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Autism: a novel form of mercury poisoning

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Summary Autism is a syndrome characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recent epidemiological studies suggest that autism may affect 1 in 150 US children. Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Austic spectrum disorder (ASD) is a neurodevelopmental syndrome with onset prior to age 36 months. Diagnostic criteria consist of impairments in sociality and communication plus repetitive and stereotypic behaviors (1). Traits strongly associated with autism include movement disorders and sensory dysfunctions (2). Although autism may be apparent soon after birth, most autistic children experience at least several months, even a year or more of normal development – followed by regression, defined as loss of function or failure to progress (2–4).

The neurotoxicity of mercury (Hg) has long been recognized (5). Primary data derive from victims of contaminated fish (Japan – Minamata disease) or grain (Iraq, Guatemala, Russia); from acrodynia (Pink disease) induced by Hg in teething powders; and from individual instances of mercury poisoning (HgP), many occurring in occupational settings (e.g. Mad Hatter's disease). Animal and in vitro studies also provide insights into the mechanisms of Hg toxicity. More recently, the Food and Drug Administration (FDA) and the American Academy of Pediatrics (AAP) have determined that the typical amount of Hg injected into infants and toddlers via childhood immunizations has exceeded government safety guidelines on an individual (6) and cumulative vaccine basis (7). The mercury in vaccines derives from thimerosal (TMS), a preservative which is 49.6% ethylmercury (eHg) (7).

Past cases of HgP have presented with much inter-individual variation, depending on the dose, type of mercury, method of administration, duration of exposure, and individual sensitivity. Thus, while commonalities exist across the various instances of HgP, each set of variables has given rise to a different disease manifestation (8–11). It is hypothesized that the regressive form of autism represents another form of mercury poisoning, based on a thorough correspondence between autistic and HgP traits and physiological abnormalities, as well as on the known exposure to mercury through vaccines. Furthermore, other phenomena are consistent with a causal Hg-ASD relationship. These include: (a) symptom onset shortly after immunization; (b) ASD prevalence increases corresponding to vaccination increases; (c) similar sex ratios of affected individuals; (d) a high heritability rate for autism paralleling a genetic predisposition to

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Hg sensitivity at low doses; and (e) parental reports of autistic children with elevated Hg.

TRAIT COMPARISON

ASD manifests a constellation of symptoms with much inter-individual variation (3,4). A comparison of traits defining, nearly universal to, or commonly found in autism with those known to arise from mercury poisoning is given in Table 1. The characteristics defining or strongly associated with autism are also more fully described.

Autism has been conceived primarily as a psychiatric condition; and two of its three diagnostic criteria are based upon the observable traits of: (a) impairments in sociality, most commonly social withdrawal or aloofness; and (b) a variety of perseverative or stereotypic behaviors and the need for sameness, which strongly resemble obsessive–compulsive tendencies. Differential diagnosis may include childhood schizophrenia, depression, obsessive–compulsive disorder (OCD), anxiety disorder, and other neuroses. Related behaviors commonly found in ASD individuals are irrational fears, poor eye contact, aggressive behaviors, temper tantrums, irritability, and inexplicable changes in mood (1,2,12–17). Mercury poisoning, when undetected, is often initially diagnosed as a psychiatric disorder (18). Commonly occurring symptoms include: (a) 'extreme shyness', indifference to others, active avoidance of others, or 'a desire to be alone'; (b) depression, 'lack of interest' and 'mental confusion'; (c) irritability, aggression, and tantrums in children and adults; (d) anxiety and fearfulness; and (e) emotional

Table 1 Summary comparison of traits of autism and mercury poisoning (ASD references in bold; *HgP references in italics*)

Psychiatric disturbances
Social deficits, shyness, social withdrawal (**1,2,130,131**; *21,31,45,53,132*)
Repetitive, perseverative, stereotypic behaviors; obsessive-compulsive tendencies (**1,2,43,48,133**; *20,33–35,132*)
Depression/depressive traits, mood swings, flat affect; impaired face recognition (**14,15,17,103,134,135**; *19,21,24,26,31*)
Anxiety; schizoid tendencies; irrational fears (**2,15,16**; *21,27,29,31*)
Irritability, aggression, temper tantrums (**12,13,43**; *18,21,22,25*)
Lacks eye contact; impaired visual fixation (HgP)/problems in joint attention (ASD) (**3,36,136,137**; *18,19,34*)

Speech and language deficits
Loss of speech, delayed language, failure to develop speech (**1–3,138,139**; *11,23,24,27,30,37*)
Dysarthria; articulation problems (**3**; *21,25,27,39*)
Speech comprehension deficits (**3,4,140**; *9,25,34,38*)
Verbalizing and word retrieval problems (HgP); echolalia, word use and pragmatic errors (ASD) (**1,3,36**; *21,27,70*)

Sensory abnormalities
Abnormal sensation in mouth and extremities (**2,49**; *25,28,34,39*)
Sound sensitivity; mild to profound hearing loss (**2,47,48**; *19,23–25,39,40*)
Abnormal touch sensations; touch aversion (**2,49**; *23,24,45,53*)
Over-sensitivity to light; blurred vision (**2,50,51**; *18,23,31,34,45*)

Motor disorders
Flapping, myoclonal jerks, choreiform movements, circling, rocking, toe walking, unusual postures (**2,3,43,44**; *11,19,27,30,31,34,39*)
Deficits in eye-hand coordination; limb apraxia; intention tremors (HgP)/problems with intentional movement or imitation (ASD) (**2,3,36,181**; *25,29,32,38,70,87*)
Abnormal gait and posture, clumsiness and incoordination; difficulties sitting, lying, crawling, and walking; problem on one side of body (**4,41,42,123**; *18,25,31,34,39,45*)

Cognitive impairments
Borderline intelligence, mental retardation – some cases reversible (**2,3,151,152**; *19,25,31,39,70*)
Poor concentration, attention, response inhibition (HgP)/shifting attention (ASD) (**4,36,153**; *21,25,31,38,141*)
Uneven performance on IQ subtests; verbal IQ higher than performance IQ (**3,4,36**; *31,38*)
Poor short term, verbal, and auditory memory (**36,140**; *21,29,31,35,38,87,141*)
Poor visual and perceptual motor skills; impairment in simple reaction time (HgP)/lower performance on timed tests (ASD) (**4,140,181**; *21,29,142*)
Deficits in understanding abstract ideas & symbolism; degeneration of higher mental powers (HgP)/sequencing, planning & organizing (ASD); difficulty carrying out complex commands (**3,4,36,153**; *9,18,37,57,142*)

Unusual behaviors
Self injurious behavior, e.g. head banging (**3,154**; *11,18,53*)
ADHD traits (**2,36,155**; *35,70*)
Agitation, unprovoked crying, grimacing, staring spells (**3,154**; *11,23,37,88*)
Sleep difficulties (**2,156,157**; *11,22,31*)

Physical disturbances
Hyper- or hypotonia; abnormal reflexes; decreased muscle strength, especially upper body; incontinence; problems chewing, swallowing (**3,42,145,181**; *19,27,31,32,39*)
Rashes, dermatitis, eczema, itching (**107,146**; *22,26,143*)
Diarrhea; abdominal pain/discomfort, constipation, "colitis" (**107,147–149**; *18,23,26,27,31,32*)
Anorexia; nausea (HgP)/vomiting (ASD); poor appetite (HgP)/restricted diet (ASD) (**2,123**; *18,22*)
Lesions of ileum and colon; increased gut permeability (**147,150**; *57,144*)

lability. Neuroses, including schizoid and obsessive–compulsive traits, problems in inhibition of perservation, and stereotyped behaviors, have been reported in a number of cases; and lack of eye contact was observed in one 12-year-old girl with mercury vapor poisoning (18–35).

The third diagnostic criterion for ASD is impairment in communication (1). Historically, about half of those with classic autism failed to develop meaningful speech (2), and articulation difficulties are common (3). Higher functioning individuals may have language fluency but still show semantic and pragmatic errors (3,36). In many cases of ASD, verbal IQ is lower than performance IQ (3). Similarly, mercury-exposed children and adults show a marked difficulty with speech (9,19,37). In milder cases, scores on language tests may be lower than those of unexposed controls (31,38). Iraqi children who were postnatally poisoned developed articulation problems, from slow, slurred word production to an inability to generate meaningful speech; while Iraqi babies exposed prenatally either failed to develop language or presented with severe language deficits in childhood (23,24,39). Workers with Mad Hatter's disease had word retrieval and articulation difficulties (21).

Nearly all cases of ASD and HgP involve disorders of physical movement (2,30,40). Clumsiness or lack of coordination has been described in many higher functioning ASD individuals (41). Infants and toddlers later diagnosed with autism may fail to crawl properly or may fall over while sitting or standing; and the movement disturbances typically occur on the right side of the body (42). Problems with intentional movement and imitation are common in ASD, as are a variety of unusual stereotypic behaviors such as toe walking, rocking, abnormal postures, choreiform movements, spinning; and hand flapping (2,3,43,44). Noteworthy because of similarities to autism are reports in Hg literature of: (a) children in Iraq and Japan who were unable to stand, sit, or crawl (34,39); (b) Minamata disease patients whose movement disturbances were localized to one side of the body, and a girl exposed to Hg vapor who tended to fall to the right (18,34); (c) flapping motions in an infant poisoned from contaminated pork (37) and in a man injected with thimerosal (27); (d) choreiform movements in mercury vapor intoxication (19); (e) toe walking in a moderately poisoned Minamata child (34); (f) poor coordination and clumsiness among victims of acrodynia (45); (g) rocking among infants with acrodynia (11); and (h) unusual postures observed in both acrodynia and mercury vapor poisoning (11,31). The presence of flapping motions in both diseases is of interest because it is such an unusual behavior that it has been recommended as a diagnostic marker for autism (46).

Virtually all ASD subjects show a variety of sensory abnormalities (2). Auditory deficits are present in a minority of individuals and can range from mild to profound hearing loss (2,47). Over- or under-reaction to sound is nearly universal (2,48), and deficits in language comprehension are often present (3). Pain sensitivity or insensitivity is common, as is a general aversion to touch; abnormal sensation in the extremities and mouth may also be present and has been detected even in toddlers under 12 months old (2,49). There may be a variety of visual disturbances, including sensitivity to light (2,50,51,52). As in autism, sensory issues are reported in virtually all instances of Hg toxicity (40). HgP can lead to mild to profound hearing loss (40); speech discrimination is especially impaired (9,34,). Iraqi babies exposed prenatally showed exaggerated reaction to noise (23), while in acrodynia, patients reported noise sensitivity (45). Abnormal sensation in the extremities and mouth is the most common sensory disturbance (25,28). Acrodynia sufferers and prenatally exposed Iraqi babies exhibited excessive pain when bumping limbs and an aversion to touch (23,24,45,53). A range of visual problems has been reported, including photophobia (18,23,34).

COMPARISON OF BIOLOGICAL ABNORMALITIES

The biological abnormalities commonly found in autism are listed in Table 2, along with the corresponding pathologies arising from mercury exposure. Especially noteworthy similarities are described.

Autism is a neurodevelopmental disorder which has been characterized as 'a disorder of neuronal organization, that is, the development of the dentritic tree, synaptogenesis, and the development of the complex connectivity within and between brain regions' (54). Depressed expression of neural cell adhesion molecules (NCAMs), which are critical during brain development for proper synaptic structuring, has been found in one study of autism (55). Organic mercury, which readily crosses the blood–brain barrier, preferentially targets nerve cells and nerve fibers (56); primates accumulate the highest Hg-levels in the brain relative to other organs (40). Furthermore, although most cells respond to mercurial injury by modulating levels of glutathione (GSH), metallothionein, hemoxygenase, and other stress proteins, neurons tend to be 'markedly deficient in these responses' and thus are less able to remove Hg and more prone to Hg-induced injury (56). In the developing brain, mercury interferes with neuronal migration, depresses cell division, disrupts microtubule function, and reduces NCAMs (28,57–59).

While damage has been observed in a number of brain areas in autism, many nuclei and functions are spared (36). HgP's damage is similarly selective (40). Numerous studies link autism with neuronal atypicalities within the amygdala, hippocampi, basal ganglia, the Purkinje and

Table 2 Summary comparison of biological abnormalities in autism and mercury exposure

Mercury exposure	Autism
Biochemistry	
Binds -SH groups; blocks sulfate transporter in intestines, kidneys (40,93)	Low sulfate levels (91,92)
Reduces glutathione availability; inhibits enzymes of glutathione metabolism; glutathione needed in neurons, cells, and liver to detoxify heavy metals; reduces glutathione peroxidase and reductase (97,100,161,162)	Low levels of glutathione; decreased ability of liver to detoxify xenobiotics; abnormal glutathione peroxidase activity in erythrocytes (91,94,95)
Disrupts purine and pyrimidine metabolism (10,97,158,159)	Purine and pyrimidine metabolism errors lead to autistic features (2,101,102)
Disrupts mitochondrial activities, especially in brain (160,163,164)	Mitochondrial dysfunction, especially in brain (76,172)
Immune system	
Sensitive individuals more likely to have allergies, asthma, autoimmune-like symptoms, especially rheumatoid-like ones (8,11,18,24,28,31,111,113)	More likely to have allergies and asthma; familial presence of autoimmune diseases, especially rheumatoid arthritis; IgA deficiencies (103,106–109,115)
Can produce an immune response in CNS; causes brain/MBP autoantibodies (18,111,165)	On-going immune response in CNS; brain/MBP autoantibodies present (104,105,109,110)
Causes overproduction of Th2 subset; kills/inhibits lymphocytes, T-cells, and monocytes; decreases NK T-cell activity; induces or suppresses IFNg & IL-2 (100,112,117–120,166)	Skewed immune-cell subset in the Th2 direction; decreased responses to T-cell mitogens; reduced NK T-cell function; increased IFNg & IL-12 (103,108,114–116,173,174)
CNS structure	
Selectively targets brain areas unable to detoxify or reduce Hg-induced oxidative stress (40,56,161)	Specific areas of brain pathology; many functions spared (36)
Accummulates in amygdala, hippocampus, basal ganglia, cerebral cortex; damages Purkinje and granule cells in cerebellum; brain stem defects in some cases (10,34,40,70–73)	Pathology in amygdala, hippocampus, basal ganglia, cerebral cortex; damage to Purkinje and granule cells in cerebellum; brain stem defects in some cases (36,60–69)
Causes abnormal neuronal cytoarchitecture; disrupts neuronal migration, microtubules, and cell division; reduces NCAMs (10,28,57–59,161)	Neuronal disorganization; increased neuronal cell replication, increased glial cells; depressed expression of NCAMs (4,54,55)
Progressive microcephaly (24)	Progressive microcephaly and macrocephaly (175)
Neuro-chemistry	
Prevents presynaptic serotonin release and inhibits serotonin transport; causes calcium disruptions (78,79,163,167,168)	Decreased serotonin synthesis in children; abnormal calcium metabolism (76,77,103,179)
Alters dopamine systems; peroxidine deficiency in rats resembles mercurialism in humans (8,80)	Either high or low dopamine levels; positive response to peroxidine, which lowers dopamine levels (2,177,178)
Elevates epinephrine and norepinephrine levels by blocking enzyme that degrades epinephrine (81,160)	Elevated norepinephrine and epinephrine (2)
Elevates glutamate (21,171)	Elevated glutamate and asparate (82,176)
Leads to cortical acetylcholine deficiency; increases muscarinic receptor density in hippocampus and cerebellum (57,170)	Cortical acetylcholine deficiency; reduced muscarinic receptor binding in hippocampus (83)
Causes demyelinating neuropathy (22,169)	Demyelination in brain (105)
Neurophysiology	
Causes abnormal EEGs, epileptiform activity, variable patterns, e.g., subtle, low amplitude seizure activities (27,31,34,86–89)	Abnormal EEGs, epileptiform activity, variable patterns, including subtle, low amplitude seizure activities (2,4,84,85)
Causes abnormal vestibular nystagmus responses; loss of sense of position in space (9,19,34,70)	Abnormal vestibular nystagmus responses; loss of sense of position in space (27,180)
Results in autonomic disturbance: excessive sweating, poor circulation, elevated heart rate (11,18,31,45)	Autonomic disturbance: unusual sweating, poor circulation, elevated heart rate (17,180)

granule cells of the cerebellum, brainstem, basal ganglia, and cerebral cortex (*36,60–69*). Each of these areas can be affected by HgP (10,34,40,70–73). Migration of Hg, including eHg, into the amygdala is particularly noteworthy, because in primates this brain region has neurons specific for eye contact (74) and it is implicated in autism and in social behaviors (*65,66,75*).

Autistic brains show neurotransmitter irregularities which are virtually identical to those arising from Hg exposure: both high or low serotonin and dopamine, depending on the subjects studied; elevated epinephrine and norepinephrine in plasma and brain; elevated glutamate; and acetylcholine deficiency in hippocampus (*2,21,76–83*).

Gillberg and Coleman (2) estimate that 35–45% of autistics eventually develop epilepsy. A recent MEG study reported epileptiform activity in 82% of 50 regressive autistic children; in another study, half the autistic children expressed abnormal EEG activity during sleep (84). Autistic EEG abnormalities tend to be non-specific and have a variety of patterns (85). Unusual epileptiform activity has been found in a number of mercury poisoning cases (18,27,34,*86–88*). Early mHg exposure enhances tendencies toward epileptiform activity with a reduced

level of seizure-discharge amplitude (89), a finding consistent with the subtlety of seizures in many autism spectrum children (84,85). The fact that Hg increases extracellular glutamate would also contribute to epileptiform activity (90).

Some autistic children show a low capacity to oxidize sulfur compounds and low levels of sulfate (91,92). These findings may be linked with HgP because: (a) Hg preferentially binds to sulfhydryl molecules (-SH) such as cysteine and GSH, thereby impairing various cellular functions (40); and (b) mercury can irreversibly block the sulfate transporter NaSi cotransporter NaSi-1, present in kidneys and intestines, thus reducing sulfate absorption (93). Besides low sulfate, many autistics have low GSH levels, abnormal GSH-peroxidase activity within erythrocytes, and decreased hepatic ability to detoxify xenobiotics (91,94,95). GSH participates in cellular detoxification of heavy metals (96); hepatic GSH is a primary substrate for organic-Hg clearance from the human (40); and intraneuronal GSH participates in various protective responses against Hg in the CNS (56). By preferentially binding with GSH, preventing absorption of sulfate, or inhibiting the enzymes of glutathione metabolism (97), Hg might diminish GSH bioavailability. Low GSH can also derive from chronic infection (98,99), which would be more likely in the presence of immune impairments arising from mercury (100). Furthermore, mercury disrupts purine and pyrimidine metabolism (97,10). Altered purine or pyrimidine metabolism can induce autistic features and classical autism (2,101,102), suggesting another mechanism by which Hg can contribute to autistic traits.

Autistics are more likely to have allergies, asthma, selective IgA deficiency (sIgAd), enhanced expression of HLA-DR antigen, and an absence of interleukin-2 receptors, as well as familial autoimmunity and a variety of autoimmune phenomena. These include elevated serum IgG and ANA titers, IgM and IgG brain antibodies, and myelin basic protein (MBP) antibodies (103–110). Similarly, atypical responses to Hg have been ascribed to allergic or autoimmune reactions (8), and genetic predisposition to such reactions may explain why Hg sensitivity varies so widely by individual (88,111). Children who developed acrodynia were more likely to have asthma and other allergies (11); IgG brain autoantibodies, MBP, and ANA have been found in HgP subjects (18,111,112); and mice genetically prone to develop autoimmune diseases 'are highly susceptible to mercury-induced immunopathological alterations' even at the lowest doses (113). Additionally, many autistics have reduced natural killer cell (NK) function, as well as immune-cell subsets shifted in a Th2 direction and increased urine neopterin levels, indicating immune system activiation (103,114–116). Depending upon genetic predisposition, Hg can induce immune activation, an expansion of Th2 subsets, and decreased NK activity (117–120).

POPULATION CHARACTERISTICS

In most affected children, autistic symptoms emerge gradually, although there are cases of sudden onset (3). The earliest abnormalities have been detected in 4-month-olds and consist of subtle movement disturbances; subtle motor-sensory disturbances have been observed in 9-month-olds (49). More overt speech and hearing difficulties become noticeable to parents and pediatricians between 12 and 18 months (2). TMS vaccines have been given in repeated intervals starting from infancy and continuing until 12 to 18 months. While HgP symptoms, may arise suddenly in especially sensitive individuals (11), usually there is a preclinical 'silent stage' in which subtle neurological changes are occuring (121) and then a gradual emergence of symptoms. The first symptoms are typically sensory-and motor-related, which are followed by speech and hearing deficits, and finally the full array of HgP characteristics (40). Thus, both the timing and nature of symptom emergence in ASD are fully consistent with a vaccinal Hg etiology. This parallel is reinforced by parental reports of excessive amounts of mercury in urine or hair from younger autistic children, as well as some improvement in symptoms with standard chelation therapy (122).

The discovery and rise in prevalence of ASD mirrors the introduction and spread of TMS in vaccines. Autism was first described in 1943 among children born in the 1930s (123). Thimerosal was first introduced into vaccines in the 1930s (7). In studies conducted prior to 1970, autism prevalence was estimated, at 1 in 2000; in studies from 1970 to 1990 it averaged 1 in 1000 (124). This was a period of increased vaccination rates of the TMS-containing DPT vaccines among children in the developed world. In the early 1990s, the prevalence of autism was found to be 1 in 500 (125), and in 2000 the CDC found 1 in 150 children affected in one community, which was consistent with reports from other areas in the country (126). In the late 1980s and early 1990s, two new TMS vaccines, the HIB and Hepatitis B, were added to the recommended schedule (7).

Nearly all US children are immunized, yet only a small proportion develop autism. A pertinent characteristic of mercury is the great variability in its effects by individual, so that at the same exposure level, some will be affected severely while others will be asymptomatic (9,11,28). An example is acrodynia, which arose in the early 20th century from mercury in teething powders and afflicted only 1 in 500–1000 children given the same low dose (28). Studies in mice as well as humans indicate that susceptibility to Hg effects arises from genetic status, in some

cases including a propensity to autoimmune disorders (113,34,40). ASD exhibits a strong genetic component, with high concordance in monozygotic twins and a higher than expected incidence among siblings (4); autism is also more prevalent in families with autoimmune disorders (106).

Additionally, autism is more prevalent among boys than girls, with the ratio estimated at 4:1 (2). Mercury studies in mice and humans consistently report greater effects on males than females, except for kidney damage (57). At high doses, both sexes are affected equally; at low doses only males are affected (38,40,127).

DISCUSSION

We have shown that every major characteristic of autism has been exhibited in at least several cases of documented mercury poisoning. Recently, the FDA and AAP have revealed that the amount of mercury given to infants from vaccinations has exceeded safety levels. The timing of mercury administration via vaccines coincides with the onset of autistic symptoms. Parental reports of autistic children with measurable mercury levels in hair and urine indicate a history of mercury exposure. Thus the standard primary criteria for a diagnosis of mercury poisoning – observable symptoms, known exposure at the time of symptom onset, and detectable levels in biologic samples (11,31) – have been met in autism. As such, mercury toxicity may be a significant etiological factor in at least some cases of regressive autism. Further, each known form of HgP in the past has resulted in a unique variation of mercurialism – e.g. Minamata disease, acrodynia, Mad Hatter's disease – none of which has been autism, suggesting that the Hg source which may be involved in ASD has not yet been characterized; given that most infants receive eHg via vaccines, and given that the effect on infants of eHg in vaccines has never been studied (129), vaccinal thimerosal should be considered a probable source. It is also possible that vaccinal eHg may be additive to a prenatal mercury load derived from maternal amalgams, immune globulin injections, or fish consumption, and environmental sources.

CONCLUSION

The history of acrodynia illustrates that a severe disorder, afflicting a small but significant percentage of children, can arise from a seemingly benign application of low doses of mercury. This review establishes the likelihood that Hg may likewise be etiologically significant in ASD, with the Hg derived from thimerosal in vaccines rather than teething powders. Due to the extensive parallels between autism and HgP, the likelihood of a causal relationship is great. Given this possibility, TMS should be removed from all childhood vaccines, and the mechanisms of Hg toxicity in autism should be thoroughly investigated. With perhaps 1 in 150 children now diagnosed with ASD, development of HgP-related treatments, such as chelation, would prove beneficial for this large and seemingly growing population.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington DC.: American Psychiatric Association, 1994.
2. Gillberg C., Coleman M. The Biology of the Autistic Syndromes, 2nd edn. London: Mac Keith Press, 1992.
3. Filipek P., Accardo P., Baranek G. et al. The screening and diagnosis of autistic spectrum disorders. *J Autism Dev Disord* 1999; **29**(6): 439–484.
4. Bailey A., Phillips W., Rutter M. Autism: towards an integration of clinical, genetic, neuro-psychological, and neurobiological perspectives. *J Child Psychol Psychiatry* 1996; **37**(1): 89–126.
5. Suzuki T., Takemoto T. I., Kashiwazaki H., Miyama T. Metabolic fate of ethylmercury salts in man and animal. In: Miller M. W., Clarkson T. W., (eds) Mercury, Mercurials, and Mercaptans. Springfield: Charles C. Thomas, 1973: 209–233.
6. Halsey N. A. Perspective on the use of thimerosal-containing vaccines. Presentation at the National Vaccine Advisory Committee Workshop on Thimerosal and Vaccines, August 11–12, 1999. Institute of Vaccine Safety website; www.vaccinesafety.edu.
7. Egan, W. M. Thimerosal in Vaccines. Presentation to the FDA, September 14, 1999.
8. Gosselin R. E., Smith R. P., Hodge H. C. Mercury. Clinical Toxicology of Commercial Products, Section III, Therapeutic Index, 5th edn. Baltimore: Williams & Wilkins, 1984: 262–271.
9. Dales L. D. The neurotoxicity of alkyl mercury compounds. *Am J Med* 1972; **53**: 219–232.
10. Koos B. J., Longo L. D., Mercury toxicity in the pregnant woman, fetus, and newborn infant. *Am J Obstet Gynecol* 1976; **126**(3): 390–406.
11. Warkany J., Hubbard D. H. Acrodynia and mercury. *J Pediatrics* 1953; **42**: 365–386.
12. McDougle C. J., Brodkin E. S., Yeung P. P., Naylor S. T., Cohen D. J., Price L. H. Risperidone in adults with autism or pervasive developmental disorder. *J Child Adolesc Psychopharmacol* 1995; **5**(4): 273–282.
13. Jaselskis C., Cook E., Fletcher K., Bennett L. Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Pharmacol 1992.
14. Piven J., Palmer P. Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families. *Am J Psychiatry* 1999; **156**(4): 557–563.
15. Clarke D., Baxter M., Perry D., Prasher V. The diagnosis of affective and psychotic disorders in adults with autism: seven case reports. *Autism* 1999; **3**(2): 149–164.
16. Muris P., Steerneman P., Merckelbach H., Holdrinet I., Meesters C. Comorbid anxiety symptoms in children with pervasive developmental disorders. *J Anxiety Disord* 1998; **12**(4): 387–393.
17. Wing L., Attwood A. Syndromes of autism and atypical development. In: Handbook of Autism and Pervasive Developmental Disorders, New York: John Wiley & Sons, 1987: 3–19.
18. Fagala G. E., Wigg C. L. Psychiatric manifestions of mercury poisoning. *J Am Acad Child Adolesc Psychiatry* 1992; **31**(2): 306–311.

19. Kark R. A., Poskanzer D. C., Bullock J. D., Boylen G. Mercury poisoning and its treatment with N-acetyl-D., L-penicillamine. *N Engl J Med* 1971; **285**: 10–16.
20. White R. F., Feldman R. G., Moss M. B., Proctor S. P. Magnetic resonance imaging (MRI), neurobehavioral testing, and toxic encephalopathy: two cases. *Environ Res* 1993; **61**: 117–123.
21. O'Carroll R. E., Masterton G., Dougnall N., Ebmeier K. P. The neuropsychiatric sequelae of mercury poisoning: the Mad Hatters disease revisited. *Br J Psychiatry* 1995; **167**(1): 95–98.
22. Florentine M. J., Sanfilippo II D. J. Grand rounds: elemental mercury poisoning. *Clin Pharm* 1991; **10**: 213–221.
23. Amin-Zaki, L., Elhassani S., Majeed M. A., Clarkson T. W., Doherty R. A., Greenwood M., Intra-uterine methylmercury poisoning in Iraq. *Pediatrics* 1974; **54**(5): 587–595.
24. Amin-Zaki L., Majeed M. A., Elhassani S. B., Clarkson T. W., Greenwood M. R., Doherty R. A., Prenatal methylmercury poisoning. *Am J Disabled Child* 1979; **133**: 172–177.
25. Joselow M. M., Louria D. B., Browder A. A., Mercurialism: environmental and occupational aspects. *Ann Intern Med* 1972; **76**: 119–130.
26. Smith D. Mental Effects of Mercury Poisoning. Presentation before the Section on Family Practice, Southern Medical Association, 71st Annual Scientific Assembly, November 6–9, 1977.
27. Lowell J. A., Burgess S., Shenoy S., Curci J. A., Peters M., Howard T. K. Mercury poisoning associated with high-dose hepatitis-B immune globulin administration after liver transplantation for chronic hepatitis B. *Liver Transpl Surg* 1996; **2**(6): 475–478.
28. Clarkson, T. The toxicology of mercury. *Crit Rev Clin Lab Sci* 1997; **34**(3): 369–403.
29. Camerino D., Cassito M. G., Desideri E., Angotzi G. Behavior of some psychological parameters of a population of a Hg extraction plant. *Clin Toxicol* 1981; **18**(11): 1299–1309.
30. Snyder R. D. The involuntary movements of chronic mercury poisoning. *Arch Neurol* 1972; **26**: 379–381.
31. Vroom F. Q., Greer M. Mercury vapour intoxication. *Brain* 1972; **95**: 305–318.
32. Adams C. R., Ziegler D. K., Lin J. T. Mercury intoxication simulating amyotrophic lateral sclerosis. *JAMA* 1983; **250**: 642–643.
33. Cuomo V., Ambrosi L., Annau Z., Cagiano R., Brunello N., Racagni G. Behavioural and neurochemical changes in offspring of rats exposed to methylmercury during gestation. *Neuobehav Toxicol Teratol* 1984; **6**(3): 249–254.
34. Tsubaki T., Irukayama K., eds. Minamata Disease. Amsterdam: Elsevier Scientific Publishing 1977.
35. Elsner J. Testing strategies in behavioral teratology. III. Microanalysis of behavior. *Neurobehav Toxicol Teratol* 1986; **8**: 573–584.
36. Dawson G. Brief report: neuropsychology of autism: a report on the state of the science. *J Autism Dev Disord* 1996; **26**(2): 179–184.
37. Pierce P. E., Thompson J. F., MPH, Likosky W. H. MD, Nickey L. N. MD, Barhtel W. F., Hinman A. R. MD, MPH. Alkyl mercury poisoning in humans. *JAMA* 1972; **220**(11): 1439–1442.
38. Grandjean P., Weihe P., White R. F., Debes F. Cognitive performance of children prenatally exposed to "safe" levels of methylmercury. *Environ Res* 1998; **77**(2): 165–172.
39. Amin-Zaki L., Majeed M. A., Clarkson T. W., Greenwood M. R. Methylmercury poisoning in Iraqi children: clinical observations over two years. *BMJ* 1978; March 1: 613–616.
40. Clarkson T. W. Mercury: major issues in environmental health. *Environ Health Perspect* 1992; **100**: 31–38.
41. Kugler B. The differentiation between autism and Asperger syndrome. *Autism* 1998; **2**(1): 11–32.
42. Teitelbaum P., Teitelbaum O., Nye J., Fryman J., Maurer R. G. Movement analysis in infancy may be useful for early diagnosis of autism. *Proc Natl Acad Sci USA* 1998; **95**: 13982–13987.
43. Tsai L. Y. Brief report: comorbid psychiatric disorders of autistic disorder. *J Autism Dev Disord* 1996; **26**(2): 159–164.
44. Cesaroni L., Garber M. Exploring the experience of autism through firsthand accounts. *J Autism Dev Disord* 1991; **21**(3): 303–313.
45. Farnsworth D. *Pink Disease Survey Results*. Pink Disease Support Group Site, 1997; www.users.bigpond.com/difarnsworth.
46. Brasic J. R. Movements in autistic disorder. *Med Hypotheses* 1999; **53**: 48–49.
47. Rosenhall U., Nordin V., Sandstrom M., Ahlsen G., Gillberg C. Autism and hearing loss. *J Autism Dev Disord* 1999; **29**(5): 349–358.
48. Roux S., Adrien J-L., Bruneau N., Malvy J., Barthelemy C. Behavior profiles within a population of 145 children with autism using the Behaviour Summarized Evaluation scale: influence of developmental age. *Autism* 1998; **2**(4): 345–366.
49. Baranek G. Autism during infancy: a retrospective video analysis of sensory-motor and social behaviors and 9–12 months of age. *J Autism Dev Disord* 1999; **29**(3): 213–224.
50. ONeill M., Jones R. S. P. Sensory-perceptual abnormalities in autism: a case for more research? *J Autism Dev Disord* 1997; **27**(3): 283–293.
51. Sperry V. W. Family and personal section: from the inside out – a view of the world as seen by one with Asperger syndrome. *Autism* 1998; **2**(1): 81–86.
52. Cass H. Visual impairment and autism: current questions and future research. *Autism* 1998; **2**(2): 117–138.
53. Manser N. *Neville's (a Pinkie) Recollection of Pink Disease*. Pink Disease Support Group; www.users.bigpond.com/difarnsworth.
54. Minshew N. J. Brief report: brain mechanisms in autism: functional and structural abnormalities. *J Autism Dev Disord* 1996; **26**(2): 205–209.
55. Plioplys A. V., Hemmens S. E., Regan C. M. Expression of a neural cell adhesion molecule serum fragment is depressed in autism. *J Neuropsychiatry Clin Neurosci* 1990; **2**(4): 413–417.
56. Sarafian T. A., Bredesen D. E., Verity M. A. Cellular resistance to methylmercury. *Neurotoxicology* 1996 Spring Abstract; **17**(1): 27–36.
57. Hassett-Sipple B., Swartout J., Schoeny R. Vol. V. Health effects of mercury and mercury compounds. *Mercury Study Report to Congress*. Environmental Protection Agency (EPA), December 1997.
58. Pendergrass J. C., Haley B. E., Vimy M. J., Winfield S. A., Lorscheider F. L. Mercury vapor inhalation inhibits binding of GTP to tubulin in rat brain: similarity to a molecular lesion in Alzheimer diseased brain. *Neurotoxicology* 1997; **18**(2): 315–324.
59. Dey P. M., Gochfeld M., Reuhl K. R. Developmental methymercury administration alters cerebellar PSA-NCAM expression and Golgi sialyltransferase activity. *Brain Res* 1999; **845**(2): 139–151.
60. Courchesne E. et al. More evidence links autism, cerebellar defects. reviewed in *Autism Research Review International* 1994; **8**(2): 1, 7.
61. Ritvo E. R., Freeman B. J., Scheibel A. B. et al. Lower Purkinje cell counts in the cerebella of four autistic subjects: intitial findings of the UCLA-NSAC Autopsy Research Report. *Am J Psychiatry* 1986; **143**: 862–866.
62. Hoon A. H., Riess A. L. The mesial-temporal lobe and autism: case report and review. *Dev Med Child Neurol* 1992; **34**: 252–265.

63. Piven J., Berthier M., Starkstein S., Nehme E., Pearlson G., Folstein S. Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. *Am J Psychiatry* 1990; **147**(*6*): 734–739.
64. Abell F., Krams M., Ashburner J. et al. The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. *Neuroreport* 1999; **10**(8): 1647–1651.
65. Aylward E. H., Minshew N. J., Goldstein G. et al. MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology* 1999; **53**(*9*): 2145–2150.
66. Otsuka H. Brain metabolites in the hippocampus-amygdala region and cerebellum in autism: an 1H-MR spectroscopy study. *Neuroradiology* 1999; July.
67. Sears L. L. An MRI study of the basal ganglia in autism. *Prog Neuropsychopharmacol Biol Psychiatry* 1999; May.
68. Hashimoto T., Tayama M., Murakawa K. et al. Development of the brainstem and cerebellum in autistic patients. *J Autism Dev Disord* 1995; **25**(1): 1–18.
69. McClelland R. J., Eyre D., Watson D., Calvert J. A neuro-physiological study of autistic children. *Electroencephalogr Clin Neurophysiol* 1985; **61**: 16.
70. Davis L. E., Kornfeld M., Mooney H. S. et al. Methylmercury poisoning: long term clinical, radiological, toxicological, and pathological studies of an affected family. *Ann Neurol* 1994; **35**(*6*): 680–688.
71. Larkfors L., Oskarsson A., Sundberg J., Ebendal T. Methyl-mercury induced alterations in the nerve growth factor level in the developing brain. *Brain Res Dev Brain Res* 1991; **62**(2): 287–291.
72. Lorscheider F. L., Vimy M. J., Summers A. O. Mercury exposure from "silver" tooth fillings: emerging evidence questions a traditional dental paradigm. *FASEB J* 1995; **9**: 504–508.
73. Magos L., Brown A. W., Sparrow S., Bailey E., Snowden R. T., Skipp W. R. The comparative toxicology of ethyl-and methylmercury. *Arch Toxicol* 1985; **57**(4): 260–267.
74. Rolls E. T. Memory systems in the brain. *Ann Rev Psychol* 2000; **51**: 599–630.
75. Bachevalier J. Medial temporal lobe structures: a review of clinical and experimental findings. *Neuropsychologia* 1994; **32**: 627–648.
76. Chugani D. C., Muzik O., Behen M. et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann Neurol* 1999; 45.
77. Cook E. H. Autism: review of neurochemical investigation. *Synapse* 1990; **6**: 292–308.
78. OKusky J. R., Boyes B. E., McGeer E. G. Methylmercury-induced movement and postural disorders in developing rat: regional analysis of brain catecholamines and indoleamines. *Brain Res* 1988; **439**(1–2): 138–146.
79. Nishio H., Nezasa K., Hirano J., Nakata Y. Effects of thimerosal, an organic sulfhydryl modifying agent, on serotonin transport activity into rabbit blood platelets. *Neurochem Int* 1996; **29**(4): 391–396.
80. McKay S. J., Reynolds J. N., Racz W. J. Effects of mercury compounds on the spontaneous and potassium-evoked release of [3H]dopamine from mouse striatal slices. *Can J Physiol Pharmacol* 1986; **64**(12): 1507–1514.
81. Hrdina P. D., Peters D. A., Singhal R. L. Effects of chronic exposure to cadmium, lead and mercury of brain biogenic amines in the rat. *Research Communications in Chemistry, Pathology and Pharmacology* 1976; **15**(3): 483–493.
82. Moreno H., Borjas L., Arrieta A. et al. Clinical heterogeneity of the autistic syndrome: a study of 60 families (Spanish). *Invest Clin* 1992; **33**(1): 13–31.
83. Perry E., Lee M., Court J., Perry R. *Cholinergic Activities in Autism: Nicotinic and Muscarinic Receptor Abnormalities in the Cerebral Cortex*. Presentation to Cure Autism Now, 2000.
84. Lewine magnetoenchalography in children with an autistic epileptiform regression. *J Pediatrics* 1999; 405–418.
85. Nass R., Gross A., Devinsky O. Autism and autistic epileptiform regression with occipital spikes. *Dev Med Child Neurol* 1998; **40**(7): 453–8.
86. Brenner R. P., Snyder R. D. Late EEG finding and clinical status after organic mercury poisoning. *Arch Neurol* 1980; **37**(5): 282–284.
87. Piikivi L., Tolonen U. EEG findings in chlor-alkali workers subject to low long term exposure to mercury vapor. *Br J Ind Med* 1989; **46**(6): 370–375.
88. Rohyans J., Walson P. D., Wood G. A., MacDonald W. A. Mercury toxicity following merthiolate ear irrigations. *J Pediatr* 1984: 311–313.
89. Szasz A., Barna B., Szupera Z. et al. Chronic low-dose maternal exposure to methylmercury enhances epileptogenicity in developing rats. *Int J Devl Neurosci* 1999; **17**(7): 733–742.
90. Scheyer R. D. Involvement of glutamate in human epileptic activities. *Prog Brain Res* 1998; **116**: 359–369.
91. OReilly B. A., Waring R. Enzyme and sulfur oxidation deficiencies in autistic children with known food/chemical intolerances. *Journal of Orthomolecular Medicine* 1993; **4**: 198–200.
92. Alberti A., Pirrone P., Elia M., Waring R. H., Romano C. Sulphation deficit in "low-functioning" autistic children: a pilot study. *Biol Psychiatry* 1999; **46**(3): 420–424.
93. Markovich D., Knight D., Renal Na-Si cotransporter NaSi-1 is inhibited by heavy metals. *American Journal of Renal Physiology* 1998; **274**(2): 283–289.
94. Golse B., Debray-Ritzen P., Durosay P., Puget K., Michelson A. M. Alterations in two enzymes: superoxide dismutase and glutathion peroxidase in developmental infantile psychosis. *Rev Neurol* (Paris) 1978; **134**(11): 699–705.
95. Edelson S. B., Cantor D. S. Autism: xenobiotic influences. *Toxicol Ind Health* 1998; **14**(4): 553–563.
96. Fuchs J., Packer L., Zimmer G. Lipoic Acid in Health and Disease. Marcel Dekker, 1997.
97. Williams M. V., Winters T., Waddell K. S. *In vivo* effects of Mercury (II) on deoxyuridine triphosphate nucleotidohydrolase, DNA polymerase (α,β), uracil-DNA glycosylase activities in cultured human cells: relationship to DNA damage, DNA repair, and cytotoxicity. *Mol Pharmacol* 1987; **31**(2): 200–207.
98. Aukrust P. et al. Decreased levels of total and reduced glutathione in CD4+ lymphocytes in common variable immunodeficiency are associated with activation of the tumor necrosis factor system: possible immunopathogenic role of oxidative stress. *Blood* 1995; **86**(4): 1383–1391.
99. Jaffe J. S. et al. Functional abnormalities of CD8+ t cells define a unique subset of patients with common variable immunodeficiency. *Blood* 1993; **82**(1): 192–201.
100. Shenker B. J., Guo T. L., Shapiro I. M. Low-level methylmercury exposure causes human T-cells to undergo apoptosis: evidence of mitochondrial dysfunction. *Environ Res* 1998; Section A **77**(2): 149–159.
101. Page T., Yu A., Fontanesi J., Nyhan W. L. Developmental disorder associated with increased cellular nucleotidase activity. *Proc Natl Acad Sci USA* 1997; **94**: 11601–11606.
102. Page T., Coleman M. Purine metabolism abnormalities in a hyperuricosuric subclass of autism. *Biochim Biophys Acta* 2000; **1500**(3): 291–296.

103. Plioplys A. *Autism: Biomedical Perspectives*. Presentation for the Autism Society of America meeting, July 1989.
104. Connolly A. M. et al. Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders. *J Pediatr* 1999; **134**(5): 607–613.
105. Singh V., Warren R., Odell J., Warren W., Cole P. Antibodies to myelin basic protein in children with autistic behavior. *Brain Behav Immun* 1993; **7**(1): 97–103.
106. Comi A. M., Zimmerman A. et al. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J Child Neurol* 1999; **14**: 388–394.
107. Whiteley P., Rogers J., Shattock P. Clinical features associated with autism: observations of symptoms outside the diagnostic boundaries of autistic spectrum disorders. *Autism* 1998; **2**(4): 415–422.
108. Warren R. P., Margaretten N. C., Pace N. C., Foster A. Immune abnormalities in patients with autism. *J Autism Dev Disord* 1986; **16**(2): 189–197.
109. Zimmerman A., Frye V. H., Potter N. T. Immunological aspects of autism. *International Journal of Pediatrics* 1993; **8**: 199–204.
110. Weitzman A., Weisman R., Szekely G. A., Wijsenbeek H., Livni E. Abnormal immune response to brain tissue antigen in the syndrome of autism. *Am J Psychiatry* 1982; **139**(11): 1462–1465.
111. Nielsen J. B., Hultman P. Experimental studies on genetically determined susceptibility to mercury-induced autoimmune response. *Ren Fail* 1999; **21**(3&4): 343–348.
112. Hu H., Abedi-Valugerdi M., Moller G. Pretreatment of lymphocytes with mercury *in vitro* induces a response in T cells from genetically determined low-responders and a shift of the interleukin profile. *Immunology* 1997; **90**: 198–204.
113. Al-Balaghi S., Möller E., Möller G., Abedi-Valugerdi M. Mercury induces polyclonal B cell activation, autoantibody production and renal immune complex deposits in young (NZB × NZW) F1 hybrids. *Eur J Immunol* 1996; **26**(7): 1519–1526.
114. Warren R. P., Margaretten N. C., Foster A., Reduced natural killer cell activity in autism. *J Am Acad Child Adolesc Psychiatry* 1987; **26**(3): 333–335.
115. Gupta S., Aggarwal S., Heads C., Brief report: dysregulated immune system in children with autism: beneficial effects of intravenous immune globulin on autistic characteristics, *J Autism Dev Disord* 1996; **26**(4): 439–452.
116. Messahel S., Pheasant A. E., Pall H., Ahmed-Choudhury J., Sungum-Paliwal R. S., Vostanis P. Urinary levels of neopterin and biopterin in autism. *Neurosci Lett* 1998; **241**(1): 17–20.
117. Johansson U., Hansson-Georgiadis H., Hultman P. The genotype determines the B cell response in mercury-treated mice. *Int Arch Allergy Immunol* 1998; **116**(4): 295–305.
118. Bagenstose L. M., Salgame P., Monestier M. Murine mercury-induced autoimmunity: a model of chemically related autoimmunity in humans. *Immunol Res* 1999; **20**(1): 67–78.
119. Hu H., Moller G., Abedi-Valugerdi M. Mechanism of mercury-induced autoimmunity: both T helper 1- and T helper 2-type responses are involved. *Immunology* 1999; **96**(3): 348–357.
120. Ilback N. G. Effects of methyl mercury exposure on spleen and blood natural-killer (NK) cell-activity in the mouse. *Toxicology* 1991; **67**(1): 117–124.
121. Mattsson J. R., Miller E., Alligood J. P., Koering J. E., Levin S. G. Early effects of methylmercury on the visual evoked response of the dog. *Neurotoxicology* 1981; **2**(3): 499–514.
122. Redwood, L. *Chelation case histories*. Http://tlredwood.home.mindspring.com/case_studies.htm.
123. Kanner L. Autistic disturbances of affective contact. *The Nervous Child* 1942–1943; **2**(3): 217–250.
124. Gilberg C., Wing L. Autism: not an extremely rare disorder. *Acta Psychiatr Scand* 1999; **99**(6): 399–406.
125. Bristol M., Cohen D., Costello E. et al. State of the science in autism: report to the National Institutes of Health. *J Autism Dev Disord* 1996; **26**(2): 121–157.
126. *Prevalence of Autism in Brick Township, New Jersey, 1998: Community Report*. Centers for Disease Control and Prevention, April 2000; www.cdc.gov/nceh/cddh/dd/rpttoc.
127. Sager, P. R., Aschner, M., Rodier, P. M. Persistent differential alteration in developing cerebellar cortex of male and female mice after methylmercury exposure. *Dev Brain Res* 1984; **12**: 1–11.
128. Rossi A. D., Ahlbom E., Ogren S. O., Nicotera P., Ceccatelli S. Prenatal exposure to methylmercury alters locomotor activity of male but not female rats. *Exp Brain Res* 1997; **117**(3): 428–436.
129. Uproar over a little-known preservative, thimerosal, jostles U. S. hepatitis B vaccination policy. *Hepatitis Control Report* 1999 Summer; **4**(2).
130. Capps L., Kehres J., Sigman M. Conversational abilities among children with autism and children with developmental delays. *Autism* 1998; **2**(4): 325–44.
131. Tonge B. J., Brereton A. V., Gray K. M., Einfeld S. L. Behavioural and emotional disturbance in high-functioning autism and Aspergers syndrome. *Autism* 1999; **3**(2): 117–130.
132. Ross W. Donald, Gechman A., Sholiton M., Paul H. Alertness to neuropsychiatric manifestations. *Compr Psychiatry* 1977; **18**(6): 595–598.
133. Howlin P. Outcome in adult life for more able individuals with autism or Asperger syndrome. *Autism* 2000; **4**(1): 63–84.
134. Klin A., Sparrow S. S., de Bilt A. et al. A normed study of face recognition in autism and related disorders. *J Aut Dev Disorders* 1999; **29**(6): 499–508.
135. DeLong G. R. Autism: new data suggest a new hypothesis. *Neurology* 1999; **52**(5): 911–916.
136. Bernabei P., Camaioni L., Levi G. An evaluation of early development in children with autism and pervasive developmental disorders from home movies: preliminary findings. *Autism* 1998; **2**(3): 243–258.
137. Baron-Cohen S., Allen J., Gillberg C. Can autism be detected at 18 months: the needle, the haystack, and the CHAT. *Br J Psychiatry* 1992; **161**: 839–843.
138. Eisenmayer R. et al. Delayed language onset as a predictor of clinical symptoms in pervasive developmental disorders. *J Autism Dev Disord* 1998; **28**(6): 527–533.
139. Prizant B. M. Brief report: communication, language, social, and emotional development. *J Autism Dev Disord* 1996; **26**(2): 173–178.
140. Grandin T. The learning style of people with autism: an autobiography. *Teaching Children with Autism*. Kathleen Ann Quill, ed., 1995: 33–52.
141. Hua M. S., Huang C. C., Yang Y. J. Chronic elemental mercury intoxication: neuropsychological follow up case study. *Brain Inj* 1996; **10**(5): 377–384.
142. Yeates K. O., Mortensen M. E. Acute and chronic neuropsychological consequences of mercury vapor poisoning in two early adolescents. *J Clin Exp Neuropsychol* 1994; **16**(2): 209–222.
143. Aronow R., Fleischmann L. Mercury poisoning in children. *Clin Pediatr* 1976; **15**(10): 936–945.
144. Watzl B., Abrahamse S. L., Treptow-van Lishaut S. et al. Enhancement of ovalbumin-induced antibody production and mucosal mast cell response by mercury. *Food Chem Toxicol* 1999; **37**(6): 627–637.

145. Church C., Coplan J. The high functioning autistic experience: birth to preteen years. *J Pediatr Health Care* 1995; **9**: 22–29.
146. O'Neill J. L. Through the Eyes of Aliens. Jessica Kingsley Publishers, 1999.
147. Deufemia P., Celli M., Finocchiaro R. et al. Abnormal intestinal permeability in children with autism. *Acta Paediatr* 1996; **85**: 1076–1079.
148. Horvath K., Papadimitriou J. C., Rabsztyn A., Drachenberg C., Tildon J. T. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr* 1999; **135**(5): 559–563.
149. Wakefield A. J., Murch S. H., Anthony A., et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637–641.
150. Shattock P., Savery D. *Autism as a Metabolic Disorder.* Sunderland, UK: Autism Research Unit, University of Sunderland, 1997.
151. Edelson M. G., Schubert D. T., Edelson S. M. Factors predicting intelligence cores on the TONI in individuals with autism. *Focus on Autism and Other Developmental Disabilities* 1998; **13**(1): 17–26.
152. Long term follow-up: early intervention effects lasting. *ARI Newsletter*, review 1993; **7**(1): 1&6.
153. Rumsey J. Conceptual problem-solving in highly verbal, nonretarded autistic men. *J Autism Dev Disord* 1985; **15**(1): 23–36.
154. Gedye A. Anatomy of self-injurious, stereotypic, and aggressive movements: evidence for involuntary explanation. *J Clin Psychol* 1992; **48**(6): 766–778.
155. Kim J. A., Szatmari P., Bryson S. E., Streiner D. L., Wilson F. J. The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. *Autism* 2000; **4**(2): 117–133.
156. Richdale A. L. Sleep problems in autism: prevalence, cause, and intervention. *Dev Med Child Neurol* 1999; **41**(1): 60–66.
157. Stores G., Wiggs L. Abnormal sleeping patterns associated with autism: a brief review of research findings, assessment methods and treatment strategies. *Autism* 1998; **2**(2): 157–170.
158. Sarafian T., Verity M. A. Altered patterns of protein phosphorylation and synthesis caused by methyl mercury in cerebellar granule cell culture. *J Neurochem* 1990; **55**(3): 922–929.
159. Rosenspire A. J., Bodepudi S., Mathews M., McCabe M. J. Jr. Low levels of ionic mercury modulate protein tyrosine phosphorylation in lymphocytes. *Int J Immunopharmacol* 1998; **20**(12): 697–707.
160. Rajanna B., Hobson M. Influence of mercury on uptake of [3H]dopamine and [3H]norepinephrine by rat brain synaptosomes. *Toxicol Lett* 1985; **27**(1–3): 7–14.
161. Aschner M., Mullaney K. J., Wagoner D., Lash L. H., Kimelberg H. K. Intracellular glutathione (GSH) levels modulate mercuric chloride (MC)- and methylmercuric chloride (MeHgCl)-induced amino acid release from neonatal rat primary astrocytes cultures. *Brain Res* 1994; (664); 133–140.
162. Ashour H., Abdel-Rahman M., Khodair A. The mechanism of methyl mercury toxicity in isolated rat hepatocytes. *Toxicol Lett* 1993; **69**(1): 87–96.
163. Atchison W. D., Hare M. F. Mechanisms of methylmercury-induced neurotoxicity, *FASEB J* 1994; **8**(9): 622–629.
164. Faro L. R. F., Nascimento J. L. M., Alfonso M., Duran R. Acute administration of methylmercury changes *in vivo* dopamine release from rat striatum. *Bull Environ Contam Toxicol* 1998; **60**: 632–638.
165. El-Fawal H. A., Waterman S. J., De Feo A., Shamy M. Y. Neuroimmunotoxicology: humoral assessment of neurotoxicity and autoimmune mechanisms. *Environ Health Perspect* 1999; **107**(Suppl 5): 767–775.
166. Tan X. X., Tang C., Castoldi A. F., Manzo L., Costa L. G. Effects of inorganic and organic mercury on intracellular calcium levels in rat T lymphocytes. *J Toxicol Environ Health* 1993; **38**(2): 159–170.
167. Elferink J. G. Thimerosal: a versatile sulfhydryl reagent, calcium mobilizer, and cell function-modulating agent. *Gen Pharmacol* 1999; **33**(1): 1–6.
168. Atchison W. D., Joshi U., Thornburg J. E. Irreversible suppression of calcium entry into nerve terminals by methylmercury. *J Pharmacol Exp Ther* 1986; **238**(2): 618–624.
169. Chu C. C., Huang C. C., Ryu S. J., Wu T. N. Chronic inorganic mercury induced peripheral neuropathy. *Acta Neurol Scand* 1998; **98**(6): 461–465.
170. Coccini T., Randine G., Candura S. M., Nappi R. E., Prockop L. D., Manzo L. Low-level exposure to methylmercury modifies muscarinic cholinergic receptor binding characteristics in rat brain and lymphocytes: physiologic implications and new opportunities in biologic monitoring. *Environ Health Perspect* 2000; **108**(1): 29–33.
171. Volterra A., Trotti D., Cassutti P., et al. High sensitivity of glutamate uptake to extracellular free arachidonic acid levels in rat cortical synaptosomes and astrocytes. *J Neurochem* 1992; **59**(2): 600–606.
172. Lombard J. Autism: a mitochondrial disorder? *Med Hypotheses* 1998; **50**(6): 497–500.
173. Gupta S., Aggarwal S., Rashanravan B., Lee T. Th1- and Th2-like cytokines in CD4+ and CD8+ T cells in autism. *J Neuro-immunol* 1998; **85**(1): 106–109.
174. Singh V. K. Plasma increase of Interleuken-12 and Interferon-gamma. Pathological significance in autism. *J Neuro-immunology* 1996; **66**: 143–145.
175. Fombonne E., Rogé B., Claverie J., Courty S., Frémolle J. Microcephaly and macrocephaly in autism. *J Autism Dev Disord* 1999; **29**(2): 113–119.
176. Carlsson M. L. Hypothesis: is infantile autism a hypoglutamatergic disorder? Relevance of glutamate – serotonin interactions for pharmacotherapy. *J Neural Transm* 1998; **105**(4–5): 525–535.
177. Gillberg C., Svennerholm L. CSF monoamines in autistic syndromes and other pervasive dev. disorders of early childhood. *Br J Psychiatry* 1987; (151): 89–94.
178. Ernst M., Zametkin A. J., Matochik J. A., Pascualvaca D., Cohen R. M. Low medial prefrontal dopaminergic activity in autistic children. *Lancet* 1997; **350**(9078): 638.
179. Leboyer M., Philippe A., Bouvard M. et al. Whole blood serotonin and plasma beta-endorphin in autistic probands and their first-degree relatives. *Biol Psychiatry* 1999; **45**(2): 158–163.
180. Ornitz E. M. Neurophysiologic studies of infantile autism. *Handbook of Autism and Pervasive Developmental Disorders.* John Wiley & Sons, Inc., 1987: 148–165.
181. Schuler A. L. Thinking in autism: differences in learning and development. In: Quill K. A., ed. Teaching Children with Autism. Florence, KY: Delmer Publishers, 1995: 11–32.