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Sensible Action For Ending Mercury-Induced Neurological Disorders

Autism: a Unique Form of Mercury Poisoning.

Bernard S, Enayati A, Redwood L, Roger H, Binstock T.
Coalition of SafeMinds

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Autism: A Unique Type of Mercury Poisoning

The following pages contain an extensive literature review which compares the symptoms of mercury toxicity in humans with those of autism spectrum disorders. This landmark paper was conceived and written in 1999 by founding members of SafeMinds who felt the overlap between the physical symptoms resulting from mercury exposure and autism were too extensive to be a chance occurrence. The authors believed that mercury exposure best explains the rapid rise in prevalence behind the autism epidemic.

The Coalition for SafeMinds (Sensible Action For Ending Mercury Induced Neurological Disorders) is a private not for profit organization founded in 2000 to raise awareness and investigate the risks of mercury exposure to infants, children and pregnant women. Mercury is a well known neurotoxin and exposure can result in significant disability, particularly in the fetus, infants and children since their brains are still growing and developing.

Since its inception, SafeMinds has brought this issue to national attention by publishing peer-reviewed articles, networking with leading scientists in the fields of toxicology and autism research, testifying before Congress and the Institute of Medicine, appearing in several national news stories including Good Morning America and working with David Kirby on the publication of the award winning book, *Evidence of Harm.*

Today, ten years after the short version of "Autism: A Novel Form of Mercury Poisoning" appeared in the journal *Medical Hypothesis*, support for the autism-mercury has grown. This theory holds that in a vulnerable fetus or infant exposure to mercury can result in injury to the metabolic, immune, sensory, gastrointestinal and neurological systems creating symptoms and impairments consistently documented in those with autism. Unfortunately, our Federal health and research agencies have shown little leadership in confronting this issue. Due to political reasons, they have restricted or biased investigations into mercury-autism research.

To fill the gap, SafeMinds has sponsored over $1,000,000 dollars in scientific research on mercury and adverse neurological outcomes, including autism. This level of commitment establishes SafeMinds as the largest charitable organization funding mercury and autism related research. But there is still more good science that needs to be done. We owe it to those children who have already been tragically injured not to give up on our research efforts, because understanding mercury's effects can lead to treatments as well as prevention of future cases. But we can't do this without your help. We ask that you please support our efforts to end the devastation caused by needless exposure to mercury and offer help those that have been harmed. You can make a donation online at
http://www.safeminds.org/support-safeminds/protect-our-children-donate.html
Or by mailing a check to 16033 Bolsa Chica, #104-142, Huntington Beach, CA 92649.

Stop the Mercury, Start the Cure

AUTISM:
A UNIQUE TYPE OF
MERCURY POISONING

Sallie Bernard*
Albert Enayati, B.S., Ch.E., M.S.M.E.
Teresa Binstock
Heidi Roger
Lyn Redwood, R.N., M.S.N., C.R.N.P.**
Woody McGinnis, M.D.

Contact: sbernard@safeminds.org
****Contact: (404)932-1786***

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ABSTRACT

Autism is a syndrome characterized by impairments in social relatedness, language and communication, a need for routine and sameness, abnormal movements, and sensory dysfunction. Mercury (Hg) is a toxic metal that can exist as a pure element or in a variety of inorganic and organic forms and can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism. Thimerosal, a preservative frequently added to childhood vaccines, has become a major source of Hg in human infants and toddlers. According to the FDA and the American Academy of Pediatricians, fully vaccinated children now receive, within their first two years, Hg levels that exceed safety limits established by the FDA and other supervisory agencies. A thorough review of medical literature and U.S. government data indicates (i) that many and perhaps most cases of idiopathic autism, in which a period of developmental normalcy is followed by an emergence of symptoms, are induced by early exposure to Hg; (ii) that this type of autism represents a unique form of Hg poisoning (HgP); (iii) that excessive Hg exposure from thimerosal in vaccine injections is an etiological mechanism for causing the traits of autism; (iv) that certain genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children; and (v) that vaccinal Hg in thimerosal is causing a heretofore unrecognized mercurial syndrome.

SYNOPSIS

A review of medical literature indicates that the characteristics of autism and of mercury poisoning (HgP) are strikingly similar. Traits defining or associated with both disorders are summarized in *Table A* immediately following and are discussed and cited in the body of this document. The parallels between the two diseases are so thorough as to suggest, based on total Hg injected into U.S. children, that many cases of autism are a form of mercury poisoning.

For these children, the exposure route is childhood vaccines, most of which contain thimerosal, a preservative which is 49.6% ethylmercury by weight. Over the last decade, the amount of mercury a typical child under two years received from vaccinations equated to 237.5 micrograms injected in several bolus (or large) doses.

The total amount injected into infants and toddlers (i) is known to exceed Federal safety standards, (ii) is officially considered to be a “low” level; whereby (iii) only a small percentage of exposed individuals exhibit symptoms of toxicity. In fact, children who develop Hg-related autism are likely to have had a predisposition derived from genetic and non-genetic factors.

Importantly, the timings of vaccinal Hg-exposure and its latency period coincide with the emergence of autistic-symptoms in specific children. Moreover, excessive mercury has been detected in urine, hair, and blood samples from autistic children; and parental reports, though limited at this date, indicate significant improvement in symptoms subsequent to heavy-metal chelation therapy.

The HgP phenotype is diverse and depends upon a number of factors – including type of Hg, route of entry into the body, rate and level of dose, individual genotype, and the age and immune status of the patient. Historically, variation among these factors has caused slightly different manifestations of mercurialism; Mad Hatter's disease, Minamata disease, acrodynia, and industrial exposures provide examples.

The pathology arising from the mercury-related variables involved in autism – intermittent bolus doses of ethylmercury injected into susceptible infants and toddlers – is heretofore undescribed in medical literature. Therefore, in accord with existing HgP data and HgP's ability to induce virtually all the traits defining or associated with autism spectrum disorders, we hypothesize that many and perhaps most cases of autism represent a unique form of mercury poisoning.

This conclusion and its supporting data have important implications for the affected population of autistic individuals and their families, for other unexplained disorders with symptoms similar to those of heavy metal intoxication, for vaccine content, and for childhood vaccination programs. Due to its high potential for neurotoxicity, thimerosal should be removed immediately from all vaccine products designated for infants and toddlers.

Table A: Summary Comparison of Characteristics of Autism & Mercury Poisoning

	Mercury Poisoning	Autism
Impariments in Sociability	Social deficits, shyness, social withdrawal	Social deficits, social withdrawal, shyness
	Depression, mood swings; mask face	Depressive traits, mood swings; flat affect
	Anxiety	Anxiety
	Lacks eye contact, hesitant to engage others	Lack of eye contact, avoids conversation
	Irrational fears	Irrational fears
	Irritability, aggression, temper tantrums	Irritability, aggression, temper tantrums
	Impaired face recognition	Impaired face recognition
	Schizoid tendencies, OCD traits	Schizophrenic & OCD traits
	Repetitive, penseverative, stereotypic behaviors	Repetitive, penseverative, stereotypic behaviors
Speech & Language Deficits	Loss of speech, failure to develop speech	Delayed language, failure to develop speech
	Dysarthria; articulation problems	Dysarthria; articulation problems
	Speech comprehension deficits	Speech comprehension deficits
	Verbalizing & word retrieval problems	Echolalia; word use & pragmatic errors
	Hearing loss; deafness in very high doses	Mild to profound hearing loss
	Poor performance on language IQ tests	Poor performance on verbal IQ tests
Sensory Abnormalities	Abnormal sensation in mouth & extremities	Abnormal sensation in mouth & extremities
	Sound sensitivity	Sound sensitivity
	Abnormal touch sensations; touch aversion	Abnormal touch sensations; touch aversion
	Vestibular abnormalities	Vestibular abnormalities
	Impaired visual fixation	Problems with joint attention
Motor Disorders	Involuntary jerking movements – arm flapping, ankle jerks, myoclonal jerks, choreiform movements, circling, rocking	Stereotyped movements - arm flapping, jumping, circling, spinning, rocking; myoclonal jerks; choreiform movements
	Deficits in eye-hand coordination; limb apraxia; intention tremors	Poor eye-hand coordination; limb apraxia; problems with intentional movements
	Gait impairment; ataxia – from incoordination & clumsiness to inability to walk, stand, or sit; loss of motor control	Abnormal gait and posture, clumsiness and incoordination; difficulties sitting, lying, crawling, and walking
	Difficulty in chewing or swallowing	Difficulty chewing or swallowing
	Unusual postures; toe walking	Unusual postures; toe walking
Cognitive Impairments	Borderline intelligence, mental retardation - some cases reversible	Borderline intelligence, mental retardation - sometimes "recovered"
	Poor concentration, attention, response inhibition	Poor concentration, attention, shifting attention
	Uneven performance on IQ subtests	Uneven performance on IQ subtests
	Verbal IQ higher than performance IQ	Verbal IQ higher than performance IQ
	Poor short term, verbal, & auditory memory	Poor short term, auditory & verbal memory
	Poor visual and perceptual motor skills, impairment in simple reaction time	Poor visual and perceptual motor skills, lower performance on timed tests
	Difficulty carrying out complex commands	Difficulty carrying out multiple commands
	Word-comprehension difficulties	Word-comprehension difficulties
	Deficits in understanding abstract ideas & symbolism; degeneration of higher mental powers	Deficits in abstract thinking & symbolism, understanding other's mental states, sequencing, planning & organizing

Unusual Behaviors	Stereotyped sniffing (rats)	Stereotyped, repetitive behaviors
	ADHD traits	ADHD traits
	Agitation, unprovoked crying, grimacing, staring spells	Agitation, unprovoked crying, grimacing, staring spells
	Sleep difficulties	Sleep difficulties
	Eating disorders, feeding problems	Eating disorders, feeding problems
	Self injurious behavior, e.g. head banging	Self injurious behavior, e.g. head banging
Visual Impairments	Poor eye contact, impaired visual fixation	Poor eye contact, problems in joint attention
	"Visual impairments," blindness, near-sightedness, decreased visual acuity	"Visual impairments"; inaccurate/slow saccades; decreased rod functioning
	Light sensitivity, photophobia	Over-sensitivity to light
	Blurred or hazy vision	Blurred vision
	Constricted visual fields	Not described
Physical Disturbances	Increase in cerebral palsy; hyper- or hypo-tonia; abnormal reflexes; decreased muscle strength, especially upper body; incontinence; problems chewing, swallowing, salivating	Increase in cerebral palsy; hyper- or hypotonia; decreased muscle strength, especially upper body; incontinence; problems chewing and swallowing
	Rashes, dermatitis/dry skin, itching; burning	Rashes, dermatitis, eczema, itching
	Autonomic disturbance: excessive sweating, poor circulation, elevated heart rate	Autonomic disturbance: unusual sweating, poor circulation, elevated heart rate
Gastro-intestinal Disturbances	Gastroenteritis, diarrhea; abdominal pain, constipation, "colitis"	Diarrhea, constipation, gaseousness, abdominal discomfort, colitis
	Anorexia, weight loss, nausea, poor appetite	Anorexia; feeding problems/vomiting
	Lesions of ileum & colon; increased gut permeability	Leaky gut syndrome
	Inhibits dipeptidyl peptidase IV, which cleaves casomorphin	Inadequate endopeptidase enzymes needed for breakdown of casein & gluten
Abnormal Biochemistry	Binds -SH groups; blocks sulfate transporter in intestines, kidneys	Low sulfate levels
	Has special affinity for purines & pyrimidines	Purine & pyrimidine metabolism errors lead to autistic features
	Reduces availability of glutathione, needed in neurons, cells & liver to detoxify heavy metals	Low levels of glutathione; decreased ability of liver to detoxify heavy metals
	Causes significant reduction in glutathione peroxidase and glutathione reductase	Abnormal glutathione peroxidase activities in erythrocytes
	Disrupts mitochondrial activities, especially in brain	Mitochondrial dysfunction, especially in brain
Immune Dysfunction	Sensitivity due to allergic or autoimmune reactions; sensitive individuals more likely to have allergies, asthma, autoimmune-like symptoms, especially rheumatoid-like ones	More likely to have allergies and asthma; familial presence of autoimmune diseases, especially rheumatoid arthritis; IgA deficiencies
	Can produce an immune response in CNS	On-going immune response in CNS
	Causes brain/MBP autoantibodies	Brain/MBP autoantibodies present
	Causes overproduction of Th2 subset; kills/inhibits lymphocytes, T-cells, and monocytes; decreases NK T-cell activity; induces or suppresses IFNg & IL-2	Skewed immune-cell subset in the Th2 direction; decreased responses to T-cell mitogens; reduced NK T-cell function; increased IFNg & IL-12

CNS Structural Pathology	Selectively targets brain areas unable to detoxify or reduce Hg-induced oxidative stress	Specific areas of brain pathology; many functions spared
	Damage to Purkinje and granular cells, brainstem, corpus callosum, basal glangia, cerebral cortex	Damage to Purkinje and granular cells, brainstem, corpus callosum, basal glangia, cerebral cortex
	Accummulates in amygdala and hippocampus	Pathology in amygdala and hippocampus
	Causes abnormal neuronal cytoarchitecture; disrupts neuronal migration & cell division; reduces NCAMs	Neuronal disorganization; increased neuronal cell replication, increased glial cells; depressed expression of NCAMs
	Progressive microcephaly	Progressive microcephaly and macrocephaly
Abnormalities in Neuro-chemistry	Prevents presynaptic serotonin release & inhibits serotonin transport; causes calcium disruptions	Decreased serotonin synthesis in children; abnormal calcium metabolism
	Alters dopamine systems; peroxidine deficiency in rats resembles mercurialism in humans	Possibly high or low dopamine levels; positive response to peroxidine (lowers dopamine levels)
	Elevates epinephrine & norepinephrine levels by blocking enzyme that degrades epinephrine	Elevated norepinephrine and epinephrine
	Elevates glutamate	Elevated glutamate and aspartate
	Leads to cortical acetylcholine deficiency; increases muscarinic receptor density in hippocampus & cerebellum	Cortical acetylcholine deficiency; reduced muscarinic receptor binding in hippocampus
	Causes demyelinating neuropathy	Demyelination in brain
Neuro-physiology	Causes abnormal EEGs, epileptiform activity	Abnormal EEGs, epileptiform activity
	Causes seizures, convulsions	Seizures; epilepsy
	Causes variable patterns, eg, subtle, low amplitude seizure activity	Variable patterns, eg, subtle, low amplitude seizure activities
Population Charact-eristics	Effects more males than females	Male:female ratio estimated at 4:1
	At low doses, only affects those geneticially susceptible	High heritability - concordance for MZ twins is 90%
	First added to childhood vaccines in 1930s	First "discovered" among children born in 1930s
	Exposure levels steadily increased since 1930s with rate of vaccination, number of vaccines	Prevalence of autism has steadily increased from 1 in 2000 (pre1970) to 1 in 500 (early 1990s), higher in 2000.
	Exposure occurs at 0 - 15 months; clinical silent stage means symptom emergence delayed; symptoms emerge gradually, starting with movement & sensation	Symptoms emerge from 4 months to 2 years old; symptoms emerge gradually, starting with movement & sensation

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INTRODUCTION

Autism

Autism, or Autistic Spectrum Disorder (ASD), is considered a neurodevelopmental syndrome, emerging early in life and exhibiting a constellation of seemingly unrelated features and a wide variation in symptom expression and level of severity by individual (Filipek et al, 1999; Bailey et al, 1996). The diagnostic criteria for autism are qualitative impairments in social relatedness, deficits in verbal and nonverbal communication, and the presence of repetitive and restricted behaviors or interests (APA, 1994). As will be cited below, other traits associated with autism are movement disorder, sensory dysfunction, and cognitive impairments as well as gastrointestinal difficulties and immune abnormalities (Gillberg & Coleman, 1992; Warren et al, 1990; Horvath et al, 1999). Onset must occur before age 36 months (APA, 1994); although in some instances deficits are apparent at birth, in the great majority of cases there are at least several months of normal development followed by clear regression or failure to progress normally (Bailey et al, 1996). Formerly regarded as a rare disease, autism is now said to affect one in 500 children (Bristol et al, 1996), with some estimates suggesting one in 100 for a broader phenotype often labeled as the "autism-spectrum" of disorders and which includes both higher and lower functioning individuals (Arvidsson et al, 1997; Wing, 1996).

Autism and autistic symptoms can arise from a number of known disorders, most notably tuberous sclerosis, Rhett syndrome, Landau-Kleffner syndrome, Fragile X, Phenylketonuria, purine autism, and other purine metabolic diseases such as PRPP synthetase defects and 5'-nucleotidase superactivity. The etiology and pathogenesis of the vast majority of autism cases – 70% - 90% (Gillberg and Coleman, 1992; Bailey et al, 1996) – remain unexplained, however, despite ASD being "one of the most extensively studied disorders in child psychiatry today" (Malhotra and Gupta, 1999). Nevertheless, there is general agreement that most cases of autism arise "from the interaction of an early environmental insult and a genetic predisposition" (Trottier et al, 1999; Bristol et al, 1996).

Mercury

A heavy metal, mercury (Hg) is widely considered one of the most toxic substances on earth (Clarkson, 1997). Instances of Hg poisoning or "mercurialism" have been described since Roman times. The Mad Hatter in *Alice in Wonderland* was a victim of occupational exposure to mercury vapor, referred to as "Mad Hatter's Disease." Further human data has been derived from instances of widespread poisonings during the 20th Century. These misfortunes include outbreaks in Minamata and Niigata, Japan, caused by consumption of contaminated fish and resulting in "Minamata Disease;" outbreaks in Iraq, Guatemala and Russia due to ingestion of contaminated seed grains; and, in the first half of the century, poisoning of infants and toddlers by mercury in teething powders, leading to acrodynia or Pink Disease. Besides these epidemics, numerous instances of individual or small group cases of Hg intoxication and subsequent phenotype are described in the literature.

The constellation of mercury-induced symptoms varies enormously from individual to individual. The diversity of disease manifestations derives from a number of interacting variables which are summarized in Table I. The variables which affect phenotype include an individual's age, the total dosage, dose rate, duration of exposure, type of mercury, routes of exposure such as inhaled, subcutaneous, oral, or intramuscular, and, most importantly, individual sensitivity arising from immune and genetic factors (Dales, 1972; Koos and Longo, 1976; Matheson et al, 1980; Eto et al, 1999; Feldman, 1982; Warkany and Hubbard, 1953).

Table I: Summary of Mercury Exposure Variables Leading to Diverse & Non-Specific Symptomatology

Variable	Level of Variable
Exposure Amount	Ranges from high doses, leading to death or near death with severe impairments, to low "safe" doses, leading to subtle neurological and other physical impairments
Duration of exposure	One time vs. multiple times over the course of weeks, months, or years
Dose rate	Acute or bolus dose, daily or chronic dose
Individual sensitivity	A function of (a) the age at which exposure occurs, that is, prenatal, infant, child, adolescent, or adult, (b) genetically determined reactivity to mercury, and (c) gender
Common types of mercury	The organic alkyl forms – methylmercury and ethylmercury; and inorganic forms - metallic mercury, elemental (liquid) mercury, and ionic mercury/mercuric salt
Primary routes of exposure	Inhalation of mercury vapors, orally through the intestinal tract, subcutaneous and intramuscular injections, topically through ear drops, teething powders, skin creams and ointments, and intravenously during medical treatments

While these variations in exposure, individual status, and genotype give rise to a diverse clinical phenotype, there are nevertheless obvious commonalities across all mercury-caused disorders. Thus, for example, victims will almost always develop a movement disorder, but in some individuals this may manifest as mere clumsiness, while others will develop severe involuntary jerking movements. Likewise, psychological disturbances are usually present, but in some individuals these might manifest as anxiety while in others it might present as aggression or irritability.

Diagnosing Mercury Poisoning in Autism

Mercury poisoning can be difficult to diagnose and is commonly interpreted by clinicians as a psychiatric disorder, especially if exposure is not suspected (Diner and Brenner, 1998; Frackelton and Christensen, 1998). The difficulty in diagnosis derives primarily from two notable characteristics of this heavy metal. First, there can be a long latent period between time of exposure and onset of overt symptoms, so that the connection between the two events is often overlooked. The latency period is discussed in more detail below. Second, the diverse manifestations of the disease make it difficult for the clinician to find a precise match of his particular patient's symptoms with those described in other case reports (Adams et al, 1983, Kark et al, 1971; Florentine and Sanfilippo,

1991; Matheson et al, 1980; Frackelton and Christensen, 1998; Warkany & Hubbard, 1953).

Due to the difficulty of diagnosing mercurialism based on presentation of non-specific symptoms alone, clinicians have come to rely on the following criteria (Warkany & Hubbard, 1953; Vroom and Greer, 1972).

1. Observation of impairments in many but not all of the following domains: (a) movement/motor disorder, (b) sensory abnormalities, (c) psychological and behavioral disturbances, (d) neurological and cognitive deficits, (e) impairments in language, hearing, and vision, and (f) miscellaneous physical presentations such as rashes or unusual reflexes (Adams et al, 1983; Snyder, 1972; Vroom & Greer, 1972).

2. Known exposure to Hg (a) at a level that has been documented as causing impairment, and (b) at approximately the same time as the symptoms emerge, with allowances given for the latency period (Ross et al, 1977; Amin-Zaki et al, 1978). The dose which is considered safe has been set by various government agencies; a recently released study by the National Academy of Sciences (NAS) has validated the Environmental Protection Agency (EPA) guidelines as most consistent with existing epidemiological data (NAS, 2000).

3. Detectable levels of mercury in urine, blood, or hair (Florentine and Sanfilippo, 1991; Frackelton and Christensen, 1998; EPA, 1997, p.ES-2). Importantly, because mercury can clear from biologic samples before the patient feels symptoms or is tested, the lack of detectable Hg concentrations is insuffucuent cause for ruling out mercury poisoning; and conversely, detectable levels have been observed in asymptomatic individuals (Adams et al, 1983; Warkany & Hubbard, 1953; Cloarec, 1995).

4. Improvement in symptoms after chelation. While many patients' symptoms resolve with chelation, some clearly poisoned individuals do not improve. Other exposed subjects have also been known to improve without intervention (Vroom & Greer, 1972; Warkany & Hubbard, 1953).

Thus, none of these criteria is sufficient on its own for a certain diagnosis. Rather, observed effects within two or three domains are generally required. This paper, which reviews and compares the extensive literature available on both ASD and mercury, provides citations documenting that, based on these four diagnostic criteria, many if not most cases of autism meet the requirements for mercury poisoning. In fact, this review and its citations (i) delineate a single mechanism for inducing all of the primary domains of impairment and biological abnormalities in autism, including its genetic component, prevalence levels, and sex ratios; and (ii) identify that mechanism as arising from the "environmental insult" of early childhood exposure to mercury. Furthermore, the route of exposure is thimerosal, which is 50% ethylmercury by weight and which is a preservative used in many childhood vaccines as well as other biologics.

We are not suggesting that the previous reports of mercurialism described in the literature are in fact cases of autism; rather, we claim that autism represents its own unique form of Hg poisoning, just like acrodynia, Minamata disease, and Mad Hatter's disease represent distinct yet closely related presentations of mercurialism. A unique expression would be expected in cases of autism, given that the effects of repeated vaccinal administration of ethylmercury to infants and toddlers have never been described before in mercury-related literature. We maintain that the diverse phenotype that is autism matches the diverse phenotype that is mercurialism to a far greater degree that could reasonably be expected to occur by chance. Given the known exposure to mercury via vaccination of autistic children and the presence of mercury found in biologic samples from a number of autistic subjects, also described here, we are confident that our claim is substantiated. Our paper discusses some important medical and societal ramifications of this conclusion.

I. SYMPTOM COMPARISON

The overt symptoms of ASD and mercury poisoning, described in the literature and presented here, are strikingly similar. Summary tables have been provided after each section to aid in symptom comparisons.

a. Affect/Psychological Presentation

Since its initial description in 1943 by Leo Kanner, a psychiatrist, autism has been defined primarily as a psychiatric condition. One of the three requirements for diagnosis is a severe deficit in social interactions (APA, 1994). Self and parental reports describe children and adults who prefer to be alone and who will withdraw to their rooms if given the chance (MAAP, 1996-1999). Even high functioning autistics tend to be aloof, have poor social skills, are unable to make friends, and find conversation difficult (Tonge et al, 1999; Capps et al, 1998). Face recognition and what psychologists call "theory of mind" are impaired (Klin et al, 1999, Baron-Cohen et al, 1993). Poor eye contact or gaze avoidance is present in most cases, especially in infancy and childhood (Bernabei et al, 1998).

The second psychobehavioral diagnostic characteristic of autism is the presence of repetitive, stereotyped activities and the need for sameness (APA, 1994). Traits in this domain strongly resemble obsessive-compulsive tendencies in both thought and behavior (Lewis, 1996; Gillberg & Coleman, 1992, p.27), especially as the individual becomes more high functioning (Roux et al, 1998): "it [is] very difficult…to distinguish between obsessive ideation and the bizarre preoccupations so commonly seen in autistic individuals" (Howlin, 2000). Serotonin uptake inhibitors known to be effective for OCD also reduce repetitive behaviors in some autistic patients (Lewis, 1996). Most autistic subjects - 84% in one study - show high levels of anxiety and meet diagnostic criteria for anxiety disorder (Muris et al, 1998).

ASD has been linked to depression, based on symptoms, familial history of depression and the positive response to SSRIs among many autistics (Clarke et al, 1999; DeLong, 1999; Piven and Palmer, 1999). One subset of autistics has been described as “passive”, with flat affect, “absence of facial expression,” lack of initiative, and diminished outward emotional reactions. Some autistics have a strong family history of manic depression and mood swings, and, among those who are verbal, psychotic talk is frequently observed (Plioplys, 1989). Autism is also said to strongly resemble childhood schizophrenia. In the past it was often misdiagnosed as such (Gillberg & Coleman, 1992, p.100), and there are a number of instances of dual ASD-schizophrenia diagnoses in the literature (Clarke et al, 1999). Furthermore, irrational fears, aggressive behaviors, and severe temper tantrums are common (Muris et al, 1998; McDougle et al, 1994), as are chronic hyperarousal and irritability (Jaselskis et al, 1992). “Inexplicable changes of mood can occur, with giggling and laughing or crying for no apparent reason” (Wing & Attwood, 1987).

Mercury poisoning, when undetected, is often initially diagnosed as a psychiatric disorder in both children and adults (Fagala and Wigg, 1992; Ross et al,1977). Common psychiatric symptoms are (a) depression, including “lack of interest” and “mental

confusion;" (b) "extreme shyness," indifference to others, active avoidance of others or "a desire to be alone"; (c) irritability in adults and tantrums in children; and (d) anxiety and fearfulness. Neurosis, including schizoid and obsessive-compulsive traits, has been reported in a number of cases (Fagala and Wigg, 1992; Kark et al, 1971; O'Carroll et al, 1995; Florentine and Sanfilippo, 1991; Amin-Zaki, 1974 and 1979; Matheson et al, 1980; Joselow et al, 1972; Smith, 1972; Lowell, 1996; Tuthill, 1899; Clarkson, 1997; Camerino et al, 1981; Grandjean et al, 1997; Piikivi et al, 1984; Rice, 1996; Vroom & Greer, 1972; Adams et al, 1973; Hua et al, 1996).

Juvenile monkeys prenatally exposed to mercury exhibit decreased social play and increased passive behavior (Gunderson et al, 1986, 1988), as well as impaired face recognition (Rice, 1996). Humans exposed to mercury vapor also perform poorly on face recognition tests and may present with a "mask face" (Vroom & Greer, 1972); emotional instability can occur in children and adults exposed to Hg. For instance, Iraqi children poisoned by methylmercury had a tendency "to cry, laugh, or smile without obvious provocation" (Amin-Zaki et al, 1974 & 1979), like the autistic group described by Wing and Attwood (1987).

Table II: Summary of Psychiatric Disturbances Found in Autism & Mercury Poisoning

Mercury Poisoning	Autism
Extreme shyness, social withdrawal, feeling overly sensitive, introversion	Social deficits, social withdrawal, self reports of extreme shyness, aloofness
Mood swings; flat affect; mask face; laughing or crying without provocation; episodes of hysteria	Mood swings; flat affect in some; no facial expression; laughing or crying without reason
Anxiety; nervousness; tremulousness; somatization of anxious feelings	Anxiety, nervousness; anxiety disorder
Schizoid tendencies, neurosis, obsessive-compulsive traits, repetitive dreams	Schizophrenic traits; OCD traits; repetitive behaviors and thoughts
Lack of eye contact; being less talkative; hesitancy to engage others	Lack of eye contact, gaze avoidance; avoids conversation
Depression, lack of interest in life, lassitude, fatigue, apathy; feelings of hopelessness; melancholy	Association with depression; lack of initiative, diminished outward emotions
On the one hand, less overtly active, unwilling to go outside or be with others; on the other hand, increased restlessness	Tendency to withdraw, especially to own rooms, prefer to be alone; hyperactivity
Irrational fears	Irrational fears
Irritability, anger, and aggression; in children this may manifest as frequent and severe temper tantrums	Irritability and aggression; severe temper tantrums in children
Psychotic episodes; hallucinations, hearing voices; paranoid thoughts	Psychotic talk, paranoid thoughts
Impaired face recognition	Impaired face recognition

Since traditionally autism has been characterized and studied by researchers primarily in psychiatric terms, providing case studies illustrating the psychiatric aspects of ASD and

of mercurialism are necessary in establishing the similarities of the two disorders on this critical domain. Also included is a comparison of "Lenny," an autistic adult described by Rhea Paul (1987), and the Mad Hatter from *Alice in Wonderland*, considered to be an accurate portrayal of victims of the disease. Of particular relevance in all these cases are social withdrawal and deficits in social communication, traits (i) always prominent in autism and (ii) clearly associated with mercurialism.

Case Studies: Autism

"I am 18 years old. My parents found out I was autistic when I was 18 months old. My parents said I banged my head a lot when I got frustrated when I was young. Head banging motions help me deal with nervousness. I also take 2 medications to help me cope with stress. I have very few friends. It is also somewhat painful for me to look people in the eye. This sometimes makes people think I am not paying attention" (The MAAP, Vol. II, 1997).

"I have a high-functioning autistic eight-year-old boy. My mistake was putting him in the second grade with a teacher who was determined to 'socialize' him. After three months, the anxiety proved to be too great for him. He spent a lot of time crying, withdrawing to his room, becoming compulsive and belligerent. In another era, he would have been seen as having a 'nervous breakdown'" (The MAAP, Vol. II, 1997).

"I am writing regarding our 25 year old son who was diagnosed only a few months ago as having Asperger's Syndrome. All his life he displayed the 'classic' symptoms of Asperger's (lack of social skills, disorganization, anxiety, etc.). A few months ago, he became clinically depressed, phobic about being around people for fear of more rejection or being laughed at. He now has obsessive thoughts that our home is electronically 'bugged' and all his actions are being observed and belittled" (The MAAP, Vol. II, 1997).

"Several people have asked me what it's like to have Asperger's Syndrome. Today, I still prefer to work on my computer or with electronics rather than socialize. I've never been able to tolerate any kind of physical contact or intimacy. I like wrestling and rough-housing, but I hate being caressed or held." (The MAAP, Vol. II, 1997).

"My son Brian is a 6-year-old with high functioning autism. Our main problem now is his rigidity and obsessive/compulsive behaviors. He gets extremely upset when activities don't go as he thinks they should. He first gets mad, screaming and yelling, then begins to obsessively talk about how he can remedy the situation, then often begins to cry uncontrollably. These tantrums can go on for hours" (The MAAP, Vol. IV, 1996).

"[I'm] age 12½. I have Autism/PDD. I don't really know any real social skills, though my brother Isaiah says I am a social outcast. I do have trouble making new friends because I get real shy and nervous" (The MAAP, Vol. IV, 1997).

"I am the mother of three autistic boys. Nate was considered very shy. Poor eye contact but very smart and doing well in school. Nate was also diagnosed with Hypotonia of the face (which answered all the mumbling he did wasn't just shyness) and extremities" (The MAAP, Vol. III, 1999)

"I spent many hours sitting in the trees or under the bed or in a dark closet. I had a loud flat voice. Socialization has always been beyond me" (The MAAP, Vol. II, 1998).

"I sit in my room a prisoner to my autism. Mom and sis doing their loving best to get me out. I wanted to get out – really get out. I wanted to love, to feel, to connect. But, I couldn't. I was stuck. I was slowly dying. There were days I truly wanted to end it all. If any days were good, I didn't deserve it. I shouldn't be happy. Autism teaches you that – because it's a life sentence" (The MAAP, Vol. VI, 1996).

Case Studies: Mercury Poisoning

A 12 year old girl with recent mercury vapor poisoning was initially diagnosed as having a psychiatric disturbance. Her behavior was more normal when she was unaware of being watched. She became upset when people were around, was reluctant to speak when others were present, spoke in a soft, mumbling voice, lacked eye contact, had a flat affect, was sometimes tearful, experienced auditory hallucinations of voices laughing at her, wished to stay alone in her room with the lights off and her head covered, and had frequent temper tantrums (Fagala and Wigg, 1992).

Sufferers of Mad Hatter's disease, arising from prolonged mercury vapor exposure, were known to suffer from depression, lassitude, acute anxiety, and irrational fears. They also became nervous, timid, and shy. They blushed readily, were embarrassed in social situations, objected to being watched, and sought to avoid people. They felt a constant impulse to return home. They were easily upset, and were prone to agitation, irritability, anger, and aggressive behavior (O'Carroll et al, 1995).

A survey on an Internet site of adult acrodynia victims, which compared the symptoms of adults who suffered from acrodynia as children with controls, reported the following symptoms as seen to a greater degree in acrodynia sufferers than in controls: dislikes being touched or hugged, is a loner, lacks self confidence, feels nervousness and has a racing heart, has depression and suicidal feelings (Farnesworth, 1997). One acrodynia victim described his own situation: "not having learnt normal social skills I spent a lot of my time alone…Gradually by age 11 or so, I was becoming 'normal'…But, I have never overcome the headache problem, irritability, shyness with real people, not wanting to be touched, depression, fear of doctors, great anxiety…" (Manser, Pink Disease site)

A doctor from the 19th century described several cases of mercury poisoning from dental amalgams: "There is mental excitability as well as mental depression; perplexing events cause the highest degree of excitement, ordinary conversation sometimes causes complete confusion, headache, palpitation, intense solicitude, and anxiety, without reason for it. Such are some of the symptoms attending these cases." As an example he cites the case of a young woman who "had come to be melancholic and to withdraw herself from her family and friends, seeking the seclusion of her room -- refusing to go out or to associate with others, or even with the members of her own household." (Tuthill, 1899, Pink Disease site)

Nearly a century later, initial questioning of a 28 year old woman, subsequently found to have mercury vapor poisoning, “elicited the fact that she had become increasingly withdrawn from social activities and had felt most uncomfortable when with strangers. She also felt that her friends had turned against her. She had a repetitive disturbing dream of electric fire around the frames of the windows in her bedroom.” (Ross et al, 1977)

Lenny and The Mad Hatter

(a) Rigid literal interpretation of word meaning; word meaning and pragmatic errors which interfere with social communication

Lenny -

"He was very literal minded, and words spoken to him became matters of immutable fact. For example, he was trying on new shoes. His mother asked him if they slipped up and down. He said they didn't, and when asked again if he were sure, he replied, 'No, they don't slip up and down; they slip down and *then* they slip up.' "

The Mad Hatter -

"Take some more tea," the March Hare said to Alice, very earnestly.

"I've had nothing yet," Alice replied in an offended tone: "so I ca'n't take more."

"You mean you ca'n't take *less*," said the Hatter: "It's very easy to take *more* than nothing."

(b) Social deficits, inability to interpret social rules, leading to perceived rude behavior

Lenny -

"Although he tried working in his father's business for a time, his immaturity, self-centered behavior, and lack of social judgment required his return to a sheltered setting."

The Mad Hatter -

"Your hair wants cutting," said the Hatter. He had been looking at Alice for some time with great curiosity, and this was his first speech.

"You should learn not to make personal remarks," Alice said with some severity: "it's very rude."

The Hatter opened his eyes wide upon hearing this; but all he said was "Why is a raven like a writing desk?"

(c) Inability to engage in meaningful social conversation; poor conversational interpretation skills; perseverative thoughts

Lenny -
"During one interview he engaged in a 20 minute monologue about a broken washing mashine. The interviewer momentarily dozed off. Upon rousing, the interviewer exclaimed, 'Oh, Lenny, I'm sorry!' 'It's all right,' Lenny replied calmly, 'the washing machine got fixed."

The Mad Hatter (who talks obsessively/perseveratively about Time for a good portion of the chapter) -

"What a funny watch!" she remarked. "It tells the day of the month, and doesn't tell what o'clock it is!"

"Why should it?" muttered the Hatter. "Does *your* watch tell you what year it is?"

"Of course not, " Alice replied very readily: "but that's because it stays the same year for such a long time altogether."

"Which is just the case with *mine*," said the Hatter.

Alice felt dreadfully puzzled. The Hatter's remark seemed to her to have no sort of meaning in it, and yet it was certainly plain English.

b. Language and Hearing

The third diagnostic criterion for autism is a qualitative impairment in communication (APA, 1994), and such impairment is a primary feature of mercury poisoning.

Delayed language onset is often among the first overt signs of ASD (Eisenmajer et al, 1998). Historically, half of those with classic autism failed to develop meaningful speech (Gillberg & Coleman, 1992; Prizant, 1996); and oral-motor deficits (e.g. chewing, swallowing) are often present (Filipek et al, 1999). When speech develops, there may be "specific neuromotor speech disorders," including verbal dyspraxia, a dysfunction in the ability to plan the coordinated movements to produce intelligible sequences of speech sounds, or dysarthria, a weakness or lack of control of the oral musculature" leading to articulation problems (Filipek et al, 1999). Echolalic speech and pronoun reversals are typically found in younger children. Many ASD subjects show poorer performance on tests of verbal IQ relative to performance IQ (Dawson, 1996; Filipek at al, 1999). Higher functioning individuals, such as those with Asperger's Syndrome, may have language fluency but still exhibit semantic (word meaning) and pragmatic (use of language to communicate) errors (Filipek et al, 1999).

Auditory impairment is also common. Two separate studies, for example, both found that 24% of autistic subjects have a hearing deficit (Gillberg & Coleman, 1992). More recently Rosenhall et al (1999) have diagnosed hearing loss ranging from mild to profound, as well as hyperacusis, otitis media, and conductive hearing loss, in a minority of ASD subjects, and these traits were independent of IQ status. Among the earliest signs of autism noted by mothers were strange reactions to sound and abnormal babble (Gillberg & Coleman, 1992), and many ASD children are tested for deafness before receiving a formal autism diagnosis (Vostanis et al, 1998). "Delayed or prompted response to name" differentiates 9-12 months old toddlers, later diagnosed with autism, from mentally retarded and typical controls (Baranek, 1999). In fact, "bizarre responses"

to auditory stimuli are nearly universal in autism and may present as "either a lack of responsiveness or an exaggerated reaction to auditory stimuli" (Roux et al, 1998), possibly due to sound sensitivity (Grandin, 1996). Kanner noted an aversion to certain types of sounds, such as vacuum cleaners (Kanner, 1943). Severe deficits in language comprehension are often present (Filipek et al, 1999). Difficulties in picking out conversational speech from background noise are commonly reported by high functioning ASD individuals (Grandin, 1995; MAAP, 1997-1998).

In regard to language and auditory phenomena, autism's parallels to mercurialism are striking. Emerging signs of mercury poisoning are dysarthria (defective articulation in speech due to CNS dysfunction) and then auditory disturbance, leading to deafness in very high doses (Clarkson, 1992). In some cases, hearing impairment manifests as an inability to comprehend speech rather than an inability to hear sound (Hunter et al, 1940; Dales, 1972). Hg poisoning can also result in aphasia, the inability to understand and/or physically express words (Kark et al, 1971). Speech difficulties may arise from "intention tremor, which can be noticeable about the mouth, tongue, face, and head, as well as in the extremities" (Adams et al, 1983).

Mercury-exposed children especially show a marked difficulty with speech (Pierce et al, 1972; Snyder, 1972; Kark et al, 1971). Even children exposed prenatally to "safe" levels of methylmercury performed less well on standardized language tests than did unexposed controls (Grandjean et al, 1998). Iraqi babies exposed prenatally either failed to develop language or presented with severe language deficits in childhood. They exhibited "exaggerated reaction" to sudden noise and some had reduced hearing (Amin-Zaki, 1974 and 1979). Iraqi children who were postnatally poisoned from bread containing either methyl or ethylmercury developed articulation problems, from slow, slurred word production to the inability to generate meaningful speech. Most had impaired hearing and a few became deaf (Amin-Zaki, 1978). In acrodynia, symptoms of sufferers (vs. controls) include noise sensitivity and hearing problems (Farnsworth, 1997).

Adults also exhibit these same Hg-induced impairments. There is slurred or explosive speech (Dales, 1972), as well as difficulty in picking out one voice from a group (Joselow et al, 1972). Poisoned Iraqi adults developed articulation problems (Amin-Zaki, 1974). A 25 year old man with elemental mercury poisoning had reduced hearing at all frequencies (Kark et al, 1971). Thimerosal injected into a 44 year old man initially led to difficulty verbalizing, even though his abilities in written expression were uncompromised; he then progressed to slow and slurred speech, although he could still comprehend verbal language; and he finally lost speech altogether (Lowell et al, 1996). In Mad Hatter's disease, there were word retrieval and articulation difficulties (O'Carroll et al, 1995). A scientist who recently died from dimethylmercury poisoning demonstrated an inability to understand speech despite having good hearing sensitivity for pure tones (Musiek and Hanlon, 1999). Workers exposed to mercury vapor showed decreased verbal intelligence relative to performance IQ (Piikivi et al, 1984; Vroom and Greer, 1972).

Table III: Summary of Speech, Language & Hearing Deficits in Autism & Mercury Poisoning

Mercury Poisoning	Autism
Complete loss of speech in adults or children; failure to develop speech in infants	Delayed language onset; failure to develop speech
Dysarthria; speech difficulties from intention tremor; slow and slurred speech	Dysarthria; dyspraxia and oral-motor planning difficulties; unintelligible speech
Aphasia, the inability to use or understand words, inability to comprehend speech although ability to hear sound is intact	Speech comprehension deficits, although ability to hear sound is intact
Difficulties verbalizing; word retrieval problems	Echolalia; pronoun reversals, word meaning and pragmatic errors; limited speech production
Auditory disturbance; difficulties differentiating voices in a crowd	Difficulties following conversational speech with background noise
Sound sensitivity	Sound sensitivity
Hearing loss; deafness in very high doses	Mild to profound hearing loss
Poor performance on standardized language tests	Poor performance on verbal IQ tests

c. Sensory Perception

Sensory impairment is considered by many researchers to be a defining characteristic of autism (Gillberg and Coleman, 1992; Williams, 1996). Baranek (1999) detected sensory-motor problems - touch aversion, poor non-social visual attention, excessive mouthing of objects, and delayed response to name - in 9-12 month old infants later diagnosed with autism, and suggests that these impairments both underlie later social deficits and serve to differentiate ASD from mental retardation and typical controls. Besides sensitivity to sound, as previously noted, ASD often involves insensitivity to pain, even to a burning stove (Gillberg & Coleman, 1992), while on the other hand there may be an overreaction to stimuli, so that even light to moderate touches are painful. Pinprick tests are usually normal. Children with autism have been described as "stiff to hold," and one of the earliest signs reported by mothers is an aversion to being touched (Gillberg & Coleman, 1992). Abnormal sensation in the extremities and mouth are common. Toe-walking is frequently seen. Oral sensitivity often results in feeding difficulties (Gillberg & Coleman, 1992, p.31). Autistic children frequently have vestibular impairments and difficulty orienting themselves in space (Grandin, 1996; Ornitz, 1987).

As in ASD, sensory issues are reported in nearly all cases of mercury toxicity, and serve to demonstrate the similarities between the two conditions. Paresthesia, or abnormal sensation, tingling, and numbness around the mouth and in the extremities, is the most common sensory disturbance in Hg poisoning, and is usually the first sign of toxicity (Fagala and Wigg, 1992; Joselow et al, 1972; Matheson et al, 1980; Amin-Zaki, 1979). In Japanese who ate contaminated fish, there was numbness in the extremities, face and tongue (Snyder, 1972; Tokuomi et al, 1982). Iraqi children who ate bread experienced sensory changes including numbness in the mouth, hands and feet, and a feeling that there were "ants crawling under the skin." These children could still feel a pinprick (Amin-Zaki, 1978). Loss of position in space has also been noted (Dales, 1972). Acrodynia sufferers describe excessive pain when bumping limbs, numbness, and poor circulation (Farnsworth, 1997). One adult acrodynia victim described himself as a boy as "shying away from people wanting to touch me" due to extreme touch sensitivity (Manser, Pink Disease Support Group). Iraqi babies exposed to mercury prenatally showed excessive crying, irritability, and exaggerated reaction to stimulation such as sudden noise or when touched (Amin-Zaki et al, 1974 and 1979).

Table IV: Summary of Sensory Abnormalities in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Abnormal sensation or numbness around mouth and extremities (paresthesia); burning feet	Abnormal sensation in mouth and extremities; excessive mouthing of objects (infants); toe walking; difficulty grasping objects
Sound sensitivity	Sound sensitivity
Excessive pain when bumping; abnormal touch sensations; touch aversion	Insensitivity or overreaction to pain and touch; touch aversion; stiff to hold
Loss of position in space	Vestibular system abnormalities; difficulty orienting self in space
Normal pinprick tests	Normal pinprick tests

d. Movement/Motor Function

Nearly all cases of autism include disorders of physical movement. Movement disturbances have been detected in infants as young as four to six months old who were later diagnosed as autistic: Teitelbaum et al (1998) have observed that these children do not lie, roll over, sit up or crawl like normal infants; impairment in motor control sometimes caused these babies to fall over while sitting, consistently to avoid using one of their arms, or to rest on their elbows for stability while crawling. Later, when trying to walk their gait was abnormal, and some degree of asymmetry, mostly right-sided, was present in all cases studied. Kanner noted in several of his subjects the absence of crawling and a failure to assume an anticipatory posture preparatory to being picked up in infancy (Kanner, 1943). Arm flapping, abnormal posture, jumping, hand-finger mannerisms (choreiform movements), circling or spinning, rocking, toe walking, and other perseverative, repetitive or stereotypic movements are among the diagnostic criteria for ASD (APA, 1994). Many individuals with Asperger's syndrome are characterized as

uncoordinated or clumsy (Kugler, 1998). Other autism movement disorders include praxis (problems with intentional movement), myoclonal jerks, difficulty swallowing and chewing, difficulty writing with or even holding a pen, limb apraxia, and poor eye-hand coordination (Caesaroni and Garber, 1991; Gillberg and Coleman, 1992; Filipek et al, 1999).

Like ASD, movement disorders have been a feature of virtually all descriptions of mercury poisoning in humans (Snyder, 1972). Even children prenatally exposed to "safe" levels of methylmercury had deficits in motor function (Grandjean et al, 1998). The movement-related behaviors are extremely diverse: Iraqi infants and children exposed postnatally, for example, developed ataxia that ranged from clumsiness and gait disturbances to an "inability to stand or even sit" (Amin-Zaki et al, 1978). The various movement behaviors are listed more fully in Table V (Adams et al, 1983; Kark et al, 1971; Pierce et al, 1972; Snyder, 1972; O'Carroll et al, 1995; Tokuomi et al, 1982; Amin-Zaki, 1979; Florentine and Sanfilippo, 1991; Rohyans et al, 1984; Fagala and Wigg, 1992; Smith, 1977; Grandjean et al, 1998; Farnesworth, 1997; Dales, 1972; Matheson et al, 1980; Lowell et al, 1996; O'Kusky et al, 1988; Vroom and Greer, 1972; Warkany and Hubbard, 1953).

Noteworthy because of similarities to movement disorders in autism are reports in the Hg literature of (a) an infant with "peculiar tremulous movements of the extremities which were principally proximal and can best be described as flapping in nature" (Pierce et al, 1972; Snyder, 1972); (b) "jerking movements of the upper extremities" in a man injected with thimerosal (Lowell et al, 1996); (c) "constant choreiform movements affecting the fingers and face" in mercury vapor intoxication (Kark et al, 1971); (d) myoclonal jerks, associated with epilepsy among Iraqi subjects (Amin-Zaki et al, 1978); (e) poor coordination and clumsiness among victims of acrodynia (Farnesworth, 1997); (f) rocking among infants with acrodynia (Warkany and Hubbard, 1953); (g) "unusual postures" observed in both acrodynia and mercury vapor poisoning (Vroom and Greer, 1972; Warkany and Hubbard, 1953); (h) toe walking by a moderately poisoned child in the Minamata epidemic (Tsubaki and Irukayama, 1977); and (i) problems with inhibiting perseveration in an adult exposed to inorganic Hg (White et al, 1993). In animal studies, cats exposed to mercury by eating fish developed "circling movements" (Snyder, 1972); subcutneous administration of methylmercury to rats during postnatal development has resulted in postural disorders (O'Kusky et al, 1988); and rats exposed to MeHg prenatally exhibited significant increases in stereotyped locomotion (Elsner, 1986).

As summarized in Table V, movement similarities in autism and Hg poisoning are clear.

Table V: Summary of Motor Disorder Behaviors in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Involuntary jerking movements, e.g., arm flapping, ankle jerks, myoclonal jerks; choreiform movements; circling (cats); rocking; purposeless movement of extremities; twitching, shaking; muscular spasticity	Stereotyped movements such as arm flapping, jumping, circling, spinning, rocking; myoclonal jerks; choreiform movements
Unsteadiness in handwriting or an inability to hold a pen; deficits in eye-hand coordination; limb apraxia; intention tremors; loss of fine motor skills	Difficulty in writing with or holding a pen; poor eye-hand coordination; limb apraxia; problems carrying out intentional movements (praxia)
Ataxia: gait impairment; severity ranging from mild incoordination, clumsiness to complete inability to walk, stand, or sit; staggering, stumbling; loss of motor control	Abnormal gait and posture, clumsiness and incoordination; difficulties sitting, lying, crawling, and walking in infants and toddlers
Toe walking	Toe walking
Difficulty in chewing or swallowing	Difficulty chewing or swallowing
Unusual postures	Unusual postures
Areflexia	None described
Tremors in general, tremors of the face and tongue, hand tremors	None described

e. Cognition/Mental Function

Nearly all autistic individuals show impairment in some aspects of mental function, even as other cognitive abilities remain intact. Most individuals may test in the retarded range, while others have normal to above average IQs. These characteristics are true in mercurialism. Moreover, the specific areas of impairment are similar in the two disorders.

The impaired areas in autism are generally in (a) short term or working memory and auditory and verbal memory; (b) concentration and attention, particularly attention shifting; (c) visual motor and perceptual motor skills, including eye-hand coordination; (d) language/verbal expression and comprehension; and (e) using visually presented information when constraints are placed on processing time. Relatively unimpaired areas include rote memory skills, pattern recognition, matching, perceptual organization, and stimuli discrimination. Higher level mental skills requiring complex processing are typically deficient; these include (a) processing and filtering of multiple stimuli; (b) following multiple step commands; (c) sequencing, planning and organizing; and (d) abstract/conceptual thinking and symbolic understanding (Rumsey & Hamburger, 1988; Plioplys, 1989; Bailey et al, 1996; Filipek et al, 1999; Rumsey, 1985; Dawson, 1996; Schuler, 1995; Grandin, 1995; Sigman et al, 1987). Younger or more mentally impaired children may have difficulties with symbolic play and understanding object permanence or the mental state of others (Bailey et al, 1996). Some autistic children are hyperlexic, showing superior decoding skills while lacking comprehension of the words being read

(Prizant, 1996). As mentioned before, for most autistic individuals verbal IQ is lower than performance IQ.

As in autism, Hg exposure causes some level of impairment primarily in (a) short term memory and auditory and verbal memory; (b) concentration and attention, including response inhibition; (c) visual motor and perceptual motor skills, including eye-hand coordination; (d) language/verbal expression and comprehension; and (e) simple reaction time. Hg-affected individuals may present as "forgetful" or "confused." Performance IQ may be higher than verbal IQ. "Degeneration of higher mental powers" has resulted in (a) difficulty carrying out complex commands; (b) impairment in abstract and symbolic thinking; and (c) deficits in constructional skills and conceptual abstraction. One study mentions alexia, the inability to comprehend the meaning of words, although reading of the words is intact (Yeates & Mortensen, 1994; O'Carroll et al, 1995; Pierce et al, 1972; Snyder, 1972; Adams et al, 1983; Kark et al, 1971; Amin-Zaki, 1974 and 1979; Davis et al, 1994; Grandjean et al, 1997 & 1998; Myers & Davidson, 1998; Gilbert & Grant-Webster 1995; Dales, 1972; Fagala and Wigg, 1992; Farnesworth, 1997; Tuthill, 1899; Joselow et al, 1972; Rice, 1997; Piikivi et al, 1984; Vroom and Greer, 1972). Even children exposed prenatally to "safe" levels of methylmercury show lower scores on selective subtests of cognition, especially in the domains of memory and attention, relative to unexposed controls (Grandjean et al, 1998). In exposed juvenile monkeys, tests have revealed delays in the development of object permanence, or the ability to conceptualize the existence of a hidden object (Rice, 1996).

Research on mental retardation in autism is contradictory (Schuler, 1995). The finding that "mental retardation or borderline intelligence often co-exists with autism" (Filipek et al, 1999) is based on using standard measures of intelligence (Gillberg & Coleman, 1992, p.32; Bryson, 1996); other intelligence tests, designed to circumvent the language and attentional deficits of autistic children, show significantly higher intelligence test scores (Koegel et al, 1997; Russell et al, 1999). One study using such a modified rating instrument has found 20% of autistic children to be mentally retarded (Edelson et al, 1998), rather than the 70%-80% so scored on standard tests. ASD individuals also show "strikingly uneven scores" on IQ subtests, "unlike other disorders involving mental retardation, in which subtest scores seem to be more or less even" (Bailey et al, 1996). Also unlike typical cases of mental retardation, which is nearly always noted in the peri- or neonatal periods, most parents of ASD children report infants of seemingly normal appearance and development who were later characterized as mentally retarded on tests. For example, one study compared early developmental aberrations in mentally retarded children with and without autism. Findings indicated that, whereas nearly all parents of the non-autistic mentally retarded study group were aware of their child's impairment by age 3 months, nearly all parents of the autistic children failed to notice *any* developmental delays or issues until after 12 months of age (Baranek, 1999). Finally, there are several case reports of autistic adults who were labeled mentally retarded as children based on tests, who later "emerged" from their autism and had normal IQs (ARI Newsletter, 1993, review).

As in autism, symptomatic mercury-poisoned victims can present with normal IQs, borderline intelligence, or mental retardation; some may be so impaired as to be untestable (Vroom and Greer, 1972; Davis et al, 1994). When lowered intelligence is

found, it is always reported as an obvious deterioration among previously normally functioning people; this includes children exposed as infants or toddlers (Dale, 1972; Vroom and Greer, 1972; Amin-Zaki, 1978). Once the Hg-exposure source is removed, many (although not all) of these patients "recover" their normal IQ, suggesting that "real" IQ was not affected (Vroom and Greer, 1972; Davis et al, 1994). Infant monkeys given low doses of Hg, while clearly impaired in visual, auditory, and sensory functions, had intact central processing speed, which has been shown to correlate with IQ in humans (Rice, 1997).

Table VI: Summary of Areas of Mental Impairment in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Some aspect of mental impairment in all symptomatic cases	Some aspect of mental impairment in all cases
Borderline intelligence on testing among previously normal individuals; mental retardation occurring in severe cases of pre-/postnatal exposure; some cases of MR reversible; primate studies indicate core intelligence spared with low exposures	Borderline intelligence or mental retardation on standard tests among previously normally appearing infants; some cases of MR "reversible"; indications that normal IQ might be present in MR-labeled individuals
Uneven performance on subtests of intelligence	Uneven performance on subtests of intelligence
Verbal IQ higher than performance IQ; compromised language/verbal expression and comprehension	Verbal IQ higher than performance IQ; compromised language/verbal expression and comprehension
Poor concentration, shortened attention span, general lack of attention; poor response inhibition	Lack of concentration, short attention span, lack of attention, difficulty shifting attention
Forgetfulness, loss of memory, particularly short term, verbal and auditory memory; mental confusion	Poor short term/working memory; poor auditory and verbal memory; lower verbal encoding abilities
Poor visual and perceptual motor skills, poor eye-hand coordination; impairment in simple reaction time	Poor visual and perceptual motor skills, poor eye-hand coordination; lowered performance on timed tests
Not reported as being tested	Difficulty processing multiple stimuli
Difficulty carrying out complex commands	Difficulty carrying out multiple commands
Alexia (inability to comprehend the meaning of written words)	Hyperlexia (ability to decode words while lacking word comprehension)
Deficits in constructional skills, conceptual abstraction, understanding abstract ideas and symbolism; degeneration of higher mental powers	Deficits in abstract/conceptual thinking, symbolism, understanding other's mental states; impairment in sequencing, planning, organizing
Lack of understanding of object permanence (primates)	Deficient understanding of object permanence (children)

f. Behaviors

Autism is associated with difficulties initiating and/or maintaining sleep; hyperactivity and other ADHD traits; and self injurious behavior such as head banging, even in the absence of mental retardation. Agitation, screaming, crying, staring spells, stereotypical behaviors, and grimacing are common (Gaedye, 1992; Gillberg and Coleman, 1992; Plioplys, 1989; Kanner, 1943; Richdale, 1999; Stores & Wiggs, 1998). Kanner (1943) made a point of noting excessive and open masturbation in two of the eleven young children comprising his initial cases. Feeding and suckling problems are typical (Wing, 1980), and restricted diets and narrow food preferences "are the rule rather than the exception" (Gillberg and Coleman, 1992; Clark et al, 1993); some autistics show a preference for salty foods (Shattock, 1997). Kanner, in his 1943 article, noted feeding problems from infancy, including vomiting and a refusal to eat, in six of the eleven autistic children he described. There are case studies of anorexia nervosa occurring in ASD patients, as well as an increased likelihood of this eating disorder in families with ASD (Gillberg & Coleman, 1992, p.99).

Humans and animals exposed to mercury develop unusual, abnormal, and "inappropriate" behaviors (Florentine and Sanfilippo, 1991). Rats exposed to mercury during gestation have exhibited stereotyped sniffing (Cuomo et al, 1984) and hyperactivity (Fredriksson et al, 1996). "Restlessness" has already been noted, and Davis et al (1994) found poor response inhibition in their human subjects; both of these behaviors are closely associated with ADHD in children. Babies and children with Hg poisoning exhibit agitation, crying for no observable reason, grimacing, and insomnia (Pierce et al, 1972; Snyder, 1972; Kark et al, 1971; Amin-Zaki, 1979; Florentine and Sanfilippo, 1991; Aronow and Fleischmann, 1976). An 18 month old toddler with otitis media, exposed to thimerosal in ear drops, had staring spells and unprovoked screaming episodes (Rohyans et al, 1984). Symptoms of acrodynia in babies and toddlers include continuous crying, anorexia and insomnia (Matheson et al, 1980; Aronow and Fleischmann, 1976). These children were said to bang their heads, have difficulty falling asleep, be irritable, and either refuse to eat or only eat a few foods (Neville Recollection, Pink Disease Support Group Site; Farnesworth, 1997). The frequent temper tantrums of a previously normal 12 year old, poisoned by mercury vapor, included hitting herself on the head and screaming; furthermore, she had extreme genital burning and was observed to masturbate even in front of others (Fagala and Wigg, 1992). Similarly, priapism, persistent erection of the penis due to a pathologic condition resulting in pain and tenderness, has been noted in boys with mercury poisoning (Amin-Zaki et al, 1978).

Adults with mercury poisoning present with insomnia, agitation, and poor appetite (Tuthill, 1899; Adams et al, 1983; Fagala and Wigg, 1992). Relative to controls, more adults who had acrodynia in childhood have eating idiosyncrasies, particularly a preference for salty foods to sweet ones (Farnesworth, 1997), possibly because mercury causes excessive sodium excretion, as shown in studies of dental amalgam placed in monkeys and sheep (Lorscheider et al, 1995).

Table VII: Summary of Unusual Behaviors in Mercury-Poisoned Animals and Humans & in Autism

Mercury Poisoning	Autism
Stereotyped sniffing (rats)	Stereotyped, repetitive behaviors
Hyperactivity (rats); poor response inhibition (humans), restlessness	Hyperactivity; ADHD-traits
Agitation (humans)	Agitation
Insomnia; difficulty falling asleep (humans)	Insomnia; difficulty falling or staying asleep
Eating disorders: anorexia, poor appetite, food aversion, narrow food preferences, decided food preferences (salty food) (humans)	Eating disorders: anorexia; restricted diet/narrow food preferences; feeding and suckling problems
Masturbation, priapism (children)	Masturbatory tendencies
Unintelligible cries; continuous crying; unprovoked crying (infants and children)	Unprovoked crying
Self injurious behavior, including head banging and hitting the head (toddlers and children)	Self injurious behavior, including head banging and hitting the head
Grimacing (children)	Grimacing
Staring spells (infants and children)	Staring spells

g. Vision

In autism, one of the earliest signs detected by mothers is a lack of eye contact (Gillberg & Coleman, 1992), and an early diagnostic behavior is failure to engage in joint attention based on the ability to "look where you are pointing" (CHAT, Baron-Cohen et al, 1992). Of 11 autistic children studied, ten had inaccurate or slow visual saccades (Rosenhall et al, 1988). Although some adults with ASD report exceptional visual acuity, visual problems are common, with two separate studies reporting 50% of ASD subjects having some type of unusual visual impairment (Steffenburg, in Gillberg & Coleman, 1992). Ritvo et al (1986) and Creel et al (1989) found decreased function of the rods in a study of autistic people, including a retinal sheen, and noted that many such individuals tend to use peripheral vision because of this. A number of case reports describe over-sensitivity to light and blurred vision (Sperry, 1998; Gillberg & Coleman, 1992, p.29; O'Neill & Jones, 1997).

Mercury can lead to a variety of vision problems, especially in children (Pierce et al, 1972; Snyder, 1972). Children who ate high doses of mercury from contaminated pork developed blindness (Snyder, 1972). In Iraqi babies exposed prenatally there was blindness or impaired vision (Amin-Zaki, 1974 and 1979). Iraqi children exposed postnatally developed visual disturbances, which ranged from blurred or hazy vision to constriction of the visual fields to complete blindness (Amin-Zaki et al, 1978). Two girls with mercury vapor poisoning were found to have visual field defects (Snyder, 1972), and, as previously noted, one child with Hg poisoning developed gaze avoidance (Fagala & Wigg, 1992). Acrodynia sufferers report vision problems, including near-sightedness

and light sensitivity or photophobia (Diner and Brenner, 1998; Manser, Pink Disease site; Farnsworth, 1997; Matheson et al, 1980; Aronow and Fleischmann, 1976). A 25 year old man with elemental mercury poisoning exhibited decreased visual acuity, difficulty with visual fixation, and constricted visual fields (Kark et al, 1971). In Japanese victims, there was blurred vision as well as constriction of visual fields (Snyder, 1972; Tokuomi et al, 1982). Iraqi mothers exposed to Hg had visual disturbance (Amin-Zaki, 1979).

In dogs exposed to daily doses of methylmercury, distortion of the visual evoked response from the visual cortex was the first sign. Damage occurred in the preclinical silent stage, demonstrating that CNS damage is occurring before overt symptoms appear (Mattsson et al, 1981). Monkeys treated at birth with low level methylmercury exhibited impaired spatial vision and visual acuity at age 3 and 4 years (Rice and Gilbert, 1982). Disturbances caused by methylmercury in rat optic nerves were observed (Kinoshita et al, 1999).

Table VIII: Summary of Visual Impairments Seen in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Lack of eye contact; difficulties with visual fixation	Lack of eye contact; gaze abnormalities; problems in joint attention
"Visual impairments," blindness, near-sightedness, decreased visual acuity	"Visual impairments"; inaccurate or slow saccades; decreased functioning of the rods; retinal sheen
Light sensitivity, photophobia	Over-sensitivity to light
Blurred or hazy vision	Blurred vision
Constricted visual fields	Not described

h. Physical Presentations

There is a much higher rate of autism among children with cerebral palsy than would be expected by chance (Nordin and Gillberg, 1996). Many autistic children have abnormal muscle tone including hyper- and hypotonia, and many are incontinent or have difficulty being toilet trained (Filipek et al, 1999; Church and Coplan, 1995). Several of the infants which Teitelbaum and colleagues (1998) observed showed decreased arm strength, and Schuler (1995) describes greater muscle weakness in the upper than the lower body. Impairments in oral-motor function, including problems chewing and swallowing, are common, as noted previously.

These impairments are seen in mercurialism as well. In the Iraqi and Japanese epidemics, many children developed clinical cerebral palsy (Amin-Zaki, 1979; Myers & Davidson, 1998; Gilbert & Grant-Webster 1995; Dale, 1972). Amin-Zaki et al (1978) reported muscle wasting and lack of motor power and control in most cases, complete paralysis in several cases, and athetotic movements in 2 cases, of postnatally exposed children. In the Iraqi babies and children, some had increased muscle tone, while others had decreased muscle tone. Abnormal reflexes, spasticity, and weakness were common. One child said "my hands are weak and do not obey me" (Amin-Zaki et al, 1974 and 1978). The 12 year old who inhaled mercury vapor exhibited weakness and decreased muscle strength

(Fagala and Wigg, 1992). As in autism, muscle weakness from mercury poisoning is most prominent in the upper body (Adams et al, 1983). Acrodynia, for example, is marked by poor muscle tone in general and loss of arm strength in particular (Farnesworth, 1997). Finally, difficulty in chewing and swallowing, salivation, and drooling are common in children as well as adults; incontinence was observed in children in the Iraqi Hg-crisis (Amin-Zaki, 1974 and 1978; Pierce et al, 1972; Snyder, 1972; Joselow et al, 1972; Smith, 1977).

The presence of rashes and dermatitis is sometimes reported in descriptions of ASD subjects. Whiteley et al (1998) found that 63% of the ASD children had a history of eczema or other skin complaints. "Some children with autism are frequent scratchers. Gentle rubbing and scratching can become a calming self-stimulation; but when it becomes clawing, and there are rashes and open scrapes on the skin, a tactile intolerance can be responsible" (O'Neill, 1999).

Rashes and itching are common disturbances in mercury toxicity as well (Kark et al, 1971). A 4 year old with Hg poisoning developed an itchy, peeling rash on the extremities (Florentine and Sanfilippo, 1991). Mercury vapor inhalation caused a rash and peeling on the palms and soles of a pre-adolescent (Fagala and Wigg, 1992). An acrodynia victim described himself as a child as having severe itching and a constant burning sensation at the extremities, resulting in him rubbing his hands and feet raw (Neville Recollection, Pink Disease Support Group). Acrodynia symptoms in an adult poisoned by ethylmercury injection included pink scaling palms and soles, flushed cheeks, and itching (Matheson et al, 1980). In acrodynia the skin may be rough and dry, and the soles and palms are usually but not necessarily red (Aronow and Fleischmann, 1976). Thimerosal ingested by 44 year old man led to dermatitis (Pfab et al, 1996).

In autism, "signs of autonomic disturbance may be noticed at times, including sweating, irregular breathing, and rapid pulse" (Wing and Attwood, 1987). There may be elevated blood flow and heart rate (Ornitz, 1987). An increased incidence of acrocyanosis has been observed in Asperger's syndrome. Acrocyanosis is an uncommon disorder of poor circulation in which skin on the hands and feet turn red and blue; there is profuse sweating; and the fingers and toes are persistently cold (Carpenter and Morris, 1991).

Sweating and circulatory abnormalities are also common in some forms of mercury poisoning. Acrodynia in adults and children results in excessive sweating, poor circulation, and rapid heart rate (Farnesworth, 1997; Matheson et al, 1980; Cloarec et al, 1995; Warkany and Hubbard, 1953). The 12 year old with mercury vapor poisoning sweated profusely, especially at night (Fagala and Wigg, 1992), and elevated blood pressure has been reported in exposed workers (Vroom and Greer, 1972). Autonomic system abnormalities can be caused by disturbances in acetylcholine levels, known to be deficient in both autism and Hg poisoning (see neurotransmitter section below).

Table IX: Physical Disturbances in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Increase in cerebral palsy; hyper- or hypotonia; paralysis, abnormal reflexes; spasticity; decreased muscle strength and motor power, especially in the upper body; incontinence; problems chewing, swallowing, and salivating	Increase in cerebral palsy; hyper- or hypotonia; decreased muscle strength, especially in the upper body; incontinence/toilet training difficulties; problems chewing and swallowing
Rashes, dermatitis, dry skin, itching; burning sensation	Rashes, dermatitis, eczema; itching
Autonomic disturbances: excessive sweating; poor circulation; elevated heart rate	Autonomic disturbances: sweating abnormalities; poor circulation; elevated heart rate

j. Gastrointestinal Function

Many if not most autistic individuals have gastrointestinal problems, the most common complaints being chronic diarrhea, constipation, gaseousness, and abdominal discomfort and distention (D'Eufemia et al, 1996; Horvath et al, 1999; Whitely et al, 1998). Colitis is not uncommon (Wakefield et al, 1998). As noted previously, anorexia is sometimes associated with ASD (Gillberg & Coleman, 1992). Kanner noted that over half his initial cases had feeding difficulties and excessive vomiting as infants (1943). O'Reilly and Waring (1993) have described sulfur deficiencies in autism, an effect of which can be clumping of proteins on the gut wall, which is lined with sulfated proteins. The clumping can lead to increased intestinal permeability, or leaky gut syndrome (Shattock, 1997), found in many autistic individuals (D'Eufemia, 1996). Some ASD individuals have unusual opioid peptide fragments in urine; these peptides are believed to enter the bloodstream due to a leaky gut and to result from an incomplete breakdown of gluten and casein in the diet possibly arising from "inadequacy of the [endopeptidase] enzyme systems which are responsible for their breakdown" (Shattock, 1997).

Mercury, which binds to sulfur groups (Clarkson, 1992), is known to cause gastroenteritis (Kark et al, 1971). For example, a four year old with diarrhea was initially diagnosed with gastroenteritis (Florentine and Sanfilippo, 1991). A pre-adolescent with mercury vapor poisoning developed nausea, abdominal pain, poor appetite, rectal itching, and diarrhea; she frequently strained to have a bowel movement, and was at one point diagnosed with colitis (Fagala and Wigg, 1992). Acrodynia is marked by both constipation and diarrhea (Diner and Brenner, 1998). Incontinence of urine and stool are observed in infants and children exposed pre- and postnatally in Iraq (Amin-Zaki, 1974 and 1978). In another case, a 28 year old woman with occupational exposure to mercury vapor developed watery stools (Ross et al, 1977). Diarrhea and digestive disturbance were seen in a dentist with measurable mercury levels; there was obesity in another dentist (Smith, 1977). A 44 year old man poisoned with thimerosal given intramuscularly developed gastrointestinal bleeding, which looked like hemorrhaging colitis (Lowell et al, 1996). Intense exposure to mercury vapor can cause abdominal

pain, nausea, and vomiting (Feldman, 1982). Severe constipation, anorexia, weight loss, and other "disturbances of gastrointestinal function" have been noted in other cases (Adams et al, 1983; Joselow et al, 1972). Rats tested with mercuric chloride were observed with "lesions of the ileum and colon with abnormal deposits of IgA in the basement membranes of the intestinal glands and of IgG in the basement membranes of the lamina propria" (Andres, 1984, reviewed in EPA, 1997, p.3-36). In another rat experiment, Hg was found to increase the permeability of intestinal epithelial tissues (Watzl et al, 1999). Mercury also inhibits the peptidase - dipeptidyl peptidase IV - which cleaves, among other substances, casomorphin during the digestive process (Puschel et al, 1982).

There is no reported increase in incidence in kidney problems in autism. Although renal function is commonly impaired from Hg exposure, such impairment would not be expected if the mercury exposure occurred from thimerosal injections, since kidney function may be unaffected when mercury is injected or inhaled (Davis et al, 1994; Fagala and Wigg, 1992). For example, although thimerosal ingested orally by a 44 year old man resulted in renal tubular failure and gingivitis (Pfab et al, 1996), renal function was normal in another 44 year old man injected intramuscularly with thimerosal (Lowell et al, 1996).

Table X: Summary of Gastrointestinal Problems in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Gastroenteritis, diarrhea; abdominal pain, rectal itching, constipation, "colitis"	Diarrhea, constipation, gaseousness, abdominal discomfort, colitis
Anorexia, weight loss, nausea, poor appetite	Anorexia; feeding difficulties, vomiting as infants
Lesions of the ileum and colon; increased intestinal permeability	Leaky gut syndrome from sulfur deficiency
Inhibits dipeptidyl peptidase IV, which cleaves casomorphin	Inadequate endopeptidase enzymes responsible for breakdown of casein and gluten

II. COMPARISON OF BIOLOGICAL ABNORMALITIES

Like the similarities seen in observable symptoms, parallels between autism and mercury poisoning clearly exist even at cellular and subcellular levels. These similarities are summarized in tables after each individual section.

a. Biochemistry

Sulfur: Studies of autistic children with known chemical or food intolerances show a low capacity to oxidize sulfur compounds and low levels of sulfate (O'Reilly & Waring, 1993; Alberti et al, 1999). These findings were interpreted as suggesting that "there may be a fault either in the manufacture of sulfate or that sulfate is being used up dramatically on an unknown toxic substance these children may be producing" (O'Reilly and Waring, 1993). Alternatively, these observations may be linked to mercury, since mercury preferentially forms compounds with molecules rich in sulfhydryl groups (--SH), such as cysteine and glutathione, making them unavailable for normal cellular and enzymatic functions (Clarkson, 1992). Relatedly, mercury may cause low sulfate by its ability to irreversibly inhibit the sulfate transporter Na-Si cotransporter NaSi-1 present in kidneys and intestines, thus preventing sulfate absorption (Markovitch and Knight, 1998).

Among the sulfhydryl groups, or thiols, mercury has special affinity for purines and pyrimidines, as well as other subcellular substances (Clarkson, 1992; Koos and Longo, 1976). Errors in purine or pyrimidine metabolism are known to result in classical autism or autistic features in some cases (Gillberg and Coleman, 1992, p.209; Page et al, 1997; Page & Coleman, 2000; The Purine Research Society), thereby suggesting that mercury's disruption of this pathway might also lead to autistic traits.

Likewise, yeast strains sensitive to Hg are those which have innately low levels of tyrosine synthesis. Mercury can deplete cellular tyrosine by binding to the SH-groups of the tyrosine uptake system, preventing colony growth (Ono et al, 1987), and Hg-depleted tyrosine would be particularly significant in cells known to accumulate mercury (e.g., neurons of the CNS, see below). Similarly, disruptions in tyrosine production in hepatic cells, arising from a genetic condition called Phenylketonuria (PKU), also results in autism (Gillberg & Coleman, 1992, p.203).

Glutathione: Glutathione is one of the primary means through which the cells detoxify heavy metals (Fuchs et al, 1997), and glutathione in the liver is a primary substrate by which body clearance of organic mercury takes place (Clarkson, 1992). Mercury, by preferentially binding with glutathione and/or preventing absorption of sulfate, reduces glutathione bioavailability. Many autistic subjects have low levels of glutathione. O'Reilly and Waring (1993) suggest this is due to an "exotoxin" binding glutathione so it is unavailable for normal biological processes. Edelson and Cantor (1998) have found a decreased ability of the liver in autistic subjects to detoxify heavy metals. Alternatively, low glutathione can be a manifestation of chronic infection (Aukrust et al, 1996, 1995; Jaffe et al, 1993), and infection-induced glutathione deficiency would be more likely in the presence of immune impairments derived from mercury (Shenkar et al, 1998).

Glutathione peroxidase activities were reported to be abnormal in the erythrocytes of autistic children (Golse et al, 1978). Mercury generates reactive oxygen species (ROS) levels in cells, which increases ROS scavenger enzyme content and thus glutathione, to relieve oxidative stress (Hussain et al, 1999). At high enough levels, mercury depletes rat hepatocytes of glutathione (GSH) and causes significant reduction in glutathione peroxidase and glutathione reductase (Ashour et al, 1993).

Mitochondria: Disturbances of brain energy metabolism have prompted autism to be hypothesized as a mitochondrial disorder (Lombard, 1998). There is a frequent association of lactic acidosis and carnitine deficiency in autistic patients, which suggests excessive nitric oxide production in mitochondria (Lombard, 1998; Chugani et al, 1999), and again, mercury may be a participant. Methylmercury accumulates in mitochondria, where it inhibits several mitochondrial enzymes, reduces ATP production and Ca2+ buffering capacity, and disrupts mitochondrial respiration and oxidative phosphorylation (Atchison & Hare, 1994; Rajanna and Hobson, 1985; Faro et al, 1998). Neurons have increased numbers of mitochondria (Fuchs et al, 1997), and since Hg accumulates in neurons of the CNS, an Hg effect upon neuronal mitochondria function seems likely - especially in children having substandard mercury detoxification.

Table XI: Abnormalities in Biochemistry
Arising from Hg Exposure & Present in Autism

Mercury	Autism
Ties up sulfur groups; prevents sulfate absorption	Low sulfate levels
Has special affinity for purines and pyrimidines	Errors in purine and pyrimidine metabolism can lead to autistic features
Depletes cellular tyrosine in yeast	PKU, arising from disruption in tyrosine production, results in autism
Reduces bioavailability of glutathione, necessary in cells and liver for heavy metal detoxification	Low levels of glutathione; decreased ability of liver to detoxify heavy metals
Can cause significant reduction in glutathione peroxidase and glutathione reductase	Abnormal glutathione peroxidase activities in erythrocytes
Disrupts mitochondrial activities, especially in brain	Mitochondrial dysfunction, especially in brain

b. Immune System

A variety of immune alterations are found in autism-spectrum children (Singh et al, 1993; Gupta et al, 1996; Warren et al, 1986 & 1996; Plioplys et al, 1994), and these appear to be etiologically significant in a variety of ways, ranging from autoimmunity to infections and vaccination responses (e.g., Fudenberg, 1996; Stubbs, 1976). Mercury's effects upon immune cell function are well documented and may be due in part to the ability of Hg to reduce the bioavailability of sulfur compounds:

> "It has been known for a long time that thiols are required for optimal primary in vitro antibody response, cytotoxicity, and proliferative

> response to T-cell mitogens of murine lymphoid cell cultures. Glutathione and cysteine are essential components of lymphocyte activation, and their depletion may result in lymphocyte dysfunction. Decreasing glutathione levels profoundly affects early signal transduction events in human T-cells" (Fuchs & Schöfer, 1997).

Allergy, asthma, and arthritis: Individuals with autism are more likely to have allergies and asthma, and autism occurs at a higher than expected rate in families with a history of autoimmune diseases such as rheumatoid arthritis and hypothyroidism (Comi and Zimmerman, 1999; Whitely et al, 1998). Relative to the general population, prevalence of selective IgA deficiency has been found in autism (Warren et al); individuals with selective IgA deficiency are more prone to allergies and autoimmunity (Gupta et al, 1996). Furthermore, lymphocyte subsets of autistic subjects show enhanced expression of HLA-DR antigens and an absence of interleuken-2 receptors, and these findings are associated with autoimmune diseases like rheumatoid arthritis (Warren et al). These observations suggest autoimmune processes are present in ASD (Plioplys, 1989; Warren et al); and this possibility is reinforced by Singh's findings of elevated antibodies against myelin-basic protein (Singh et al, 1993).

Atypical responses to mercury have been ascribed to allergic or autoimmune reactions (Gosselin et al, 1984; Fournier et al, 1988), and a genetic predisposition for Hg reaction may explain why sensitivity to this metal varies so widely by individual (Rohyans et al, 1984; Nielsen & Hultman, 1999). Acrodynia can present as a hypersensitivity reaction (Pfab et al, 1996), or it may arise from immune over-reactivity, and "children who incline to allergic reactions have an increased tendency to develop acrodynia" (Warkany & Hubbard, 1953). Those with acrodynia are also more likely to suffer from asthma, to have poor immune system function (Farnesworth, 1997), and to experience intense joint pains suggestive of rheumatism (Clarkson, 1997). Methylmercury has altered thyroid function in rats (Kabuto, 1991).

Rheumatoid arthritis with joint pain has been observed as a familial trait in autism (Zimmerman et al, 1993). A subset of autistic subjects had a higher rate of strep throat and elevated levels of B lymphocyte antigen D8/17, which has expanded expression in rheumatic fever and may be implicated in obsessive-compulsive behaviors (DelGiudice-Asch & Hollander, 1997).

Mercury exposure frequently results in rheumatoid-like symptoms. Iraqi mothers and children developed muscle and joint pain (Amin-Zaki, 1979), and acrodynia is marked by joint pain (Farnesworth, 1997). Sore throat is occasionally a presenting sign in mercury poisoning (Vroom and Greer, 1972). A 12 year old with mercury vapor poisoning, for example, had joint pains as well as a sore throat; she was positive on a streptozyme test, and a diagnosis of rheumatic fever was made; she improved on penicillin (Fagala and Wigg, 1992). Acrodynia, which is almost never seen in adults, was also observed in a 20 year old male with a history of sensitivity reactions and rheumatoid-like arthritis, who received ethylmercury via injection in gammaglobulin (Matheson et al, 1980). One effective chelating agent, penicillamine, is also effective for rheumatoid arthritis (Florentine and Sanfilippo, 1991).

Mercury can induce an autoimmune response in mice and rats, and the response is both dose-dependent and genetically determined. Mice "genetically prone to develop spontaneous autoimmune diseases [are] highly susceptible to mercury-induced immunopathological alterations" (al-Balaghi, 1996). The autoimmune response depends on the H-2 haplotype: if the strain of mice does not have the susceptibility haplotype, there is no autoimmune response; the most sensitive strains show elevated antibody titres at the lowest dose; and the less susceptible strain responds only at a medium dose (Nielsen & Hultman, 1999). Interestingly, Hu et al (1997) were able to induce a high proliferative response in lymphocytes from even low responder mouse strains by washing away excess mercury after pre-treatment, while chronic exposure to mercury induced a response only in high-responder strains.

Autoimmunity and neuronal proteins: Based upon research and clinical findings, Singh has been suggesting for some time an autoimmune component in autism (Singh, Fudenberg et al, 1988). The presence of elevated serum IgG "may suggest the presence of persistent antigenic stimulation" (Gupta et al, 1996). Connolly and colleagues (1999) report higher rates in autistic vs. control groups of elevated antinuclear antibody (ANA) titers, as well as presence of IgG and IgM antibodies to brain endothelial cells. On the one hand, since mercury remains in the brain for years after exposure, autism's persistent symptoms may be due to an on-going autoimmune response to mercury remaining in the brain; on the other hand, activation and continuation of an autoimmune response does not require the continuous presence of mercury ions: in fact, once induced, autoimmune processes in the CNS might remain exacerbated because removal of mercury after an initial exposure can induce a greater proliferative response in lymphocytes than can persistent Hg exposure (Hu et al, 1997).

In sera of male workers exposed to mercury, autoantibodies (primarily IgG) to neuronal cytoskeletal proteins, neurofilaments (NFs), and myelin basic protein (MBP) were prevalent. These findings were confirmed in rats and mice, and there were significant correlations between IgG titers and subclinical deficits in sensorimotor function. These findings suggest that peripheral autoantibodies to neuronal proteins are predictive of neurotoxicity, since histopathological findings were associated with CNS and PNS damage. There was also evidence of astrogliosis (indicative of neuronal CNS damage) and the presence of IgG concentrated along the bbb (El-Fawal et al, 1999). Autoimmune response to mercury has also been shown by the transient presence of antinuclear antibodies (ANA) and antinucleolar antibodies (ANolA) (Nielsen & Hultman, 1999; Hu et al, 1997; Fagala and Wigg, 1992).

A high incidence of anti-cerebellar immunoreactivity which was both IgG and IgM in nature has been found in autism, and there is a higher frequency of circulating antibodies directed against neuronal antigens in autism as compared to controls (Plioplys, 1989; Connolly et al, 1999). Furthermore, Singh and colleagues have found that 50% to 60% of autistic subjects tested positive for the myelin basic protein antibodies (1993) and have hypothesized that autoimmune responses are related to an increase in select cytokines and to elevated serotonin levels in the blood (Singh, 1996; Singh, 1997). Weitzman et al

(1982) have also found evidence of reactivity to MBP in autistic subjects but none in controls.

Since anti-cerebellar antibodies have been detected in autistic blood samples, ongoing damage may arise as these antibodies find and react with neural antigens, thus creating autoimmune processes possibly producing symptoms such as ataxia and tremor. Relatedly, the cellular damage to Purkinje and granule cells noted in autism (see below) may be mediated or exacerbated by antibodies formed in response to neuronal injury (Zimmerman et al, 1993).

T-cells, monocytes, and natural killer cells: Many autistics have skewed immune-cell subsets and abnormal T-cell function, including decreased responses to T-cell mitogins (Warren et al, 1986; Gupta et al, 1996). One recent study reported increased neopterin levels in urine of autistic children, indicating activation of the cellular immune system (Messahel et al, 1998).

Workers exposed to Hg^o exhibit diminished capacity to produce the cytokines TNF (alpha) and IL-1 released by monocytes and macrophages (Shenkar et al, 1998). Both high dose and chronic low-level mercury exposure kills lymphocytes, T-cells, and monocytes in humans. This occurs by apoptosis due to perturbation of mitochondrial dysfunction. At low, chronic doses, the depressed immune function may appear asymptomatic, without overt signs of immunotoxicity. Methylmercury exposure would be especially harmful in individuals with already suppressed immune systems (Shenker et al, 1998). Mercury increases cytosolic free calcium levels [Ca2+]i in T lymphocytes, and can cause membrane damage at longer incubation times (Tan et al, 1993). Hg has also been found to cause chromosomal aberrations in human lymphocytes, even at concentrations below those causing overt poisoning (Shenkar et al, 1998; Joselow et al, 1972), and to inhibit rodent lymphocyte proliferation and function in vitro.

Depending on genetic predisposition, mercury causes activation of the immune system, especially Th2 subsets, in susceptible mouse strains (Johansson et al, 1998; Bagenstose et al, 1999; Hu et al, 1999). Many autistic children have an immune portrait shifted in the Th2 direction and have abnormal CD4/CD8 ratios (Gupta et al, 1998; Plioplys, 1989). This may contribute to the fact that many ASD children have persistent or recurrent fungal infections (Romani, 1999).

Many autistic children have reduced natural killer cell function (Warren et al, 1987; Gupta et al, 1996), and many have a sulfation deficiency (Alberti, 1999). Mercury reduces --SH group/sulfate availability, and this has immunological ramifications. As noted previously, decreased levels of glutathione, observed in autistic and mercury poisoned populations, are associated with impaired immunity (Aukrust et al, 1995 and 1996; Fuchs and Schöfer, 1997). Decreases in NK T-cell activity have in fact been detected in animals after methylmercury exposure (Ilback, 1991).

Singh detected elevated IL-12 and IFNg in the plasma of autistic subjects (1996). Chronic mercury exposure induces IFNg and IL-2 production in mice, while intermittent presence of mercury suppresses IFNg and enhances IL-4 production (Hu et al, 1997).

Interferon gamma (IFNg) is crucial to many immune processes and is released by T lymphocytes and NK cells, for example, in response to chemical mitogens and infection; sulfate participates in IFNg release, and "the effector phase of cytotoxic T-cell response and IL-2-dependent functions is inhibited by even a partial depletion of the intracellular glutathione pool" (Fuchs & Schöfer, 1997). A mercury-induced sulfation problem might, therefore, impair responses to viral (and other) infections - via disrupting cell-mediated immunity as well as by impairing NK function (Benito et al, 1998). In animals, Hg exposure has led to decreases in production of antibody-producing cells and in antibody titres in response to inoculation with immune-stimulating agents (EPA, 1997, review, p.3-84).

Table XII: Summary of Immune System Abnormalities in Mercury Exposure & Autism

Mercury	Autism
Individual sensitivity due to allergic or autoimmune reactions; sensitive individuals more likely to have allergies and asthma, autoimmune-like symptoms, especially rheumatoid-like ones	More likely to have allergies and asthma; familial presence of autoimmune diseases, especially rheumatoid arthritis; IgA deficiencies
Can produce an immune response, even at low levels; can remain in CNS for years	Indications of on-going immune response in CNS
Presence of autoantibodies (IgG) to neuronal cytoskeletal proteins, neurofilaments, and myelin basic protein; astrogliosis; transient ANA and AnolA	Presence of autoantibodies (IgG and IgM) to cerebellar cells, myelin basis protein
Causes overproduction of Th2 subset; diminishes capacity to produce TNF(alpha) and IL-1; kills lymphocytes, T-cells, and monocytes; inhibits lymphocyte production; decreases NK T-cell activity; may induce or suppress IFN(gamma) and IL-2 production	Skewed immune-cell subset in the Th2 direction and abnormal CD4/CD8 ratios; decreased responses to T-cell mitogens; increased neopterin; reduced NK T-cell function; increased IFN(gamma) and IL-12

c. CNS Structure

Autism is primarily a neurological disorder (Minshew, 1996), and mercury preferentially targets nerve cells and nerve fibers (Koos and Longo, 1976). Experimentally, primates have the highest levels in the brain relative to other organs (Clarkson, 1992). Methylmercury easily crosses the blood-brain barrier by binding with cysteine to form a molecule that is nearly identical to methionine. This molecule - methylmercury cysteine - is transported on the Large Neutral Amino Acid across the bbb (Clarkson, 1992).

Once in the CNS, organic mercury is converted to the inorganic form (Vahter et al, 1994). Inorganic mercury is unable to cross back out of the bbb (Pedersen et al, 1999) and is more likely than the organic form to induce an autoimmune response (Hultman and Hansson-Georgiadis, 1999). Furthermore, although most cells respond to mercurial injury by modulating levels of glutathione, metallothionein, hemoxygenase, and other

stress proteins, "with few exceptions, neurons appear to be markedly deficient in these responses" and thus more prone to injury and less able to remove the metal (Sarafian et al, 1996).

While damage has been observed in a number of brain areas in autism, many functions are spared (Dawson, 1996). In mercury exposure, damage is also selective (Ikeda et al, 1999; Clarkson, 1992), and the list of Hg-affected areas is remarkably similar to the neuroanatomy of autism.

Cerebellum, Cerebral Cortex, & Brainstem: Autopsy studies of carefully selected autistic individuals revealed cellular changes in cerebellar Purkinje and granule cells (Bauman and Kemper, 1988; Ritvo et al, 1986). MRI studies by Courchesne and colleagues (1988; reviewed in ARI Newslett, 1994) described cerebellar defects in autistic subjects, including smaller vermal lobules VI and VII and volume loss in the parietal lobes. The defects were present independently of IQ. "No other part of the nervous system has been shown to be so consistently abnormal in autism." Courchesne (1989) notes that the only neurobiological abnormality known to precede the onset of autistic symptomatology is Purkinje neuron loss in the cerebellum. Piven found abnormalities in the cerebral cortex in seven of 13 high-functioning autistic adults using MRI (1990). Although more recent studies have called attention to amygdaloid and temporal lobe irregularities in autism (see below), and cerebellar defects have not been found in all ASD subjects studied (Bailey et al, 1996), the fact remains that many and perhaps most autistic children have structural irregularities within the cerebellum.

Mercury can induce cellular degeneration within the cerebral cortex and leads to similar processes within granule and Purkinje cells of the cerebellum (Koos and Longo, 1976; Faro et al, 1998; Clarkson, 1992; see also Anuradha, 1998; Magos et al, 1985). Furthermore, cerebellar damage is implicated in alterations of coordination, balance, tremors, and sensations (Davis et al, 1994; Tokuomi et al, 1982), and these findings are consistent with Hg-induced disruption in cerebellar synaptic transmission between parallel fibers or climbing fibers and Purkinje cells (Yuan & Atchison, 1999).

MRI studies have documented Hg-effects within visual and sensory cortices, and these findings too are consistent with the observed sensory impairments in victims of mercury poisoning (Clarkson, 1992; Tokuomi et al, 1982). Acrodynia, a syndrome with symptoms similar to autistic traits, is considered a pathology mainly of the CNS arising from degeneration of the cerebral and cerebellar cortex (Matheson et al, 1980). In monkeys, mercury preferentially accumulated in the deepest pyramidal cells and fiber systems.

Mercury causes oxidative stress in neurons. The CNS cells primarily affected are those which are unable to produce high levels of protective metallothionein and glutathione. These substances tend to inhibit lipid peroxidation and thereby suppress mercury toxicity (Fukino et al, 1984). Importantly, granule and Purkinje cells have increased risk for mercury toxicity because they produce low levels of these protective substances (Ikeda et al, 1999; Li et al, 1996). Naturally low production of glutathione, when combined with mercury's ability to deplete usable glutathione reserves, provides a mechanism whereby

mercury is difficult to clear from the cerebellum -- and this is all the more significant because glutathione is a primary detoxicant in brain (Fuchs et al, 1997).

Mercury's induction of cerebellar deterioration is not restricted to high-doses. Micromolar doses of methylmercury cause apoptosis of developing cerebellar granule cells by antagonizing insulin-like growth factor (IGF-I) and increasing expression of the transcription factor c-Jun (Bulleit and Cui, 1998).

Several researchers have found evidence of a brainstem defect in a subset of autistic subjects (Hashimoto et al, 1992 and 1995; McClelland et al, 1985); and MRI studies have revealed brainstem damage in a few cases of mercury poisoning (Davis et al, 1994). The peripheral polyneuropathy examined in Iraqi victims was believed to have resulted from brain stem damage (Von Burg and Rustam, 1974).

Amygdala & Hippocampus: Atypicalities in other brain areas are remarkably similar in ASD and mercury poisoning. Pathology affecting the temporal lobe, particularly the amygdala, hippocampus, and connected areas, is seen in autistic patients and is characterized by increased cell density and reduced neuronal size (Abell et al, 1999; Hoon and Riess, 1992; Otsuka, 1999; Kates et al, 1998; Bauman and Kemper, 1985). The basal ganglia also show lesions in some cases (Sears, 1999), including decreased blood flow (Ryu et al, 1999).

Mercury can accumulate in the hippocampus and amygdala, as well as the striatum and spinal chord (Faro et al, 1998; Lorscheider et al, 1995; Larkfors et al, 1991). One study has shown that areas of hippocampal damage from Hg were those which were unable to synthesize glutathione (Li et al, 1996). A 1994 study in primates found that mercury accumulates in the hippocampus and amygdala, particularly the pyramidal cells, of adults and offspring exposed prenatally (Warfvinge et al, 1994).

The documenting of temporal lobe mercury provides a direct link between autism and mercury because, as cited previously, (i) mercury alters neuronal function, and (ii) the temporal lobe, and the amygdala in particular, are strongly implicated in autism (e.g., Aylward et al, 1999; Bachevalier, 1994; Baron-Cohen, 1999; Bauman & Kemper, 1985; Kates et al, 1998; Nowell et al, 1990; Warfvinge et al, 1994). Bachevalier (1996) has shown that infant monkeys with early damage to the amygdaloid complex exhibit many autistic behaviors, including social avoidance, blank expression, lack of eye contact and play posturing, and motor stereotypies. Hippocampal lesions, when combined with amygdaloid damage, increases the severity of symptoms.

Also noteworthy is the fact that amygdala findings in autism and mercury literatures are paralleled in fragile X syndrome, a genetic disorder wherein many affected individuals have traits worthy of an autism diagnosis. These traits include sensory alterations, emotional lability, appetite dysregulation, social deficits, and eye-contact aversion (Hagerman). Not only are fraX-related proteins (FRM1, FMR2) implicated in amygdaloid function (Binstock, 1995; Yamagata, 1999), but neurons involved in gaze- and eye-contact-aversion have been identified within the primate temporal lobe and amygdaloid subareas (Rolls 1992, reviewed in Binstock 1995). These various findings in

ASD, mercury poisoning, and fragile X suggest that amygdaloid mercury is a mechanism for inducing traits central to or associated with autism and the autism-spectrum of disorders.

Neuronal Organization & Head Circumference: Several autism brain studies have found evidence of increased neuronal cell replication, a lowered ratio of glia to neurons, and an increased number of glial cells (Bailey et al, 1996). Based on these and other neuropathological findings, autism can be characterized as "a disorder of neuronal organization, that is, the development of the dendritic tree, synaptogenesis, and the development of the complex connectivity within and between brain regions" (Minshew, 1996).

Mercury can interfere with neuronal migration and depress cell division in the developing brain. Post-mortem brain tissue studies of exposed Japanese and Iraqi infants revealed "abnormal neuronal cytoarchitecture characterized by ectopic cells and disorganization of cellular layers" (EPA, 1997, p.3-86; Clarkson, 1997). Developmental neurtoxicity of Hg may also be due to binding of mercury to sulfhydryl-rich tubulin, a component of microtubules (Pendergrass et al, 1997). Intact microtubules are necessary for proper cell migration and cell division (EPA, review, 1997, p.32-88).

Rat pups dosed postnatally with methylmercury had significant reductions in neural cell adhesion molecules (NCAMs), which are critical during neurodevelopment for proper synaptic structuring. Sensitivity of NCAMs to methylmercury decreased as the developmental age of the rats increased. "Toxic perturbation of the developmentally-regulated expression of NCAMs during brain formation may disturb the stereotypic formation of neuronal contacts and could contribute to the behavioral and morphological disturbances observed following methylmercury poisoning" (Deyab et al, 1999). Plioplys et al (1990) have found depressed expression of NCAM serum fragments in autism.

Abnormalities in neuronal growth during development are implicated in head size differences found in both autism and mercury poisoning. In autism, Fombonne and colleagues (1999) have found a subset of subjects with macrocephaly and a subset with microcephaly. The circumference abnormalities were progressive, so that, while micro- and macrocephaly were present in 6% and 9% respectively of children under 5 years, among those age 10-16 years, the rates had increased to 39% and 24% respectively. Another study, by Stevenson et al (1997), had found just one subject out of 18 with macrocephaly who had this abnormality present at birth. The macrocephaly in autism is generally believed to result from "increased neuronal growth or decreased neuronal pruning." The cause of microcephaly has not been investigated.

The most detailed study of head size in mercury poisoning, by Amin-Zaki et al (1979), involved 32 Iraqi children exposed prenatally and followed up to age 5 years. Eight (25%) had progressive microcephaly, i.e., the condition was not present at birth. None had developed macrocephaly, at least at the time of the study. The microcephaly has been ascribed to neuronal death or apoptosis from Hg intoxication.

Table XIII: CNS Lesions
in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Primarily impacts CNS	Neurological impairments primary
Selectively targets brain areas - those unable to detoxify heavy metals or reduce Hg-induced oxidative stress	Specific areas of brain pathology; many functions spared
Damage to Purkinje and granular cells	Damage to Purkinje and granular cells
Accummulates in amygdala and hippocampus	Pathology in amygdala and hippocampus
Causes abnormal neuronal cytoarchitecture; interferes with neuronal migration and depresses cell division in developing brains; reduces NCAMs	Neuronal disorganization; increased neuronal cell replication, small glia to neuron ration, increased glial cells; depressed expression of NCAMs
Head size differences: progressive microcephaly	Head size differences: progressive microcephaly and macrocephaly
Brain stem defects in some cases	Brain stem defects in some cases

d. Neurons & Neurochemicals

The brains of autistic subjects show disturbances in many neurotransmitters, primarily serotonin, catecholamines, the amino acid neurotransmitters, and acetylcholine. Mercury poisoning causes disturbances in these same neurotransmitters: primarily serotonin, the catecholamines, glutamate, and acetlycholine.

Serotonin: Serotonin synthesis is decreased in the brains of autistic children and increased in autistic adults, relative to age-matched controls (Chugani et al, 1999), while whole blood serotonin in platelets is elevated regardless of age (Leboyer; Cook, 1990). Autistic patients frequently respond well to SSRIs as well as Risperidone (McDougal; 1997; Zimmerman et al, 1996). Likewise, a number of animal studies have found serotonin abnormalities from mercury exposure. For example, subcutaneous administration of methylmercury to rats during postnatal development increases tissue concentration of 5-HT and HIAA in cerebral cortex (O'Kusky et al, 1988).

Findings about serotonin abnormalities in mercury literature implicate interactions between mercury and intracellular calcium as well as mercury and sulfhydral groups:

> Many researchers have documented disruptions of intra- and extra-cellular calcium in neurons from mercury exposure (Atchison & Hare, 1994), including thimerosal (Elferink, 1999), and calcium metabolism abnormalities have been identified in autism (Plioplys, 1989; Coleman, 1989).
>
> Intracellular concentrations of Ca2+ are critical for controlling gene expression in neurons and mediating neurotransmitter release from presynaptic vesicles (Sutton, McRory et al, 1999). 5-HT re-uptake

> activity and intrasynaptic concentration of 5-HT are regulated by Ca2+ in nerve terminals. Methylmercury causes a rapid, irreversible block of synaptic transmission by suppression of calcium entry into nerve terminal channels (Atchison et al, 1986). Thimerosal inhibits 5-HT transport activity in particular through interaction with intracellular sulfhydryl groups associated with Ca2+ pump ATPase (Nishio et al, 1996), for example, by modifying cysteine residues of the Ca(2+)-ATPase (Sayers et al, 1993; Thrower et al, 1996).

Dopamine: Studies have found indications both of abnormally high and low levels of dopamine in autistic subjects (Gillberg & Coleman, 1992, p288-9). For example, Ernst et al (1997) reported low prefrontal dopaminergic activity in ASD children, while Gillberg and Svennerholm (1987) reported high concentrations of homovanillic acid (HVA), a dopamine metabolite, in cerebro-spinal fluid of autistic children, suggesting greater dopamine synthesis. Pyridoxine (vitamin B6) has been found to improve function in some autistic patients by lowering dopamine levels through enhanced DBH function (Gillberg & Coleman, 1992, p289; Moreno et al, 1992; Rimland & Baker, 1996). Dopamine antagonists such as haloperidol improve some antipsychotic symptoms in ASD subjects, including motor stereotypies (Lewis, 1996).

Rats exposed to mercury during gestation show major alterations in synaptic dynamics of brain dopamine systems. The effects were not apparent immediately after birth but showed a delayed onset beginning at the time of weaning (Bartolome et al, 1984). A variety of mercuric compounds increase the release of [3H]dopamine, possibly by disrupting calcium homeostasis or calcium-dependent processes (McKay et al, 1986). Minnema et al (1989) found that methylmercury increases spontaneous release of [3H]dopamine from rat brain striatum mainly due to transmitter leakage caused by Hg-induced synaptosomal membrane permeability. SH groups may also be involved in the inhibition of dopamine binding in rat striatum (Bonnet et al, 1994). Pyridoxine deficiency in rats causes acrodynia, with features similar to human acrodynia (Gosselin et al, 1984).

Epinephrine and norepinephrine: Studies on autistic subjects have consistently found elevated norepinephrine and epinephrine in plasma, which suggests elevated levels of these transmitters in brain, as plasma and CSF norepinephrine are closely correlated (Gillberg and Coleman, 1992, p.121-122). Recently, Hollander et al (2000) have noted improvement in function in about half of their ASD subjects with administration of venlafaxine, a norepinephrine reuptake inhibitor. Mercury also disrupts norepinephrine levels by inhibiting sulfhydryl groups and thus blocking the function of O-methyltransferase, the enzyme that degrades epinephrine (Rajanna and Hobson, 1985). In acrodynia, blocking this enzyme resulted in high levels of epinephrine and norepinephrine in plasma (Cheek, Pink Disease Website). In rats, chronic exposure to low doses of methylmercury increased brain-stem norepinephrine concentration (Hrdina et al, 1976).

Glutamate: It has been observed that many autistics have irregularities related to glutamate (Carlsson ML, 1998). In autism, glutamate and aspartate have been found to be significantly elevated relative to controls (Moreno et al, 1992); and in a more recent

study of ASD subjects, plasma levels of glutamic acid and aspartic acid were elevated even as levels of glutamine and asparagine were low (Moreno-Fuenmayor et al, 1996).

Mercury inhibits the uptake of glutamate, with consequent elevation of glutamate levels in the extracellular space (O'Carroll et al, 1995). Prenatal exposure to methylmercury of rats induced permanent disturbances in learning and memory which could be partially related to a reduced functional activity of the glutamatergic system (Cagiano et al, 1990). Thimerosal enhances extracellular free arachidonate and reduces glutamate uptake (Volterra et al, 1992). Excessive glutamate is implicated in epileptiform activities (Scheyer, 1998; Chapman et al, 1996), frequently present in both ASD and mercurialism (see below).

Acetylcholine: Abnormalities in the cortical cholinergic neurotransmitter system have recently been reported in a post mortem brain study of adult autistic subjects (Perry et al, 2000). The problem was one of acetylcholine deficiency and reduced muscarinic receptor binding, which Perry suggests may reflect intrinsic neuronal loss in hippocampus due to temporal lobe epilepsy (see section below for discussions of epilepsy and ASD/Hg). Mercury alters enzyme activities (Koos and Longo, 1976, p.400), including choline acetyltransferase, which may lead to acetylcholine deficiency (Diner and Brenner, 1998), or Hg may inhibit acetylcholine release due to its effects on Ca2 homeostasis and ion channel function (EPA, 1997, p.3-79). In rats, chronic exposure to low doses of methylmercury decreased cortical acetylcholine levels (Hrdina et al, 1976). Methylmercury has also been found to increase spontaneous release of [3H]acetylcholine from rat brain hippocampus (Minnema et al, 1989) and to increase muscarinic cholinergic receptor density in both rat hippocampus and cerebellum, suggesting upregulation of these receptors in these selected brain regions (Coccini, 2000).

Demyelination: Evidence of demyelination has been observed in the majority of autistic brains (Singh, 1992). This is true of mercury poisoning as well. Mild demyelinating neuropathy was detected in two girls (Florentine and Sanfilippo, 1991), and an adult showed axonal degeneration with Hg-related demyelination (Chu et al, 1998). Methylmercury can alter the fatty acid composition of myelin cerebrosides in suckling rats (Grundt et al, 1980).

Table XIV: Abnormalities in Neurons & Neurochemicals from Mercury & in Autism

Mercury	Autism
Can increase tissue concentration of serotonin in newborn rats; causes calcium disruptions in neurons, preventing presynaptic serotonin release and inhibiting serotonin transport activities	Serotonin abnormalities: decreased serotonin synthesis in children; over-synthesis in adults; elevated serotonin in platelets; positive response to SSRIs; calcium metabolism abnormalities present
Alters dopamine systems; disrupts calcium and increases synaptosome membrane permeability, which affect dopamine activities; peroxidine deficiency in rats results in acrodynia	Indications of either high or low dopamine levels; positive response to peroxidine by lowering dopamine levels; positive response to dopamine antagonists
Increases epinephrine and norepinephrine levels by blocking the enzyme which degrades epinephrine	Elevated norepinephrine and epinephrine; positive response to norepinephrine reuptake inhibitors
Elevates glutamate; decreases glutamate uptake; reduces functional activity of glutamatergic system	Elevated glutamate and aspartate
Alters choline acetyltransferase, leading to acetylcholine deficiency; inhibits acetylcholine neurotransmitter release via impact on calcium homeostasis; causes cortical acetylcholine deficiency; increases muscarinic receptor density in hippocampus and cerebellum	Abnormalities in cholinergic neurotransmitter system: cortical acetylcholine deficiency and reduced muscarinic receptor binding in hippocampus
Causes demyelating neuropathy	Demyelation in brain

e. EEG Activity/Epilepsy

Abnormal EEGs are common in mercury poisoning as well as autism. In one study, half the autistic children expressed abnormal EEG activity during sleep (reviewed in LeWine, 1999). Gillberg and Coleman (1992) estimate that 35%-45% of autistics eventually develop epilepsy. A recent study by LeWine and colleagues (1999) using MEG found epileptiform activity in 82% of 50 regressive-autistic children. EEG abnormalities in autistic populations tend to be non-specific and consist of a variety of epileptiform discharge patterns (Nass, Gross, and Devinsky, 1998).

Unusual epileptiform activity has been found in a variety of mercury poisoning cases (Brenner & Snyder, 1980). These include (i) the Minamata outbreak - generalized convulsions and abnormal EEGs (Snyder, 1972); (ii) methylmercury ingestion through contaminated pork - all four affected children had epileptiform features and disturbances of background rhythms; two had seizures (Brenner & Snyder, 1980); (iii) mercury vapor poisoning - abnormal EEG in a 12 year old girl (Fagala and Wigg, 1992) and slower and attenuated EEGs in chloralkali workers with long term exposure (Piikivi & Tolonen, 1989); and (iv) exposure from thimerosal in ear drops and through IVIG - EEG with generalized slowing in an 18 month old girl with otitis media (Rohyans et al, 1984) and a 44 year old man (Lowell et al, 1996). More recently, Szasz and colleagues (1999), in a

study of early Hg-exposure, described methylmercury's ability to enhance tendencies toward epileptiform activity and reported a reduced level of seizure-discharge amplitude, a finding which is at least consistent with the subtlety of seizures in many autism spectrum children (LeWine, 1999; Nass, Gross, and Devinsky, 1998).

Processes whereby neuronal damage is induced by epileptiform discharges are elucidated in a number of studies, many of which focus upon brain regions affected in autism. Importantly, neuronal damage in the amygdala can be an "ongoing delayed process," even after the cessation of seizures (Tuunanen et al, 1996, 1997, 1999). Alterations of cerebral metabolic function last long after seizures have occurred. In a model of seizure-induced hippocampal sclerosis, Astrid Nehlig's group describes hypometabolism having its regional boundaries "directly connected" to seizure-damaged locus (Bouilleret et al, 2000). That Hg increases extracellular glutamate would also contribute to epileptiform activity (Scheyer, 1998; Chapman et al, 1996).

These findings support a rationale:

> In susceptible individuals, mercury can potentiate or induce Hg-related epileptiform activity, which can have lower amplitude and be harder to identify. Furthermore, this low-level but persisting epileptiform activity would gradually induce cell death in the seizure foci and in brain nuclei neuroanatomically related to the seizure foci.

These studies have a more direct relevance to the possibility of Hg-induced cases of autism (i) because the amygdala are implicated in regard to core traits in autism, as described above, and (ii) because mercury finds its way into the amygdala (see above). Furthermore, these theoretical relationships are consistent with SPECT imaging studies by Mena, Goldberg, and Miller, who have demonstrated areas of regional hypoperfusion neuroanatomically associated with trait deficits in autism-spectrum children (Goldberg et al, 1999).

Table XV: EEG Activity & Epilepsy in Mercury Poisoning & Autism

Mercury Poisoning	Autism
Causes abnormal EEGs and unusual epileptiform activity	Abnormal EEG activity; epileptiform activity
Causes seizures, convulsions	Seizures; epilepsy
Causes subtle, low amplitude seizure activity	Subtle, low amplitude seizure activities

III. MECHANISMS, SOURCES & EPIDEMIOLOGY OF EXPOSURE

a. Exposure Mechanism

Vaccine injections are a known source of mercury (Plotkin and Orenstein, 1999), and the typical amount of mercury given to infants and toddlers in this manner exceeds government safety limits, according to Neal Halsey of the American Academy of Pediatrics (1999) and William Egan of the Biologics Division of the FDA (1999).

Most vaccines given to children 2 years and under are stored in a solution containing thimerosal, which is 49.6% mercury by weight. Once inside humans, thimerosal (sodium ethylmercurrithio–salicylate) is metabolized to ethylmercury and thiosalicylate (Gosselin et al, 1984). The vaccines mixed with this solution are DTaP, HIB, and Hepatitis B (Egan, 1999). Thimerosal is not an integral component of vaccines, but is a preservative added to prevent bacterial contamination. Many vaccine products are available without the thimerosal preservative; however, these alternatives have not been widely used (Egan, 1999). In addition, thimerosal is used during the manufacturing process for a number of vaccines, from which trace amounts are still present in the final injected product (FDA, personal communication; Smith-Kline press release on Hepatitis B, March 31, 2000).

Since at least 1977 clinicians have recognized thimerosal as being potentially dangerous, especially in situations of long term exposure (Haeney et al, 1979; Rohyans et al, 1984; Fagan et al, 1977; Matheson et al, 1980). For nearly twenty years the US government has also singled out thimerosal as a potential toxin (FDA, 1982). In response to the Food and Drug Administration (FDA) Modernization Act of 1997, which called for the FDA to review and assess the risk of all mercury containing food and drugs (*MMWR*, 1999, July 9), the FDA issued a final rule in 1998 stating that over-the-counter drug products containing thimerosal and other mercury forms "are not generally recognized as safe and effective" (FDA, 1998). In December 1998 and April 1999, the FDA requested US vaccine manufacturers to provide more information about the thimerosal content in vaccines (*MMWR*, 1999, July 9); and in July 1999, the CDC asked manufacturers to start removing thimerosal from vaccines and rescheduled the Hepatitus B vaccine so it is given at 9 months of age instead of at birth (CDC, July 1999). In November 1999, the CDC repeated its recommendation that vaccine manufacturers move to thimerosal-free products (CDC, November 1999).

Importantly, based on the CDC's own recommended childhood immunization schedule (and excluding any trace amounts), the amount of mercury a typically vaccinated two year old child born in the 1990s would receive is 237.5 micrograms; and a typical six month old might receive 187.5 micrograms (Egan, 1999). These amounts equate to 3.53×10^{17} molecules and 2.79×10^{17} molecules of mercury respectively (353,000,000,000,000,000 and 279,000,000,000,000,000 molecules). Since thimerosal is injected during vaccinations, the mercury is given intermittently in large, or 'bolus', doses: at birth and at 2, 4, 6, and approximately 15 months (Egan, 1999). The amount of mercury injected at birth is 12.5 micrograms, followed by 62.5 micrograms at 2 months,

50 micrograms at 4 months, another 62.5 micrograms during the infant's 6-month immunizations, and a final 50 micrograms at about 15 months (Halsey, 1999).

Although infancy is recognized as a time of rapid neurological development, to the best of our belief and knowledge, there are no published studies on the effect of injected ethylmercury in intermittent bolus doses in infants from birth to six months or to 2 years (Hepatitis Control Report, 1999; *Pediatrics*, 1999; EPA, 1997, p.6-56). In contrast, four government agencies have set safety thresholds for daily mercury exposure based on ingested fish or whale meat containing methylmercury. Two of these guidelines are based on adult values and two are for pregnant women/fetuses (Egan, 1999). Applying these guidelines to a bolus dose scenario (see Halsey, 1999 for bolus vs. daily dose discussion), the sum of Hg-doses given at 6 months of age or younger, correlated to infant weights, exceed all of the Hg-total guidelines for all infants. The 2 month dose is especially high relative to the typical infant body weight. Halsey (1999) has calculated the 2 month dose to be over 30 times the recommended daily maximum exposure, with babies of the smallest weight category receiving almost three months worth of daily exposures on a single day.

Halsey's observation is all the more important because even at doses which were not previously thought to be associated with adverse affects, mercury has resulted in some damage to humans (Grandjean et al, 1998; NAS, 2000). Given that ethylmercury is equally neurotoxic as methylmercury (Magos et al, 1985; Suzuki et al, 1973), and that injected mercury is more harmful than ingested mercury (EPA, 1997, p.3-55; Diner and Brenner, 1998), the amount of injected ethylmercury given to young children is cause for concern. The potential for Hg-induced harm is compounded by the special vulnerability of infants (Gosselin et al, 1984). Mercury, which primarily affects the central nervous system, is most toxic to the developing brain (Davis et al, 1994; Grandjean et al, 1999; Yeates and Mortensen, 1994), and neonates exposed to methyl (organic) mercury have been shown to accumulate significantly more Hg in the brain relative to other tissues than do adults (EPA, 1997, p.4-1). Mercury may also be more likely to enter the infant brain because the blood-brain barrier has not fully closed (Wild & Benzel, 1994). In addition, infants under 6 months and suckling animals excrete little to no mercury, most likely due to their inability to produce bile, the main excretion route for organic mercury, and once excretion begins, it is slower than adult rates (Koos and Longo, 1976; Clarkson, 1992; Thomas et al, 1982, 1988; Walsh, 1981). Bakir et al (1973) have shown that those with the longest half-time of clearance are most likely to experience adverse sequelae, while Aschner and Aschner (1990) have demonstrated that the longer that organic mercury remains in neurons, the more it is converted to its inorganic irreversibly-bound form, which has greater neurotoxicity.

b. Population Susceptibility

Nearly all children in the United States are immunized, yet only a small proportion of children develop autism. The NIH (Bristol et al, 1996) estimates the current prevalence of autism to be 1 in 500. A pertinent characteristic of mercury is the great variability in its effects by individual. At the same exposure level of mercury, some will be affected severely, while others will be asymptomatic or only mildly impaired (Dale, 1972; Warkany and Hubbard, 1953; Clarkson, 1997). A ten-fold difference in sensitivity to the

same exposure level has been reported (Koos and Longo, 1976; Davis et al, 1994; Pierce et al, 1972; Amin-Zaki, 1979). An example of variability in children is the mercury-induced disease called acrodynia. In the earlier half of this century, from one in 500 to one in 1000 children exposed to the same chronic, low-dose of mercury in teething powders developed this disorder (Matheson et al, 1980; Clarkson, 1997), and the likelihood of developing the disease "appears to be dominated more by individual susceptibility and possibly age rather than the dose of the mercury" (Clarkson, 1992). Given the documented inter-individual variability of responses to Hg, and the young age at which exposure occurs, the doses of mercury given concurrently with vaccines are such that only a certain percentage of children will develop overt symptoms, even as other children might have trait irregularities sufficiently mild as to remain unrecognized as having been induced by mercury.

c. Sex Ratio

Autism is more prevalent among boys than girls, with the ratio generally recognized as approximately 4:1 (Gillberg & Coleman, 1992, p.90). Mercury studies have consistently shown a greater effect on males than females, except in instances of kidney damage (EPA, 1997). At the highest doses, both sexes are affected equally, but at lower doses only males are affected. This is true of mice as well as humans (Sager et al, 1984; Rossi et al, 1997; Clarkson, 1992; Grandjean et al, 1998; McKeown-Eyssen et al, 1983; see also review in EPA, 1997, p.6-50).

d. Exposure Levels & Autism Prevalence

Perhaps not coincidentally, autism's initial description and subsequent epidemiological increase mirror the introduction and use of thimerosal as a vaccine preservative. In the late 1930s, Leo Kanner, an experienced child psychologist and the "discoverer" of autism, first began to notice the type of child he would later label "autistic." In his initial paper, published in 1943, he remarked that this type of child had never been described previously: "Since 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits…a detailed consideration of its fascinating peculiarities." All these patients were born in the 1930s. Thimerosal was introduced as a component of vaccine solutions in the 1930s (Egan, 1999).

Not only does the effect of mercury vary by individual, as noted above, it also varies in a dose-dependent manner, so that the higher the exposure level, the more individuals that are affected. At higher dose levels, the most sensitive individuals will be more severely impaired, and the less sensitive individuals will be only moderately impaired, and the majority of individuals may still show no overt symptoms (Nielson and Hultman, 1999). The vaccination rate, and hence the rate of mercury exposure via thimerosal, has steadily increased since the 1930s. In 1999 it was the highest ever, at close to 90% or above, depending on the vaccine (CDC, 1999, press release). The rate of autism has increased dramatically since its discovery by Kanner: prior to 1970, studies showed an average prevalence of 1 in 2000; for studies after 1970, the average rate had doubled to 1 in 1000 (Gillberg and Wing, 1999). In 1996, the NIH estimated occurrence to be 1 in 500 (Bristol et al, 1996). A large increase in prevalence, yet to be confirmed by stricter epidemiological analysis, appears to be occurring since the mid-1990s, as evidenced by

several state departments of education statistics reflecting substantial rises in enrolment of ASD children (California, Florida, Maryland, Illinois, summarized by Yazbak, 1999). These increases have paralleled the increased mercury intake induced by mandatory innoculations: in 1991, two vaccines, HIB and Hepatitis B, both of which generally include thimerosal as a preservative, were added to the recommended vaccine schedule (Egan, 1999).

e. Genetic Factors

ASD is one of the most heritable of developmental and psychiatric disorders (Bailey et al, 1996). There is 90% concordance in monozygotic twins and a 3-5% risk of autism in siblings of affected probands (Rogers et al, 1999), a rate 50 to 100 times higher than would be expected in the general population (Smalley & Collins, 1996; Rutter, 1996). From 2 to 10 genes are believed to be involved (Bailey et al, 1996).

Individual differences in susceptibility to mercury are said to arise from genetic factors and these too may be multiple in nature (Pierce et al, 1972; Amin-Zaki, 1979). They include innate differences in (i) the ability to detoxify heavy metals, (ii) the ability to maintain balanced gut microflora, which can impair detoxification processes, and (iii) immune over-reactivity to mercury (Nielson and Hultman, 1999; Hultman and Nielson, 199; Johansson et al, 1998; Clarkson, 1992; EPA, review 1997, p.3-26). Many autistic children are described as having (i) difficulties with detoxification of heavy metals (Edelson & Cantor, 1998), possibly due to low glutathione levels (O'Reilly and Waring, 1993), (ii) intestinal microflora imbalances that can impede excretion (Shattock, 1997), and (iii) autoimmune dysfunction (Zimmerman et al, 1993). These characteristics might be reflective of the underlying "susceptibility genes" that predispose to mercury-induced sequelae and hence to autism.

As noted above, autism family studies show an exceptionally high concordance rate of 90% for identical twins. Most environmental factors, such as a postnatal viral infection, tend not to be present at exactly the same time or at the same level or rate for each twin. This would cause a difference in phenotype expression, and thus postnatal environmental influences in general reduce the concordance rate for identical twins. However, given the extremely high vaccination rate and the high likelihood of vaccination of one twin at the same time and with the same vaccines as the other twin, mercury-induced autism via vaccination injection, even though it is an environmental factor, would still lead to the high concordance rate seen in twins.

Furthermore, among identical twin pairs, the 90% concordance rate is for the milder phenotype: if one twin has pure classic autism, there is (i) a 60% chance that the other twin will have pure classic autism; (ii) a 30% chance that the other twin will exhibit some type of impairment falling on the autism spectrum, but with less severe symptoms; and (iii) a 10% chance the other twin will be unimpaired. The difference in symptom severity among the 40% of monozygotic pairs who do not exhibit classic autism may arise from either (i) a different vaccination history within pairs, or (ii) the tendency of thimerosal to "clump" or be unevenly distributed in solution, so that one twin might receive more or less mercury than the other. One study found a 62% difference in the mercury

concentration of ampoules drawn from the same container of immunoglabulin batches containing thimerosal (Roberts and Roberts, 1979).

f. Course of Disease

Age of onset: Autism emerges during the same time period as infant and toddler thimerosal injections during vaccinations. As noted above, the recommended childhood vaccination schedule from 1991 to 1999 has called for injections of thimerosal starting at birth and continuing at 2, 4, 6, and approximately 15 months (Halsey, 1999); a similar schedule occurred prior to this time but for DTP alone. In the great majority of cases, the more noticeable symptoms of autism emerge between 6 and 20 months old – and mostly between 12 and 18 months (Gillberg & Coleman, 1992). Teitelbaum et al (1998), who have claimed the ability to detect subtle abnormalities at the youngest age so far, have observed these abnormalities at 4 months old at the earliest, the exception being a "Moebius mouth" seen at birth in a small number of subjects. Other retrospective studies using videotapes of children later diagnosed with autism report abnormalities at a later age, from 9 to 12 months (Werner et al, 2000).

Symptoms of mercury poisoning do not usually appear immediately upon exposure, although in especially sensitive individuals or in cases of excessive exposure they can (Warkany and Hubbard, 1953; Amin-Zaki, 1978). Rather, there is generally a preclinical "silent stage," seen in both animals and humans, during which subtle neurological changes are occurring (Mattsson et al, 1981). The delayed reaction between exposure and overt signs can last from weeks to months to years (Adams et al, 1983; Clarkson, 1992; Fagala & Wigg, 1992; Davis et al, 1994; Kark et al, 1971). Consequently, mercury given in vaccines before age 6 months would not in most individuals lead to an observable or recognizable disorder, except for subtle signs, prior to age 6-12 months, and for some individuals, symptoms induced by early vaccinal Hg might not emerge until the infant had become a toddler (Joselow et al, 1972).

A few autism researchers have suggested a prenatal onset for autism (Rodier et al, 1997; Bauman & Kemper, 1994), which would preclude a vaccinal-mercury etiology. Others, however, have evidence that suggest post-natal timings (Bailey, 1998; Courchesne, 1999; Bristol Power, NICHD, Dateline Interview, 1999). The general consensus at this point is that the timing cannot be determined (Bailey et al, 1996; Bristol et al, 1996); and, further, that there is "little evidence" that prenatal or perinatal events "predict to later autism" (Bristol et al, 1996), even though clustering of adverse effects (suboptimality factors) are associated with autism (Prechtel, 1968; Bryson et al, 1988; Finegan and Quarrington, 1979). There is also a general agreement that, in the great majority of cases, autistic signs emerge among infants and toddlers who had looked "normal", developed normally, met major milestones, and had unremarkable pediatric evaluations (Gillberg & Coleman, 1992; Filipek et al, 1999; Bailey et al, 1996), so that autism presents as an obvious deterioration or regression, occurring sometime between 9 months to 3 years of age (Baranek, 1999; Bristol Power, NICHD, Dateline Interview, 1999; LeWine, 1999; Werner, 2000).

It is worthwhile to note that early and intensive educational and behavioral intervention can produce dramatic gains in function, and the gains made by these children "may be

somewhat unique among the more severe developmental disabilities" (Rogers, 1996). This phenomenon further suggests that autism arises from an environmental overlay rather than being purely an organic disease. Additionally, at least one paper has described a case of acute mercury poisoning in which improvement in function was observed as a result of re-education and physical therapy (Hunter et al, 1940).

Emergence of symptoms: The manner in which symptoms emerge in many cases of autism is consistent with a multiple low-dose vaccinal exposure model of mercury poisoning. From a parent's and pediatrician's perspective, such an individual is a "normal" looking child who regresses or fails to develop after thimerosal administration. Clinically relevant symptoms generally emerge gradually over many months, although there have been scattered parental reports of sudden onset (Filipek, et al, 1999). The initial signs, occurring shortly after the first injections, are subtle, suggesting disease emergence, and consist of abnormalities in motor behavior and in sensory systems, particularly touch sensitivity, vision, and numbness in the mouth (excessive mouthing of objects) (Teitelbaum et al, 1998; Baranek, 1999). These signs persist and are followed by parental reports of speech and hearing abnormalities appearing before the child's second birthday (Prizant, 1996; Gillberg & Coleman, 1992), that is, within several months of when additional and final injections are given. Finally, in year two, there is a full blossoming of ASD traits and a continuing regression or lack of development, so that the most severe expression of symptoms occurs at approximately 3-5 years of age. These symptoms then begin to ameliorate (Church & Coplan, 1995; Wing & Attwood, 1987; Paul, 1987). The exceptions are the subset of those with regression during adolescence or early adulthood, which may involve onset of seizures and associated neurodegeneration (Howlin, 2000; Paul, 1987; Tuunanen et al, 1996, 1997, 1999).

As in autism, onset of Hg toxicity symptoms is gradual in some cases, sudden in others (Amin-Zaki et al, 1979 & 1978; Joselow et al, 1972; Warkany and Hubbard, 1953). In the case of organic poisoning, the first signs to emerge are abnormal sensation and motor disturbances; as exposure levels increase, these signs are followed by speech and articulation problems and then hearing deficits (Clarkson, 1992), just like autism. Once the mercury source is removed symptoms tend to ameliorate (though not necessarily disappear) except in instances of severe poisoning, which may lead to a progressive course or death (Amin-Zaki et al, 1978). As in autism, epilepsy in Hg exposure also predicts a poorer outcome (Brenner & Snyder, 1980).

Long term prognosis: The long term outcomes of ASD and mercury poisoning show the same wide variation. Autism is viewed as a lifelong condition for most; historically, three-fourths of autistic individuals become either institutionalized as adults or are unable to live independently (Paul, 1987). There are, however, many instances of partial to full recovery, in which autistic traits persist in a much milder form or, in some individuals, disappear altogether once adulthood is reached (Rogers, 1996; Church & Coplan, 1994; Szatmari et al, 1989; Rimland 1994; Wing & Attwood, 1987).

Upon exposure, mercury entering the bloodstream tends to accumulate in tissues and organs, primarily the brain (Koos and Long, 1976; Lorscheider et al, 1995). Once inside tissues, and particularly the brain, mercury will linger for years, as shown on X rays of a

poisoned man 22 years after exposure (Gosselin et al, 1984), as well as autopsies of humans with known mercury exposure (Pedersen et al, 1999; Joselow et al, 1972) and primate studies (Vahter et al, 1994). The continued presence of mercury in organs and the CNS in particualr would explain why autistic symptoms might persist, why researchers such as Zimmerman or Singh would detect an on-going immune reaction, why epilepsy might not emerge until adolescence, or why sulfate transporters in the intestine or kidney might continue to be blocked.

Nevertheless, despite the continued presence of Hg in tissue, the degree of recovery from mercurialism varies greatly. Even in severe cases, there are reports of full or partial recovery (e.g., Adams et al, 1983; Vroom & Greer, 1972; Amin-Zaki et al, 1978). In less severe cases, especially those in which exposure occurs early in life, the more severe symptoms may ameliorate over time, but milder impairments remain, especially neurological ones (Feldman, 1982; Yeates & Mortensen, 1994; Amin-Zaki, 1974 & 1978; Mathiesin et al, 1999; Vroom and Greer, 1972; EPA 1997, pp.3-10, 3-14, and 3-75). The wide variation in outcome is believed to be due, again, to individual sensitivity to mercury, in this case, the ability of some victims to develop "immunity" or a "tolerance" to Hg even when the metal is still present in tissue (Warkany & Hubbard, 1953).

Course of Disease:
Typical Autism & Ingested Organic Mercury

Typical Autism Progression & Thimerosal Administration

Birth	**2 mos**	**4 mos**	**6 mos**	**15 mos**	**2 yrs**	**3-5 yrs**	**6-18 yrs**	**Adults**
Hg dose	Hg dose	Hg dose	Hg dose	Hg dose				
Delay (no signs)	Delay (no signs)	subtle signs – move-ment	subtle signs - sensory	definite signs - hearing & speech	full array of symptoms	Height of symptom severity	Sympto m amelio ra-tion	Occasion -al full or partial recovery

Temporal & Dose-Response Relationship for Effects of Ingested Methylmercury

Hg dose	Delay (no signs)	1st sign – sensory	2nd sign – move-ment	3rd sign – speech/ art-iculation	4th sign – hearing	full array of symp-toms	Sympto m amelio ra-tion (or death)	full or partial recovery

g. Thimerosal Interaction with Vaccines

As noted above, for most ASD children symptom onset is gradual, but for a significant minority it is sudden. Additionally, many parents believe there is a connection between their child's autism and his or her immunizations. The Cure Autism Now Foundation, for example, reports that half the parents who call its hotline mention such a connection (Portia Iversen, CAN president, personal communication). The association extends not only to the mercury-containing vaccines – DTP/DTaP, HIB, and Hepatitis B – but also to those without thimerosal, particularly the MMR (Bernard Rimland, president, Autism Research Institute, personal communication). Parents may describe a variety of post-vaccine scenarios: a fever followed by a short recovery period and then a more gradual symptom onset; onset of symptoms immediately and suddenly after inoculation with or

without fever; or even a mildly impaired child whose condition worsened after vaccination (CAN Parent Advisory Board Internet list; St. John's Autism Internet list).

While it is possible that any temporal association between vaccination and emergence of autism is due to chance, Warkany and Hubbard, who successfully proved the connection between acrodynia and mercury poisoning to the medical community 50 years ago, offer alternate explanations. In their 1953 article in *Pediatrics*, they made the following points:

(a) They noted that high fever accompanied by a rash after mercury administration can be signs of a "typical, acute, mercurial reaction," and "acrodynia may follow, immediately or after short intervals, acute idiosyncratic reactions to mercury." This reaction was independent of hypersensitivity to mercury, as detected from skin tests, as they reported that only 10% of acrodynia victims responded positively to Hg on patch tests.

Thus in ASD, the fevers and deteriorations seen by parents immediately after a thimerosal-containing vaccine injection may be a systemic reaction (and not a hypersensitivity response) to the mercury content, and this reaction may subsequently progress to the emergence of autism, just as topical mercury administration produced fever and then acrodynia over 50 years ago.

(b) Warkany and Hubbard provided some tentative observations that the administration of a vaccine, irrespective of whether or not it contains thimerosal, can set off a reaction to any mercuric compound that may also be given to a child, which in the case of acrodynia, would be topical mercury in powders or rinses. This inter-reactivity might explain the pronounced effects from the MMR among subsequently-diagnosed autistic children:

> "[One patient] underwent a fourteen day course of antirabies injections six weeks before outbreak of acrodynia. Ten days after completion of the therapy she was treated with ammoniated mercury ointment and subsequently acrodynia developed...[In another case] antirabies treatment preceded the disease by three months. In several children various immunization procedures preceded the onset of acrodynia in addition to [topical] mercurial exposure. This could be purely coincidental or the vaccination material may play a role as an accessory factor. It is noteworthy that many vaccines and sera contain small amounts of mercury as preservatives which are injected together with the biologic material. These small amounts of mercurial compounds could act as sensitizing substances. In several instances vaccination against smallpox preceded the development of acrodynic symptoms, and some patients were exposed to bismuth, arsenic, lead, and antimony in addition to mercury. Such observations deserve attention."

(c) Finally, these two researchers observed that some individuals would react to mercury and then, upon re-exposure, not show any effects, i.e., they had acquired an unexplained tolerance to it. In other cases, Hg sensitivity would be maintained. Rarely, though, would reactivity occur with the first dose: "more often the patient tolerates several" before the reaction occurs.

> "The organism can harbor appreciable amounts of mercury while remaining in perfect health, and then, for unknown reasons, these innocuous stores of mercury become toxic. It seems in such cases as if the barriers which held the mercury in check break down without provocation, or as if the mercury had been converted from a nontoxic to a toxic form..."

In ASD, this delayed sensitivity would explain why some might develop autism later, not after the first few vaccines, and it would also explain in part why the more vaccines that are given, the more likely it is that a given individual will develop a reaction since there are more "sensitizing" opportunities. Importantly, in susceptible individuals, the reactions described by Warkany and Hubbard are likely to occur if mercury's presence occurred via injected thimerosal.

IV. DETECTION OF MERCURY IN AUTISTIC CHILDREN

In the past, hair, urine, or blood tests from autistic subjects have mostly found lead rather than mercury (Wecker et al, 1985), but this is likely due (i) to lead's pervasiveness in our environment, coupled with autistic children's pica tendencies and general inability to detoxify *any* heavy metal (LaCamera and LaCamera, 1987; Edelson & Cantor, 1998); (ii) to the difficulty in detecting Hg, especially in older children exposed early in life, since remaining mercury is sequestered in tissue; and (iii) to the greater affinity of standard chelators used in challenge tests (e.g., DMSA) for lead over mercury, making lead more readily detectable in such exams (Frackelton and Christenson, 1998).

More recently, a number of parents of younger autistic children, in whom mercury is more likely to be detectable, have reported higher than expected levels of mercury in hair, blood, and urine samples. Cases studies are listed below, and more are in the process of documentation. Several parents have also noted improved function after chelation.

The Case Studies

We are providing data from several retrospective case studies of autistic children with associated tissue mercury burdens. In each case we have tried to identify potential sources of exposure, although we have not been able to identify the exact amounts in some cases due to inadequate documentation. This information does not purport to be a rigid scientific study, but rather an initial effort to demonstrate that there may be a problem with mercury toxicity in children with autism. Our primary objective is to show that considerable amounts of mercury are found in the bodies of some autistic children. The data we present were derived from many sources: hair, urine and blood. Some of the samples were baseline and others were obtained utilizing a provocative agent, either DMPS or DMSA. Typically a single dose of DMPS will provoke more mercury from the tissue than a single oral dose of DMSA. Excretion levels will also vary depending on the amount of DMPS or DMSA given. There are also variations among these factors in the case studies.

Identifier: 0001SM **Sex**: M **Age**: 5 **DOB**: 4-25-94

Prenatal and Postnatal History: Premature contractions, which required bedrest during the 2nd and 3rd trimesters. Scheduled C-section at term with good apgars. Birth weight 8 lbs. 3 oz. Vomiting milk based formula, which subsided with a switch to soy formula at 2 months.

Developmental Landmarks: Completely normal development, meeting all developmental milestones until 20 months of age. Speech present with two word phrases.

Regression and Symptoms: At 20 months an unexplained loss of speech and eye contact (lateral gaze). He began lining up trains, developed preservations, and showed a marked decrease in attention. Diagnosed autistic at 26 months of age. Formal psychological evaluation at 30 months found expressive speech at 14-16 months, cognitive at 12-18 months, fine motor at 18 months, and play skills at 12 months. He

was described as withdrawn with alternating inattention or repetitive manipulation of objects.

Exposure Sources: He received multiple vaccines with thimerosal preservatives his first year, including influenza vaccine. The documented exposure the first year was 136.5mcg mercury. Mother with 1 amalgam filling and minimal dietary exposure. Child with no dietary exposure the first year of life. Families estimated consumption of seafood 3 times monthly.

Mercury Levels: Hair mercury 2.6 mcg with a norm reference of less than 2mcg. DMPS provacation (3mg per kg. IV) 7-7-99 resulted in 87 mcg mercury per g urinary creatine. Intermittent treatment with oral DMSA continued for 2 months with normalization of hair mercury levels.

Response to Treatment: Parents claim significant improvement in speech and behavior, also documented on neuropsychological evaluation on 1-14 and 1-21-00. "His ability to use language for social purposes has clearly increased and he could maintain exchanges for several turns without excessive difficulty. He has improved in his ability to initiate interactions and invitation to other children to play. Academic function at or above grade level. Impressive and highly encouraging rate of progress."

Identifier: 0002CM **Sex**: M **Age**: 5 **DOB**: 12-1-94

Prenatal and Postnatal History: Unremarkable prenatal course. Birth weight 8lbs.8oz. Maintained above the 95th percentile for height and weight the first year of life.

Developmental Landmarks: All early developmental landmarks - crawling, walking, and talking - were obtained on schedule.

Regression and Symptoms: Child went from age appropriate to severe autistic regression between 18 to 20 months. He lost speech, eye contact and became inattentive and withdrawn. Symptoms at 3 years include extreme thirst, echolalia, toe walking, high pain threshold, sleep disturbances, hyperactivity and obsessive behaviors.

Exposure Sources: No maternal amalgam history and minimal dietary exposure. He received all recommended vaccines, although without manufacturer data we are unable to calculate total exposure at this time. Known exposure from hepatitis B vaccine, 37.5 mcg mercury.

Mercury Levels: Hair mercury was 2.21ppm at 3 years and 3 months of age with a lab reference of 0-1.5ppm. DMPS provocation utilizing 3 mg. DMPS/kg given IV revealed:

46 micrograms of mercury / g creatine on 12-18-98
86 micrograms of mercury / g creatine on 3-25-99
46 micrograms of mercury / g creatine on 7-27-99
36 micrograms of mercury / g creatine on 9-30-99
Normal reference for urinary mercury 0-3 micrograms / g creatine.

Between DMPS infusions the child received DMSA 100 mg. orally two days a week, with glutathione 75 mg. twice daily, glycine 900 mg. on day prior to DMSA and glycine 900 mg. on DMSA treatment days.

Response to treatment: On 3-22-00 the parents reported marked behavioral improvement, particularly over the past two months. He now responds to his name and follows instructions. He has developed original speech without echolalia, and obsessive behaviors have declined.

Identifier: 0003HC **Sex**: M **Age**: 3yr. 11mo. **DOB**: 4-11-96

Prenatal and Postnatal History: Prenatal history was unremarkable. Infant was thought to be 4 weeks premature, although birth weight was that of a term infant at 8lbs. 6oz. He developed jaundice shortly after birth and was treated with phototherapy. He was briefly given antibiotics for a suspected infection the first 3 days of life.

Developmental Landmarks: Parents report that his development was normal until 12 months. He was crawling but did not begin to walk until 18 months of age with the support of a walker.

Regression and Symptoms: Some concerns at 13 months, marked regression at 16 months. Six to seven spoken words in use at 12 months were entirely lost. Vacant stares predominated and he began biting his hands. Officially diagnosed autistic at 2 1/2 years of age.

Exposure Sources: Mother had 8 amalgams. He also received exposure via vaccine, but total dose is not available at this time.

Mercury Levels: Hair mercury at 2 years 7 months was below detection limits. DMSA provacative protocol with 10 mg per kg per dose three times daily for three days with 24 hr urine screen for heavy metals day 2 revealed:

3.2 micrograms of mercury / g creatine on 6-21-99
28 micrograms of mercury / g creatine on 9-13-99
13 micrograms of mercury / g creatine on 10-12-99
Normal lab reference 0-3 mcg Hg per g creatine.

Response to treatment: Parents feel certain that DMSA chelation has resulted in improvement in their son. They noticed almost immediate improvement during the three days of treatment along with dramatic improvement the past six months. He is "much more with it and curious about his world". Although he is still not talking, he is having frequent vocalizations. He just started running for the first time 6 weeks ago.

Identifier: 0004WR **Sex**: M **Age**: 6 **DOB**: 2-2-94

Prenatal and Postnatal History: Prenatal history unremarkable with the exception of breech presentation. C-section preformed and apgars were 9 and 10. Birth weight, 8lbs. 11oz. Normal postnatal course.

Developmental Landmarks: He easily met and exceeded all early developmental landmarks and was described as a pleasant, happy baby.

Regression and symptoms: Shortly after his first birthday he developed numerous infections and was hospitalized for a respiratory illness. He received antibiotics, steroids, and oxygen and was discharged on day three. By 15 months he had lost speech and

interaction. At 18 months he developed a very limited diet with bouts of bloody, culture negative diarrhea. Officially diagnosed autistic at 5 yrs, although he had been receiving services for autism from the school system since age 3.

Exposure sources: This child received all early vaccines with thimerosal preservative. At 2 months of age he received 62.5 mcg of mercury which represented a 125 fold increase above EPA guidelines based on his weight. This occurred again at 4 months, 62.5 mcg mercury and 50 mcg mercury at 6 months, 11 months 12.5mcg mercury and at 18 months, 50 mcg mercury for a total of 237.5 mcg of mercury. Mother also reports 5 dental amalgams and minimal dietary exposure. Child has never eaten fish or seafood.

Mercury Levels: Hair analysis from 20 months revealed 4.8 ppm mercury with a reference range of 0-1ppm and aluminum 40.2 with a reference of 0-9ppm. Note this sample was not sent for analysis until the child was already 5 1/2 years at which time the mother became aware of his early mercury exposure from vaccines. A subsequent analysis at 5 ½ years revealed normal levels of mercury and elevated lead 1.14 ppm with a normal reference 0-0.5, aluminum 23.2, and antimony 0.017 with reference of 0-0.03 and bismuth 0.19 with reference of 0-0.11. Initial treatment with oral DMSA removed 17 mcg per g creatine lead with reference 0-15 mcg per g creatine. Oral cyclic chelation was continued for 5 cycles with lead again present at 15 mcg per g creatine down to normal levels at the 5th cycle.

Response to treatment: Parents report marked improvement with each round of chelation. The last two cycles were not as pronounced as the first 3 cycles of treatment. An increase in spontaneous language and a general overall increase in all areas of functioning were also noted.

Identifier: 0005ZH **Sex**: M **Age**: 10 **DOB**: 5-28-89

Prenatal and Postnatal History: Unremarkable pre- and postnatal course. Term vaginal delivery. Pitocin given for failure to progress. Birth weight 7 lbs. 14 oz., good apgars.

Developmental Landmarks: Mother reports he was a very alert and pleasant infant who easily obtained all his early developmental landmarks with the exception of crawling. He progressed directly to walking at 8 ½ months. He began to babble and had developed some speech the first year of life, which did not progress.

Regression and Symptoms: Parents were concerned about his speech delay but attributed it to other factors. He also developed a very picky diet with a preference for starches. He also would line up toys and repeat phrases but was not officially diagnosed autistic until 5 years of age.

Exposure Sources: Mother with multiple dental amalgams. DPT vaccine known to have mercury 25 mcg per dose at 2,4,and 6 months. Child did eat fish sticks as a toddler but parents switched to only farm raised fish.

Mercury Levels: A 24 hour heavy metal challenge at 9 years of age removed 67 mcg of mercury. Unfortunately, the parents were not able to financially afford further treatment at that time.

Identifier: 0006MA **Sex**: M **Age**: 4 ½ yrs. **DOB**: 8-24-95

Prenatal and Postnatal History: Uncomplicated pregnancy, term vaginal delivery, apgars 9 and 10, birth weight 7 lbs. 6 oz. Quickly learned to breast feed, unremarkable postnatal history.

Developmental Landmarks: Easily met all early developmental milestones. Described as being very social with good eye contact. He was saying Mama, bye-bye, and babbling at 14 months.

Regression and Symptoms: According to the parents, at 16 to 17 months he began to slide into his own world. He stopped responding to his name and making eye contact. He also lost language and social interactions. Parents also report muted emotions.

Exposure Sources: This infant was exposed to 100 mcg mercury the first six months of life via vaccines. No dietary exposure from seafood or fish to the child. Mother with 9 amalgam fillings and only occasional fish consumption during pregnancy.

Mercury Levels: Hair analysis without mercury detection. Heavy metals challenge urine 8.6 mcg / g / creatine with a norm reference of 0-2.5 mcg / g / creatine at 3 years 8 months of age. He is currently undergoing cyclic chelation therapy with oral DMSA.

Response To Treatment: Parents report that his level of awareness, eye contact, emotions, and receptive and expressive language have all improved since starting the chelation program.

Identifier: 0007EK **Sex**: M **Age**: 5 **DOB**:12-10-94

Prenatal and Postnatal History: Uncomplicated prenatal and postnatal history. Birth weight 8 lbs., apgars 9 and 9.

Developmental Landmarks: Easily met all early milestones. Parents report precocious language skills. At 10 months he was talking with phrases "oh, there it is."

Regression and Symptoms: At 12 months there was a major and obvious reversal in behavior. Speech, social interaction, and laughter began to fade away rapidly. He began toe walking, lost eye contact, grew inattentive, and developed repetitive behaviors.

Exposure Sources: Mother with 8 dental amalgams, no fish consumption. Infant received thimerosal in vaccines, but unable to calculate exposure at this time. At 3 years of age 8 amalgam fillings were placed with an initial improvement in behavior for 3 weeks, then a decline to a level much worse than before the dental work with progressive decline.

Mercury Levels: Prior to chelation non-detectable, 12-27-99. DMPS IM + oral DMSA/EDTA and DMSA/EDTA supp. (unspecified doses).

2-19-99 41 mcg / g creatine of urinary mercury.

DMSA supp. 250mg bid were used 3 x week, every other week subsequent to provocation testing. Oral DMSA provocation for urinary Hg pending.

Response to Treatment: Multiple dietary and secretin infusions are concurrent to the DMPS/DMSA chelation, but mother is firmly convinced that the latter are contributing to

excellent behavioral and somatic gains. Improvement in eye contact within 2 days of DMSA is evident. Improvement in speech, sociability and playing with toys are seen consistently right after DMSA and are reported to be on a gradual upward trend. A full sentence was uttered on or about 3-1-00.

In addition to the above case studies, we have collected preliminary data on three autistic children who have not undergone chelation. These children also exhibit elevated levels of mercury.

Data on Non-Chelated ASD Children

Age	Sex	Mercury level and source of sample
2 ½ yrs.	Female	Heavy metal hair analysis 5.6ppm (ref.range 0-2)
4 ½ yrs.	Male	Hair analysis 1.2ug/g (ref. <0.4) PRBC 18.4 (ref <9)
5 yrs.	Male	Hair analysis 1.8 ppm PRBC 18.3 (ref.<9)

Discussion

Several observations from these case studies deserve mention. One is that all of the children experienced a regressive form of autism. Other findings are that (i) low levels of mercury in hair may be associated with large amounts of mercury excretion on provocation and (ii) initial levels of provoked mercury may not be as high as subsequent ones. Mercury in the hair will only reflect a current or recent exposure of approximately one year or the body's active detoxification of mercury. This was evident in a child with non-detectable levels of mercury in the hair and positive levels on provocation.

In the case studies there is also a trend of higher numbers for mercury in younger children (20 month hair sample of 4.8 ppm and 2 ½ year hair sample of 5.6 ppm). This may be related to the fact that the testing was performed closer to the time of exposure. Hair levels of mercury greater than 5.0 ppm are considered diagnostic for mercury poisoning (*Applied Toxicology*, 1992). Among the majority of these case studies much more modest elevations of mercury, if detected at all, were associated with high levels of provoked mercury.

There are no standards for provoked levels of mercury in children in the context of behavioral disorders. Therefore, we surveyed a large number of physicians treating adults with chronic health problems diagnosed as secondary to mercury. These clinicians advise that tolerable limits may vary according to the general health of the patient and associated health problems. All consulted agreed that in adults excretion of 50 mcg of mercury per gm creatine after intravenous DMPS challenge is worrisome. We submit that the concern level for children should be even more stringent. High levels of mercury are demonstrated in some children without a history of fish consumption, amalgam burden, or known environmental exposure, suggesting the role of vaccines as a contribution to body burden.

The families who submitted these case histories wanted to tell their stories because their children are noticeably improved after treatment for mercury. Whether this improvement was sudden or gradual, the parents are convinced that lessening the mercury and heavy metal burden has helped their child. They ask us to request support for much needed research in this area.

DISCUSSION

How reasonable is it to claim that the most common form of autism, where there is normal development and then regression, could be caused by mercury poisoning? There are several reasons to believe that this process has indeed occurred.

Diagnostic Criteria Are Met

Medical literature demonstrates that mercury can induce autism-spectrum traits, and this association extends to mercury's localization within specific brain nuclei. In attempting to address "the totality of the syndrome" (Bailey et al, 1996), we have shown that every major characteristic of autism has been exhibited in at least several cases of documented mercury poisoning, and that every major area of biological and neurological impairment implicated in ASD has been observed with Hg exposure. Recently, government-directed studies have revealed that the amount of mercury given to infants receiving vaccinations exceeds safety levels. The timing of mercury administration via vaccines coincides with the onset of autistic symptoms. Case reports of autistic children with measurable mercury levels in hair, blood, and urine indicate a history of mercury exposure along with inadequate detoxification. Thus the standard criteria for a diagnosis of mercury poisoning in autism, as outlined at the beginning of this paper, are met. In other words, mercury toxicity is a significant contributing factor or primary etiological factor in many or most cases of autism.

Unique Form Would be Expected, Implicates Vaccinal Thimerosal

Symptoms manifested in mercury poisoning are diverse and vary by the interaction of variables such as type of mercury, age of patient, method of exposure, and so forth. Thus, although it could be argued that in all the thousands of cases of past Hg poisonings, no instance of autism could be found, such an argument fails to take into account the possibility of unique expression. It would be comparable to saying that, because in all the cases of Minamata disease no instance of acrodynia could be found, then acrodynia could not be caused by mercury poisoning. Since there are no case reports or systematic studies in the literature of the effects of intermittent bolus doses of injected ethylmercury on "susceptible" infants and toddlers, it would be reasonable to expect that symptoms arising from this form of mercury poisoning would present as a novel disease. In fact, given the high neurotoxicity of organic mercury, its known psychological effects, and the age at which it has been given in vaccines, it would almost be a given that the "novel disease" would present as a neurodevelopmental disorder like autism.

Conversely, the fact that autism meets the diagnostic criteria for mercury poisoning, yet has never been described as a mercury-induced disease, requires that the disorder must arise from a mode of mercury administration which has not been studied before. This would rule out other known sources of Hg like fish consumption or occupational mercury hazards, as these have been well characterized. It is possible that another under-investigated mercury route, such as maternal Hg exposures (e.g., from vaccinations, thimerosal-containing RhoGam injections during pregnancy, or dental fillings) or infant exposures to thimerosal-containing eardrops or eyedrops, might be a factor, and this cannot be ruled out.

Historical Precedent Exists

There is a precedent for large scale, undetected mercury poisoning of infants and toddlers in the syndrome that came to be known as acrodynia or pink disease. For over 50 years, tens of thousands of children suffered the bewildering, debilitating, and often life-long effects of this disease before its mercury etiology was established, as Ann Dally relates in *The Rise and Fall of Pink Disease* (1997, excerpts):

> "Acrodynia is a serious disease that was common, at least in children's clinics, during the first half of the present (20th) century. Reports abound of children too miserable to acknowledge their mothers, such as the child who kept repeating, "I am so sad." One unhappy mother was quoted as saying, "My child behaves like a mad dog." In most cases the condition improved spontaneously, but was often regarded as chronic. Mortality varied from 5.5% to 33.3% and was usually about 7%. Most physicians who speculated on the causes of pink disease believed in either the infective or the nutritional theory. No one seems to have suggested that it might be due to poisoning. It was a tradition to advise student doctors to treat cases of difficult teething with the mercury powders that were eventually to be revealed as the cause of the disease. The ill-effects of mercury on the mouth had been known at least since the time of Paraclesus, but it was not until 1922 that the pediatrician, John Zahorsky, commented on the similarity between pink disease and mercury poisoning. He dismissed rather than pursued his new idea of possible mercury poisoning and suggested a theory that was more in tune with current fashion. Most doctors, even those skilled in the use of calomel, associated mercury poisoning with adults (syphilis, industrial poisoning, hatters shakes) rather than with infants. By 1935 the disease was seen in every children's out-patient clinic.
>
> The mystery began to be solved in 1945 by Dr. Josef Warkany, of the Cincinnati Children's Hospital. He and his assistant found large amounts of mercury in the urine of a child with pink disease. They did not publish their findings until 1948, but it is noteworthy that the news seems not to have spread through the small and tightly knit pediatric world, where everyone knew everyone else. It was probably because the idea was unfashionable and contrary to the conventional wisdom. The theory that mercury poisoning caused pink disease was gradually accepted, but against resistance, particularly by older men and those in powerful positions. Mercury was withdrawn from most teething powders after 1954, initially through voluntary action by the manufacturers because of adverse publicity and probably in the hope of avoiding statutory prohibition. Pink disease almost disappeared. Later in the decade the theory was widely accepted and soon pink disease was no longer part of the usual pediatric out-patient clinic."

Thus, like acrodynia before it, autism may in fact be "just another" epidemic of mercury poisoning, this time caused by childhood vaccinal mercury rather than infant teething powders.

Barriers Preventing Earlier Discovery Are Removed

The priorities and methods of research experts in the autism and mercury fields have prevented the association between mercurialism and ASD to be recognized until recently.

The effects on humans of mercury-containing medicinals and home remedies used to be studied quite regularly by medical researchers (Warkany and Hubbard, 1953); but since, aside from vaccinal thimerosal, such products have declined dramatically in number since the 1950s and 1960s, most mercury researchers today focus on biochemical studies or environmental sources like fish and coal plants. Some mercury experts seem surprised to learn that Hg is present in infant vaccines (authors' personal experience), and as recently as 1997, when the EPA released its massive review of extant mercury research, vaccines were not even mentioned as a potential source. Thus it is not surprising that mercury experts have never investigated thimerosal as they have, say, contaminated whale meat consumption in the Faroes Islands or Hg exposure from Amazonian goldmines (NAS, 2000).

Likewise, it is not surprising that neither mercury experts nor autism professionals have ever investigated autism as a possible disease of mercury exposure. Since its discovery by Kanner, autism has been characterized in almost exclusively psychological terms. The descriptions have been such that the symptoms would be essentially unrecognizable as manifestations of poisoning to any mercury expert not looking closely. A perfect example is Kanner himself, who recorded feeding problems and vomiting in infants and concluded: "Our patients, anxious to keep the outside world away, indicated this by the refusal of food." Bruno Bettleheim, who dominated autism discourse in the 1950s and 1960s and blamed the entire disorder on "refrigerator mothers" who forced the withdrawal of the child, asserted, "the source of the anxiety is not an organic impairment but the child's evaluation of his life as being utterly destructive" (1967, reported in ARI Newsletter). In 1987, Robert Sternberg would propose a "unified theoretical perspective on autism" by defining the disorder in terms of a "triarchic theory of intelligence," and in the same publication Lorna Wing and Anthony Attwood would write:

> "Sometimes young autistic children will stand in a dejected posture, with tears streaming down their faces, as if they suddenly felt their helplessness in the face of a world they cannot understand."

Even as recently as 1995, a typical slate of articles in the dominant *Journal of Autism and Developmental Disorders* (April 1995) would consist of eight psychological pieces (example: "Generativity in the Play of Young People with Autism") and one biomedical one (on biopterin). Thus biomedical research in autism existed, but it was mostly relegated to the margins as psychology held center stage, and the symptomatic characteristics of autism continued to be presented in accord with psychological biases.

In the latter part of the 1990s, the situation on both sides changed. Congressional mandate led to the public quantification of the cumulative amount of mercury in vaccines, raising interest in understanding its effects. Parent organizations like CAN, NAAR, and ARI, working with the NIH and other researchers, engineered an autism research agenda which is more heavily focused on underlying physiological mechanisms of the disease. With parents already suspecting a vaccine-autism link, the environment was right for investigations focused on the link between vaccinal mercury and autism.

MEDICAL & SOCIETAL IMPLICATIONS

Affected Population

The NIH (1999, web site) estimates that there are nearly half a million Americans who suffer from autism, a devastating, debilitating, and lifelong disorder. Given the role of thimerosal as a major contributing factor in ASD, basic and clinical research efforts should be focused on understanding how mercury leads to autism in susceptible individuals and on finding effective methods to address the resulting Hg damage. Such research might focus on the following areas, with others undoubtedly still to be identified:

(a) Chelation methods which will work across all body tissues and especially the brain. The current standard chelators – DMPS and DMSA - appear unable to cross the blood-brain barrier. Other promising but less studied chelators like alpha lipoic acid can cross the bbb (Fuchs et al, 1997) and should be studied in autism.

(b) Mechanisms to induce immunity to Hg and which might possibly reverse the Th2 shift or IFNg expression which mercury causes. The work of Hu and colleagues suggests that Hg can cause an immune reaction in any individual, but some are protected by a counteractive immunosuppressive response, and Warkany and Hubbard have pointed out that individuals who are Hg-sensitive can later become "immune". It may be possible to engineer these responses in autistic individuals through careful research.

(c) Mechanisms which might reverse Na-Si transporter blockage in the intestines and kidney, thereby normalizing sulfate absorption.

(d) Techniques to eliminate the Hg-induced epileptiform activities found in the majority of autistic children, as outlined by LeWine et al.

(e) Stem cell applications in autism to repair brain damage that occurred during development.

Other Disorders

As pointed out by David Hartman (1998), mercury's ability to cause a wide range of common psychiatric disturbances should be considered in their diagnosis, and it might also be productive in developing hypotheses about and designing research studies for these other disorders. The disorders might include depression, OCD, dementia, anxiety, ADHD/ADD, Tourette's, and schizophrenia. Mercury may play a role in the etiology of some cases of these conditions. Conversely, investigating mercury's wide ranging effects upon neurobiological processes may lead to a quicker understanding of the organic etiologies in these other diseases which are now seen with increasing frequency.

Vaccination Programs

Universal compliance with the recommended vaccine schedule is a governmental, medical, and societal goal, since "vaccines save lives" (CDC). Our goal is not to negatively impact childhood immunization rates. Instead, we have been careful to

distinguish between thimerosal and vaccines. Thimerosal is not a vaccine; it is a preservative. Except for trace amounts, vaccines without thimerosal are currently available for all routinely recommended immunizations for children under 6 years (Institute for Vaccine Safety, 1999). Furthermore, it is possible to remove mercury from existing products. Merck, for example, delivered and received FDA approval for a thimerosal-free Hepatitis B vaccine in a record-breaking two months from the time the FDA publicly encouraged manufacturers to develop thimerosal-free alternatives (Pless, 1999; Merck, 1999). Thus, any issues being raised here are related to how vaccine programs are run, not with vaccines themselves.

The issues, of course, are: (i) first, how thimerosal was allowed to remain a component of the immunization program, even after 1953 when Warkany and Hubbard specifically named vaccinal mercury as a possible factor in acrodynia, or 1982 when the FDA issued a notice singling out thimerosal as especially neurotoxic as well as ineffective as a preservative (Federal Register, 1982); and (ii) second, why thimerosal remains in over 30 vaccine products today (FDA, 1999), and why the FDA, as of March 2000, has only "encouraged" rather than required the vaccine manufacturers to remove the thimerosal (William Egan personal communication). Although the CDC has stated that no adverse effects from thimerosal have been found other than hypersensitivity reactions, the sad fact is there have been no direct studies on the long term effects of intermittent bolus doses of ethylmercury injected in infants and toddlers. As Altman and Bland have aptly demonstrated (1995), “absence of evidence is not evidence of absence.”

These lapses in vaccine program oversight suggest that vaccine safety studies need to be bolstered. Current practice is to track adverse reactions only if they occur within one month of the vaccination. The experience with mercury clearly shows that an adverse event may not manifest for months if not years. Studies on adverse reactions must involve long term tracking of patients; they should investigate the impact of multiple injections as well as compare reactions to vaccines with and without various additives; and sample sizes need to be large enough to include especially sensitive groups. Finally, the FDA should require manufacturers to remove all remaining thimerosal from their vaccines immediately, so that another child is not lost to this terrible disease.

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