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Health Risks from Increases in Methylmercury Exposure

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Our present knowledge of the human health effects of methylmercury exposure is derived from study of major outbreaks of human poisonings in Japan and Iraq and experimental studies on primates. Methylmercury readily passes through such physiological barriers as the blood–brain barrier, blood–testes barrier, and the placenta. Its major pathological effects are on the nervous and reproductive systems and the developing embryo/fetus. The neurotoxicity of methylmercury is well established in both humans and non-human primates. Lesions in the cerebral and cerebellar gray matter consist of necrosis and lysis of neurons, phagocytosis and gliosis. The changes are most prominent in the deep sulci and may have a vascular component. A late effect is cerebral atrophy. At high dose levels the liver, kidneys, and other organs may also have degenerative changes.

Although not yet described in humans, a major effect of exposure of female primates is an adverse effect on pregnancy. Maternal female *M. fascicularis* blood mercury levels above 1 ppm are associated with a decreased pregnancy rate and increased abortion rate. To date our experimental data lack sufficient numbers to detect infrequent pregnancy effects below 1 ppm. Preliminary studies also reveal that methylmercury may also decrease the number and function (swim speed) of sperm.

Both human and primate studies demonstrate deleterious effects of methylmercury on the developing embryo/fetus. Autopsies on human and primate infants reveal retarded brain development and the occurrence of a cerebral palsy-like behavior in the newborns, whereas the mother may be free of signs and symptoms of methylmercury toxicity. The fetal blood level of mercury is higher than the maternal level. Many features of physical and behavioral development of the newborn and infant have been reported from relatively high exposure levels. Behavioral tests of infant primates (object permanence; visual preference) revealed a retardation of cognitive development. Further research is needed to define the level at which methylmercury begins to have significant neurotoxic, reproductive, or fetal developmental effects. The increased level of methylmercury in some fish due to acid precipitation and the demonstration of significant lesions at clinically nontoxic levels suggest that the margin of safety may be narrow.

The chemical form of mercury and the dose alters the selection of the target organ (*1*). For example, inhalation of metallic mercury (Hg^0) vapor in sufficient quantity leads to severe toxic injury to the lung alveoli and blood vessels which, in turn, produces pulmonary edema. The edema fluid interferes with the respiratory exchange of oxygen and carbon dioxide. This pathological sequence with the lung as target organ is often the result of occupational exposures and misadventure (*2,3*). The kidneys are the main target organ of bichloride of mercury ($HgCl_2$). The Hg^{2+} ion is rapidly concentrated in the kidneys and liver (*4,5*). If the concentration is sufficient it will cause necrosis of the epithelial cells lining the kidney proximal convoluted tubules (*6*) and may produce renal failure. Although poisoning by inorganic mercurials has been known since ancient times only relatively recently has there been greater attention paid to the organic mercury compounds. Methylmercury passes through physiologic barriers such as the blood-brain barrier, blood-testes barrier, and placenta with ease, in contrast to the inorganic forms (*4*). Thus, methylmercury is much more likely to target the nervous system, testes and the developing embryo/fetus and will be described in detail.

The reports of Stokes and of Jernelov at this conference presented data on the increased bioavailability of methylmercury to fish due to acid precipitation. It now is well established by researchers in Japan (*7*), Sweden (*8,9*), and the United States (*10–12*), that bacteria in the soil and lakes as well as in the intestinal tract (*13*) can convert metallic and inorganic mercury forms to methylmercury. Methylmercury enters the food chain and is concentrated in fish and shellfish. The amount in the environment of these creatures determines, for the

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main part, the amount in their tissues and thus the amount we consume. Approximately 80% of our daily intake of mercury is methylmercury, and the principal source of mercury is seafood (*14–16*). The average methylmercury intake varies from 20 μg/day to 80 μg/day or more in heavily contaminated food (*15,17,18*). Clinical and epidemiologic studies on some human subpopulations with high methylmercury intake have been done by Clarkson et al. (*18–22*).

Effects of Methylmercury

Three methylmercury environmental poisonings of large populations in recent decades and some occupational reports have provided much of the clinical and pharmacodynamic information (*22–24*) about the effects of high level exposure especially as they relate to the nervous system (*25–28*) and congenital injury (*21,25,26,28*). However, some aspects of methylmercury injury may have not come to light during these poisonings because of limitations inherent in the field conditions of the populations studied. Thus, subclinical and low dose cases with subtle effects were less likely to be discovered (*29*). The biologic differences such as blood clearance (*30–32*), placental structure and function between laboratory rodents and humans has made it necessary to use primates to uncover some of the subtle but important pathologic changes. Therefore, the following summary of the health effects includes some data we have derived from nonhuman primate experiments to add to our understanding of the effects of intermediate (1–2 ppm) and low (< 1 ppm) blood levels of methylmercury

Neurotoxicity

That methylmercury in high doses, i.e., blood levels above 2 ppm, is a severe neurotoxin was well established in Japan (*28*), by Jalili in Iraq in 1961 (*27*), and Bakir et al. in Iraq in 1972 (*26*). Much of the human neuropathology was defined by Takeuchi (*33*). The widespread brain lesions lead to signs and symptoms characteristically referable to that organ. They are (1) parasthesia, a numbness and tingling sensation around the mouth, lips, and extremities, particularly the fingers and toes; (2) ataxia, a clumsy stumbling gait, difficulty in swallowing and articulating words; (3) neurasthenia, a generalized sensation of weakness, fatigue and inability to concentrate; (4) vision and hearing loss; (5) spasticity and tremor; and finally (6) coma and death. Except for the brief reports of Al-Saleem (*34*) and Choi (*35*), scant pathologic studies have been reported from Iraq. Neuropathologic observations reveal the cortex of the cerebrum and cerebellum to be selectively involved with focal necrosis of neurons, their lysis and phagocytosis and replacement with supporting glial cells (Fig. 1). These changes are most prominent in the deeper fissures (sulci) such as in the visual cortex and insula. The overall acute effect of these destructive changes is cerebral edema. However, with prolonged destruction of gray matter and subsequent gliosis, cerebral atrophy results. (Fig 2). Observations on primate brains by Shaw (*36–38*), Berlin (*39*), and others (*40*) are consistent with the above and provide a time, dose, and tissue burden relationship. Shaw observed that in autopsies done more than a year after the cessation of exposure, cerebral atherosclerosis occurred in 4 of 27 animals in small arteries and arterioles (Fig. 3.) overlying sites of mercury parenchymal degeneration.

Sacrifice of methylmercury-exposed monkeys that lacked signs of mercury poisoning (normal cage behavior) revealed in a few instances neuronolysis in the cerebral cortex and cerebral atrophy (of the type reported in the human clinical deaths) occurred at blood mercury levels below 2 ppm in our primates. However, our data are incomplete to establish whether "silent damage" occurs at lower levels.

Observations from Minamata, Japan suggest that the lowest whole blood level of mercury in which symptoms had occurred was 0.2 ppm (*1*). However, Bakir et al. (*26*) and Kutsuma (*27*) suggest that symptoms may occur in susceptible individuals at 0.1 ppm.

Pregnancy Outcome

The groups studying the poisonings in Japan and Iraq have not reported data on the effects of methylmercury on pregnancy outcome. A surprise finding in our primate studies was that methylmercury decreased the pregnancy rate and increased the abortion rate at relatively moderate maternal blood levels (*41*).

Our experimental design is as follows: Two colonies of *M. fascicularis* monkeys were studied in tandem. Each colony consisted of three groups (seven control females received apple juice vehicle by oral administration daily; seven females received 50 μg MeHg/kg/day orally in apple juice, which produced blood mercury levels of 1.0 ± 0.13 ppm. Seven females received 90μg MeHg/kg daily, which produced mercury blood levels of 2.0 ± 0.33 ppm. The females were selected from our large center which enabled us to match these groups for parity, weight, and other standard obstetrical characteristics. Half of each group was colony-born and -reared and half were wild-born but colony-reared, with a proven successful pregnancy history. One male used in all of the experiments did not receive mercury. The study consisted of 4 months of baseline observations (clinical evaluation, menstrual cycles, menses, blood chemistry, liver and kidney function tests and hemogram, and blood mercury assay biweekly). Methylmercury was administered on the preplanned schedule for 4 months; the animals were then mated and continued on mercury throughout pregnancy and after. Each individual at a given dose established a blood mercury level after 2 months of exposure which remained relatively constant throughout the experiment. The mid-menstrual cycle was established during the baseline and the day of ovulation calculated (*42*). After 4 months of methylmercury administration, the male was placed in the cage with the female at ovulation for one night. If

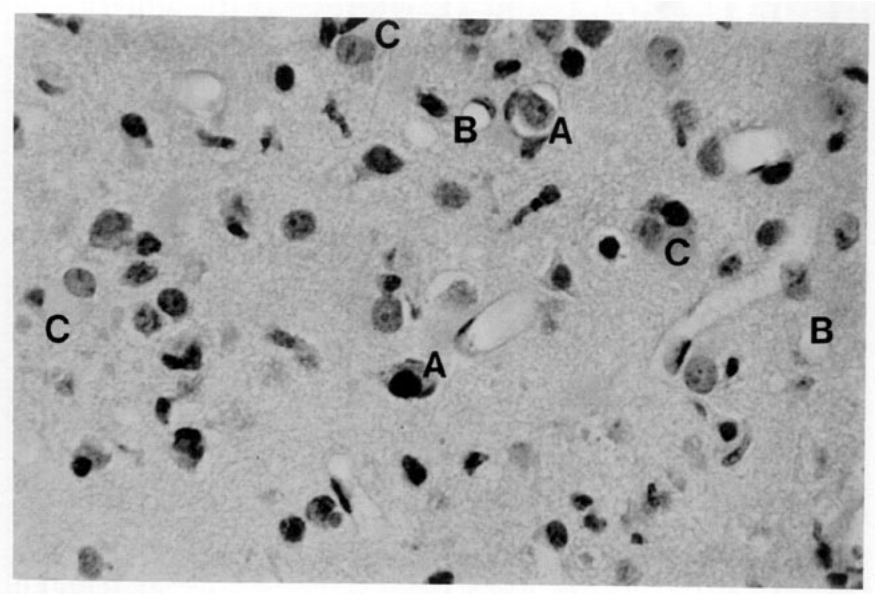

FIGURE 1. Primate cerebrum (occipital pole) following methylmercury exposure. Degenerating neurons (A) are accompanied by phagocytic cells (B) and increased numbers of glial cells (C). ×100.

pregnancy did not occur, mating would be repeated for the two subsequent cycles. If pregnancy did not occur in three matings it was recorded as nonconception. Mating, gestation (*165–168* days) labor, and delivery were recorded by video camera. After delivery the experimental females were continued on methylmercury for one year, then the study was repeated. Four of the first colony of seven animals at the 90 μg MeHg dose level developed slight tremor after a year of MeHg; therefore, the second colony high dose was reduced to 70 μg MeHg/kg/day. None of the females had symptoms of mercury intoxication during pregnancy.

To date (12/31/84), the pregnancy outcome data of 29 experimental and 15 control animals are available. An increase in nonconceptions, abortions and stillbirths is seen at blood mercury levels above 1 ppm (Table 1). We obtained no viable offspring above 2 ppm, but our N at this level is too small to be statistically significant. This type of methylmercury effect can easily be overlooked in the human exposures. The many variables in the

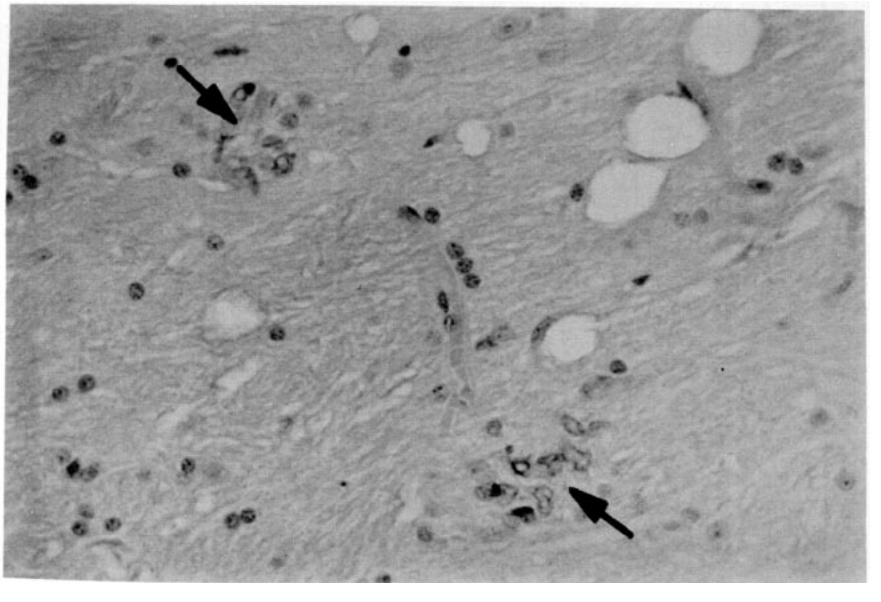

FIGURE 2. Primate cerebrum late lesions following methylmercury exposure. Clusters of glial cells surround remnants of neurons. ×100.

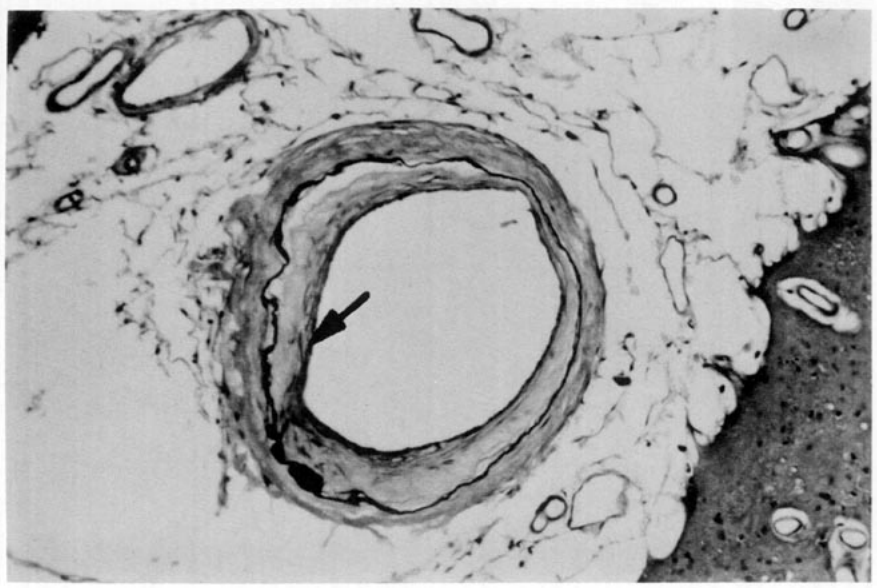

FIGURE 3. Cerebral sulcus arteriole. A thick layer of intima (↑) overlies internal elastic lamina (black layer).

Table 1. Meand Hg concentration in whole blood and reproductive failure.

$\bar{X}$ Hg concentration, ppm[a]	Reproductive failure[b] % and (absolute number)
0.6[c]–1.0 (N = 6)	0.0% (0/6)
1.0–1.5 (N = 7)	28.6 (2/7)
1.5–2.0 (N = 13)	69.2 (9/13)
>2.0 (N = 3)	100.0 (3/3)

[a] $\bar{X}$ Hg concentration during breeding and/or pregnancy.
[b] Total nonconceptions, abortions, stillbirths.
[c] Lowest $\bar{X}$ Hg concentration for exposed females.

MeHg-exposed human populations make data of this type difficult to derive.

Abnormal Spermatogenesis

There appears to be only one report in the literature (*43*) describing decreased spermatogenesis in the humans due to alkylmercury exposure. Lee and Dixon (*44*) have shown in mice that methylmercury breaches the blood–testes barrier much more readily than inorganic mercury. We have followed these reports with a primate pilot study which is currently in progress. A preliminary study by M. Mohamed in my laboratory has shown *in vitro* that methylmercury at levels above 1 ppm decreases the motility of sperm over a 3-hr period (Fig. 4). The speed was quantitated by a new laser light scatter method in microns per second (*45*). (*In vivo* exposure of male monkeys on a dose schedule comparable to the above results in abnormal sperm structure (Fig. 5). Much more remains to be done to determine whether male fertility is decreased.

Embryopathic Effects

The fourth principal effect of methylmercury is on the unborn child. The poisonings in Japan (*28*) and in Iraq (*25,26*) clearly established mercury to be a human teratogen in relatively high doses, with major effects on the developing nervous system. A cerebral palsy-like syndrome is produced. Autopsies by Takeuchi on three fetal deaths (*33*) revealed a decreased number of nerve cells in the cerebral cortex and a generalized hypoplasia of the cerebellum. The total brain weight was markedly decreased. Choi et al. (*35*) autopsied two fetal brains from Iraqi fetal deaths. High levels of brain mercury were associated with abnormal neuron migration and deranged organization of brain centers and layers were described. At the levels and period of congenital exposure, the women in Japan and Iraq produced offspring that tended to be smaller than normal; however, many uncontrolled variables make the human data difficult to interpret. In laboratory rodents there is a dose-related decrease in size/weight of the methylmercury congenitally exposed offspring (*46,47*).

We have examined the physical and behavioral development of offspring born to primate females with blood levels of mercury between 0.5 and 2 ppm and have found some very interesting structural and functional changes not reported at the lower dose levels in the humans. At any of the given maternal mercury blood levels within the range studied, the maternal level was lower than the fetal (umbilical cord blood) by a ratio of 1:1.5–2.0. The data from our observations on the physical characteristics of the offspring are comparable in

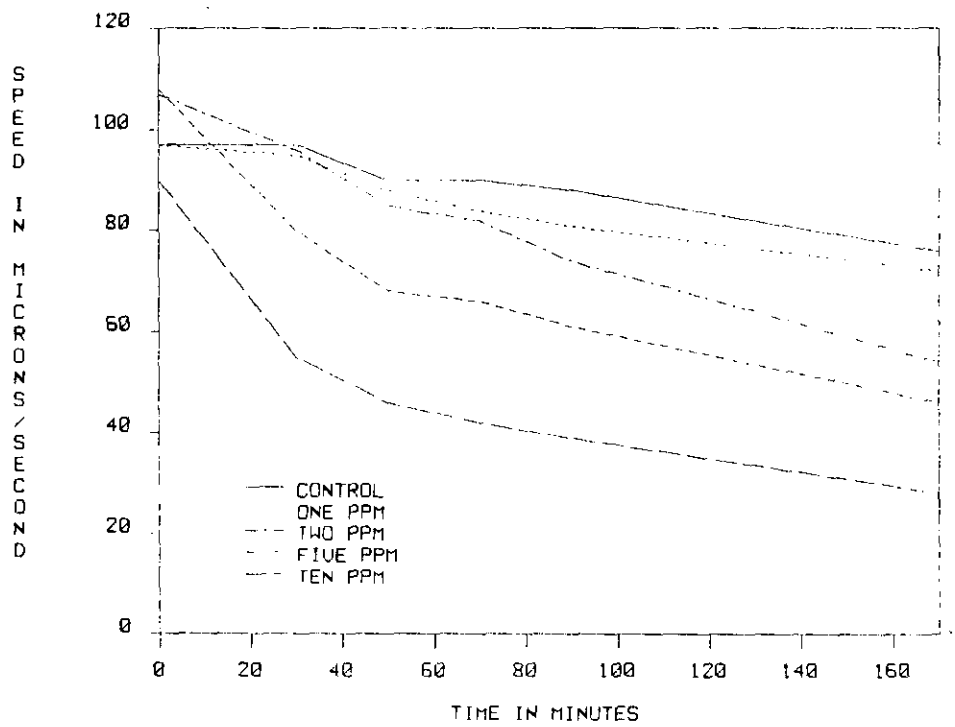

FIGURE 4. Methylmercury level and sperm speed.

experimental and control groups and for male and female offspring (Table 2). There is a trend towards lower birth weights, shorter crown-rump length, microcephaly, and other physical parameters of decreased size. However, one must be cautious in interpreting these data because as indicated we separate the offspring into male and female which have an inherent difference in size in primates. We must gather further data to be sure that maternal weight, which is an important variable in birthweight, be carefully controlled. Above the maternal blood level of 2 ppm one sees a pattern of brain changes similar to that described in humans.

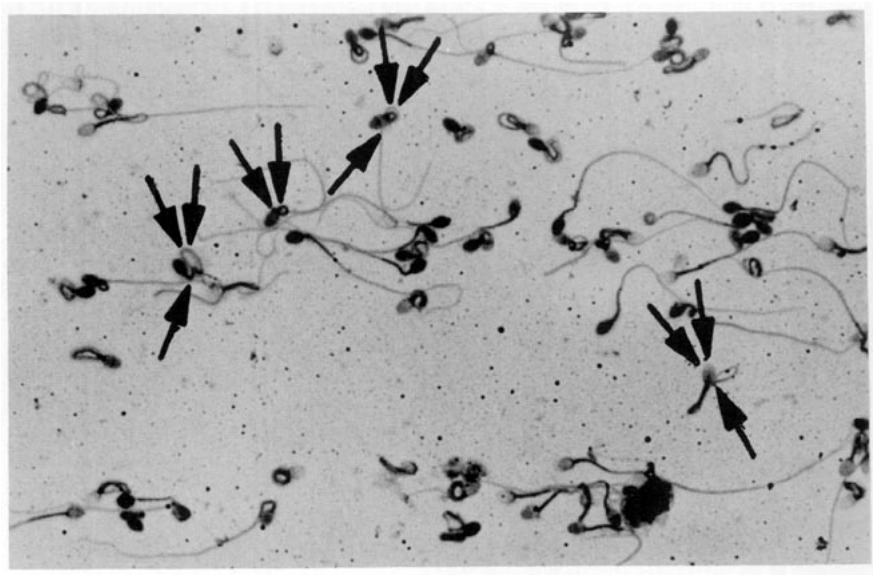

FIGURE 5. Primate spermatozoa following methylmercury exposure. Frequent kinking of flagella (↑) and persistent cycoplasmic droplets (↑ ↑). Kinked areas are inflexible.

Table 2. Physical characteristics of offspring at birth.[a]

	Females		Males	
	Controls (N = 6)	50 μg/kg/day (N = 5)	Controls (N = 9)	50 μg/kg/day (N = 7)
Gestation, days	160 ± 2.5	157 ± 2.8	163 ± 1.5	160 ± 1.7
Birthweight, g	348 ± 21	316 ± 45	380 ± 24	344 ± 11
Crown-rump length, mm	178 ± 4	171 ± 3	181 ± 4	174 ± 3
Head width, mm	48 ± 0.8	47 ± 0.5	49 ± 0.6	49 ± 0.5
Head length, mm	61 ± 0.7	59 ± 0.7	62 ± 0.6	61 ± 0.6
Head circumference, mm	171 ± 3	164 ± 3	174 ± 2	172 ± 1
Left foot length, mm	68 ± 1	66 ± 2	70 ± 1	67 ± 1

[a] All values X ± SE.

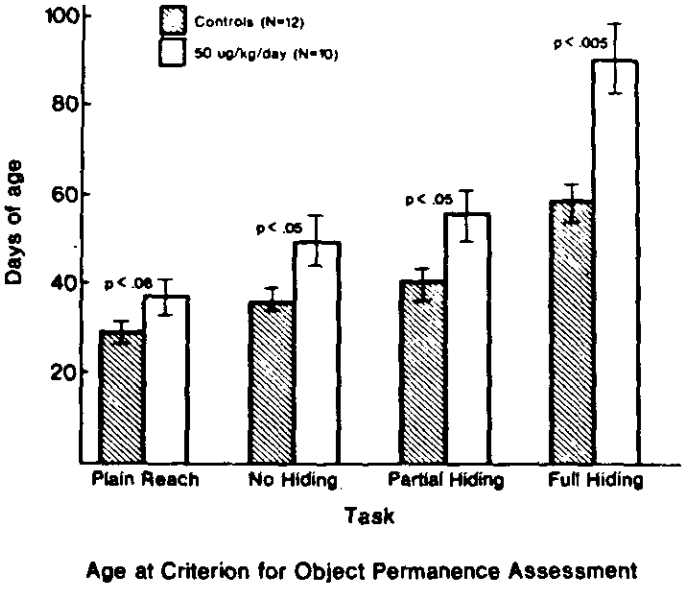

FIGURE 6. Primate infant object permanence test performance.

Behavioral Effects

In addition to recording the usual milestones of behavioral development such as the onset of reflexes, strength of suckling, play pattern, etc., that are done on humans and on our primate offsprings alike, some behavioral tests have been done on these monkeys. One of the most important findings that occurs in the offspring of mothers with 0.5 ppm blood level is a decrement in object permanence test performances.

The object permanence test is a generally recognized (*48*) milestone in cognitive development based on the concepts developed by the late Professor Piaget (*49*). Basically, in early infancy, objects that cannot be seen do not exist until cognitive ability matures enough to recognize that the object may still be present but hidden behind a screen. The test is simple. Primate responses are remarkably similar to those of humans. Assessment is done with almost identical procedures.

The test is begun at 14 days of age. It was done double-blind by Burbacher and co-workers (*50*). The object is a brightly colored toy with a nipple at one end. The nipple is dipped in apple sauce and the infant instinctively puts it in his mouth and sucks (the reward). The toy is then placed on a platform within reach and the infant grasps, picks up the toy and puts it in his mouth (plain reach task). When the infant can accomplish this task four out of five times in 15 seconds, it has reached criterion (*51*). Control infants achieved criterion at 29 days of age, whereas the prenatally methylmercury-exposed infants took 36 days of age to achieve criterion (Fig. 6). After criterion was achieved, the infants were tested two times per week with a battery of no hiding, partial hiding, and full hiding tasks (total 15 trials each day). There is a statistically significant retardation with the prenatally mercury-exposed infants for each task. With the full hiding task the prenatally mercury-exposed infants reached criterion at 91 days, whereas the controls reached criterion at 58 days.

Time does not permit description of another cognition test—the visual preference or Fagan Test (*52,53*). It is increasingly regarded as a valid predictor of mental retardation (*54*). This test is based on timing the gaze to

Table 3. Primate infant visual preference test (Fagan) performance.

	Control (N = 10)		MeHg exposed (N = 8)	
Measure	Familiar	Novel	Familiar	Novel
Percentage of looking time to novel stimuli ± SD*	—	67.7 ± 7.9	—	57.1 ± 7.3
Frequency of looks ± SD†	4.34 ± 1.28	6.13 ± 1.81	4.43 ± 1.72	5.31 ± 2.02
Duration per look, sec ± SD‡	1.07 ± 0.34	1.66 ± 0.44	1.34 ± 0.39	1.35 ± 0.34

* $p < 0.02$ for groups.
† $p < 0.001$ for stimulus type (familiar vs. novel).
‡ $p < 0.01$ for group × stimulus type interaction.

determine how quickly the offspring gazes at a novel visual stimulus (Table 3). A decrement in the mercury-exposed group in comparison with the controls was found (*55*).

At the present time one cannot define precisely the margin of safety between the level of methylmercury exposure of some subpopulations of people and the level at which the developing embryo and fetus or adults may be adversely affected. From the data presented, the margin appears to be sufficiently narrow to be cause for concern and to warrant continued investigation. The minimal exposure level at which subtle decrements in male and female fertility, brain structural and functional development and offspring growth and development occur in humans and primates awaits further investigation.

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