

TOXICOLOGY OF NEURODEVELOPMENTAL DISORDERS**The neuropathogenesis of mercury toxicity**

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Elemental and inorganic mercury (Hg) are found in scientific instruments, electrical equipment, dental amalgams, felt making, disinfectants, production of caustic soda, and disk batteries. Environmental Hg contamination has increased dramatically since the beginning of the Industrial Revolution. The largest contributor to atmospheric contamination is coal burning. Mining, smelting, and refining processes also contribute locally to Hg contamination. Through natural processes and direct commercial discharge, most Hg settles in the marine environment. In the waterways, methylation of inorganic mercury to methylmercury (MeHg) leads to its accumulation in the food chain. Anthropogenic sources resulting in the acidification of freshwater streams and lakes, and the impoundment of water for large hydroelectric schemes have led to increasingly higher MeHg concentrations in fish. A considerable degree of bio-concentration takes place as MeHg moves up the aquatic food chain. Most marine fish contain <0.5 ppm MeHg, but sharks, sailfish, marlin, and other billfish frequently have levels of over 1 ppm. When local waters are polluted with MeHg, levels may be much higher.

The clinical manifestations of organic mercury poisoning depend on the type of Hg compound involved. Ethylmercury (EthylHg; the additive in thimerosal) mimics the neurotoxicity of MeHg, whereas phenylmercury mimics the toxicity of inorganic Hg salts. MeHg, at high concentrations, causes a toxic encephalopathy with severe congenital form resulting from prenatal exposure. The correlation between clinical symptoms and whole blood Hg depends both on the Hg species and/or the duration of exposure. Whole-blood mercury levels are the best measure of recent inorganic Hg and elemental Hg vapor absorption. Normal blood levels of Hg do not exceed 1–3 $\mu\text{g dl}^{-1}$. Hair analysis indicates past exposure, and the Hg blood to hair ratio is ~2:250.

Comparative studies on the neurotoxicity of MeHg and EthylHg are limited. Three or 10 days after the last of five treatments with either 8.0 or 9.6 mg EthylHg kg^{-1} , rats had higher total or organic Hg concentrations in blood, and lower concentrations of Hg in brain than rats treated with 8 mg kg^{-1} MeHg. There appears to be

little difference in the neurotoxicity of MeHg and EthylHg.¹

Given that contaminated fish represent a common source for human MeHg exposure, considerable attention in the scientific and health policy fora is focused on the question of whether MeHg intake from a diet high in fish is associated with aberrant CNS function. The human database on the neurodevelopmental effects of MeHg is extensive, and has been recently summarized by the National Research Council.² These studies provide little evidence that the ages at which children achieve major language and motor milestones are affected appreciably by low-dose prenatal MeHg exposure.² An association of low-dose MeHg exposure on early childhood development was reported in only two of the four studies using the Denver Developmental Screening Test. The Faroes study reports associations between low-dose prenatal MeHg exposure and children's performance on standardized neuro-behavioral tests, particularly in the domains of attention, fine-motor function, confrontational naming, visual-spatial abilities, and verbal memory, but it is the only one to report such effects of the three major prospective long-term studies. In contrast, the Seychelles study failed to reveal such associations. The smaller New Zealand study also observed associations, as did a large pilot study conducted in the Seychelles.²

In 1957, Margoshes and Vallee reported the isolation of a protein from horse kidney, which showed a high affinity for cadmium.³ This protein was subsequently biochemically characterized, and, due to its high content of metals and cysteine residues, it was named metallothionein (MT). Putative physiological functions, such as transport and storage of essential heavy metals (zinc, copper) and detoxification of non-essential ones (mercury) were proposed. The ability of heavy metals to induce MT synthesis was described by Piscator,⁴ demonstrating increased MT levels in the livers of rabbits exposed to cadmium. This form of regulation has been recognized in all species and cells that synthesize MTs. MT synthesis is inducible in several tissues by a variety of heavy metal ions, such as Cd, Pb, Zn, Co and Hg.⁵ Although the number of studies on the ability of MTs to protect against neurotoxicity is rather limited, recent reports corroborate the cytoprotective effects of these proteins. For example, in an ischemic experimental model, van Lookeren Campagne and colleagues⁶ demonstrate that increased expression of MT-1 protects against focal cerebral ischemia and reperfusion. Mammalian MTs are genetically polymorphic. Thus, in human tissues and cell lines closely related structures of ten functional isoMTs have been identified either by amino acid or nucleotide sequencing.