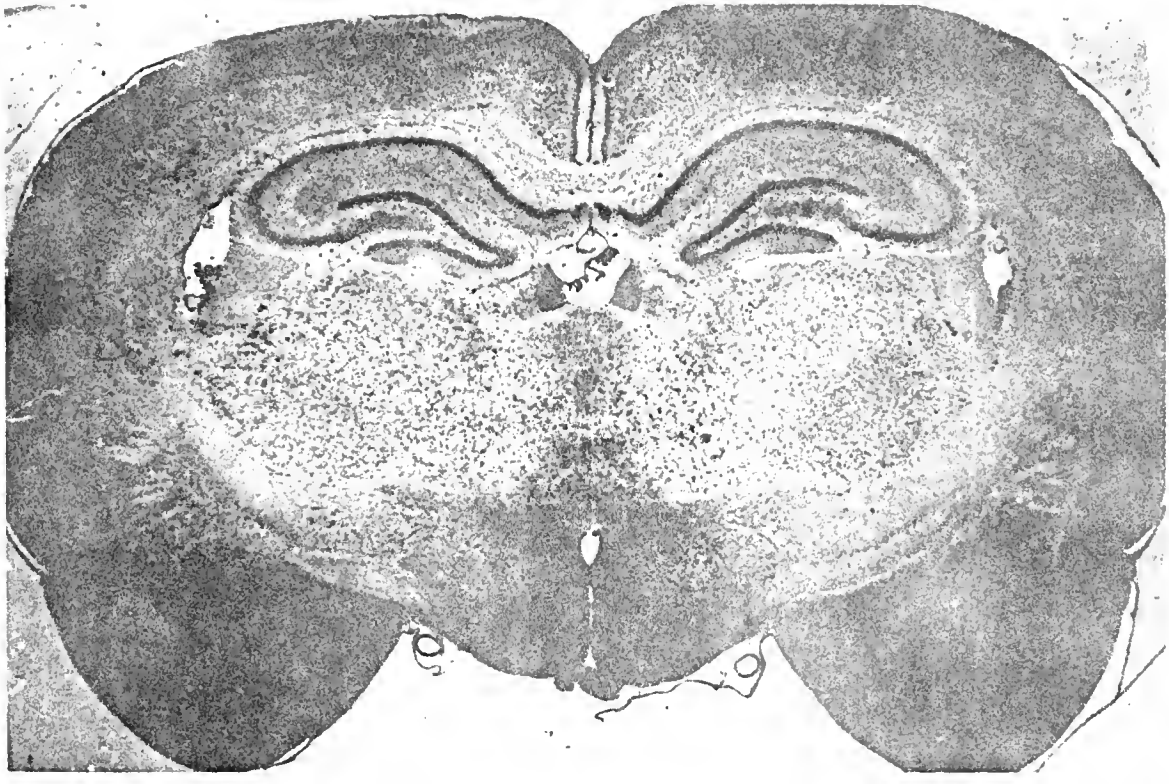

Figure 1. Frontal section of the brain of an adult rat from Group C (X-7.5: thionin).

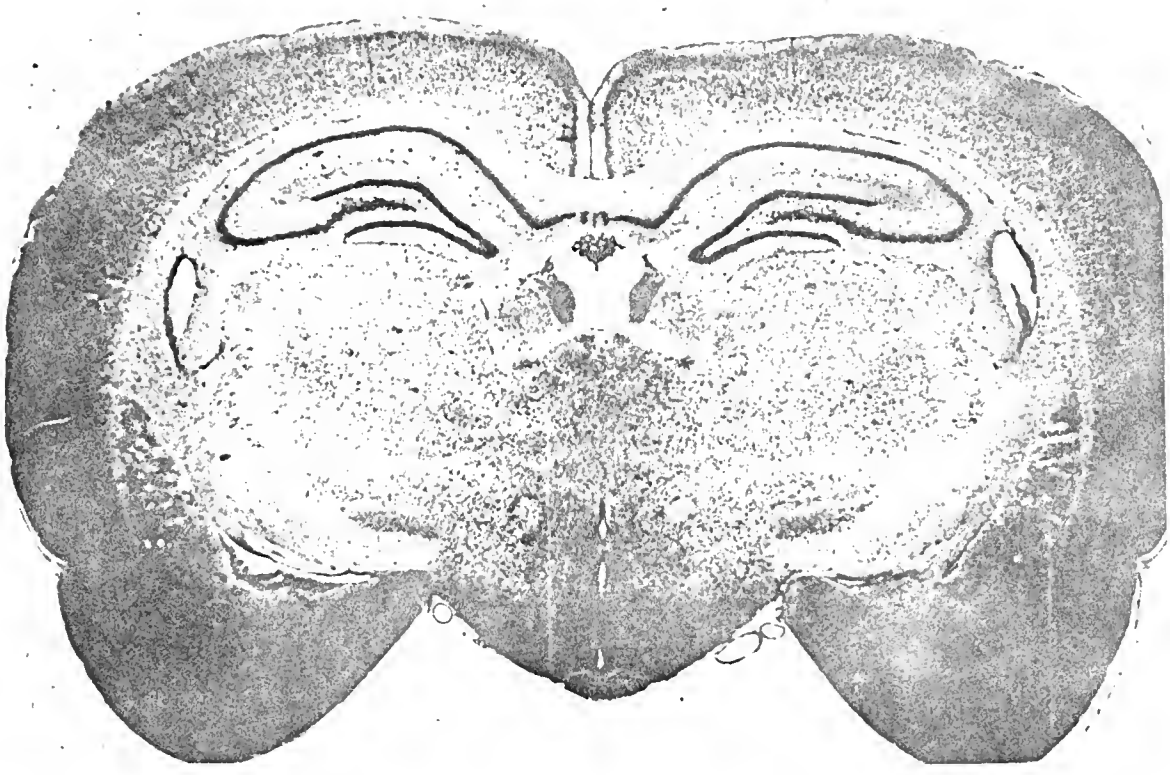

Figure 2. Frontal section of the brain of an adult rat from Group 10-11 (X-7.5: thionin).

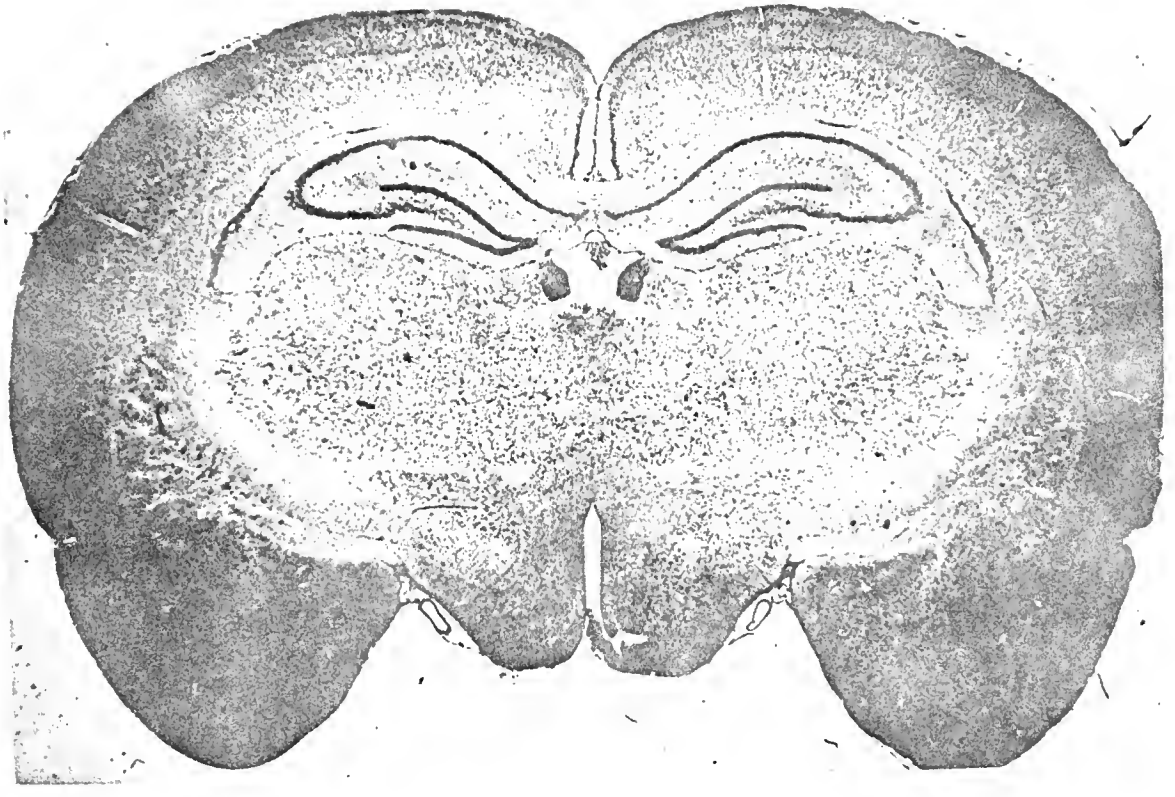

Figure 3. Frontal section of the brain of an adult rat from Group 13-14 (X-7.5: thionin).

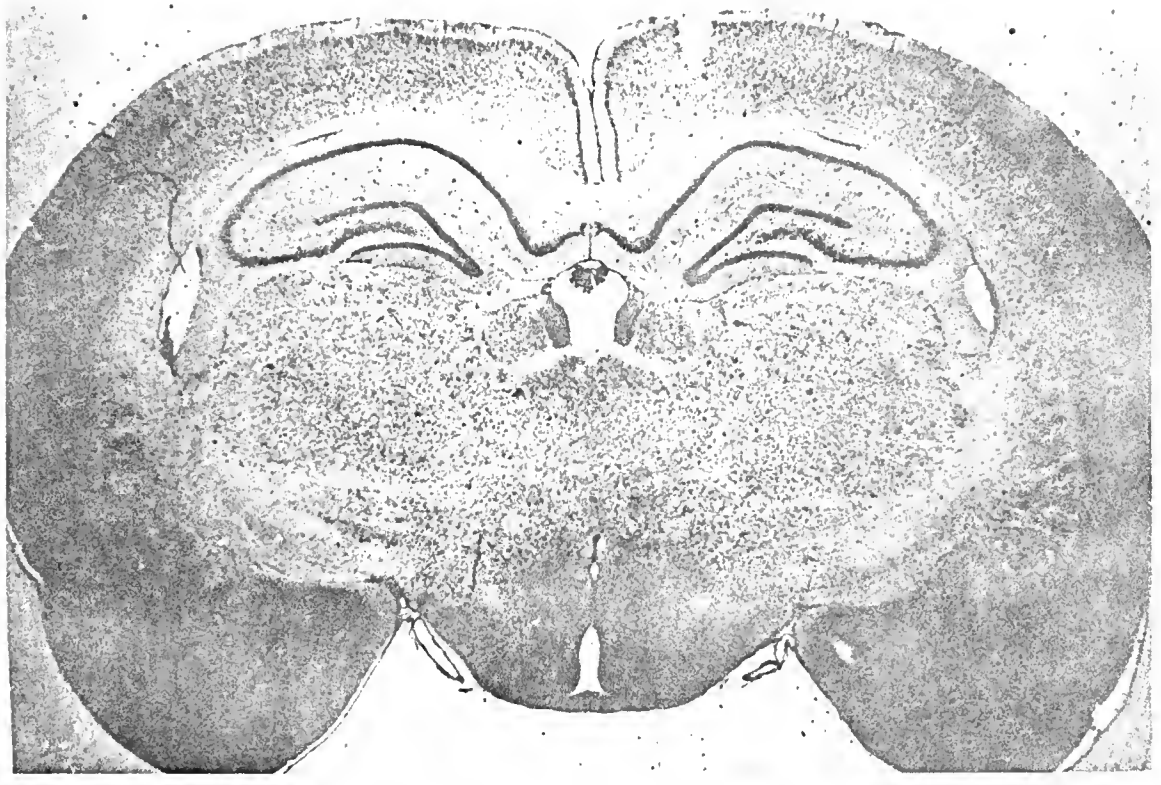

Figure 4. Frontal section of the brain of an adult rat from Group 16-17 (X-7.5: thionin).

TABLE 2

Mean Scores on Behavioral Tests

	Activity	T Maze Errors				Parallel Bar walking	
		Original Learning	Reversal 1	Reversal 2	Reversal 3	Seconds	Falls
Group C n=48	73.5	8.6	4.9	2.6	2.1	37.7	3.0
Group 10-11 n=16	59.3[a]	7.2	3.6	1.9	1.8	65.7[b]	5.4[a]
Group 13-14 n=16	105.3[b]	7.4	8.8[b]	6.8[a]	7.3[a]	83.4[a]	7.2[a]
Group 16-17 n=16	103.0[b]	8.3	5.9	5.1[a]	3.2[b]	72.8[a]	6.0[a]

a = significantly different from Group C at the .05 level.
b = significantly different from Group C at the .01 level.

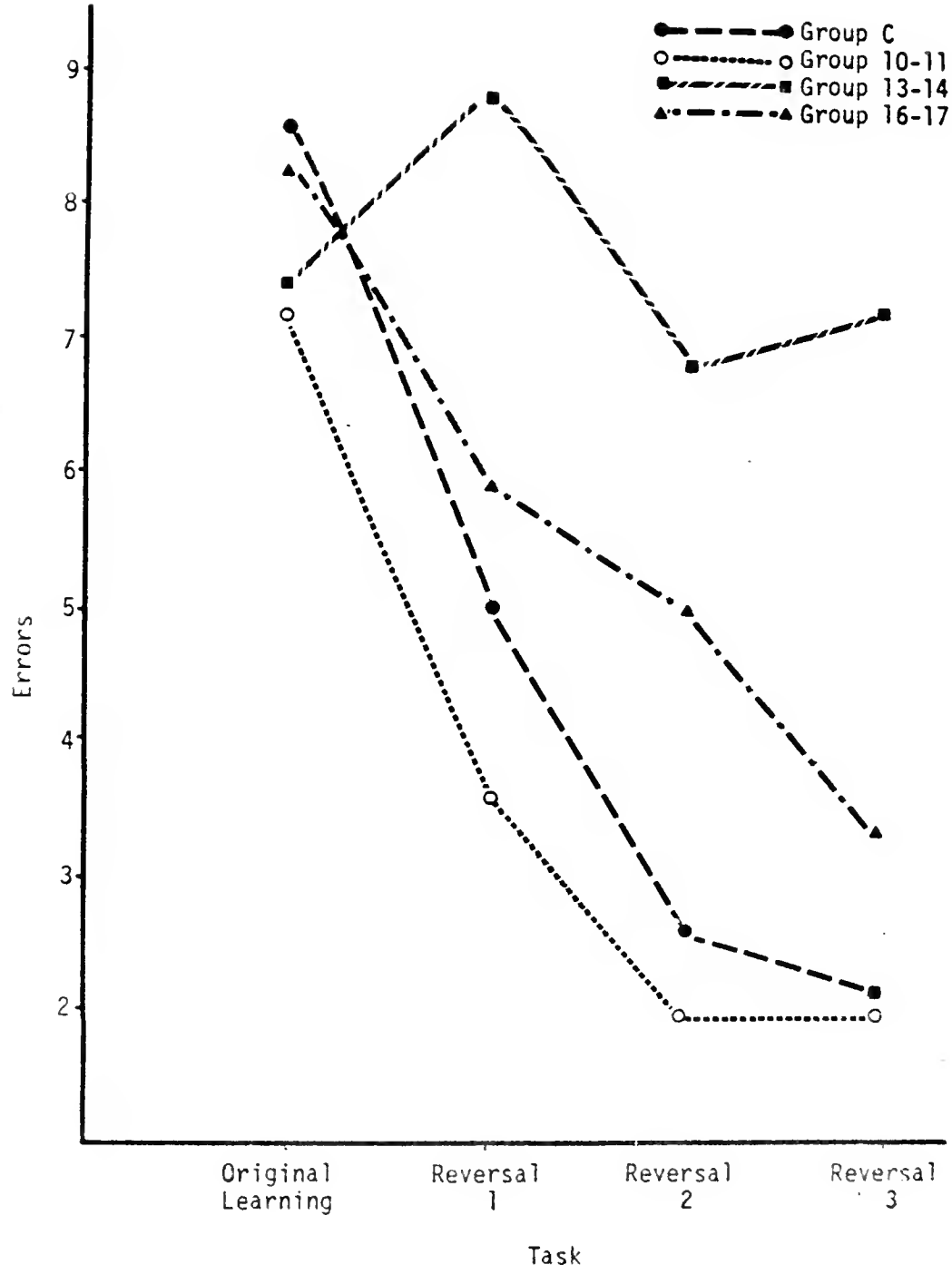

Figure 5. Mean error scores on T-maze learning and rehearsal for all groups.

On all three reversals, Group 13-14 made more errors than Group C ($p < .01$). Group 16-17 made more errors only on reversal two ($p < .01$) and three ($p < .05$). While Group C and Group 10-11 showed a consistent drop in the number of errors made over the three reversals, Group 13-14 continued to make approximately the same number of errors as original learning throughout the three reversals. Group 16-17 showed a drop in the mean number of errors across the three reversals, but the drop was not as great as in Group C.

Inspection of Figure 5 indicates that Group 13-14 performed more poorly on reversal learning than Group 16-17. Group 13-14 made more errors than Group C on all three reversals, while the Group 16-17 error scores were higher only on the last two reversals. During the last two reversals, Group 13-14 made more errors than Group 16-17 ($p < .01$, Duncan's post-ANOVA test, Edwards, 1968).

Parallel Bar Walking

Performance on the parallel bars was measured in terms of seconds taken to transverse the bars and number of complete or partial falls. All three experimental groups were inferior to Group C on both measures.

Audiogenic Seizure Susceptibility

For purposes of evaluation, all animals were divided into two groups: those animals that had a score of 6 or 7 (clonic or tonic movements) on either of the two test trials, and those animals that never had a score higher than 5 (hopping).

Using a Chi-Square analysis, no differences were found between the groups. In the control group, 25.5 percent of the animals had scores above 5 while 33.3 percent of Group 10-11, 33.3 percent of Group 13-14, and 7.1 percent of Group 16-17 had scores above 5.

DISCUSSION

The results of this study indicate that administration of FUDR at three different points in pregnancy results in different behavioral consequences in the offspring. Activity decreases were seen in Group 10-11, while an increase in activity was seen in Group 13-14 and Group 16-17. Although all groups learned the spatial discrimination in the T-maze with little difficulty, animals in Group 13-14 and Group 16-17 performed poorly on the position reversals, with Group 13-14 performing more poorly than Group 16-17. Problems in motor performance were seen in all three experimental groups, while no differences in audiogenic seizure susceptibility could be detected in any of the experimental groups.

Although a significant reduction in brain size and weight was found in Group 16-17, no anatomical anomalies could be detected in the brains of any of the treated animals. Anatomical effects frequently can not be detected in offspring treated with teratogens, despite great behavioral differences (Butcher, Brunner, Roth & Kimmel, 1970; Butcher, Vorhees, & Kimmel, 1972; Hutchings, Gibbon, & Kaufman, 1973; Vorhees, 1974; Butcher, Hawver, Burbacker, & Scott, 1974; Hutchings & Gaston, 1974). Proliferating cells can partially restitute cell populations which are destroyed or prevented from forming by a teratogen (Altman & Anderson, 1971; Andreoli, Rodier, & Langman, 1973). Therefore, cells depleted by FUDR treatment

could have been replenished at least in part after the FUDR treatment had been terminated. Butcher et al. (1974) have suggested three progressive effects of increases in teratogenic drug dosage: functional, anatomical, and lethal levels. They postulated that at low doses there could be functional, i.e., behavioral, effects of teratogens without producing anatomical effects. Hutchings & Gaston (1974) have also emphasized the lack of correlation between teratologically produced brain damage and behavioral impairment. Noting the similarity in behavioral, but not anatomical, impairments found after treatments with a variety of agents, the authors suggested a common underlying mechanism, possibly of a biochemical rather than structural nature.

Activity changes in offspring subjected to teratogens appear to be correlated with the time of prenatal intervention. Treatment during early prenatal CNS formation with hypervitaminosis A on E8, 9, and 10 (Vorhees, 1974), X-irradiation on E10 (Werboff, Havlena, & Sikov, 1962), or FUDR on E10 and 11 (present study) leads to reduced activity levels in the offspring. Intervention during the middle of the prenatal period of CNS formation with methylazoxymethanol on E14, 15, or 16 (Haddad, Rabe, Laquer, Spatz, & Valsamis, 1969), X-irradiation on E15 (Furchtgott, Tacker, & Draper, 1968; Furchtgott & Echols, 1958a; Werboff, Havlena, & Sikov, 1962) or FUDR on E13-14 (present study) causes hyperactivity in the offspring. Activity differences are also found following intervention during late prenatal CNS formation. Animals treated with

FUDR on E16-17 (present study) were found to be hyperactive. Furchtgott & Echols (1958b) irradiated animals on E13 through 17 and tested them in tilting cages and an open field. They found maximal activity enhancement in animals treated on E15-16. Irradiation on E17 produced increased activity levels, whereas neonatal irradiation produced decreased activity levels. Petit & Isaacson (in press) tested animals treated with colchicine on E17, 18, and 19 in an open field on Days PN25, 26, and 45. The animals were not found to differ from the controls on PN25 or 45, but were hypoactive on PN26. It appears that the hyperactivity found from intervention during mid-prenatal CNS formation is seen after intervention during the early part of this period. As intervention time nears birth, however, a drop in activity level of the treated animal is seen.

Animals in Group 13-14 and Group 16-17 made more errors during spatial reversal learning in the T-maze than the controls. Previous researchers have reported that animals treated with methylazoxymethanol (Rabe & Haddad, 1972), or X-irradiation (Furchtgott, Jones, Tacker, & Deagle, 1970) on E15 learned a spatial discrimination in a T-maze as quickly as controls; but when reversal learning was required the treated animals performed significantly worse than controls. However, in a WGTA adapted for rats, a series of visual pattern discriminations of increasing difficulty and their reversal were mastered by the treated as well as control rats (Rabe & Haddad, 1972). This is in contrast to the reversal learning deficits in the T-maze shown by these same animals. These authors concluded

that the animals had a deficit in spatial reversal learning, rather than a general cognitive impairment. The deficits found in reversal learning in this study are consistent with earlier findings and indicate that animals treated with FUDR during early prenatal CNS formation, E10-11, do not show deficits in reversal learning, while animals treated with FUDR during late pregnancy, E16-17, although showing a spatial reversal deficit, may not perform as poorly on this task as animals treated during mid-prenatal CNS formation, E13-14.

Animals treated on E10-11, E13-14, or E16-17 showed an increase in falls and time taken to traverse the parallel bars. This is consistent with earlier reports. Similar results on this same task were found by Werboff, Goodman, Havlena, & Sikov (1961) in animals irradiated on E10, 15, or 20, and by Furchtgott & Echols (1958b) in animals irradiated on E13. Thus deficits in motor performance can be produced in animals after teratological intervention at several points in pregnancy.

Audiogenic seizure susceptibility was not found to be affected by treatment with FUDR at any of the three points in pregnancy. Geller (1973) has shown that audiogenic seizure susceptibility was not altered in irradiated animals regardless of the time of administration. Butcher, Smith, Kazmaier, & Scott (1973) were unable to find differences in this measure in animals treated with hydroxyurea on E12. Petit & Isaacson (in press), however, found a decrease in audiogenic seizure susceptibility in animals treated with colchicine on E17, 18, and 19. The results of the latter authors may be specific to

the drug colchicine. Thus, although X-irradiation and FUDR administration during different periods of pregnancy may not affect seizure susceptibility, results on this test may be specific to the teratogen used.

In conclusion, this study indicates that while certain behaviors are affected in a similar fashion after FUDR intervention at any point in pregnancy (motor behaviors), some behaviors are not affected at any point in pregnancy (audiogenic seizure susceptibility), and other behaviors are differentially affected depending on the time of intervention (activity and reversal learning). FUDR intervention during early prenatal CNS formation (E10-11) produces hypoactivity and no deficits in reversal learning. Intervention during mid-prenatal CNS formation (E13-14) results in hyperactivity and large deficits in reversal learning. Intervention later in pregnancy (E16-17) results in a mild deficit in reversal learning and hyperactivity.

The results of this study indicate that different behavioral syndromes are associated with teratological intervention on different days of gestation. Additional studies using a variety of agents administered at different gestational ages are needed to fully understand the principles involved in this area of research. If it were possible to identify the behavioral consequences of interference with cell proliferation at different stages of gestation and postnatal life, it might be possible to specify the etiology of some brain damage syndromes.

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BIOGRAPHICAL SKETCH

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Robert L. Isaacson, Chairman
Professor of Psychology

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Frederick A. King
Professor of Neuroscience

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