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Behavioral Consequences of Perinatal Hypothyroidism in Postnatal and Adult Rats

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COMER, C. P. AND S. NORTON. *Behavioral consequences of perinatal hypothyroidism in postnatal and adult rats.* PHARMACOL BIOCHEM BEHAV **22**(4) 605–611, 1985.—The long-term effects of perinatal hypothyroidism on spontaneous locomotor behaviors were assessed after exposure to the antithyroid drug, methimazole. Perseveration was observed in methimazole-treated rats in a spatial maze. Locomotor activity in residential mazes was examined at 6 weeks, 4 months, and 6 months of age. Treated rats were hypoactive at some intervals compared with controls and were hyperactive at others. These paradoxical differences resulted from changes in exploratory, diurnal, and nocturnal locomotor activity in control rats both with increasing age and on repeated exposures to residential mazes; rats after perinatal hypothyroidism had relatively constant levels of activity on repeated days of exposure to residential mazes and at different ages. These results may be related to perseveration noted in the spatial maze. In an analysis of walking patterns, treated rats tended to have a more pronounced asymmetry in gait than controls.

Hypothyroid Methimazole Perinatal exposure Spatial maze activity Gait analysis Perseveration

A variety of agents are known to decrease thyroid function as measured by decreased serum levels of thyroid hormones (T_3 or T_4) or elevated levels of thyroid stimulating hormone (TSH) including cobalt [19], lead [14], PBB's [1,37], PCB's [3], DDT and DDE [2,25], oxalic acid [15], and goitrin [19]. The almost ubiquitous distribution of some of these goitrogens in the environment suggests the possibility that low levels of these agents might affect thyroid function in the developing fetus.

The fetus is dependent on thyroid hormones produced by fetal thyroid gland since maternal thyroid hormones do not cross the placenta in significant amounts [13]. Levels of goitrogen producing asymptomatic maternal thyroid suppression may have the potential for fairly complete suppression of fetal thyroid [12,21]. Therefore, placental transfer of goitrogens may have serious consequences to the developing fetal nervous system, particularly if developmental hypothyroidism is not corrected in the early postnatal period.

Perinatal administration of goitrogens to pregnant and lactating dams has been used experimentally to produce a reversible thyroidectomy in neonates. Thiouracils have poor water solubility and may be administered in the diet [7,23]. Methimazole is stable, freely soluble in water, and can be administered in drinking water [16, 20, 36]. The placental transfer of methimazole is more efficient than that of propylthiouracil. A fetal/maternal serum ratio of methimazole approaches 1.0 within 20 minutes after an IV injection into pregnant rats during the third trimester; the maximum serum ratio reached after propylthiouracil is 0.7 at 60 minutes after injection [22].

Considerable, but sometimes contradictory, information has been accumulated which suggests that perinatal hypothyroidism may produce persistent effects on various types of behavior in experimental animals [4, 5, 6, 7, 8, 9, 10, 23, 32, 34]. Few studies have been performed which have evaluated long-term changes in spontaneous behaviors after early hypothyroidism. In the present study three methods have been compared to evaluate spontaneous behavior in post-weanling rats: activity in residential mazes, exploration of a spatial maze, and gait analysis. The methods have been chosen because they presumably represent three different types of central nervous systems function and hence may reflect effects on diverse systems.

Activity in a residential maze consists of three components: exploratory activity on introduction to the maze, diurnal activity during the light cycle, and nocturnal activity during the dark cycle when most feeding behavior occurs in rats. The corridors of the maze offer a method for examining the efficiency with which a naive animal traverses the complex space until it is completely explored. When animals are placed in a novel environment the exploratory process depends on recall of recent location. Spatial recognition during brief exposure to a novel maze has been described as a method for evaluation of brain damage [30,31].

Abnormal gait has been described clinically as a neurological consequence of cretinism [11,17]. A walking behavior described as a "high stepping" gait has been described in rats after perinatal exposure to goitrogens [35]. This description may apply either to ankle weakness or rigidity and either condition may exist in the cretin [17]. The report that hypothyroid rats have some abnormality in walking [35] has

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led to a more quantitative analysis of locomotion in the present study.

METHOD

Breeding and Methimazole Administration

Female, Charles River, Sprague-Dawley-derived rats were bred to males of the same strain.

Sixteen pregnant rats were randomly assigned to either control or experimental groups. Gestational day 1 was the day on which the female was sperm positive. Starting on gestational day 15, tap water was replaced with distilled water and the volume consumed was recorded daily. Beginning on gestational day 17, eight animals (controls) continued to drink distilled water and eight animals (treated) were given a 0.1 mg/ml solution of methimazole (provided by Dr. Gerard Poore, The Lilly Laboratories, Indianapolis, IN) in distilled water until postnatal day 10. This concentration was calculated to provide a daily methimazole dose of approximately 20 mg/kg, a dose close to those reported in the literature to inhibit the thyroid [16, 20, 36].

At 24 hours after birth, litters were culled to eight pups. Equal numbers of male and female pups were retained as far as possible. Control and treated litters were weaned at 30 days of age and were housed in groups of 4 with litter mates of the same sex.

Behavioral Tests

Rats were tested in behavioral experiments from five weeks to six months of age. Each rat was used for only one test unless specified otherwise.

Spatial maze exploration. At five weeks of age, exploration of a spatial maze was recorded for 26 control and 28 treated maze-naive rats from the eight control and eight methimazole-treated litters. One of two rats of each sex were selected randomly from each litter. The maze consisted of six corridors radiating out from a central starting area. Corridors 1 and 4 had cul-de-sacs which were visible from the starting area. The four remaining corridors had cul-de-sacs obscured by bends in the corridors (Fig. 1). This spatial maze is based conceptually on mazes described by Olton [30,31] and is adapted from the residential maze which has been described by Norton and co-workers [27,28].

Animals were placed in the center starting area and each corridor entered by the rat during a ten minute period of observation was recorded. Rats crossing the point of a photocell located ten cm down the corridors from the starting area were recorded as having made a "complete" entry into a corridor; rats retreating from a corridor before the photocell was crossed were recorded as having made an incomplete entry into the corridor.

The distribution of individual corridors entered was analyzed by Chi-square to detect patterns in repeated entries into corridors by control or treated animals. The mean number of complete, incomplete, and total entries for control and treated rats was tested by *t*-test comparison of means.

Residential maze activity. The figure-8 residential maze used in these experiments consisted of two low connecting corridors which intersected in an elevated central area to form a continuous figure-8-shaped run. Two straight corridors extended laterally out from the central area. The four long, discontinuous corridors illustrated for the spatial maze in Fig. 1 were connected in the residential maze. Six photocells were located along each corridor ten cm from the central area, and two additional photocells were located at the sites of discontinuity in the long arms of the spatial maze in Fig. 1. An electronic counter provided hourly cumulative counts for all eight photocells in the maze. Five mazes were available and control and treated rats were alternately assigned to each maze.

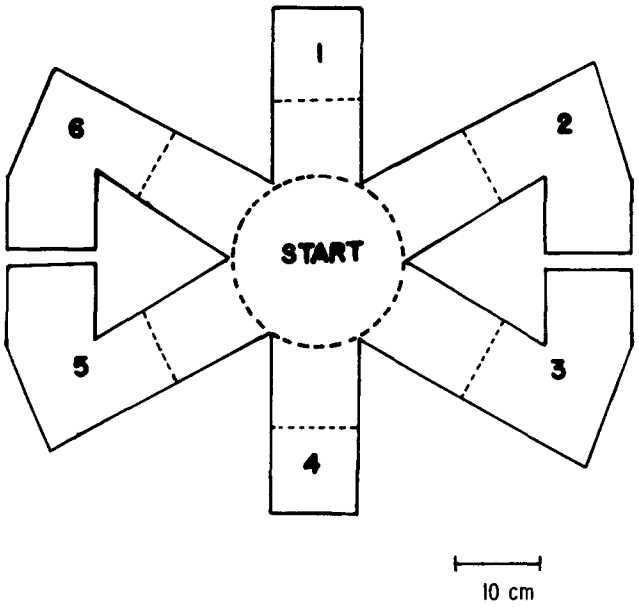

FIG. 1. Top view of the Spatial Maze Exploratory Apparatus. Numerals indicate assigned arm numbers. Rats were placed in the center starting area; the number of complete arm entries (beyond the level of photocells indicated by hash marks approximately 10 cm down each arm) and incomplete arm entries (retreats to the starting area prior to crossing the level of photocell) were recorded during a 10 minute period of obsesrvation.

Animals were housed in a 6:00 a.m. to 6:00 p.m. diurnal light cycle. Food and water were freely available and mazes were cleaned daily prior to placing a single rat into a maze before 9:00 a.m. Animals tested for multiple days were placed in a different maze on each day of testing. The hourly counts for each 24 hour cycle were divided into three periods: the "exploratory period" was the first three hour interval after an animal was introduced into a maze; the "diurnal period" was the remainder of the light cycle; and the "nocturnal period" was the 12 hour dark period from 6:00 p.m. to 6:00 a.m.

At 6 weeks of age, 20 control and 19 treated rats (one or two rats of each sex from each litter) were exposed to the residential mazes for a 24 hour period. These same animals were exposed to the mazes again for a 48 hour period at four months of age. At six months of age, one maze-naive control and methimazole-treated female rat from eight litters and males from six litters were exposed to the mazes for a 48 hour period. Statistical inferences were made by a *t*-test comparison of means.

Walking pattern analysis. Walking patterns obtained from four month old control and methimazole-treated rats of both sexes (one from each litter) were analyzed by the method of Mullenix and co-workers [24]. Hind paws of the rats were

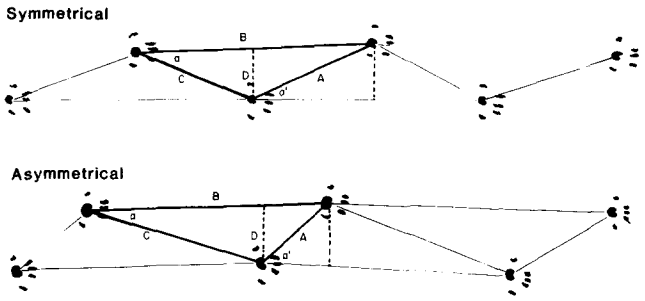

FIG. 2. Examples of symmetrical (top) and asymmetrical (bottom) walking patterns from female adult rats. In the symmetrical pattern, the sine of angle "a" equals the sine of angle "a'." Lines A and C are approximately equal and describe an isosceles triangle along with line B (length of stride). Line D is the calculated perpendicular to line B and is the width of rat's stride. In the lower asymmetrical example, the sine of angle "a'" is greater than the sine of angle "a." The length of line C is also much greater than that of line A.

dipped in water-soluble ink and the animal was allowed to walk on ink-absorbent paper through a covered Plexiglas corridor, ten cm square and 80 cm long. The corridor, which had black opaque sides and a clear top, was elevated at a ten degree angle by propping it on the edge of the rat's home cage. After several trials, control animals with freshly inked feet would walk from the lower end of the corridor to the upper end and jump into the home cage without stopping. Treated animals would usually walk through the corridor and jump into the home cage without stopping on the first trial. Barriers were dropped as the animal progressed through the corridor to prevent backtracking. All animals were given three trials prior to obtaining footprints. Then two tests with inked feet were recorded for each rat. Four consecutive left-right pairs of footprints were analyzed for each test.

A sample of walking patterns obtained in this manner is illustrated in Fig. 2. Records were analyzed as follows. The distance between successive placement of the same hind foot (lines D in Fig. 2) and the distances between the intervening placement of the opposite foot (lines A and C in Fig. 2) were recorded. Alterations in walking patterns caused by treatment may be detected by the symmetry of the walking pattern (how closely angle "a" approximates angle "a'"), by differences in the sines of the angles formed by placement of the hind feet, and by differences in the length or width of the stride. Measurements were made separately for the triangles thus generated by left and right hind paws to detect any asymmetry in walking pattern. The sines of the angles formed by the rear feet of control and methimazole-treated rats were tested for asymmetry by comparing the mean sines by the left and right rear feet by paired *t*-test.

RESULTS

Body weights but not growth rates of both male and female rats were slightly depressed after perinatal exposure to methimazole (Fig. 3). No recovery was noted up to four months of age.

Spatial Maze Exploration

Treated and control rats at five weeks of age randomly distributed entries into maze corridors during a ten minute

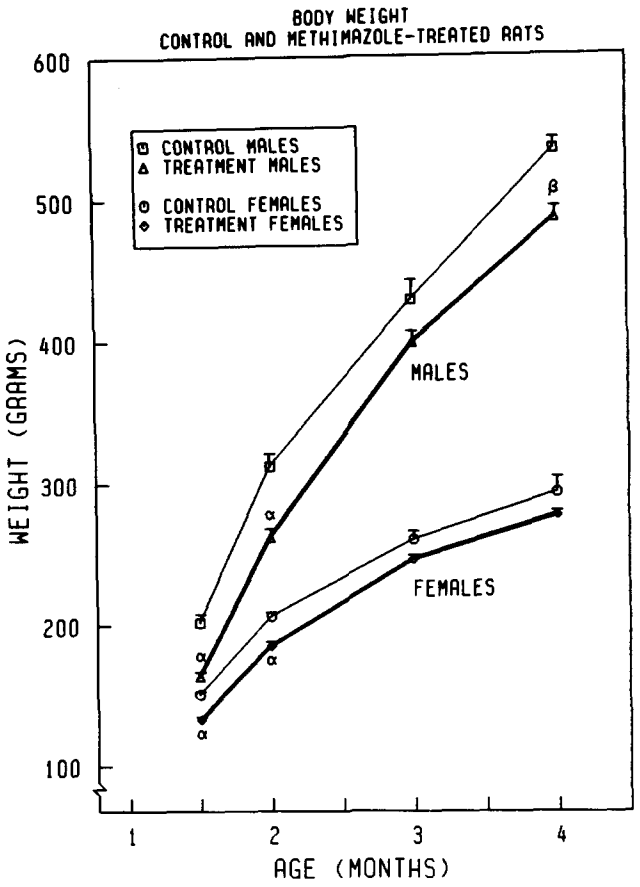

FIG. 3. Body weight gain of young adult rats. Heavy lines are methimazole-treated rats, lighter lines are control animals. Points are means (±S.E.). The N's of control females range from 18 to 26; treated females from 17 to 27; control males from 10 to 15; and treated males from 14 to 18. Alphas=$p<0.001$; beta=$p<0.005$ by *t*-test comparison of means.

period of observation. No preference was shown for short or long corridors. Differences between treated and control animals were significant when complete and incomplete arm entries were compared (Table 1). There were no sex-related differences in spatial maze exploration for control or treated rats. Despite the marked differences in complete and incomplete entries for control and treated rats, the total number of corridor entries was virtually identical for all groups.

Residential Maze Activity

At six weeks of age, the activity of female control and methimazole-treated rats did not differ significantly during any portion of the 24 hour period in residential mazes (Table 2). Methimazole-treated males of the same age were significantly more active than controls during the diurnal and nocturnal periods of the 24 hour activity measurement (Table 2).

Control animals showed decreased activity during exploratory, diurnal, and nocturnal periods from four months to six months of age (Table 2). In contrast, methimazole-treated rats showed a pattern of more consistent activity levels for all experimental periods between six weeks and six

TABLE 1

SPATIAL MAZE EXPLORATION*

Sex	Control	Methimazole	
Complete entries into corridors			
Female	33.0 ± 1.5	42.4 ± 2.8	$p<0.01$†
Male	33.3 ± 1.9	44.3 ± 1.7	$p<0.001$
Incomplete entries into corridors			
Female	13.1 ± 1.0	1.4 ± 0.5	$p<0.001$
Male	14.7 ± 1.8	2.0 ± 0.6	$p<0.001$
Total entries into corridors			
Female	46.1 ± 1.8	43.7 ± 2.7	N.S.
Male	48.0 ± 2.6	46.3 ± 1.9	N.S.

5 Week old control and methimazole-treated rats.

*Number of entries (±S.E.) summed for 6 corridors during a 10 minute observation period.

†t-Test comparison of means; N=12 for control males, N=14 for all other groups.

months of age; the result was that treated rats became hyperactive relative to controls with aging.

Walking Pattern Analysis

At four months of age there were no significant differences between length of stride or width of stride for control or treated rats of the same sex. Treated rats tended to have a longer stride although they were lighter than control rats (treated males=140.6±5.1 mm; control males=127.4±5.8 mm; treated females=131.6±6.4 mm; control females =124±2.5 mm).

The means for sines from both feet, the greater sine, the lesser sine, and the mean differences obtained by subtracting greater from lesser sines for individual animals are recorded in Table 3. No significant differences were obtained between mean sines for control or treated rats of either sex. Treated rats of both sexes had significant left-right asymmetry in walking patterns by paired t-test comparison (females, $t=5.1$, $p<0.005$; males, $t=3.4$, $p<0.025$). Control females, however, also showed a significant left-right asymmetry ($t=3.1$, $p<0.025$).

A further indication of asymmetry in gait is obtained by examining the correlation between length of stride and the angle formed by placement of the rear feet. The relationship of sine and length of stride is expected to show no negative or positive correlation in normal rats where stride length and width vary together with changes in body weight during walking [26]. The correlation coefficients for the sine of the angle formed by the rear feet and the length of stride for treated females was −0.80 ($p<0.01$) and for treated males was −0.64 ($p=0.05$); corresponding values for control rats were +0.01 for females and −0.46 for males. Correlations of stride length and angles of foot placement are not significant for control rats. The pronounced asymmetry in the walking pattern of treated rats is indicated by these strong negative correlations between the length of stride and the sine of the angle formed by the rear feet as well as by the significant of difference in angle of foot placement.

TABLE 2

RESIDENTIAL MAZE ACTIVITY AVERAGE PHOTOCELL COUNTS ± S.E.

	Control			Treated		
	Exploratory	Diurnal	Nocturnal	Exploratory	Diurnal	Nocturnal
Time in maze			6 week old rats			
Female		(N=11)			(N=10)	
Day 1	1305 ± 152	1151 ± 101	3010 ± 349	1225 ± 142	1202 ± 75	2397 ± 198
Male		(N=9)			(N=9)	
Day 1	911 ± 126	750 ± 98	2048 ± 151	1109 ± 146	1105 ± 76*	2650 ± 197†
			4 month old rats			
Female		(N=11)			(N=8)	
Day 1	2407 ± 252	1694 ± 189	3925 ± 434	1714 ± 169†	1655 ± 98	3239 ± 244
Day 2	650 ± 73	1290 ± 238	3047 ± 170	1051 ± 147*	1247 ± 152	2076 ± 92*
Male		(N=6)			(N=8)	
Day 1	1356 ± 149	1078 ± 152	2246 ± 203	1228 ± 210	1309 ± 215	2628 ± 926
Day 2	389 ± 74	753 ± 124	1404 ± 114	503 ± 76	627 ± 96	2148 ± 271†
			6 month old rats			
Female		(N=4)			(N=4)	
Day 1	1522 ± 98	1024 ± 76	2477 ± 297	1793 ± 121	1731 ± 176†	3502 ± 422
Day 2	574 ± 269	627 ± 48	2511 ± 221	831 ± 27	1326 ± 124*	2449 ± 648
Male		(N=3)			(N=3)	
Day 1	911 ± 179	549 ± 66	1512 ± 225	1291 ± 79	1025 ± 125*	1805 ± 197
Day 2	377 ± 74	242 ± 26	1319 ± 149	312 ± 120	527 ± 83†	1984 ± 175*

*$p<0.01$; †$p<0.05$, t-test comparison of treated and control means.

TABLE 3

SINES OF ANGLES FORMED BY PLACEMENT OF HIND FEET IN 4 MONTH OLD CONTROL AND METHIMAZOLE-TREATED RATS

Female		Male	
Control (N=8)	Methimazole (8)	Control (7)	Methimazole (7)
	Mean Sine		
0.480* ±0.020	0.497 ±0.025	0.545 ±0.031	0.526 ±0.023
	Greater Sine		
0.506 ±0.021	0.530 ±0.072	0.567 ±0.032	0.565 ±0.028
	Lesser Sine		
0.453 ±0.022	0.465 ±0.027	0.524 ±0.033	0.487 ±0.022
	Difference Between Sines		
0.052 ±0.016 $p<0.025$†	0.064 ±0.012 $p<0.005$	0.042 ±0.019 N.S.	0.078 ±0.023 $p<0.025$

*Mean sine ± S.E.

†Paired *t*-test comparison between greater and lesser sines for each animal.

DISCUSSION

Long-term functional changes were found following perinatal goitrogen administration. This is not unexpected, since the consequences of early hypothyroidism on behavior may be irreversible due to permanent effects on neuronal differentiation.

Spatial Maze Exploration

Perinatally hypothyroid rats significantly differed from controls when complete and incomplete arm entries were compared. Control rats frequently retreated to the starting area after initially entering an arm; treated rats after entering an arm rarely returned to the starting area before the end-barrier was encountered. This appeared to be a form of perseveration in both male and female treated rats. Altered distribution of arm entries following lesions of the hippocampus [30,31] or after perinatal undernutrition [18] also takes the form of perseveration, but of a more severe degree. In these cases of perseveration rats will repeatedly explore a few arms of the maze as if the remainder of the maze did not exist. The recording of "complete" and "incomplete" arm entries in a spatial maze may provide a sensitive measure of mild perseveration. Olton's subjective impression was that rats with hippocampal lesions tended to run the length of the arms faster than did controls and that they did not "hesitate" in the arms of the maze [30]; determination of "complete" and "incomplete" entries may provide an objective measure for similar types of observations.

Other evidence has been reported which suggests perseveration in mature rats after perinatal hypothyroidism. Eayrs and Lishman [10] reported that perinatally hypothyroid rats never retraced their steps and had a 100 percent success rate in traversing a tapering spar. Control rats, however, hesitated and would cross a tapering spar in only 75 percent of the trials.

The comment has been frequently made that after perinatal hypothyroidism, rats adapt more readily to novel testing situations than do control animals [8, 9, 10, 34]. In contrast, normal animals tend to "freeze" in novel environments [33]. In a test which required rats to leave a start box, traverse an alley, and enter a goal box, Davenport and Hennies [8] found perinatally hypothyroid rats readily completed the task but control rats were reluctant to leave the starting box. The authors interpreted this as reduced "fearfulness" in rats after early hypothyroidism. A similar phenomenon was observed in the present study during the walking pattern procedure. Both male and female control rats required several trials before a rat would walk through a corridor with inked feet, and jump into the home cage without stopping. Methimazole-treated rats of both sexes would readily walk through the corridor without stopping and jump into the home cage usually on the first trial.

Residential Maze Activity

Unlike Morgan and Einon [23] who reported no difference in exploratory activity in an open field between control and treated rats, Schalock and co-workers [34] observed hyperactivity in perinatally hypothyroid animals on the second day of testing in an open field. This was due to a marked decrease in open field activity by control animals on the second day in an open field. In a study of activity in running wheels female rats after early hypothyroidism were clearly hyperactive. Control and treated males initially did not differ in running wheel activity, but after several weeks, treated males were hyperactive compared with controls [8].

In the present study, differences in locomotor activity between control and methimazole-treated rats can be accounted for by the fact that exploratory, diurnal, and nocturnal locomotor activity tended to decrease in adult control rats during the time examined and on repeated days of exposure to residential mazes, as has been previously reported [26,27]. Male and female rats after perinatal hypothyroidism tended to show more constant levels of activity both on repeated days of exposure to residential mazes and at different ages. The dynamic changes seen in levels of activity of control animals were considerably blunted in rats after perinatal treatment with methimazole.

Walking Pattern Analysis

No significant differences were observed between control and methimazole-treated rats in length or width of strides although treated rats tended to have a longer stride. Treated rats also showed greater asymmetry in gait than controls. In the walking pattern of normal rats, the hind feet make two parallel path-lines and the placement of each rear paw along the path-line tends to fall half-way between sucessive placements of the opposite rear foot. As asymmetry increases, the placement of opposing rear feet comes closer together and the spontaneous left-right alternation of gait becomes partially restricted. Body weight is not fully shifted from left to right with each step; this restriction in alternation is observed in the gait as a "limp." Schwark [35] described rats after early hypothyroidism as having a "high stepping" gait. Hetzel and Hay [17] have described human cretins as having a "shuffling" gait with "spastic and bradybasic walking, and

a general clumsiness of movement," and suggested that the abnormality was "probably of cerebral origin." The present study suggests that an abnormality in gait may also be present in adult rats after perinatal hypothyroidism.

Conclusions

No evidence was found in the present study to support the contention of Davenport and Hennies [8] that female rats are more severely affected than males by early hypothyroidism. The perseverative tendency in the spatial maze was identical in both sexes after perinatal methimazole treatment. The failure of treated rats to habituate to the residential mazes may also be attributable to perseveration. Animals after early hypothyroidism have variously been described as "consistent responders" in behavioral testing situations [8,34], as being resistant to extinction of operant bar pressing behavior [7, 8, 34], as showing consistent movement in maze testing situations [10], and as showing decreased fearfulness [8]. All of these behaviors attributed to hypothyroid rats may reflect perseverative tendencies. In contrast, evaluation of rats in behavioral testing situations not as sensitive to detecting perseverative tendencies may lead to concluding that there are no long-term effect of early hypothyroidism on spontaneous behavior [23]. Detailed examination of locomotor walking patterns indicates that early hypothyroidism may result in permanent deficits in gait in addition to alterations in spatial and temporal components of behavior.

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