More Evidence of Mercury Effects in Children

In research published last summer, scientists revealed that prenatal exposure to methylmercury, an organic form of mercury that accumulates in animal tissues, may affect the blood pressure and ability to respond to sensory stimuli in exposed children later in life. The team is now also confirming findings of mercury-related neurodevelopmental effects among the Faroese subjects by studying a cohort of Madeiran children.

The reports are the latest work of Philippe Grandjean, an adjunct professor of public health at Boston University in Massachusetts, and Pál Weihe, medical director of the Faroese Hospital System in Tórshavn, who, with their colleagues, have performed extensive analysis of a longitudinal study on the effects of prenatal methylmercury exposure among the inhabitants of the Faroe Islands. The Faroe Islands study was funded by the NIEHS along with European grant-making bodies including the European Commission Environment Research Programme and the Danish Medical Research Council. The Faroese were chosen as study subjects because their diet is rich in pilot whale meat, a prime source of methylmercury. In the study of 917 Faroese children, prenatal exposure to methylmercury was assessed by analyzing mercury concentrations in cord blood and maternal hair. At age 7, the children underwent extensive neurobehavioral testing as well as a general health examination.

A whale of a meal. The meat and blubber of the long-finned pilot whale have been staples of the Faroese diet for centuries. People who eat a whale meal may be exposed to methylmercury, which has been found to cause neurodevelopmental and other effects in children exposed *in utero*.

A paper published in the July 1999 issue of *Epidemiology* describes mercury-related cardiovascular risk factors that were identified among the Faroese children during the general health exam. Because of earlier case reports and experimental findings of cardiovascular effects of mercury, the children were examined for blood pressure, heart rate, and heart rate variability. As a whole, the children had normal blood pressure for their age. But among children whose cord blood mercury content had been measured at 1–10 µg/L, the scientists found that blood pressure was raised by an average of 14 points. The effect was magnified in children with lower birth weights, whose blood pressure was raised by as much as 21 points. No additional increase was seen in children whose cord blood mercury concentration had been higher than 10 µg/L.

Implantation: Timing Is Everything

Understanding the many facets of human reproduction has long been considered a guessing game. According to Allen Wilcox, chief of the Epidemiology Branch at the NIEHS, until now, knowing exactly when implantation of an egg into the uterine wall occurs has been impossible because the event has never been observed in humans. However, Wilcox and his team have recently taken some of the guessing out of the process by shedding light on how the timing of implantation may affect a pregnancy's outcome. The results of their research were published in the 10 June 1999 issue of the *New England Journal of Medicine*.

Allen J. Wilcox

When the time is right. A human blastocyst is ready for implantation.

The NIEHS team collected urine samples for up to 100 days from 221 women who were trying to conceive. The scientists pinpointed the time of ovulation by studying the ratio of estrogen metabolites to progesterone metabolites. By studying levels of the hormone chorionic gonadotropin (hCG), the team was able to detect when a fertilized egg was implanted into the uterine lining.

Of the 189 women who yielded sufficient data for the team's analysis, 75% carried their pregnancies at least 6 weeks past their last menstrual cycle. The remaining 25% of pregnancies resulted in early loss that was strongly related to the time of implantation. The initial rise in hCG occurred 6–12 days after ovulation, with 84% occurring specifically 8–10 days after ovulation. On average, surviving eggs were implanted 1 day earlier than nonsurviving eggs—9.1 days versus 10.5 days from fertilization to implantation.

When implantation occurred by day 9, there was only a 13% chance of embryonic loss. By day 10, however, 26% of embryos had died. The percentage of loss rose on day 11 to 52%, and to 82% beyond day 12. In the study, the three implantations that occurred after day 12 ended in early loss. Not only does the receptivity of the mucous membrane lining the uterus decrease, but the body is less responsive to hCG by 11 or 12 days after ovulation. What this shows, according to Wilcox, is that "the uterus may be receptive to pregnancy only during a limited time-window, shutting out defective embryos that arrive too late. This would spare a mother the physiologic burden of supporting a nonviable embryo."

The study says that the data may provide implications for efforts to manipulate receptivity of the uterus, offering new possibilities for infertile women. For example, fertility might be increased by extending the window of time during which implantation could occur.

The scientists also found that heart rate variability decreased with increasing mercury exposures, particularly in boys in the 1–10 µg/L exposure range. Grandjean explains, "The heart rate must vary in accordance with the varying needs for oxygen of the peripheral tissues. This variation is regulated through the autonomic nervous system. A decreased variability is a sign of abnormality, as the heart then is slower in responding to the body needs."

The *Epidemiology* findings are especially interesting from a public health perspective because childhood blood pressure has been shown to be an important predictor for hypertension later in life. The findings also indicate that prenatal exposure to methylmercury at concentrations below current exposure limits can cause adverse health effects. The daily intake reference dose of the U.S. Environmental Protection Agency is 0.1 µg/kg body weight per day, an intake that Grandjean says would correspond to mercury concentrations of about 5 µg/L in cord blood and about 1 µg/g in hair.

In a related study (not funded by the NIEHS), that was published in the July/August 1999 issue of *Neurotoxicology and Teratology*, Grandjean and colleagues examined 149 children on the island of Madeira, off the coast of Morocco. The Madeiran children were exposed to methylmercury when their mothers ate the deep-sea fish black scabbard while pregnant.

The children's hair mercury concentration at the time of the test was measured to determine current exposure level. Hair samples were also collected from the mothers, with the hair of those whose diet hadn't changed over the past seven years (some 80% of the mothers) serving as an indicator of methylmercury exposure at the time of pregnancy.

The children then underwent neuropsychological and neurophysiological testing, including assessment of evoked potentials (electrical signals from the brain that are evoked by sensory stimuli). The results of prenatal exposure would logically be linked to the maternal hair mercury concentrations, which in the Madeiran cohort were found to vary from 1.1 to 54.1 µg/g. The scientists found that certain evoked potentials tended to be slower in children who had been exposed to higher concentrations of mercury. According to the report, children of mothers with hair mercury concentrations higher than 10 µg/g experienced delays of as much as 10% in auditory and visual latencies. Says Grandjean, "[Evoked potentials] represent an objective assessment of nervous system function, and they are relatively independent of confounders. They therefore provide support for the observations of neuropsychological deficits previously reported. The clinical implications of these findings, in total, is that children with increased prenatal exposure to methylmercury are likely to suffer delays in neurological development."

In Grandjean's opinion, two primary points emerge from the Faroe Islands and Madeira findings. "First," he says, "the evidence is accumulating that prenatal methylmercury exposure from seafood may cause subtle neurotoxicity even though current exposure limits are not exceeded. Second," he continues, "the effects on brain function should not be looked at in isolation, as the autonomic nervous system may also be involved, thereby affecting cardiovascular function."

Minority Children at Risk from ETS

Researchers at Columbia University in New York have found new molecular evidence to show that young children are more vulnerable than adults to genetic damage caused by environmental tobacco smoke (ETS). The study was published in the May 1999 issue of *Cancer Epidemiology, Biomarkers & Prevention.* According to the study, cancer risks from ETS to young children and minorities have not been adequately characterized up to this point.

The Columbia researchers attempted to characterize cancer risks further by determining if biomarkers, specific chemicals in the body that have particular molecular features for measuring a disease's progress, are associated with ETS exposure in young children. The study also examined possible ethnic differences in biomarkers. The innovative study, led by Frederica Perera, director of the Columbia Center for Children's Environmental Health, which is funded by the NIEHS, was the first to evaluate ETS's effect on minority groups.

The teams measured four different biomarkers in the blood cells of 109 Hispanic and African-American children, ages 1 to 6. The specific biomarkers measured were cotinine (a metabolite of nicotine), two different carcinogenic protein complexes, and sister chromatid exchanges. This study was the first of its kind to use this set of biomarkers to characterize the cancer risk of ETS in young children

The children studied were divided into three main exposure groups: children with no ETS exposure, children with ETS exposure from a household member other than the mother, and children with ETS exposure via maternal smoking. The results indicated that the four biomarkers increased with ETS exposure in all exposure groups. Says Perera, "Young children and infants *in utero* are likely to be more vulnerable than adults to genetic damage from carcinogens, and carcinogenic exposures during early development can increase the risk of cancer later in life."