The Effect of the Administration of Trace Amounts of Metals to Pregnant Mice upon the Behavior and Learning of Their Offspring

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There exists a considerable literature on the effect of certain metals administered to laboratory animals, but little work has been done on the detection of the effects of trace amounts of metals on animals except by ARUTYUNOV[1]. He described that oxygen absorption was increased with injection of trace amounts of Ni (0. 5μ/kg/day) in guinea pig.

The object of our study is to detect the biological actions of trace amounts of metals on animals, which are kept in nutritionally and physiologically normal conditions.

Previous work in our laboratory has shown that trace amounts of metals injected in mice caused a change in the preference taste threshold for bitter, sour, salty and sweet substances[2~5,8]. In our successive experiments, effects of trace amounts of metals on the locomotivity of mice in the swimming, treadmill, driving-wheel and motility test were observed[6,7,9~11]. These experiments showed that behavioral techniques were very sensitive tools to determine the effects of trace amount of metals on animals.

It is also suggested that subtle functional deviations in offspring of exposed mothers during pregnancy may be one of the most sensitive indicators of potential harm from many environmental contaminants[12]. The offspring of metal-injected mothers were used to avoid the unfavorable effects of the injection and to detect the effects of the metals more sensitively than using older animals.

The purpose of this experiment is to study the effects of trace amounts of metals administered to pregnant animals on the behavior of their offspring during preweaning period and to detect the effects of the metals administered to mothers on maze learning of young animals, five to seven weeks old.

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Methods

1) Experimental animals

The animals used in the study were mice of CFW strain obtained from our breeding colony. Six naive females of 8 weeks of age and two males were mated (three females per male). The males were of the same litter. The female mice received a daily intraperitoneal injection of 0.1 ml metal soltuion of various concentrations for three consecutive days and eight times every other day (totalling eleven times) during pregnancy. Table 1 shows the doses of metals. Doses of 22 kinds of metals of minimum effect concentration for each element required to change the taste threshold for 6-n-propy1-2-thiouracil according to the two-bottle preference technique were administered[4,8]. The metals tested were Al, Be, Cd, Co, Cu, F, Fe, Hg, In, La, Mg, Mn, Mo, Ni, Pb, Sb, Sc, Se, Ti, V, Y and Zr. The metals were employed as chlorides with the exception of Be and Mo (as $BeSO_4$ and Na_2MoO_4 respectively), and F as sodium salt. Control animals were injected with distilled water.

Pregnancies were determined by inspection for sperm plugs each morning. Each female was placed in a cage at least one day before giving birth. The day of birth was designated Day 1. Three of either sex were picked out of the litter wherever possible. The offspring were reared by their mothers until weaning at twenty-one days of age. Twenty-four offspring from each of the groups were tested for the development of reflex and behavior from the day after birth to 16 days of age.

At weaning, animals were divided into two groups of different environmental conditions, enriched (E) and non-enriched (NE) cages. E cage was constructed of

Table 1. Dosis

(Nano-gr/mouse/day)			
Al	0.00004	Mn	220.0
Be	140.0	Mo	12600.0
Cd	10.0	Ni	1000.0
Co	70.0	Pb	0.0015
Cu	21.0	Sb	0.008
F	12000.0	Sc	4500.0
Fe	1040.0	Se	1580.0
Hg	73900.0	Ti	2.4
In	12.0	V	2.0
La	2.78	Y	9.0
Mg	1250.0	Zr	0.0135

three polyproplylene bottles, which were connected by stainless steel pipes (30m/m inside diameter). Two blind pipes were also set into E cage to promote the enrichment. Subjects of NE cage were housed in a polypropyrene rectangular cage. Animals were housed in same sex groups of six per E or NE cage.

2) Test procedure

The stages of development of reflex and behavior were adapted from McCLEARN et al.[13] and including the geotaxis behavior test in suckling mice (Fig 1).

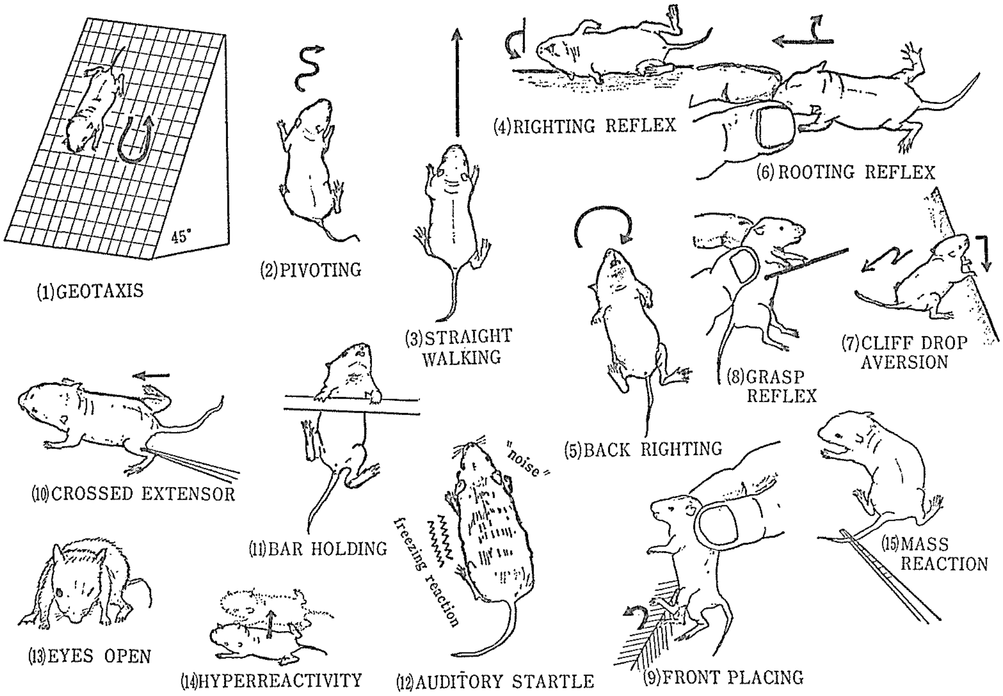

Fig. 1. Drawing illustrates reflex and behavior.

(1) Geotaxis test : CROZIER and PINCUS[14] first presented their observations on the behavior of young rats in inclined planes. In this study, the geotaxis apparatus consisted of 30×40 cm plexiglas board, and was fixed at a slope 45°[15]. The observation was whether animals attempted to turn head up and creep upward during a 1 min. interval, when placed upon the center of the board with its head pointing downward. (2) Pivoting (3) Straight walking (4) Righting reflex (5) Back righting (6) Rooting reflex (7) Cliff drop aversion (8) Grasp reflex (9) Front placing (10) Crossed extensor (11) Bar holding (12) Auditory startle (13) Eyes open (14) Hyperreactivity (15) Mass reaction (16) Body weight.

Each pup was subjected to the same order in reflex and behavioral test and body weighed each day. In the reflex and behavioral tests from (2) to (16) each pup was assigned a score on each test described by McCLEARN et al.[13] The age at which a given response was present in the mature from showed the score for each mouse. The average weight of individuals within a group was calculated for each metal group.

At 5 weeks of age, four animals of each sex in E and NE cage were selected and maze learning test was started. According to the patterns of the apparatus described by RABINOVITCH and ROSVOLD[16] for rating intelligence in the rat, the size of the apparatus was modified to suit the mouse. After 14 hrs of food deprivation the animals were given practice and test problems. The practice problems were run on the first five days, and then the test problems were given two per day for the next six days, five trials per problem. An error is scored when an animal's two forefeet cross into the error zone. Running time is the length of time elasped between starting from the start box and the first bite of food in the goal box. The scores in this maze learning test were the summation of all errors and running time during 12 test problems.

All subjects were maintained under E or NE environment throughout this maze learning test.

All data of the development of reflex and scores of the maze learning were analyzed statistically using the Student t test, and all but insignificant scores were shown in Table 2–5, and illustrated in Fig. 2.

Results

1) The reflex and developmental test in suckling mice.

Tables 2 and 3 show the results in male and female mice, respectively. The offspring of metal treated animals had no apparent morphological abnormalities. The birth weight of offspring of metal injected mice was not significantly different when compared to values in control animals. However, offspring of mice injected with the following metals showed slightly higher weaning weights than the control group: Cd, Co, Cu, F, Fe, La, Mn, Ni, Sc, Se, Y and Zr in males; Cd, F, Fe, La, Mg, Pb, Sb, Sc, Se, V, Y and Zr in females. Geotaxis : The offspring of animals injected with the following metals showed delayed response in turning head up, when compared to values in control animals : Be, Cd, Co, Cu, Fe, In, Mg, Mn, Ni, Pb, Sc, Ti, V and Y in males ; Mn and Ni in females. The offspring of animals injected with the following metals resulted in significant acceleration in the response of upward creeping : F, Mo and Zr in males ; Al, Cd, Cu, F, Fe, Mg, Mo, Pb, Sb, Sc, Se and Zr in females. While, offspring of animals injected

Table 2. The growth and the development of reflex responses in suckling mice ; male.

	21-day body wt.	geotaxis		straight walking	bar holding	
		A	B		1 sec.	60 sec.
H_2O	12.7g	8.0 day	12.2 day	14.8 day	3.3 day	13.8 day
Al						
Be		●●		○○	●●	○
Cd	○○	●●		○○	○○	○
Co	○	●●●*		○○	●●	
Cu	○	●●		○○	●●	
F	○○		○			○
Fe	○○	●●		○○	●●	○
Hg			●	○○	●●	○
In		●●●		○○		
La	○○			○○	●●*	
Mg		●		○		
Mn	○	●●●	●	○	●●	○○
Mo			○	○○	●●	○
Ni	○○	●●●		○	●●*	●
Pb		●●	●	○○		
Sb				○○	○○	○
Sc	○○	●●●*		○○		
Se	○○			○○○		○
Ti		●●●*	●	○		
V		●●		○		●
Y	○○	●		○○	●●	
Zr	○○		○○	○○	●●	○

A : turn head up B : upward creeping
○ : higher score ● : lower score
○, ● : 1–15 % ○○, ●● : 16–30 % ○○○, ●●● : 31–50 %
* : sex difference

with Hg, Mn, Pb and Ti in males and Mn in the females showed significant delay in the response of upward creeping. The offspring of animals injected with the following metals resulted in significant acceleration in the straight walking test for distance at least equal to body length : Be, Cd, Co, Cu, Fe, Hg, In, La, Mg, Mn,

Table 3. The growth and the development of reflex responses in suckling mice ; female.

	21-day body wt.	geotaxis		straight walking	bar holding	
		A	B		1 sec.	60 sec.
H_2O	13.1 g	8.4 day	12.7 day	14.8 day	3.4 day	13.8 day
Al			○			
Be				○○		○○
Cd	○		○	○○		○
Co					●●	
Cu			○	○○○		○
F	○○		○○			○
Fe	○○		○		●●	○
Hg					●●●	
In						○
La	○○					○
Mg	○		○		●●●	○
Mn		●●●	●		●●	
Mo			○	○○		○
Ni		●●●			●●●	○
Pb	○		○	○○		○
Sb	○		○		●●	○
Sc	○		○	○○		○
Se	○○		○	○○○		○
Ti						
V	○					
Y	○				●●	○
Zr	○		○○	○○	●●	○

A : turn head up　　B : upward creeping

○ : higher score　　● : lower score

○, ● : 1–15 %　　○○, ●● : 16–30 %　　○○○, ●●● : 31–50 %

Mo, Ni, Pb, Sb, Sc, Se, Ti, V, Y and Zr in males : Be, Cd, Cu, Mo, Pb, Sc, Se and Zr in females. The offspring of mothers injected with the following metals in the bar-holding (for a moment support) showed significant delay : Be, Co, Cu, Fe, Hg, La, Mn, Mo, Ni, Y and Zr in males ; Co, Fe, Hg, Mg, Mn, Ni, Sb, Y and Zr in females, while male offspring of mice injected with Cd and Sb in the same

Table 4. Total errors and running time of male mice in maze learning test.

Treatment	Total errors		Time (sec.)		NE vs. E	
	NE	E	NE	E	Errors	Time
H_2O	168	189	1179	1582		
Al	●		●●			
Be						
Cd	●		●●			
Co	M<F*		M<F*	M<F*		
Cu						
F	●●		●●●		NE>E	
Fe						
Hg						
In						
La						
Mg	M<F*		●●			
Mn						
Mo				M<F*		NE<E
Ni					NE<E	NE<E
Pb						
Sb		M<F*	M<F*	M<F*		
Sc	●		●●●	M<F*		
Se	●	M<F*				
Ti	M<F*					
V						
Y					NE<E	NE<E
Zr	●					

● : lower score ● : 1–50 %, ●● : 51–100 %, ●●● : 101 %–
* : sex difference

test showed significant acceleration. The offspring of mice injected with the following metals in the bar-holding (60 sec.) resulted in significant acceleration : Be, Cd, F, Fe, Hg, Mn, Mo, Sb, Se and Zr in males ; Be, Cd, Cu, F, Fe, In, La, Mg, Mo, Ni, Pb, Sb, Sc, Se, Y and Zr in females.

In this experiment, the offspring of injected mice in other reflex and development tests, such as pivoting, rooting reflex, grasp reflex, crossed extensor and

Table 5. Total errors and running time of femle mice in maze learning test.

Treatment	Total errors		Time (sec.)		NE vs. E	
	NE	E	NE	E	Errors	Time
H_2O	173	187	1320	1565		
Al	●		●●			
Be						
Cd		●		●●		
Co	●●	●	●●●	●●		
Cu						
F		●		●●●		
Fe						
Hg	●●		●●●	●●		
In			●●			NE＜E
La		●		●●		
Mg	●●	●	●●●	●●●		
Mn						
Mo				●		
Ni		●		●	NE＜E	
Pb						
Sb	●	●	●●	●●		
Sc	●	●	●●	●●		NE＜E
Se		●				
Ti	●●		●●●			
V	●		●			
Y		●				
Zr		●		●		

● : lower score ● : 1–50 %, ●● : 51–100 %, ●●● : 101 %–

auditory startle resulted in significant acceleraton compared with the control due to the metal treatment. Otherwise the offspring of metal injected mice in righting reflex showed significant delay compared with control.

2) Maze learning test.

Mean number of errors and running time were presented in Table 4 (male) and 5 (female). Significant increases of the errors were observed in males from mothers injected with Al, Cd, F, Sc, Se and Zr, housed in NE cage. In females, significant numbers of errors were observed in the cases of Al, Co, Hg, Mg, Sb, Sc, Ti and V under NE cage, and also observed in the cases of Cd, Co, F, La, Mg, Ni, Sb, Sc, Se, Y and Zr under E cage. There were no significant differences of the errors in the cases of E caged males.

The influences of different housing conditions, NE and E cages, on the score were also determined (Table 4, 5). Mice in E cage made more errors than those in NE cage in the cases of Ni (male and female), and Y (female) administration groups. On the contrary, males from mothers administered F made more errors in NE cage than E cage. Female mice made more errors than males from mothers administered Co, Mg, Ti in NE cage, and Sb and Se in E cage.

It was shown that running times tended to prolong in mice from mothers administered Al, Cd, F, Mg and Sc in NE caged males. The time was also prolonged in mice from mothers administered Al, Co, Hg, In, Mg, Sb, Sc, Ti and V in NE, and Cd, Co, F, Hg, La, Mg, Mo, Ni, Sb, Sc and Zr in E caged females. The times were not significantly different from controls in males of E cage.

The environmental differences of the running time were observed in mice from mothers receiving Mo, Ni and Y in males ; In and Sc in females, in which mice in E cage required more time than those in NE cage.

Male-female differences in running time were observed in mice from mothers receiving Co, Sb in NE, Co, Mo, Sb, Sc in E cage. Female mice had significantly greater running time than males in these sex differentiated scores.

Fig. 2. shows significant effects of metals in the scores of females.

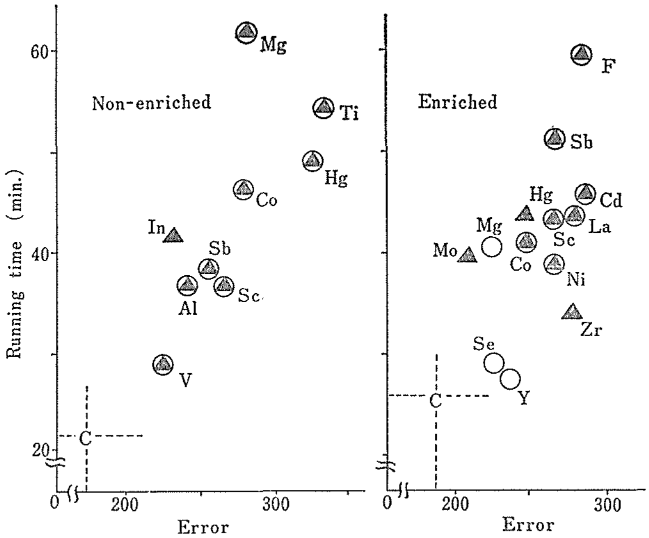

Fig. 2. Score of maze learning, female.
○ : Error ▲ : Running time C : Control

Discussion

This study clearly established that the mice injected with trace amounts of metals during pregnancy produced long lasting behavioral changes in offspring of both sexes and affected the maze learning behavior in mature offspring. Behavioral changes noted in the absence of overtly recognizeable morphological abnormalities in this study. Injections of cadmium[17], lead[18~22] or methylmercury[23,24] during pregnancy have also been reported to produce long lasting behavioral changes in offspring. These results demonstrate the effect of metals on the behavior of offspring of animals administered these metals, although the animals administered such high doses of metals during gestation exhibited marked neuromuscular impairment and some offspring died as a result.

We have used in this study much lower doses of metals injected to mothers than those used in the above studies. Nevertheless, we could observe significant effects of the trace amounts of metals on the development of reflex and behavior in preweaning offspring and on scores of maze learning at postweaning period which were inferior.

VENCHIKOV[25] has suggested that trace elements in approximately the same concentrations usually found in living organisms or in the environment exerted a stimulating effect on the course of number of physiological processes. If the trace element concentration was increased, the action was weakened or discontinued. A further increase of concentration brought about a resumption of the action in a number of cases. This effect, moreover, exhibited the usual pharmacotoxicological action, that is, the trace element exerted an irritating effect. This fact is in good agreement with biological action of trace amounts of metals in this study.

The offspring of mice injected with trace amounts of metals increased in weaning weight compared to the control. This finding suggests no debilitation associated with these trace amounts of metals in these doses.

KEINO et al.[17], is the only study in which the offspring of animals injected with metals were used for geotaxis test. Offspring mice injected with cadmium ($CdSO_4$ 5mg/kg i. p.) resulted in a turn head up and creep upward response which was compared with the control. In this paper, male offspring of mice injected with cadmium showed significant delay in the reflex to turn head up compared with control animals. However, female offspring of mice with cadmium showed significant acceleration in the reflex to turn head up compared with control animals. There was no significant difference in the development of the reflex to turn head up for male offspring of mice injected with cadmium group compared with control. Thus, there is not the least doubt about behavioral toxicology in the offspring of metal injected mice using cadmium dose (10 ng/mouse/day). The offspring showed accelerated development of number of reflex and behavior, such as response of geotaxis (turn head up), pivoting, straight walking, rooting reflex, grasp reflex, crossed extensor, bar holding (60 sec.) and auditory startle. CASTELLANO and OLIVERIO[26] have described that delayed development of number of reflex and electrocortical activities is clearly related to the degree of postnatal undernutrition. MAKER et al[27] described that brain development in the mouse, however, is less dependent on differences in litter size. Although the growth rate of mice slows during the second week of life, the behavior of the pups changes continually throughout the late nursing period, particularly marked changes occuring at the time of eye opening (14–15 day in mice used in this study). However, developmental land marks, i. e., eye opening and full incidence of body hair were not changed in offspring of mice injected with trace amounts of metals. The extent to which metals taken during pregnacy are implicated in this problem is not known but clearly the first step is to carry out such research with animals.

In this study, sex differnce of the response to turn head up was observed in offspring from mothers injected with Co, Sc and Ti. This difference was observed at about 10 days and female pups were earlier than male pups in this case. It is said that sexual differentiation of the brain occurs during a critical period between birth and about 10 days in mice[28]. Sex difference for bar holding (1 sec.) was observed in 5 day old offspring of mothers administered La and Ni.

It is known that certain metals affect the learning behavior in animals, especially animals that have been metal-exposed prenatally. It is not always clear, however, which particular metals have deleterious effects on the behavior of offspring from mothers treated with the metals in this experiment. Accordingly, it is shown that the learning behavior of animals is recognized to be a more sensitive tool to determine the effects of trace amounts of metals.

It is well established that housing conditions effect the learning behavior in experimental animals[16,29,30]. In general animals housed in enriched environment after weaning, made fewer errors than impoverished counterparts in the learning test. The environmental differences of the score in the cases of males in E cage showed more errors than did males in NE cage in this experiment, which does not agree with the previous data. But it was also found that compared with controls, males in NE cage showed neither significant increased errors nor running time. The effects of metal injection to mothers on the scores of the female offspring were recognized in both cages. The female offspring in E cage showed inferior performance as indicated by their scores for mothers receiving In, Ni, Sc, respectively, the reasons which are yet unclear.

It is well-documented that sex differences are present in learning behavior, in which males have better scores than females in rats[30,31]. In this experiment, males from mothers administered Co, Mg, Sb, Sc, Se and Ti showed better scores in maze learning than females, in good agreement with the above studies.

It is known that females after puberty show significantly greater activity[31,32] or exploratory behavior[33] than males in mice. It is suggested that this higher mobility or exploratory behavior in females could be related to the inferior scores of the maze learning test[34]. These experiments may suggest that hyperactivity such as great mobility and exploratory behavior are induced in offspring of mothers administered metals and this shows up in the inferior scores in the learning test. Especially it seemed that females were more susceptible to the influences of metals than males, because in controls sex differences were not significant in the two learning scores.

The mechanism mediating the long-term behavioral changes is currently unknown. Possibly, changes in mother-foetus interaction essential for normal development may have contributed to the observed behavioal changes in neonate and adult offspring. It is also known that metal can cross the placenta in animals, and is reported to be highly concentrated in fetal liver, adrenal and brain stem tissue. Hence, it is possible that metal may be interfering with the development of the brain and/or pituitary adrenal system to produce the long-term behavioral effects.

Although this study provides no information regarding the mechanism by which metal injected into pregnant animals produces the long lasting changes in offspring behavior, it does clearly establish the existence of such alterations and should prompt further investigation of the extent and mechanism of the change.

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Summary

The effect of 22 kinds of metals on the response of reflex and behavioral test in suckling mice and on maze learning test of the mature pups was investigated. CFW mice were injected intraperitoneally with trace amounts of metals 11 times during pregnancy. The metals tested were Al, Be, Cd, Co, Cu, F, Fe, Hg, In, La, Mg, Mn, Mo, Ni, Pb, Sb, Sc, Se, Ti, V, Y and Zr.

The offspring of mice injected with trace amounts of metals clearly accelerated as to response of straight walking, pivoting, rooting reflex, grasp reflex, crossed extensor and auditory startle in the reflex and behavioral tests. Later on offspring of mice injected with trace amounts of metals were affected so as to influence their maze learning behavior at 5–7 weeks age.

This study clearly established that mice from mothers receiving trace amounts

of metals during pregnancy produced long lasting behavioral changes from birth to maturity in offspring of both sexes.

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妊娠マウスへの22種の微量の金属投与が子の行動および学習に与える影響

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要　　約

微量な金属投与が，成熟マウスの行動に著明な影響を及ぼすことを報告してきた。本実験は，妊娠マウスに22種の微量な金属を11回投与し，その乳のみマウスにおける反射運動系の発達，更にその6週令よりいわゆる知能テストについて観察を行なった。

その結果，注射を受けた親よりの乳のみマウスにおいて反射運動系の発達においても知能テストにおいても影響を得えていることが示唆された。