

Mercury and Autism: A Review

Jie Zhang

The College at Brockport, SUNY

John J. Wheeler

Tennessee Technological University

Abstract: The prevalence of autism has increased approximately four times in children in nearly one decade (California Health and Human Services Agency, 2003). It has been reported that explanations such as immigration, shifts in the interpretation of diagnostic criteria, improved identification, or diagnostic accuracies cannot explain the observed increase (Geier & Geier, 2005). One potential cause that has alarmed many has been the presence of thimerosal, the mercury-based preservative found among immunizations. Although many refute this, concern has been leveled by many families and professionals concerning the potential impact of mercury poisoning as a causal factor. Researchers have proposed that autism may be in part caused by mercury, because there was cumulative mercury exposure through dental amalgam, fish consumption, environment pollution, and additionally, through increased thimerosal-containing vaccines for both mothers and newborns (Mutter, Naumann, Schneider, Walach, & Haley, 2005). The purpose of this study is to review the information from studies concerning the relationship between mercury exposure and autism.

It has been estimated that prevalence of autism has increased approximately four times in childhood autism in about one decade, from 1 in 1,333 children (7.5 per 10,000 children) among children born in the mid-1980s to 1 in 323 children (31.2 per 10,000 children) among children born in the late-1990s (California Health and Human Services Agency, 2003). In 2004, the Department of Health and Human Services and the American Academy of Pediatrics issued an Autism ALARM claiming that presently 1 in 166 children (60 per 10,000 children) has autism. In California, the autism rate increased by 634% between 1987 and 2002 (California Health and Human Services Agency). Once a rare disorder, autism has now been found to be more prevalent than childhood cancer, diabetes and Down Syndrome (California Health and Human Services Agency). It has been reported that explanations such as immigration, shifts in the interpretation of diagnostic criteria, improved identification, or diagnostic accuracies cannot explain the observed increase (Geier & Geier, 2005). Researchers have pro-

posed that autism may be in part caused by mercury, because there was cumulative mercury exposure through fish and industrial sources, amalgam and additionally, through increased thimerosal-containing vaccines for both mothers and newborns (Mutter, Naumann, Schneider, et al., 2005).

Similarities Between Autism and Mercury Poisoning

The harmful effects of mercury include impaired motor planning, decreased facial recognition, blurred vision and constricted visual fields, insomnia, irritability, tantrums, excitability, social withdrawal, anxiety, difficulty verbalizing, altered taste, impaired short-term memory, slowed reaction time and difficulty with concentration (Jepson, 2004). Bernard, a parent of a child with autism, and several other investigators compared signs and symptoms of mercury poisoning with those of autism (Bernard, Enayati, et al., 2001). Distinct similarities were found between autism and mercury exposure in their effects upon immune, sensory, neurological, motor, and behavioral dysfunctions, and these similarities extend to neuroanatomy, neurotransmitters, and biochemistry (Geier & Geier, 2005). Thus, Bernard, Enayati, et al. suggest that the

Correspondence concerning this article should be addressed to Jie Zhang, Education and Human Development, The College at Brockport, State University of New York, 350 New Campus Drive, Brockport, NY 14420. E-mail: jzhang@brockport.edu

regressive form of autism represents a form of mercury poisoning (Bernard, Enayati, et al.).

Historically, there were such illnesses caused by environmental exposure to mercury as Acrodynia or Pink's disease and Minamata's disease. Like autism, these diseases also presented with large range of variability and susceptibility among individuals in the population and were eradicated when the source of the exposure was eliminated (Jepson, 2004). In the early 20th century, Acrodynia (Pink's Disease) affected up to 1 of 500 infants in some industrial countries. Acrodynia disappeared after a frequently used teething powder, which contained mercury as calomel (Hg_2Cl_2), was removed from the market. Calomel works by poisoning the nerves in the baby's gums. When given orally, it is one of the less toxic forms of mercury and is about 100 times less toxic than ethyl mercury to neurones in vitro (Deth, 2004). From 1932 to 1968, 27 tons of organic mercury compounds were dumped into Minamata Bay, Japan by the Chisso Corporation (Stoller, 2006). Over 3,000 victims whose normal diet included fish from the bay unexpectedly developed symptoms of methyl mercury poisoning and have been recognized as having Minamata disease, a myriad of neurological and neurodevelopmental symptoms (Stoller). After the outbreaks in Minamata, congenital Minamata disease was documented. Pregnant women in Minamata who consumed the contaminated fish displayed mild or no symptoms but gave birth to infants with severe developmental disabilities such as cerebral palsy, mental retardation, and seizures. The congenital Minamata disease indicated that the fetal brain may be highly sensitive to MeHg exposure (Davidson, Myers, & Weiss, 2004).

Biochemical and Genomic Basis

Studies point to the possibility that testosterone significantly enhances mercury toxicity, whereas estrogen decreases the toxic effects. Manning, Baron-Cohen, Wheelwright, and Sanders (2001) examined 72 children with autism, including 23 children with Asperger syndrome, 34 siblings, 88 fathers, 88 mothers, and sex and age-matched controls to investigate prenatal testosterone levels in children

with autistic spectrum disorders (Lutchmaya, Baron-Cohen, Raggatt, Knickmeyer, & Manning, 2004; Manning et al.). The authors demonstrated that the more severely autism the higher the levels of prenatal testosterone. Tordjman, Ferrari, Sulmont, Duyme, and Roubertoux (1997) measured plasma testosterone and adrenal androgen in nine drug-free prepubertal children (6–10 years old) with autism and 62 neurotypical control children of same age, sex, weight (within 2 kg), and stage of puberty. Results showed that three of the nine children with autism had an abnormally high plasma testosterone concentration (Tordjman et al.). These studies may explain that autism affects males four to five times as often as females (Bertrand, Mars, et al., 2001; Yeargin-Allsopp et al., 2003). In addition, closer observation indicates that the more severe the autism the higher the male to female ratio. For example, in very severe cases males may outnumber females by 15 to 1 or even more (Holmes, Blaxill, & Haley, 2003).

Boris, Goldblatt, Galanko, and James (2004) conducted genomic studies of children with autism in comparison to normal control populations to examine genes in pathways that are responsible for the synthesis of key biochemical molecules, which are functionally relevant in the excretion and/or oxidative stress protection of mercury from the body (Boris et al.). Results demonstrated that there was approximately a twice statistically significant increase in the homozygous methylenetetrahydrofolate reductase (MTHFR) 677TT gene among children with autism compared to controls. MTHFR 677TT is one of the key genes in the biochemical pathway responsible for the synthesis of glutathione, a key molecule in the body's natural defenses against mercury, and those with the MTHFR 677TT gene have been found to have an enzyme with only 32% of the activity of normal (Chango, Boisson, & Barbe, 2000). James, Cutler, and Melnyk (2004) evaluated the methionine cycle and transsulfuration metabolites in children with autism in comparison to age- and sex-matched control children (James, 2004; James et al.). The process of cysteine and glutathione synthesis, both of which are crucial for natural mercury excretion, are reduced in children with autism

(Deth, 2004; Waly et al., 2004). Results showed that there were significant decreases in the plasma concentration of both cysteine (19% lower) and glutathione (46% lower) in children with autism (James; James et al.). The reduction of plasma level of cysteine and glutathione, among others, adversely affect the ability to detoxify and excrete metals like mercury (Deth; James et al.), which may lead to higher Hg concentrations in tissues like the nervous system and also lead to a longer half-life of mercury (Deth; Mutter, Naumann, Sadaghiani, Walach, & Drasch, 2005). The Environmental Working Group (EWG) investigated the relationship between mercury exposure, especially mercury exposure from thimerosal-containing childhood vaccines, and autistic disorders (Environmental Working Group, 2004). It is found that there is a severe metabolic imbalance in the ratio of active to inactive glutathione, the body's most important tool for detoxifying and excreting metals, in children with autism. As a result, these children would be susceptible to the harmful effects of mercury and other toxic chemical exposures. The EWG drew the conclusion that by identifying a metabolic common to nearly all children with autism that would make these children poorly equipped to mount a defense against a number of neurotoxic compounds, including mercury (Environmental Working Group). These findings significantly strengthen the possibility that mercury could cause or contribute to autism and other neurodevelopmental disorders. These are some of the biochemical and genomic basis for the increased body-burden of mercury in children with autism.

Higher Body-Burdens of Mercury

Several clinical studies evaluated the body-burden of heavy metals present in children with autism in comparison to typically developing children (Geier & Geier, 2005b). Holmes et al. (2003) and Hu, Bernard, and Che (2003) found that despite significantly higher mercury levels exposure through maternal dental amalgam and thimerosal containing immunoglobulins during pregnancy (Holmes et al.; Hu et al.), mercury levels in the first babies' haircut of 94 children with autism were about 8-fold lower than 49 con-

trol children. Interestingly, Grandjean, Weihe, White, and Debes (1998) found that infants who reached milestone criteria early had significantly higher mercury concentrations in the hair at 12 months of age (Grandjean et al.; Mutter, Naumann, Sadaghiani, Schneider, & Walach, 2004). It was also observed that the more severe the autism the lower mercury levels were present in the first baby haircut, which leads to the conclusion that the mercury levels in the first baby haircuts were inversely related to the severity of the autism (Geier & Geier). Further studies showed elevated levels of mercury, lead and uranium in haircuts from 40 older children with autism in comparison to 40 normal controls, while there was no difference for other toxic metals like aluminium, arsenic, cadmium or beryllium (Fido & Al-Saad, 2005). Bradstreet et al. evaluated the concentration of heavy metals in the urine among 221 vaccinated children with autistic spectrum disorders in comparison to a neurotypical control population (Bradstreet, Geier, & Kartzinel, 2003). Based on excretion following an identical three-day oral provocation with *meso* 2,3-dimercaptosuccinic acid (DMSA), there were approximately six times significantly greater urinary mercury concentrations among vaccinated children with autism matched to vaccinated neurotypical controls, whereas the two groups of children had similar urinary cadmium and lead concentrations. Following DMSA treatment, similar urinary mercury concentration levels were observed among matched vaccinated and unvaccinated neurotypical children. Results suggest that after exposure to mercury, children with autism are unable to properly eliminate mercury and thus have significantly higher body-burdens of mercury than neurotypical children (Bradstreet et al.).

Slikker from the FDA confirmed that thimerosal crosses the bloodbrain barrier and placental barriers, resulting in appreciable mercury content in tissues including the brain (Slikker, 2000). In addition, Sager reported the half-life of mercury in the brain of infant primates was approximately 28 days following administration of solutions containing vaccine comparable concentrations of thimerosal (Institute of Medicine, 2004).

Mercury Exposure during Pregnancy

Even before they are born, it is speculated that children with autism may have had a higher mercury exposure during pregnancy due to maternal dental amalgam, thimerosal-containing immunoglobulin shots, and fish consumption. Vahter et al. (2000) examined the different species of mercury in the blood of pregnant women. They found high correlations between inorganic mercury levels in blood and urine during early pregnancy, a significant correlation between cord and maternal blood, and decreased mercury levels during lactation, presumably due to excretion in milk (Vahter et al.).

Dental amalgam consists of about 50% of the most toxic nonradioactive element (Mutter, Naumann, Walach, & Daschner, 2005), and of other heavy metals as tin, copper, silver, zinc additionally. Amalgam fillings were first used in 1830 in the United States (Stoller, 2006). By 1840, organized dentistry denounced the use of amalgam as a poor filling material because of concerns about mercury poisoning, and the American Society of Dental Surgeons was formed and required members to sign a pledge promising not to use mercury fillings. In 1926, Dr. Alfred Stock, a chemist, noted that mercury amalgam fillings in the mouth were a source of mercury vapor (Stoller). Mercury vapor escapes during the preparation and placement of amalgam restorations. Some of the vapor may be inhaled (Davidson et al., 2004). Research indicates that mercury levels in human placentas correlate with the number of maternal amalgam fillings and a substantial amount of mercury from amalgam reaches the fetus (Stoiber et al. 2004; Their et al., 2003).

Rh-negative women were routinely given Rhogam injections several times during their pregnancies until recently. Those Rhogam injections contained significant amounts of thimerosal, which has been removed only recently (Geier & Geier, 2003). Additionally, there are other prescription drugs and over-the-counter medications that contain significant amounts of thimerosal (Geier & Geier).

As Davidson et al. (2004) pointed out, the principal source of organic mercury that humans are exposed to in the aquatic environment is atmospheric mercury deposited on

the surfaces of bodies of water that is then biomethylated by microorganisms and subsequently biomagnifies as it ascends the food chain. Some older, larger carnivorous fish at the top of the food chain can contain more than 1 ppm. Infants and children may be exposed postnatally to mercury from breast milk if their mother consumes foods that contain high levels or if they consume fish or foodstuff that contain fish products (Davidson et al.). The FDA currently recommends that pregnant women and those women who may become pregnant avoid species with the highest average amounts of methylmercury and that a balanced diet of seafood consumption should be followed to keep methylmercury levels low (Geier & Geier, 2003).

Mercury Exposure after Birth

The regressive form of autism is rising at a much higher rate than the form of autism evident from birth. The regressive form now is felt to make up close to 75% of the new cases (Jepson, 2004). Jepson uses the rise in environmental exposure to explain that more children nowadays have less severe deficits genetically.

Elemental mercury is the form of mercury represented in the hazardous air pollutant (HAP) database (Windham, Zhang, Gunier, Croen, & Grether, 2006). Every year, there are approximately 3,400 metric tons of elemental mercury released into the environment, 95% among which resides in terrestrial soils, 3% in ocean surface waters, and the remaining 2% in the atmosphere. Approximately 70% of the mercury in the environment comes from anthropogenic sources such as coal-fired electric power generation facilities and industrial waste. Natural sources, however, also deposits it in the environment from volcanos, mines, and the erosion of ores (Davidson et al., 2004).

Windham et al. (2006) linked the California autism surveillance system to estimated hazardous air pollutant (HAP) concentrations compiled by the U.S. Environmental Protection Agency (EPA) to explore possible associations between autism spectrum disorders (ASD) and environmental exposures. They included 284 children with ASD and 657 controls, born in 1994 in the San Francisco Bay

area. Results suggest a potential association between autism and estimated metal concentrations (Windham et al.). Palmer, Blanchard, Stein, Mandell, and Miller (2006) did an epidemiologic study, linking Toxic Release Inventory (TRI) data on mercury to special education data in Texas. The study reported a 61% increase in autism prevalence rates (or 17% adjusted) per 1,000 pounds of mercury released (Palmer et al.).

Thimerosal is an ethylmercury-containing compound (49.6% mercury by weight) (Geier & Geier, 2006). It is a preservative that is added to many vaccines at 0.005% to 0.01% level to prevent bacterial contamination and thus, prolonging shelflife and facilitating multi-use vials. It has become a major source of mercury among children in the United States since within their first two years of life, who may have received a quantity of mercury that exceeded Federal Safety Guidelines (Ball, Ball, & Pratt, 2001; Redwood, Bernard, & Brown, 2001). Geier and Geier pointed out that the routine childhood immunization schedule used to include five doses of Thimerosal-containing Diphtheria-Tetanus-whole-cell-Pertussis (DTP) vaccine with the first dose being administered at two months of age. From the late 1980s through the 1990s, the Centers for Disease Control and Prevention (CDC) expanded the number of doses of Thimerosal-containing vaccines to be administered to US infants. Eventually, the immunization schedule came to be composed of three doses of Thimerosal-containing hepatitis B vaccine with the first dose administered as early as the day of birth, and four doses of Thimerosal-containing Haemophilus Influenzae type b (Hib) vaccine with the first dose administered at two months of age. Additionally, the CDC also began recommended that three doses of Thimerosal-containing influenza vaccine be administered to certain infant population with the first dose administered by the sixth month of age (Geier & Geier).

As a result, if all thimerosal-containing vaccines were administered according to the immunization schedule recommended by the CDC, infants in the United States may have been exposed to 12.5 micrograms (μg) of ethylmercury at birth, 62.5 μg at two months, 50 μg at four months, 62.5 μg at six months, and 50 μg at 18 months, for a total of 237.5 μg of ethylmercury during the first 18 months of

life (Ball et al., 2001; Redwood et al., 2001). In addition, if three thimerosal-containing influenza vaccines were administered during the first 18 months of life as they were suggested to certain infant population, the total mercury exposure could have been as high as 275 μg of mercury (Ball et al.; Redwood et al.).

Geier and Geier (2004) reviewed the 2003 US Physician's Desk Reference (PDR) and found that some childhood vaccines still contain thimerosal. For example, DTaP manufactured by Aventis Pasteur contains 25 μg of mercury, b (Hib) vaccine manufactured by Wyeth contains 25 μg of mercury, and pediatric hepatitis B vaccine manufactured by Merck contains 12.5 μg of mercury. Additionally, influenza vaccine recommended for an increasing population also contains 25 μg of mercury. Therefore, possible total childhood mercury in the United States in 2003 is more than 300 μg , among which levels of mercury from thimerosal contained childhood vaccinations are higher than at any time in the past (Geier & Geier). Furthermore, injecting thimerosal into infants muscle also bypasses the GI tract, one of the body's first-line defense mechanisms (Geier & Geier).

In 1982, an expert panel at the Food and Drug Administration (FDA) reviewed thimerosal, reported it as toxic, causing cell damage, ineffective in killing bacteria or halting their replication, not as safe or effective as generally recognized (Federal Register, 1982), and thus called for its removal in over-the-counter products (Stoller, 2006). In 1988, the FDA ruled that thimerosal should be removed from OTC products, but gave the industry another 16 years to phase out its presence. In 1999, the FDA announced that under the recommended childhood immunization schedule, infants might be exposed to cumulative doses of ethylmercury from vaccines that exceed federal safety guidelines established for the oral ingestion of methylmercury (Geier & Geier, 2006). In the same year of 1999, the Public Health Service (PHS) and the American Academy of Pediatrics (AAP) issued a joint statement calling for the removal of thimerosal from all childhood vaccines as soon as possible due to any potential risk (Stoller). In 2001, the FDA required that vaccine manufacturers remove thimerosal from their vaccines. In the same year of 2001,

the Institute of Medicine (IOM) stated that it was biologically plausible for mercury from thimerosal-containing childhood vaccines to cause childhood neurodevelopmental disorders (Geier & Geier, 2004). Interestingly, thimerosal was taken out of animal vaccines a decade ago because of the safety concern (Stoller).

The Environmental Protection Agency (EPA)'s safety guideline of vicinal thimerosal is 1 part-per-million (ppm) for one-year old. Redwood et al. (2001) utilized a one compartment pharmacokinetic model to estimate hair mercury concentrations expected to result from the recommended CDC childhood immunization schedule during the 1990s, and the results indicated that modeled hair mercury concentrations in infants exposed to vicinal thimerosal were in excess of the EPA's safety guidelines for up to the first 365 days, with several peak concentrations within this period (Geier & Geier, 2005b; Redwood et al.). Nowadays in the United States, thimerosal has been removed from many vaccines administered to infants, but there is no recall of the existing thimerosal-containing product. Additionally, other thimerosal-containing vaccines are still being developed and marketed such as influenza, Tetanus-diphtheria, Rhogam, and monovalent tetanus. Thimerosal has also been present in other commercial products such as contact lens solution, which was removed in 1998, eardrops and various nasal preparations (Jepson, 2004).

Thimerosal has been recognized as a developmental toxin by the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Maternal exposure during pregnancy can disrupt the development, cause birth defects, low birth weight, biological dysfunctions, or even the death of the fetus, and exposure to it can also cause psychological or behavior deficits that become evident as the child grows (Geier & Geier, 2005). *In vitro*, mercury and thimerosal in levels reached eight days after vaccination inhibit methionine synthetase (MS) by 50%. MS is crucial in biochemical steps for brain development, attention, and production of glutathione, an important antioxidative and detoxifying agent. Subsequently, children with autism have significantly decreased level of reduced glutathione (Geier & Geier). In ad-

dition, a study reported that thimerosal was a potent inhibitor of phagocytosis, which is the first step of the innate immune system (Rampersad et al., 2005). While the acquired innate immune system can be only built up by aging, it seems likely that injection of thimerosal would inhibit an infant's immune system. Fagan, Pritchard, Clarkson, and Greenwood (1977) reported that 10 children out of 13 treated with a thimerosal containing topological "antiseptic" for umbilical cord infection died, even though this antiseptic was used world-wide on adolescents and adults and very little negative effects were reported. This strongly implied that infants were much more susceptible to thimerosal toxicity than others (Mutter, Naumann, Schneider, et al., 2005).

An ecological study evaluated birth cohorts from the mid-1980s through the late 1990s to investigate the relationship between the average mercury doses children received from thimerosal-containing vaccines in comparison to the prevalence of autism. Results showed that there was an increasing linear correlation between the amount of mercury children received from thimerosal-containing vaccines and the cohort prevalence of autism (Geier & Geier, 2004).

Epidemiological studies conducted in the United States using various databases, including the California Department of Developmental Services (CDDS), Vaccine Adverse Event Reporting System (VAERS), US Department of Education, and the Vaccine Safety Datalink (VSD) to examine the relationship between thimerosal-containing childhood vaccines and neurodevelopmental disorders (Geier & Geier, 2006). Results indicate significant links between exposure to Thimerosal-containing vaccines and neurodevelopmental disorders, showing that in comparison to children receiving thimerosal-free childhood vaccines, children receiving thimerosal-containing childhood vaccines were two- to six-fold statistically significantly increased risks to develop neurodevelopmental disorders, depending upon the specific conditions or symptoms examined (Geier & Geier, 2005b).

Geier and Geier (2003) evaluated doses of mercury from thimerosal-containing childhood immunizations in comparison to U.S. Federal Safety Guidelines. Results showed that children received mercury from thimerosal-

containing vaccines, as part of the routine US childhood immunization schedule, in excess of the Federal Safety Guidelines for the oral ingestion of methylmercury. Secondly, based upon the Vaccine Adverse Events Reporting System (VAERS) database, Geier and Geier investigated the effects of increasing doses of mercury on the incidence rates of neurodevelopment disorders reported following thimerosal-containing vaccines in comparison to thimerosal-free vaccines. Outcomes showed increasing relative risk of neurodevelopment disorders with increasing doses of mercury. Finally, the authors used data from the US Department of Education to analyze the prevalence of school children at various ages with various types of disabilities in comparison to the mercury dose that children received from thimerosal in their childhood vaccines. The analyses showed autism and speech disorders were correlated with increasing mercury from childhood vaccines (Geier & Geier).

Geier and Geier (2004) used the Biological Surveillance Summaries of the Centers for Disease Control and Prevention (CDC), the U.S. Department of Education datasets, and the CDC's yearly live birth estimates to evaluate the effects of mercury from thimerosal-containing childhood vaccines on the prevalence of autism. Results indicated that there was a close correlation between mercury doses from thimerosal-containing childhood vaccines and the prevalence of autism from the mid-to-late 1980s through the mid-1990s. Additionally, it was found that there were statistically significant odds ratios for the prevalence of autism following increasing doses of mercury from thimerosal-containing vaccines with birth cohorts of 1985 and from 1990 to 1995 in comparison to a baseline measurement with birth cohort of 1984 (Geier & Geier).

Geier and Geier (2005) did a two-phased population-based epidemiological study. Phase one examined reported neurodevelopmental disorders (NDs) to the Vaccine Adverse Event Reporting System (VAERS) following thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines administered from 1997 through 2001. Phase two evaluated the automated Vaccine Safety Datalink (VSD) for cumulative exposures to mercury from thimerosal-containing vaccines at 1-, 2-, 3-, and

6-months of age for infants born from 1992 through 1997 and the eventual risk of developing NDs to determine whether the affect from thimerosal-containing childhood vaccines on neurodevelopmental disorders observed in the VSD database was consistent with observations made in the VAERS database. Results showed that exposure to mercury from thimerosal-containing childhood vaccines administered in the United States was a consistent significant risk factor for the development of NDs (Geier & Geier).

Geier and Geier (2006) also conducted a meta-analysis epidemiological assessment of the Vaccine Adverse Event Reporting System (VAERS) for neurodevelopment disorders (NDs) reported following Diphtheria-Tetanus-whole-cell-Pertussis (DTP) vaccines in comparison to Diphtheria-Tetanus-whole-cell-Pertussis-Haemophilus Influenzae Type b (DTPH) vaccines administered from 1994 to 1997 and following Thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to Thimerosal-free DTaP vaccines administered from 1997 to 2000. Results demonstrated that a significant risk factor for the development of neurodevelopmental disorders was the amount of mercury children received from Thimerosal-containing childhood immunizations, thus there is a significant relationship between the Thimerosal-containing childhood vaccines evaluated and childhood neurodevelopmental disorders (Geier & Geier).

Conclusion

To sum up, there has been a great deal of information from different studies that seems to indicate that repetitive mercury exposure during pregnancy, through thimerosal, dental amalgam, and fish consumption, and after birth, through thimerosal-containing vaccinations and pollution, in genetically susceptible individuals is one potential factor in autism. Certainly this question continues to stir debate among professionals across the medical and behavioral sciences. It serves as a grey area for many families as they seek to quell their anxiety invoked by this debate by discovering the facts. The purpose of this article was to synthesize the findings relative to this question to hopefully serve as a resource to educa-

tors as we seek to become more well-informed on this timely issue. As the prevalence rate for autism in children continues to rise, more research is needed to better understand causal factors. It is also crucial that quality reviews be conducted to synthesize a body of knowledge pertaining to these questions if the puzzle is to be solved pertaining to the link between mercury exposure and autism.

References

- Ball, L. K., Ball, R., & Pratt, R. D. (2001). An assessment of thimerosal use in childhood vaccines. *Pediatrics*, *107*, 1147–1154.
- Bernard, S., Enayati, A., Redwood, L., Roger, H., & Binstock, T. (2001). Autism: A novel form of mercury poisoning. *Medical Hypotheses*, *56*, 462–471.
- Bertrand, J., Mars, A., Boyle, C., Bove, F., Yeargin-Allsopp, M., & Decoufle, P. (2001). Prevalence of autism in a United States population: The Brick Township, New Jersey, investigation. *Pediatrics*, *108*, 1155–1161.
- Boris, M., Goldblatt, A., Galanko, J., & James, S. J. (2004). Association of MTHFR gene variants with autism. *Journal of American Physicians and Surgeons*, *9*, 106–108.
- Bradstreet, J., Geier, D. A., & Kartzinel, J. J. (2003). A case-control study of mercury burden in children with autistic spectrum disorders. *Journal of American Physicians and Surgeons*, *8*, 76–79.
- California Health and Human Services Agency. (2003). *California Department of Developmental Services: Autism spectrum disorders: Changes in the California caseload and update: 1999 through 2002*. Sacramento, CA.
- Chango, A., Boisson, F., & Barbe, F. (2000). The effect of 677C6T and 1298A6C mutations on plasma homocysteine and 5,10-methylenetetrahydrofolate reductase activity in healthy subjects. *British Journal of Nutrition*, *83*, 593–596.
- Davidson, P. W., Myers, G. J., & Weiss, B. (2004). Mercury exposure and child development outcomes. *Pediatrics*, *113*, 1023–1029.
- Deth, R. C. (2004). *Truth revealed: New scientific discoveries regarding mercury in medicine and autism. Congressional Testimony before the U.S. House of Representatives. Subcommittee on human rights and wellness, Sept. 8*. Retrieved Nov. 13, 2007, from <http://reform.house.gov/WHR/Hearings/EventSingle.aspx?EventID=18156>
- Environmental Working Group. (2004). *Overloaded? New science, new insights about mercury and autism in susceptible children*. Washington, DC: EWG Action Fund.
- Fagan, D. G., Pritchard, J. S., Clarkson, T. W., & Greenwood, M. R. (1977). Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic. *Archives of Disease in Childhood*, *52*, 962–964.
- Federal Register (1982). *FDA panel report: Mercury containing drug products for topical antimicrobial over-the-counter human use; Establishment of a monograph*. *47*, 436–442.
- Fido, A., & Al-Saad, S. (2005). Toxic trace elements in the hair of children with autism. *Autism*, *9*, 290–298.
- Geier, D. A., & Geier, M. R. (2004). A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. *Medical Science Monitor*, *10*, 133–139.
- Geier, D. A., & Geier, M. R. (2005). A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: A follow-up analysis. *Medical Science Monitor*, *11*, 160–170.
- Geier, D. A., & Geier, M. R. (2006). A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. *Neuroendocrinology Letters*, *27*, 401–413.
- Geier, M. R., & Geier, D. A. (2003). Thimerosal in childhood vaccines, neurodevelopment disorders, and heart disease in the United States. *Journal of American Physicians and Surgeons*, *8*, 6–11.
- Geier, M. R., & Geier, D. A. (2005b). The potential importance of steroids in the treatment of autistic spectrum disorders and other disorders involving mercury toxicity. *Medical Hypotheses*, *64*, 946–954.
- Grandjean, P., Weihe, P., White, R. F., & Debes, F. (1998). Cognitive performance of children prenatally exposed to “safe” levels of methylmercury. *Environmental Research*, *77*, 165–172.
- Holmes, A. S., Blaxill, M. F., Haley, B. E. (2003). Reduced levels of mercury in first baby haircuts of autistic children. *International Journal of Toxicology*, *22*, 277–285.
- Hu, L. W., Bernard, J., & Che, J. (2003). Neutron Activation analysis of Hair Samples for the Identification of Autism. *Transactions of the American Nuclear Society*, *89*, 681–682.
- Institute of Medicine (US). (2004). *Immunization safety review: Vaccines and autism*. Washington, DC: National Academy Press.
- James, S. J. (2004). Increased oxidative stress and impaired methylation capacity in children with autism: Metabolic biomarkers and genetic predisposition. *Fall DAN! 2004 Conference*, Los Angeles, CA, 1–3, 143–159.
- James, S. J., Cutler, P., & Melnyk, S. (2004). Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *American Journal of Clinical Nutrition*, *80*, 1611–1617.
- Jepson, B. (2004). *Understanding autism: The physio-*

- logical basis and biomedical intervention options of autism spectrum disorders. Retrieved Nov. 14, 2007 from www.cbcutah.org.
- Lutchmaya, S., Baron-Cohen, S., Raggatt, P., Knickmeyer, R., & Manning, J. T. (2004). 2nd to 4th digit ratios, fetal testosterone and estradiol. *Early Human Development*, 77, 23–28.
- Manning, J. T., Baron-Cohen, S., Wheelwright, S., & Sanders, G. (2001). The 2nd to 4th digit ratio and autism. *Developmental Medicine & Child Neurology*, 43, 160–164.
- Mutter, J., Naumann, J., Sadaghiani, C., Schneider, R., & Walach, H. (2004). Alzheimer Disease: Mercury as pathogenetic factor and apolipoprotein E as a moderator. *Neuroendocrinology Letters*, 25, 275–283.
- Mutter, J., Naumann, J., Sadaghiani, C., Walach, H., & Drasch, G. (2005). Mercury and autism: Response to the letter of K. E. v. Muhlendahl. *International Journal of Hygiene and Environmental Health*, 208, 435–438.
- Mutter, J., Naumann, J., Schneider, R., Walach, H., & Haley, B. (2005). Mercury and autism: Accelerating evidence? *Neuroendocrinology Letters*, 26, 439–446.
- Mutter, J., Naumann, J., Walach, H., & Daschner, F. D. (2005). Amalgam: Eine Risikobewertung unter Berücksichtigung der neuen Literatur bis 2005. [Amalgam risk assessment with coverage of references up to 2005]. *Gesundheitswesen*, 67, 204–216.
- Palmer, R. F., Blanchard, S., Stein, Z., Mandell, D., & Miller, C. (2006). Environmental mercury release, special education rates, and autism disorder: An ecological study of Texas. *Health Place*, 12, 203–209.
- Rampersad, G. C., Suck, G., Sakac, D., Fahim, S., Fop, A., & Denomme, G. A., et al. (2005). Chemical compounds that target thioldisulfide groups on mononuclear phagocytes inhibit immune mediated phagocytosis of red blood cells. *Transfusion*, 45, 384–93.
- Redwood, L., Bernard, S., & Brown, D. (2001). Predicted mercury concentrations in hair from infant immunizations: Cause for concern. *Neurotoxicology*, 22, 691–697.
- Slikker, W. (2000). Developmental neurotoxicology of therapeutics: Survey of novel recent findings. *Neurotoxicology*, 21, 250.
- Stoiber, T., Bonacker, D., Bohm, K. J., Bolt, H. M., Their, R., & Degen, G. H., et al. (2004). Disturbed microtubule function and induction of micronuclei by chelate complexes of mercury (II). *Mutation Research*, 563, 97–106.
- Stoller, K. P. (2006). Autism as a Minamata disease variant: Analysis of a pernicious legacy. *Medical Veritas*, 3, 772–780.
- Their, R., Bonacker, D., Stoiber, T., Bohm, K. J., Wang, M., & Unger, E., et al. (2003). Interaction of metal salts with cytoskeletal motor protein systems. *Toxicology Letters*, 140–141, 75–81.
- Tordjman, S., Ferrari, P., Sulmont, V., Duyme, M., & Roubertoux, P. (1997). Androgenic activity in autism. *American Journal of Psychiatry*, 154, 1626–1627.
- Vahter, M., Akesson, A., Lind, B., Bjors, U., Schutz, A., & Berglund, M., et al. (2000). Longitudinal study of methylmercury and inorganic mercury in blood and urine of pregnant and lactating women, as well as in umbilical cord blood. *Environmental Research*, 81, 186–194.
- Waly, M., Olteanu, H., Banerjee, R., Choi, S. W., Mason, J. B., Parker, B. S., et al. (2004). Activation of methionine synthase by insulin-like growth factor-I and dopamine: A target for neurodevelopmental toxins and thimerosal. *Molecular Psychiatry*, 9, 358–70.
- Windham, G. C., Zhang, L., Gunier, R., Croen, L. A., & Grether, J. K. (2006). Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area. *Environmental Health Perspectives*, 114, 1438–1444.
- Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C., & Murphy, C. (2003). Prevalence of autism in a US metropolitan area. *Journal of the American Medical Association*, 289, 49–55.

Received: 24 September 2008

Initial Acceptance: 21 November 2008

Final Acceptance: 6 February 2009