Deposition of Mercury in Fetal and Maternal Brain[1] (36920)

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There is little doubt that mercury is deposited in the brain of cat (1), dog (2, 3), ferret (4), human (5), monkey (6), mouse (7, 8), pig (9), rabbit (2, 6, 10) and rats (11–22). The amount deposited depends to a large extent on the route of exposure, mercurial compound used, and size of dose administered. Apparently, exposure by inhalation of metallic mercury vapor caused a greater uptake and, presumably, deposition of the metal in the brain than exposure by oral or other routes (23). Generally, organic mercurial compounds were better absorbed from the gastrointestinal tract than inorganic compounds (24). The concentration in brains of rats administered with low levels of mercury, less than 2 mg Hg per kg body weight, was usually less than 1 ppm (11–22). Animals administered with larger quantities of mercury may attain higher brain levels. As much as 40 ppm in certain parts of the brain had been reported for animals treated with 30–60 mg of mercury per kg body weight (25). At this high level, many of the animals had clinical symptoms of mercury poisoning.

Studies to determine mercury deposition in brain are mainly, with only few exceptions, confined to the determination of the metal in the entire brain despite reports indicating different severity of histologic lesions in different parts of the brain after mercury poisoning (11–22). Even less work has been done to determine deposition of mercury in the fetal brain. However, poisoning of pregnant women by mercury affects the fetus, indicating that the metal crosses the placenta (26). The present experiments were thus designed specifically to determine the quantitative deposition of mercury in fetal and maternal brains following feeding of an organic mercurial compound to pregnant rats.

Procedures. Female Sprague-Dawley rats weighing on an average 270 g were mated with males of the same strain. Daily vaginal smears were taken and examined under the microscope to establish the presence of sperms. The day sperms were present in the vaginal smears was considered day one of pregnancy and the pregnant rat was then kept in a maternity cage with pine-chip bedding. The pregnant rat was fed a nutritionally adequate diet[2] and water *ad libitum*. The laboratory housing the rat was maintained near 22° and 12 hr each of light and darkness.

On the sixteenth day of pregnancy each rat was force-fed by stomach tube 4 μCi of ^{203}Hg as methyl mercuric chloride. The radioactive compound was dissolved in corn oil so that 1 g contained 4 μCi. The specific activity of the compound was 24.7 μCi/mg Hg. One, two, four, and five days after force-feeding or on the 17th, 18th, and 20th day of the pregnancy and at birth (21 days), 2, 2, 3, and 3 rats, respectively and their progeny (fetus and neonates) were killed by decapitation and brains carefully dissected free from the skull. There were 22, 21, and 39 fetuses from the mothers killed at the 17, 18, and 20th day of gestation. The three rats allowed to continue to term had 32 babies. All babies were killed at less than 12 hr of age. Any transfer of mercury to the baby via the milk was probably inconsequential because of the short nursing period and because milk production was minimal during early lactation.

Brains from all rats were dissected into several parts and determined for radioactivi-

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[2] Diet composition previously described in this journal **139**, 1312 (1972).

ties using a scintillation detector-counter and ^{203}Hg standards. Radioactivities were corrected for background and physical decay of the isotope.

Results. No clinical symptoms were expected or found after force-feeding the mercury compound. Since the specific activity of the compound was rather high, the mother rat received approximately 0.45 mg Hg/kg body weight. This level is about 2.2% of the LD_{50} dose for adult rats (26). The LD_{50} dose for pregnant rats is not known.

In the mother's brain, the highest uptake of mercury expressed as a percentage of the dose was in the cerebrum followed in decreasing order by cerebellum, pons plus midbrain, medulla and hypothalamus (Table I). The pituitary initially contained approximately the same percentage of the dose as the hypothalamus but subsequently decreased to about half the value. The percentage of the dose in all parts of the brain except pituitary did not change appreciably over the 5-day period.

There was a threefold increase in the uptake of mercury in the brain parts of fetal rats from 1 to 5 days after feeding the mercury to the pregnant rats (Fig. 1, 2). This was true when uptake was expressed as a percentage of the dose present in each fetal brain or in each litter of fetal brain. The increasing levels of mercury in the fetal brain undoubtedly reflect a withdrawal of the metal from the mother's blood. However, it is clear that the mercury did not come from the maternal brain since its concentration was unaltered over the 5-day period.

The uptake of mercury by the total brain mass in each litter of fetuses during the first 2 days after feeding the mercury compound to the mother was about the same as the uptake in the brain of the mother. This level was close to 0.2% of the dose. However, during the next 3 days, uptake in each litter of fetal brain mass exceeded that in the mothers' brain by 2.5- to 3.0-folds.

Of all brain parts, the cerebrum of the fetus like the cerebrum of the mother contained the highest percentage of the dose of mercury. In the 20- and 21-day-old fetal rat the pons plus midbrain contained the next highest percentage of the dose followed by the cerebellum of fetus of the same age. However, the difference between pons plus midbrain and cerebellum was small. In contrast to that found for fetal rats, the cerebellum of the mother contained a higher percentage of the dose than pons plus midbrain.

Discussion. Transplacental intoxication of fetus by mercury has been found in rats (20) and other species (23, 24, 26). In the rat, the fetal brain had higher concentrations of mercury than the maternal brain. Levels as high as 3.7 times that of the maternal brain have been found in the fetal brain (20). Using brains obtained from another 10 pregnant rats and their fetuses (2–3 pregnant rats at 17-, 18-, 20- and 21-day gestation), the calculated percentages of the dose per g of cerebellum, cerebrum, hypothalamus, pons

TABLE I. Average and Standard Errors of Deposition of Mercury in the Brain and Brain Parts of Pregnant Rats.

Stage of gestation[a] (day)	Brain or brain parts						
	Brain[b]	Cerebrum	Cerebellum	Pons + midbrain	Medulla	Hypothalamus	Pituitary
	(% of dose × 10^{-2})						
17	20.89 ± 3.4	14.07 ± 3.3	3.17 ± 0.5	1.52 ± 0.2	1.23 ± 0.1	0.43 ± 0.1	0.47 ± 0.1
18	21.23 ± 1.9	15.36 ± 3.5	2.63 ± 0.1	1.12 ± 0.6	1.21 ± 0.6	0.49 ± 0.1	0.42 ± 0.1
20	20.51 ± 2.3	13.08 ± 2.6	3.67 ± 0.2	1.63 ± 0.4	1.30 ± 0.3	0.54 ± 0.1	0.29 ± 0.1
21	22.14 ± 4.5	15.50 ± 3.7	3.60 ± 0.7	1.35 ± 0.1	0.94 ± 0.3	0.51 ± 0.1	0.24 ± 0.2

[a] There were 2 rats each for 17- and 18-day and 3 rats each for 20- and 21-day of gestation.

[b] Brain uptake of mercury represents the sum of the individual brain parts for each rat. Averages and standard errors were then calculated.

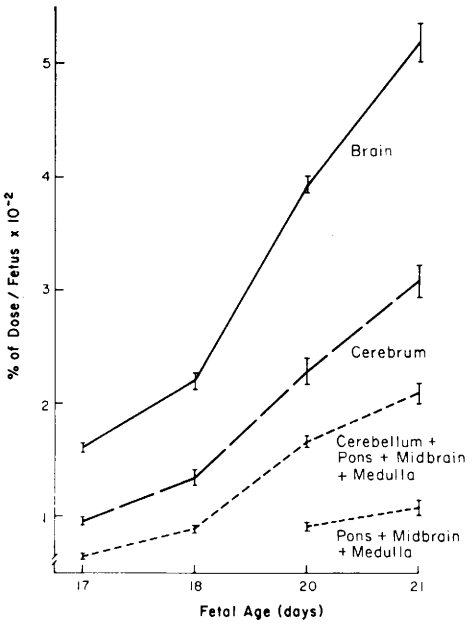

FIG. 1. Average and standard errors of deposition of mercury in the brain and brain parts in individual fetus. Each value represents the average of 22, 21, 39 and 32 fetuses for the 17-, 18-, and 20- and 21-day old fetuses, respectively.

plus midbrain, medulla, and pituitary in the mothers are 0.110, 0.114, 0.154, 0.111, 0.070 and 0.237, respectively. The mercury is thus fairly evenly distributed except in the pituitary which has the highest concentration and medulla the lowest. The concentrations expressed in a similar manner in the brain parts of the fetus were 0.43, 0.24, 0.40, and 0.51 in the cerebellum of 17-, 18-, 20- and 21-day fetus, respectively. These are 2 to 4 times higher in concentration than in the maternal cerebellum. The concentration ranged from 0.17 to 0.27% of the dose per g fetal cerebrum (fetal age, 17–21 days). These are thus 1.5 to 2.5 times higher than the concentration in the maternal cerebrum. In the 20- and 21-day fetal pons, midbrain plus medulla, the concentration was 0.29 and 0.26, respectively. These levels are again higher than that of the corresponding maternal brain parts. Thus, all indications are that fetal brain accumulates a higher concentration of mercury than the maternal brain. Furthermore, the patterns of uptake of mercury in the brain parts of mothers is different from that of their fetus. The uptake in the mother remained the same throughout the 5-day period after the oral dose of the mercury compound whereas in the fetus, the percentage of dose increased from 17 to 21 days of fetal life. However, each brain part whether fetal or maternal has its own characteristic uptake (Table 1 and Figs. 1 and 2).

Summary. Ten 16-day pregnant rats were force-fed a tracer-dose of ^{203}Hg as methyl mercury chloride. The rat was then killed at 1, 2, 4 or 5 days after force-feeding and the 10 maternal brains as well as the 114 fetal brains were each separated into several brain parts. The uptake of mercury in the maternal brain was greatest in the cerebrum followed in decreasing order by cerebellum, pons plus midbrain, medulla, and hypothalamus. The uptake expressed as a percentage of the dose remained essentially the same throughout the 5-day period after force-feeding. In the fetal brain the uptake however increased more than 3-fold from day 17 to day 21 of fetal life. Expressed on the basis of % of dose per g tissue, the fetal cerebellum contained the

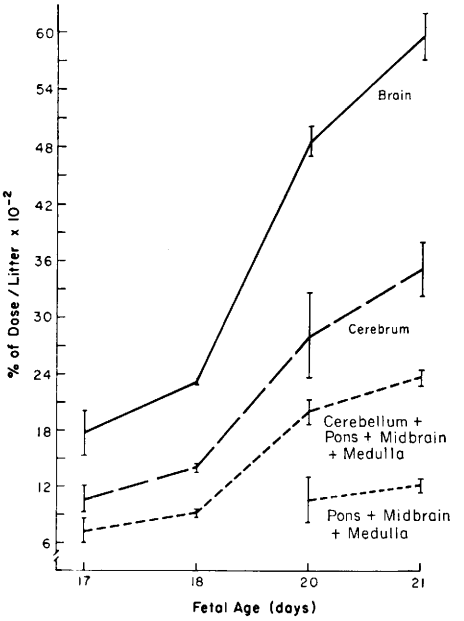

FIG. 2. Average and standard errors of deposition of mercury in the brain and brain parts in each litter of fetus. Values on the graph represent the average of 2 litters each for 17- and 18-day and 3 litters each for 19- and 21-day old fetuses.

highest concentration of mercury when compared to either fetal cerebrum or pons, midbrain plus medulla, or to any maternal brain parts. The total fetal brain mass from an average litter accumulated, during the first 2 days after force-feeding, approximately the same percentage of the dose as in the mother's brain. However, during the following 3 days, the total brain mass of each litter had 2.5 to 3.5 times the uptake level in the mother's brain.

1. Morikawa, N., Kumamoto Med. J. **14**, 71 (1961).

2. Swensson, A., Lundgren, K-D., and Lindstrom, O., Amer. Med. Assoc. Arch. Ind. Health **20**, 86/432 (1959).

3. Miller, V. L., Klavano, P. A., and Csonka, E., Toxicol. Appl. Pharmacol. **2**, 344 (1960).

4. Hanko, E., Erne, K., Wanntorp, H., and Borg, K., Acta Vet. Scand. **11**, 268 (1970).

5. Aberg, B., Ekman, L., Falk, R., Greitz, U., Persson, G., and Snihs, J-O., Arch. Environ. Health **19**, 478 (1969).

6. Berlin, M., Fazackerley, J., and Nordberg, G., Arch. Environ. Health **18**, 719 (1969).

7. Berlin, M., and Ullberg, S., Arch. Environ. Health **16**, 589, 602, and 610 (1963).

8. Berlin, M., Jerksell, L. G., and von Ubisch, H., Arch. Environ. Health **12**, 33 (1966).

9. Platonow, N., Canad. Vet. J. **10**, 202 (1969).

10. Friberg, L., Odeblad, E., and Forssman, S., Amer. Med. Assoc. Arch. Ind. Health **16**, 163 (1957).

11. Swensson, A., Lundgren, K-D., and Lindstrom, O., Amer. Med. Assoc. Arch. Ind. Health **20**, 31/467 (1959).

12. Miller, V. L., Klavano, P. A., Jerstad, A. C., and Csonka, E., Toxicol. Appl. Pharmacol. **3**, 459 (1961).

13. Magos, L., Brit. J. Ind. Med. **25**, 152 (1968).

14. Prickett, C. S., Laug, E. P., and Kunze, F. M., Proc. Soc. Exp. Biol. Med. **73**, 584 (1950).

15. Rothstein, A., and Hayes, A. D., J. Pharm. Exp. Ther. **130**, 166 (1960).

16. Magos, L., Brit. J. Ind. Med. **25**, 315 (1968).

17. Ulfvarson, U., Toxicol. Appl. Pharmacol. **15**, 517 (1969).

18. Norseth, T., and Clarkson, T. W., Arch. Environ. Health **21**, 717 (1970).

19. Ellis, R. W., and Fang, S. C., Toxicol. Appl. Pharmacol. **11**, 104 (1967).

20. Nakamura, K., and Saeki, S., Life Sci. **6**, 2321 (1967).

21. Suzuki, T., Miyama, T., and Katsunuma, H., Jap. J. Med. Progr. (Nisshin Igaku) **48**, 716 (1961).

22. Gage, J. C., Brit. J. Ind. Med. **21**, 197 (1964).

23. Nordberg, G. F., and Skerfving, S., *in* "Mercury in the Environment. A Toxicological and Epidemiological Appraisal" (L. Friberg, and J. Vostal, eds.), p. 4. Environmental Protection Agency, Triangle Park, NC (1971).

24. Nelson, N., Byerly, T. C., Kolbye, A. C., Jr., Kurland, L. T., Shapiro, R. E., Shibko, S. L., Stickel, W. H., Thompson, J. E., Van Den Berg, L. A., and Weissler, A., Environ. Res. **4**, 1 (1971).

25. Yoshino, J., Mozai, T., and Nakao, K., J. Neurochem. **13**, 397 (1966).

26. Methyl Mercury in Fish. A Toxicologic-Epidemiologic Evaluation of Risks. Report from an expert group. Nordisk Hygienisk Tidskrift Supplementum 4 (1971).

27. Takeuchi, T., International Conference on Environmental Mercury Contamination, Ann Arbor, Michigan, (1970).

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