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THE IMPACT OF MERCURY ON HUMAN HEALTH AND THE ENVIRONMENT

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The city of New Orleans was spared the wrath of hurricane Ivan. Yet, a week later, the eye of a different kind of storm stirred at the edge of the Mississippi, a muddy and polluted river, emblematic of our self-inflicted health crisis affecting children and the elderly, from autism to Alzheimer's disease. A unique international group of policymakers, environmental scientists, toxicologists, biochemists, journalists, academic physicians, practicing pediatricians, neurologists, and dentists gathered to make sense of the environmental impact, toxicology, basic science, public policy, and health implications of one of the least studied and perhaps greatest potential threats to our long-term health—mercury.

In this issue of *Alternative Therapies in Health and Medicine*, Woody McGinnis, MD, puts forth a theory of autism based on oxidative stress. In the conference it was proposed that mercury might be a key part to understanding autism and the toxin-induced oxidative stress that results from the interaction of mercury exposure with a child's unique genetic susceptibilities.

A few highlights will provide a flavor of the discussions that attempted to sift through the policy and scientific quagmire surrounding mercury. The presentations ranged from an analysis of the global cycle of mercury to the methylation cycles impaired by mercury.

THE GLOBAL CYCLE/FATE OF MERCURY

Barry Kohl, PhD, an Adjunct Professor in the Department of Earth and Environmental Sciences at Tulane University, provided a unique overview of the impact of industrialization on environmental mercury levels through a description of the levels of mercury in the ice core extracted from the pristine Fremont Glacier in Wyoming. Dr. Kohl explained that there were small peaks in mercury concentration in the ice core from the Tambora volcanic eruption in Indonesia in 1815; from the use of

mercury in smelting during the California gold rush from 1850-1884; the eruption in 1883 of the Sumatran volcano Krakatau 10,000 miles away; and the more recent Mount St. Helens eruption in 1980. However, over the past 100 years, there has been a 30-fold increase in mercury deposition, 70% of which is from anthropogenic sources. An exponential peak has occurred in the last 40 years due to major industrialization. Much of the mercury comes from coal-fired plants and from chlor-alkali plants that use mercury in the process of making chlorine used in plastics, pesticides, polyvinyl chloride (PVC) pipes, and more.

METHYLMERCURY, FISH INGESTION, AND HEALTH EFFECTS

Harvey Clewell from the ENVIRON Health Sciences Institute, Ruston, La, reviewed the epidemiologic studies from the Seychelles and Faroe islands. He presented a continuum of risk model for mercury exposures. Nearly all human exposures to methyl mercury derive from fish. In the Seychelles Islands, there seemed to be little effect from mercury on the population; however, the islander's fish consumption was predominately from low-risk, small reef fish. Maternal-fetal transmission was analyzed in the Faroe Islands. Elevated levels of mercury in umbilical cord blood correlated with decrements in neurologic studies in 5/17 tests in 917 mother-infant pairs. The mean umbilical cord blood level contained 22.9 micrograms per liter. A major source of their fish consumption was whale blubber, which contains over 3 parts per million of mercury.

The health effects from methylmercury upon infants and children depend on the dose, with severe symptoms presenting with exposure to doses of 100 mcg/kg/day, mild symptoms with greater than 10 mcg/kg/day, and sub-clinical symptoms with less than 1 mcg/kg/day. Symptoms include late development in walking and talking, and decreased performance on neurological tests.

Dr. Clewell reviewed the limitations of various forms of testing for mercury. Methylmercury is found predominately in red blood cells. Inorganic mercury from amalgams is found in plasma but is rapidly cleared. Methylmercury is converted to inorganic mercury in the body and is the main form of mercury in brain.

HEALTH EFFECTS OF MERCURY

Raoult Ratard, MD, MS, MPH, State Epidemiologist, Louisiana Department of Health, and Professor of Environmental Health Sciences at Tulane School of Public Health and Tropical Medicine, reviewed the health effects of mercury upon infants and newborns.

Sources of exposure are widespread and include mercury vapors in ambient air, ingestion via drinking water, fish, vaccines, occupational exposures, home exposures including fluorescent light bulbs, thermostats, batteries, red tattoo dye, skin lightening creams, and over-the-counter products such as contact lens fluid and neosynephrine, dental amalgams, and more. Amalgam exposure is estimated to be from 3 to 17 micrograms per day from slow corrosion, chewing, brushing and grinding.

The toxicokinetics of mercury were reviewed. Absorption is about 80% for mercury vapor and nearly 100% for oral absorption. It is primarily distributed in the kidneys and brain and readily transferred to the fetus via the placenta. It is eliminated via the urine, feces, expired air, and breast milk.

Dr. Ratard reported that the major toxicity is from mercury's ability to covalently bind to sulfhydryl groups of enzymes in microsomes and mitochondria and other enzyme binding sites including carboxyl, amide, amine, and phosphoryl groups.

Clinical manifestations were reviewed, including the historical context of mercury poisoning epidemics such as the Minamata Bay exposures in Japan, acrodynia or pink disease in children from calomel (Hg Cl) used in teething powder, mad hatter syndrome or erethism, and methylmercury fungicide grain seed exposures in Iraq and Pakistan.

The clinical manifestations are varied and mimic many other conditions. Central Nervous System (CNS) toxicity includes erethism with symptoms of shyness, emotional lability, nervousness, insomnia, memory impairment, and inability to concentrate. Other CNS symptoms may include encephalopathy, peripheral neuropathy, Parkinsonian symptoms, tremor, ataxia, impaired hearing, tunnel vision, dysarthria, headache, fatigue, impaired sexual function, and depression. Renal toxicity includes proteinuria, renal syndrome, and acute renal failure. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and colitis. Dermal toxicity includes allergic dermatitis, chelitis, gingivitis, stomatitis, and excessive salivation.

Assessment and management were discussed including the use of Dimercaptosuccinic Acid (DMSA) and Dimercaptopropane Sulfonate (DMPS).

RISK ASSESSMENT OF MERCURY-CONTAMINATED FISH, AND RESPONSE TO MERCURY EXPOSURE

William Hartley, ScD, Angela R. Machen, MS, Fred Kopfler, PhD, Dianne Dugas, Shannon Soileau, and Chris Piehler discussed public health implications of mercury.

Public health concerns were addressed in depth by various speakers who focused on research on the health effects and

exposures of populations to methylmercury through fish consumption from recreational fishing. The difficulties of assessment methods, and the determination of long-term risks, safe limits, toxic doses, and acceptable public health recommendations were clear from the presentations. One note of hope was the reduction in industrial mercury emissions from 220 million pounds to 120 million pounds a year over the last 10 years.

DENTISTRY AND MERCURY

Mike Robichaux, DDS, a practicing dentist, reviewed his experience with removal of amalgams fillings. He showed a remarkable video of mercury vapor being released from a 25-year-old tooth. It is available for viewing on the website of the International Academy of Oral Medicine and Toxicology (www.iaomt.org).

THE SWEDISH AND EUROPEAN EXPERIENCE

Anders Lindvall, MD, from the Foundation for Metal Biology in Sweden, reported on his work on the health effects of dental amalgams and presented a review of the controversial literature on dental amalgams and human health.

Many patients reported a symptom complex consistent with Chronic Fatigue Immune Dysfunction Syndrome/Epstein-Barr Virus they believed were related to dental amalgams. In 1990, Dr. Lindvall began a study at Uppsala University Hospital in Sweden to diagnose and treat patients with suspected amalgam-related illness and to develop and evaluate diagnostic tools to assess toxicity from dental amalgams. Beside conventional measures of quality of life and symptoms, unique laboratory assessments were used to determine the presence and immunological toxicity of metals. These were 1) Particle-Induced X-ray Emission (PIXE), an accelerator-based test on single blood cells that assesses intracellular levels of trace elements, which showed that, in lymphocytes, mercury is found in the nucleus, particularly in places where zinc is low; and 2) Memory Lymphocyte Immunostimulation Assay (MELISA), a test of lymphocyte reactivity to metal compounds. Information about the MELISA test is available at www.melisa.org.

The management of patients included supportive antioxidants (B complex C, E, Se), treatment of infection and jaw dysfunction, selective removal of any incompatible dental material, low-emission amalgam removal techniques, use of bio-compatible materials substituting amalgams, and laboratory follow up at one year. The cost was covered by national health insurance. It was a retrospective study of 796 patients with chronic symptoms. Over 70% of patients reported significant improvement in symptoms after amalgam removal. This correlated with improvement in the PIXE and MELISA testing. The study was limited by the lack of an adequate control group. The clinic was closed after the study was published and there was no further access allowed to the records, which contained over 1,000 untreated patients who could have served as a control. As of 1999, amalgam dental restorations in Sweden are no longer covered by insurance.

Dr. Lindvall discussed a review paper that was published on amalgam toxicity in February 2004 in the *International Journal of Hygiene and Environmental Health*. Some of the findings from European investigators may be both unfamiliar and surprising to many, but are worth further attention. Mercury vapor is continually emitted and absorbed from amalgams and accumulates in organ tissues. Humans with amalgam fillings have significantly elevated blood mercury levels, 3-5 times more mercury in the urine and 2-12 times more mercury in their tissues than those without amalgam fillings. However, blood and urine mercury levels are not necessarily indicative of mercury load in body tissues or severity of clinical symptoms. Research on sheep and monkeys with dental amalgams has shown that blood mercury levels remained low, whereas tissue mercury levels were raised. The half-life of metallic mercury in the blood is quite short (about 3 days) because it quickly penetrates other tissues. Urine mercury levels mainly reflect the cumulative dose of inorganic mercury in the kidneys and only a weak to no correlation with levels in other target tissues exists. When exposure to mercury ceases, a half-life of 1-18 years can be expected in the brain and bone structures.

Patients suffering from symptoms like fatigue, irritability, mood disorders, poor concentration, headaches, and insomnia due to their amalgam fillings exhibit the presence of apolipoprotein E 4 allele (ApoE 4) significantly more frequently than healthy controls. ApoE 4 lacks thiol groups and thus has reduced detoxifying activity. Apolipoprotein E2 and Apolipoprotein E3 can bind and detoxify heavy metals such as mercury. Patients with self-related amalgam complaints have lower selenium levels and deficiencies of trace elements than controls with amalgams that have no symptoms. The total anti-oxidant plasma activity is significantly reduced in individuals with dental amalgams. Studies cited by many authors and institutions as proof of the putative harmlessness of amalgams do not use proper non-amalgam control groups. As noted, Lindvall reported a 70% improvement in most chronic health complaints after amalgam removal. Other studies showed that patients with chronic fatigue and autoimmune thyroiditis showed improvement in their health status after the replacement of amalgam fillings with composites. In another study, 71% of patients with autoimmune diseases, including multiple sclerosis, improved after amalgam removal. Low-dose exposure to inorganic mercury may be a co-factor in the development of autoimmune diseases. Animal and *in vitro* studies confirm that exposure to inorganic and metallic mercury causes neuronal damage and that biochemical alterations including the induction of beta amyloid is found in Alzheimer's disease even at very low concentrations. These effects were not seen with other metals such as lead, aluminum, cadmium, manganese, zinc, iron, chromium, and copper.

Mercury levels in the human placenta correlate with the number of maternal amalgam fillings, and a substantial amount of mercury from amalgams reach the fetus. Mercury from dental amalgams in pregnant women may also contribute to development of autism in their children. Mothers of 94

autistic children had statistically more amalgam fillings during pregnancy than 49 mothers of normal controls. In contrast to their higher mercury exposure during pregnancy, these autistic children had reduced mercury levels in their first haircut. This may reflect a reduced capacity to excrete mercury from their body, which in turn may lead to elevated brain mercury levels.

In a recent risk analysis it was suggested that the frequency of pathological side effects from amalgams due to genetically determined high sensitivity is about 1%. The German Commission on Human Biological Monitoring states that genetically susceptible persons may develop immunological reactions to amalgams. The portion of susceptible persons in the general public is about 1%-4%. Approximately 20% of the general public may experience sub-clinical central nervous system and/or kidney function impairment due to amalgam fillings. Taken collectively, Lindvall suggests, these data question the safety of dental amalgams.

THE SCIENCE EFFECTS OF MERCURY—THE BIO EFFECTS ARE REAL

Boyd Haley, PhD, from the University of Kentucky Medical Center, is a vociferous opponent of dental amalgams. A prodigious reading of the toxicology literature and decades of his own research fuel his fervor. The National Institutes of Health (NIH) funded his research for 25 years until he began to seriously call into question safety of dental amalgams, the use of thimerosal in vaccines and their correlation with autism. The private Wallace Foundation, run by the son of President Truman's vice-president Henry Wallace who died of Amyotrophic Lateral Sclerosis (ALS) and who had been frequently exposed to mercury-containing fungicide on grain, now funds his work.

Dr. Haley believes that fish is not as big a contributor to mercury toxicity in humans as amalgams because methylmercury is generally excreted quickly while mercury vapor from amalgams is not. He reported on the dramatic rise in autism rates, over 900% in less than a generation in California and 714% nationwide. The use of drugs to treat Attention Deficit Hyperactivity Disorder (ADHD) of all ages has increased 49% in the past 3 years, while their use has increased 369% in children under five years old. He reported on the dramatic increase in autism rates in California since the introduction of the hepatitis B vaccine in 1990 and an increase in the overall vaccination schedule. In 1999, thimerosal was removed from vaccines as parents gained increased awareness of the issue. In the first three quarters of 2004 the data showed a decline in the incidence of autism in California for the first time.

Dr. Haley reported on the toxicity of thimerosal. It is quickly converted to ethylmercury in the body where it moves rapidly from blood to brain. Mercury is lipophilic and concentrates in the brain; therefore, blood levels are not an accurate measurement of total body burden of mercury. Genetic polymorphisms of glutathione disulfide (GSST) prevent excretion of mercury. Mercury can only be excreted when complexed

with glutathione (GSH). If it cannot be eliminated because GSH or GSST is lacking, then the mercury stays in tissues and does damage. Thimersol inhibits methionine synthase and methylene reductase and thus has significant effects on the body's ability to methylate and to produce glutathione.

Dr. Haley has observed that the lowest level of Hg is found in the birth hair of the most severely affected autistic children. The 4:1 ratio of autism in males:females may be in part due to the effects of testosterone on mercury excretion. Antibiotics also prevent excretion of mercury, and antibiotic use is higher among autistic children. Dr. Haley reported on striking data showing a synergistic effects of heavy metals: a (no response level) LD-1 and LD-1 lead and mercury = lethal dose (LD) 100!

Dr. Haley's website is www.testfoundation.org.

MERCURY AND AUTISM

Jane El Dahr, MD, is the Chief of Pediatric Allergy, Immunology, Rheumatology at Tulane University Health Sciences Center. She reported on the increase in autism in the last decade, its correlation with the change in the vaccine schedule and explored in detail the autism-mercury hypothesis. Dr. El Dahr discussed the immunological parallels with autism and reviewed the epidemiological and toxicological research on thimerosal.

In California, rigorous standards for reporting of autism were in place because social benefits were tied to the accurate diagnosis, so the increases are very likely to be real. During the first 25 years, 6,527 cases of autism were reported; but it took only three years during the 1990s to add 6,596 additional cases. From 1987 to 1998 there was a 273% increase in autism cases in California. The Centers for Disease Control and Prevention (CDC) and American Academy of Autism released an "Autism Alarm" stating that one in 166 children in the U.S. have autistic spectrum disorder (ASD). Currently, one-sixth of all children under the age of 18 have a developmental disability. That is nearly 20% of the population who may not be able to be productive members of society.

Much of the data she presented is available on www.safe-minds.org.

The mercury-autism hypothesis was proposed in part due to the analysis of the actual doses of thimerosal received by children after the change in the vaccination schedule. In individuals with a genetic susceptibility, such as a defect in the enzymes responsible for detoxifying heavy metals, prenatal and early postnatal exposure to mercury leads to neurologic damage resulting in autistic symptoms. Acro-dynia or pink baby syndrome from exposure to calomel or mercury in teething powder presented similarly to autism. Other potential sources of early exposure in the fetus or infant include maternal amalgams, fish consumption, eardrops, and nasal drops. Vaccines present a significant source of exposure in RhoGam, influenza vaccines during pregnancy, and childhood immunizations. The maximum exposure in the first six months of life is 187.5 micrograms of mercury, far exceeding limits set by the World

Health Organization (WHO) and the Environmental Protection Agency (EPA). These limits are set for methylmercury primarily from fish, not for ethylmercury from vaccines. Questions remain about the relative toxicity of each. According to the EPA, the "safe" daily level of mercury exposure for a 5 kg, 2-month-old infant is 0.5 micrograms or 0.1 micrograms per kg. The typical 2-month vaccination schedule includes diphtheria and tetanus (DtaP), *Haemophilus influenzae* type B (Hib), and hepatitis B vaccines. Combined, these vaccines contain 62.5 micrograms of mercury or 125 times the EPA limits for a single-day exposure. It should be remembered that, like lead, there may be no safe level and children are more susceptible to toxic effects than adults.

Dr. El Dahr advises us that there may be large variations in genetic susceptibility to exposures. She also argues that there is a strong biologic plausibility to the mercury-autism hypothesis. Symptoms of mercury toxicity parallel autism. Beside the neurotoxic effects, there appears to be correlation between the immunopathology of both autism and mercury toxicity. She defines immunopathology to include immune deficiency and dysfunction with defective or ineffective responses, hypersensitivity with an overactive response out of proportion to potential damage and autoimmunity or inappropriate reaction to self. These specific immune abnormalities have been found in 30%-70% of autistic children.

She also reviewed the problematic Institute of Medicine recommendations and analysis of the thimerosal issue. Further information can be found at www.iom.edu.

HYPERBARIC OXYGEN TREATMENT

Paul Harch, MD, is Clinical Assistant Professor and Director of the Louisiana State University Hyperbaric Medicine Fellowship and Hyperbaric Department at Medicine Center of Louisiana, New Orleans. He pioneered the application of hyperbaric oxygen therapy (HBOT) for cerebral palsy and autism. He presented his data using Single Photon Emission Computerized Tomography (SPECT) scan imaging pre and post HBOT for children from the autistic spectrum disorder. His results show both clinical and radiological improvement in brain function. He commented on the "oxygen paradox." Contrary to expectation, he reported, high-dose oxygen reduces oxidative stress. Mechanisms explored include the potential for HBOT to influence DNA expression. Dr. Harch's website is www.hyperbarics.org.

MERCURY IN CHILDREN: ASSESSMENT, DIAGNOSIS, AND TREATMENT

Stephanie Cave, MD, is on the Clinical Faculty of Louisiana State University Medical School, and since 1996 has treated over 2,300 children with autistic spectrum disorder. Her recent book, *What Your Doctor May Not Tell You About Children's Vaccinations*, outlines the data and debate in this highly charged field.

Dr. Cave also reported on the increased incidence of autism in the last 30 years from 1/10,000 children to 1/150 children and 1/30 males in the United States.

The major toxicity from mercury, she reports, is its ability to tightly bind to the sulfhydryl group's enzymatic or structural proteins, severely inhibiting enzyme function and structural integrity. Ethylmercury from vaccines exceeds WHO, EPA, FDA, and the Agency for Toxic Substances and Disease Registry (ATSDR) limits for exposure. The limits for an average 5 kg child range from 0.5 mcg/day for the EPA and FDA, to 1.5 mcg/day for ATSDR and 16.5 mcg/week for WHO. The administration of the 2-month schedule for the average child as DTaP, Hib, Hep B is 62.5 mcg, or 125 times the safe limits set by government agencies.

Dr. Cave quoted Dr Boyd's research on the paradoxically low levels of mercury (0.47 ppm in 94 cases vs 3.63 ppm in controls) in the first haircut of autistic children despite higher prenatal mercury exposure than controls from amalgams, fish consumption, and Rho D immunoglobulin. This implies an impaired detoxification and excretion capacity in autistic cases. Dr. Cave analyzed conflicting recommendations and reports from the CDC, and from epidemiologic reports concluding that there is a causal relationship between childhood vaccines containing thimerosal and neurodevelopmental disorders in children. She critiqued the *Lancet* Study, which concluded no toxic effect from thimerosal for numerous reasons including small sample size (33), blood drawn on day 7, not true peak level on day 3, variability in amounts of thimerosal exposure, and reduced exposure compared to current vaccine schedules. The population-based cohort study from Denmark published in *JAMA* reported no increased risk of autism with thimerosal. The authors of the study were affiliated with the state-run Statens Serum Institut. Eighty percent of its profits on \$120 million in annual revenue is from vaccines. The methodology was also called into question because of inconsistencies in the reporting system.

A case control study of 221 children with autism and 18 controls found that after a DMSA challenge test, vaccinated autistic children had three times the level of mercury in their urine compared to controls.

Dr. Cave reviewed her clinical approach to dealing with ASD children. Besides a thorough developmental history, she does a laboratory evaluation including a Complete Blood Count (CBC), Metabolic panel 7 (SMA7), liver functions, cellular trace minerals and toxic metals, hair metals, pre- and post-provocation urinary metals, urine organic acids, stool analysis, amino acid and fatty acids panels, serum copper, plasma zinc (often finding an elevated copper:zinc ratio), serum ceruloplasmin, glutathione and sulfate levels, Immunoglobulin G (IgG) food allergies, myelin basic protein antibodies, and viral studies (Human Herpes virus 6 [HHV6], EBV, etc.).

Her common findings include low cellular minerals, elevated cellular metals, elevated auto antibodies, positive viral titers, low plasma sulfate and glutathione, impaired detoxification chemistry, low plasma amino acids and abnormal organic acids, low unsaturated fatty acids, low vitamin A, elevated copper:zinc ratio, elevated CD4 cells, low CD8 cells and elevated CD4/CD8 ratio, low natural killer (NK) cells, imbalanced gut flora, multiple

Candida species, and parasites. Hair metals are often elevated except for mercury due to impaired detoxification and excretion.

Dr. Cave's treatment protocols include casein, gluten, allergy- and seafood-free diets, removal of amalgam fillings, and detoxification support. Key to the treatment is careful detoxification of heavy metals after repletion of cellular nutrients, repair of gut dysfunction and enhancement of liver detoxification chemistry. Supplements and treatments may include multivitamins and minerals, essential fatty acids (EPA/DHA/GLA), antioxidants, selenium, zinc, magnesium, digestive enzymes, vitamins C, E, A, and CoQ10. Bowel ecology restoration may include antifungals, antibiotics, herbs, probiotics, and glutamine. Enhancement of liver detoxification is facilitated by Epsom salt baths (MgSO₄), magnesium sulfate creams, and oral, intravenous, or topical glutathione.

Mercury and other heavy metal detoxification is achieved after a DMSA provocation challenge of 20 mg/kg with a 10-hour urine collection. DMSA is given at a dose of 10 mg/kg every 8 hours for 3 days with 11 days off. The cycle is repeated 4 times, followed by another provocation challenge test.

Another critical aspect of autistic spectrum disorder is impaired methylation chemistry, which affects methylation of proteins, repair of DNA, as well as the synthesis of glutathione affecting detoxification, synthesis of membrane phospholipids and dopamine binding to CNS receptors. Collectively, these effects can explain much of the clinical manifestations of ASD. Multiple polymorphisms of the methionine cycle pathway affect methylation capacity including MTHFR 667 C to T (methylenetetrahydrofolate reductase), combined MTHFR 677 C to T and 1298 A to C, and MTRR 66A to G (methionine synthase reductase). These are found at increased frequency in the autistic population. Mercury binds to methionine synthase causing severe downstream metabolic dysfunction. Because of these polymorphisms and the toxic effects on Hg on these enzymes, the production of methylcobalamin impaired the entire methylation cycle leading to reduced levels of homocysteine, methylmalonic acid, glutathione, and more. Methylcobalamin (B12) has multiple neuroprotective functions including enhanced methylation facilitating phosphatidyl choline formation in membrane phospholipids, and prevention of nitric oxide toxicity, which protects neurons against NMDA receptor-mediated glutamate toxicity.

Mercury further exacerbates impairment in glutathione synthesis by depleting glutathione in lymphocytes and monocytes leading to increased risk of the immuno and cytotoxic effects of mercury. The impairment in glutathione synthesis through the inhibition of the methionine cycle and the depletion of intracellular glutathione is compounded further by the increased frequency of polymorphisms affecting glutathione antioxidant capacity such as glutathione-S-transferase M1 null (GSTM1 null), glutathione-S-transferase T1 null (GSTT1 null), and a double null GST M1 and GST T1 polymorphism.

Dr. Cave presented a number of cases where these principles were applied with significant benefit and reductions in autistic symptoms.

MERCURY AND ADULT ILLNESS: FROM ALZHEIMER'S TO CARDIOMYOPATHY

Robert Nash, MD, is a practicing neurologist and the Chairman of the American Board of Metal Toxicology. After an overview, he reviewed mercury-associated diseases, mechanisms, controversies, and therapeutic options.

Major sources of mercury exposure include dental amalgams (vapor), fish (methylmercury), and vaccines (ethylmercury). Toxic effects, he suggests, spread across a broad spectrum of diseases including autism, Alzheimer's disease, ALS, multiple sclerosis, Parkinson's disease, neurodevelopmental diseases, nephrotoxicity, and cancer. Reporting on the review in the *New England Journal of Medicine*, he reports that the fetal brain is more susceptible than the adult brain to mercury-induced damage including the division and migration of neuronal cells and disruption of the cytoarchitecture of the developing brain.

The mechanism of mercury toxicity in the adult brain may be related to proteins involved in mercury excretion including glutathione, glutathione transferase, metallothionein, and Apo E. Glutathione carries Hg through biliary transport for excretion. Hg²⁺ rapidly oxidizes glutathione. Glutathione transferase is an enzyme that may be implicated in Alzheimer's disease. However, most interesting were recent findings that Apo E 4 may increase risk for Alzheimer's disease because it has an impaired ability to bind mercury and transport it from the brain. Apo E 4 has no binding sites for mercury because it contains arginine at both positions 112 and 158 of the lipoprotein. Apo E 2 has cysteine at both those sites enabling it to bind and transport mercury from the brain. Dr. Nash suggests that most if not all aberrant biochemistry in the Alzheimer's brain can be mimicked by mercury. The diagnostic hallmarks of the Alzheimer's brain can be produced by Hg concentrations lower than reported in human brain tissues. He further concludes that the biological plausibility of Hg as a causal factor in Alzheimer's disease is more complete than thimerosal causation of autism.

Regarding amalgam fillings, Dr. Nash concludes that due to the enhancement of mercury toxicity and retention by factors found in the diet, antibiotics, other toxicants such as cadmium and lead, and genetic susceptibilities, no level of mercury exposure from amalgams can be considered without risk.

He also reviewed the literature linking mercury and cardiovascular disease. Two studies have reported increased risk of myocardial infarction while another has showed no risk. However, the data presented on idiopathic cardiomyopathy was among the most compelling. Biopsy samples found 12,000 times the level of antimony and 22,000 times the level of mercury in idiopathic cardiomyopathy compared to controls with viral, ischemic or hypertensive cardiomyopathy.

Mechanisms of toxicity include damage to DNA, RNA, mitochondria, enzymes, immunopathology and autoimmunity, and generation of oxidative stress. Mercury can act as a metabolic uncoupler, hapten or immune sensitizing small molecule, enzyme inhibitor. It also depletes glutathione and ascorbate, and inhibits thiamine (B1) and pyridoxine (B6). Mercury can

also affect the CNS by concentrating in the CSF and the kidney by reducing concentrating capacity. It can also inhibit GTP binding affecting brain tubulin microtubules reducing nerve function and communication, which can lead to the development of neurofibrillary tangles. Mercury also inhibits nerve growth, and passes easily through the placental barrier. Dopaminergic activity in the brain is reduced with mercury.

Dr. Nash concluded on an optimistic note. First he suggests that there appears to be a subset of the population that cannot effectively excrete mercury and is at greater risk than the general population, and that this susceptibility is likely due to genetic differences, diet, exposure to other toxicants, antibiotics, etc. Given that susceptibility, he argues that mercury is a risk factor in many diseases, but can be safely measured, and the body detoxified, mitigating some of its toxic effects. He calls for a more research and improved detoxification agents.

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