IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

N RE: CLAIMS FOR VACCINE INJURIES RESULTING IN AUTISM SPECTRUM DISORDER, OR A SIMILAR NEURODEVELOPMENTAL DISORDER, Various Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.,	Case No. Autism Master File **NOTICE OF FILING EXPERT REPORT OF MARCEL KINSBOURNE, M.D.** Special Master George Hastings

COMES NOW, the Petitioner by and through the undersigned counsel, who is a member of the Bar of the Court, and hereby gives notice to the Court and all parties of the attached submission of Marcel Kinsbourne's Expert Report into the Autism Master File.

DATED this 21st day of, 2008.

WILLIAMS LOVE O'LEARY & POWERS P.C.

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Of Attorneys for Petitioners

Report on General Causation: Thimerosal Exposure, Neuroinflammation, and the Symptoms of Regressive Autism

Autism Omnibus Proceedings

Marcel Kinsbourne, M.D.

Qualifications

I am a pediatric neurologist. I obtained the BM. BCh. degree, a British equivalent of the M.D. degree, at Oxford University. I then undertook medical specialty training in the United Kingdom (and New York University, Bellevue Hospital) in Pediatrics, Neurology and Pediatric Neurology. At the National Hospital, Queen Square, London, I was awarded the Queen Square Prize in Neurology. I was awarded Membership of the Royal College of Physicians of London (comparable to American Specialty Board Certifications in medical specialties), and also the D.M. (Oxon), a "Higher Doctorate", based on original medical research presented by dissertation. After holding an Oxford University Lectureship in Experimental Psychology, which is the basic science on which I have most relied in my medical research, I moved to Duke University Medical Center. There I was Associate Professor of Pediatrics and Neurology, Chief of the Division of Child Neurology and Director of the Developmental Evaluation Clinic. I next moved to Canada. I was Professor of Pediatrics (Neurology) at the University of Toronto and Senior Staff Physician at the Hospital for Sick Children. During this time I was Director of the Learning Clinic and I directed research on developmental disorders, funded by the Medical Research Council and other Canadian agencies. I returned to the United States, to become Director of the Department of Behavioral Neurology at the Eunice Kennedy Shriver Center for Mental Retardation, Waltham, MA, and Clinical Associate at the Massachusetts General Hospital. At the Shriver Center I was awarded numerous NIH-funded grants for my research program on children with problems in attention, language and learning. Concurrently, I consulted on developmental disorders both on an ambulatory basis and at the Fernald State School for Mental Retardation. Since 1995, I have been a Professor of Psychology at the New School University in New York and Research Professor of Cognitive Studies at Tufts University.

I have authored or co-authored more than 400 medical and scientific articles and chapters in textbooks and monographs. I discovered a neuroimmune syndrome, Kinsbourne Disease/Opsoclonus-Myoclonus Syndrome. I have contributed the chapter, "Disorders of Mental Development", to Menkes et al.'s Textbook of Child Neurology from its first (1974) through its seventh (2006) edition, and I have contributed chapters on allied topics to other neurology, pediatrics, and psychiatry textbooks. I am an author or editor of eight books or monographs. I am Past President of the International Neuropsychology Society and Past President of the Society for Philosophy and Psychology. I have been Policy Advisor to the Communication Disorders Branch of the National Institute of Neurological Disorders and Stroke. I have served on the Advisory Board of the Max Planck Society, Germany. I have participated in numerous meetings of Study Groups and Site Visits that review grant applications for funding of research projects by the National Institutes of Health. I have served or currently serve on the Editorial Boards of 28 medical and scientific journals. Concurrently with these academic activities, I maintained a limited clinical practice for children with developmental disabilities, including Autistic Spectrum Disorder (ASD). Throughout my medical career, I have accumulated extensive experience with disorders of mental development, such as Attention Deficit Hyperactivity Disorder, developmental language disorders, specific reading disorders, autistic spectrum disorders and mental retardation.

Since the National Vaccine Injury Compensation Act came into force some 19 years ago, I have assisted the United States Court of Claims as an expert witness in Neurology with hundreds of petitions for compensation for vaccine injury. I have twice testified on vaccine injury before U.S. Congressional Committees.

By virtue of my knowledge and experience as outlined above, I feel qualified to render an expert neurological opinion to the Court. A copy of my curriculum vitae is attached.

Basis of Opinions

All my opinions are expressed to a reasonable degree of medical and scientific probability, based upon my education, training, experience, research and review of the medical literature.

Scope of this Report

This report describes the biologically plausible mechanism by which exposure to mercury contained in the thimerosal added to many pediatric vaccines can be a substantial contributing cause of the symptoms of regressive autism observed in some of the affected children. It is offered in support of the petitioners' *general* theory of causation regarding the role of thimerosal-containing vaccines (TCVs) in the appearance of regressive autistic symptoms; that is, it supports the proposition that TCVs belong on the list of potential environmental factors to consider in evaluating the etiology of cases of regressive autism where other causes have been ruled out through differential diagnosis. This report does not offer any opinion as to whether any specific child's regressive autism is related to that child's thimerosal exposure.

Specifically, this report will examine the following issues:

1. Regressive autism as an independent subtype of autism spectrum disorder;

2. Interacting genetic and environmental factors as contributing to regressive autism;

3. Exposure to thimerosal as causing inorganic mercury (Hg++) to accumulate in the brain;

4. A neuroinflammatory response within the brain due to accumulated Hg++;

5. Neuroinflammation as engendering a brain state that can cause autistic symptoms;

6. The overarousal model: Its explanatory value for autistic behavior.

1. Regressive Autism as an Independent Subtype of Autistic Spectrum Disorder

A. Diagnosis of ASD

The various medical concomitants of autistic disorders are numerous but all infrequent or rare. (See my report on Cedillo.) Most of them feature prominent additional clinically evident abnormalities that motivate a further search for genetic or metabolic disorders. In the absence of such additional features as abnormal facial appearance, abnormal neurological examination, minor congenital abnormalities, etc., an exhaustive examination to rule out all these rare syndromes that feature autistic behavior is not currently considered to be justified (Filipek et al. 2000 PMRL# 0264). Moreover, with few exceptions, the known medical conditions that feature autistic behavior do not do so in isolation, without other abnormalities. Nor do they feature the virtually unique time course of the developmental regression observed in many children who become autistic during the first 12-24 months of life.

Classical ("congenital") and regressive autism differs sharply with respect to their known medical causations. A large number of causative medical factors have been associated with children with non-regressive autism, and a differential diagnosis excluding those possible causes is possible. I do not offer an opinion here about the possible etiology of the classical or congenital cases of autism, and will discuss issues of causation that relate to regressive autism.

Only a few medical conditions that cause autism feature a regression with loss of previously attained developmental skills, leading to an autistic endpoint. Rett Syndrome, Landau-Kleffner Syndrome and Heller's Disease (Childhood Disintegrative Disorder-CDD) each do feature regression from normal to autistic functioning. Rett Syndrome is limited to females, has additional identifying characteristics, and does not remit, as regressive autism has been known to do. Rett Syndrome can be excluded as a cause of the bulk of cases of regressive autism. The regression in Landau-Kleffner Syndrome is typically ushered in by seizures, whereas in regressive autism, seizures though frequent, usually appear later in the course of the disease. Landau-Kleffner syndrome can be ruled out in the bulk of cases of regressive autism. Also, Landau-Kleffner Syndrome and, by definition, Heller's disease, are not expected to present until

after three years of age, whereas in most children with regressive autism the regression begins in the second year of life. The appearance of regressive symptoms at earlier than three years of age rules out Landau-Kleffner Syndrome and Heller's disease as the medical causes of symptoms in any given child.

When the known causative factors of a child's autistic regression are ruled out through a thorough review of the relevant medical history, a reasonable differential diagnosis would then consider other potential causes that might have contributed to the regression.

B. Autistic Regression

The majority of autistic children exhibit some level of autistic behavior in the first year of life, which, if it is not recognized at the time is recognized retrospectively, and gradually becomes increasingly apparent. However, some autistic children develop relatively normally as infants, but regress in their developmental skills and begin to exhibit the behavioral hallmarks of ASD in the second year of life, or even later (Kurita 1985 PMRL# 0350, Hoshino et al. 1987 PMRL# 0529, Rogers and Di Lalla, 1990 PMRL# 0349, Tuchman et al. 1991 PMRL# 0343, Tuchman and Rapin 1997 PMRL# 0329, Kobayashi and Murata 1998 PMRL# 0308, Richler et al. 2006 PMRL# 0279). In the course of the second year of life, children have usually acquired observable and measurable skills in language, play, and interactivity. The loss of such skills presents as cognitive and socioemotional regression, leading to the designation of a "regressive" subtype of autism, which has been said to involve about 20-40% of the ASD population (Lord et al. 2004 PMRL# 0310, Richler et al. 2006 PMRL# 0279). Autistic regression was confirmed by Woo et al. (2007) in 61 percent of children with autism that were reported to the VAERS system.

Overt seizures or epileptiform EEGs are common in ASD, but they are particularly frequent in children who had a history of regression in language (Tuchman and Rapin 1997 PMRL# 0329, McVicar et al. 2005 PMRL# 0375). Autistic children more often have gastrointestinal symptoms than children in the general population (Valicenti-McDermott et al. 2006 PMRL# 0299). However, Richler and colleagues found that children with regressive autism have still more gastrointestinal symptoms than non-regressive autistic children

An autistic endpoint is typically reached incrementally, arising indefinitely early in development and gradually becoming better defined. But in some children it is reached by regression from a previously normal developmental trajectory. In the past, when "autism" was assumed to be a unitary disorder (except for rare syndromic exceptions), it was simply taken for granted that autism could "present" in these two alternate ways. Now that the etiological heterogeneity of ASD is widely acknowledged, it can no longer be assumed without further study that these sharply contrasting natural histories arise from the same underlying pathogenesis. Autistic regression is an unexplained encephalopathy, and one can no longer legitimately extrapolate findings from "classical" ASD to autistic regression. Both epidemiologically and biomedically, each has to be studied in its own right.

Instead of broadening out into global dementia, like metabolic brain degenerations, autistic regression is self-limiting. It reaches a plateau of autistic symptoms and deficits, which varies widely in severity between individuals, and a plateau of mental function that also varies widely, ranging in level between the normal and the profoundly subnormal. The disorder may continue at that level, become more severe (especially if severe epilepsy ensues) or remit.

Do the majority of children with ASD share a common (as yet unidentified) causation? The scientific consensus no longer favors this notion. "It is time to give up on a single explanation of autism" (Happe et al. 2006 PMRL# 0326, page 1218). Bishop (Bishop 2006, PMRL# 0368) has explained how different adverse influences may cause one or another of the cardinal impairments that characterize ASD, such as language disorder or social deficit. Although autistic regression has long been recognized, the medical literature is almost devoid of attention to the mechanism of regression into autism, or the factors that trigger autistic regression.

C. Incidence of ASD

It is generally agreed that the incidence of the ASD diagnosis is rising spectacularly. Changing diagnostic criteria, improved ascertainment and diagnostic substitution may have contributed to this rise in diagnoses. But there is no proof at all that any of these factors or all of them in

combination, can account for anything like the actual rise in autism rates (Rutter 2000 PMRL# 0377). Furthermore, the proportion of ASD children of the regressive subtype remains at a level of between 20 and 30 percent. There have not been any changing diagnostic criteria for regression, and regression of development into non-autistic states, though it does occur due to certain brain degenerations, is rare. Regression is so much more striking and even shocking, as compared to slow development that it is hard to imagine that in the past it was simply not noted in many cases. Diagnostic substitution is a non-starter, since alternate descriptions, such as mental retardation and learning disabilities, are not characterized by regression, These considerations indicate that the rise in the number of cases of regressive autism is no artifact, but is very real. Genetic causation cannot explain this, but gene-environment interaction can, if exposure to provocative environmental factors is correspondingly increasing.

I make no claim as to why the incidence of ASD has been rising steeply, and I do not know the incidence of regression into ASD that is due to exposures to TCVs. I have reviewed the epidemiology with respect to ASD. I could not find any reliable epidemiological study that examined in a controlled fashion the association between regressive autism and any exposures, including TCV exposures, and I concur with Dr. Greenland's opinion in this regard. To extrapolate epidemiological findings from undifferentiated studies of ASD in general to a TCV-related regressive subtype is invalid, because of the heterogeneity of conditions subsumed by the ASD label. The epidemiological literature with respect to ASD in general is therefore not informative as to the association between TCVs and the regressive phenotypes of autism.

2. Interacting Genetic and Environmental Factors as Contributing to Regressive Autism

Autism is associated with genetic risk factors (Ritvo et al. 1989 PMRL# 0504, Bolton et al. 1994 PMRL# 0307, Bailey et al. 1995 PMRL# 0090, Bailey et al. 1998a PMRL# 0469). Identical (monozygotic) twins share an identical genome (suite of genes). Fraternal (dizygotic) twins like singleton siblings only shared 50 percent of their genomes. The extent to which it is probable that if one twin has a disorder, the other has it too, is termed the concordance between the twins. For disorders under genetic influence, concordance is expected to be much greater for identical than for fraternal twins. The strongest evidence for genetic influence derives from the repeated

observation that concordance for ASD between monozygotic (identical) twins is far greater than between dizygotic (non-identical) twins (e.g., Bailey et al. 1995 PMRL# 0090).

However, a wide differential between the concordance for autism of identical and fraternal twins does not prove that a genetic variant is the one and only cause of ASD. The same differential would be observed if the disorder were partly, or even entirely, due to gene-environment interaction. Briefly, if the autistic proband of an identical twin pair has a genetic vulnerability to react to an environmental factor by developing autism, then the other twin with an identical genome, is also vulnerable to this factor, and therefore also likely to become autistic after encountering it. The twin pair is concordant. However, if the proband in a non-identical twin pair is vulnerable to this factor and becomes autistic, then the other twin will be no more likely than other siblings are, to react to the factor by becoming autistic. Such a genetically identical twin pair would be discordant for ASD, based on differences in gene-environment interaction.

"Gene-environment interactions occur when the effect of exposure to an environmental pathogen on a person's health is conditional on his or her genotype" (Caspi and Moffit 2006 PMRL# 0336, page 583). Genetic risk factors generate vulnerabilities that remain latent unless and until they interact with non-genetic triggers to cause the clinical disorder (gene-environment interactions). Rutter (2004 PMRL# 0378) states, "Both quantitative and molecular genetics have shown the importance of gene-environment interplay with respect to the commoner disorders of emotions and behavior. In particular it has been found that genetic influences moderate people's vulnerability to environmental risks".

Bacterial or viral infections, toxins, nutritional factors and other stresses on the developing nervous system are recognized to be environmental risks (Herbert 2005 PMRL# 0371, Hertz-Picciotto et al. 2006 PMRL# 0080). Trottier et al. (1999 PMRL# 0263) point out: "the prevailing view is that autism is caused by a pathophysiological process arising from the interaction of an early environmental insult and a genetic predisposition" (page 113). Lainhart et al. (2002 PMRL# 0091) concur: "Environmental events however may act in an additive or "second hit" fashion in individuals with a genetic vulnerability to autism" (page 231). In the discussion that follows, I explain my opinion that exposure to TCVs leading to the accumulation of inorganic

(Hg++) in the brain during key periods in infant brain development is a medically reasonable candidate for having delivered this "second hit" to a vulnerable set of children who later display the symptoms of regressive autism.

The causal role of gene-environment interaction has become firmly established in the mainstream of autism research and theory. Researchers at Johns Hopkins University School of Medicine note that "although the neurobiological basis for autism remains poorly understood, several lines of research now support the view that genetic, environmental, neurological, and immunological factors contribute to its development." (Vargas 2005 PMRL# 0069, page 67). Herbert (2006 PMRL# 0079, page 681) concludes that "autism is a systemic genetically influenced condition with environmental contributors that affects the brain". The Institute of Medicine convened a two-day workshop in Washington, D.C. in April 2007 which was devoted entirely to the potential role of environmental factors in the etiology of autism spectrum disorders. Speakers emphasized the complex interplay between genetic factors or "vulnerabilities" and the environmental exposures that potentially lead to the development of autistic symptoms. Dr. Isaac Pessah, Director of the NIEHS/EPA Children's Center for Environmental Health and Disease Prevention: Environmental Factors in the Etiology of Autism, explained that "if there are many genes involved [in autism] and more than one gene in any individual that is susceptible to autism, environment must play a factor." (*Autism and the Environment: Challenges and Opportunities for Research,* Workshop Proceedings, PMRL# 0443 page 32). Later in those proceedings Dr. Tom Insel, Director of the National Institute of Mental Health, acknowledged that the NIH "had not paid enough attention to environmental factors," and explained that "it is fair to say that [this] is going to be an area of increased interest at NIH." (page 260).

When children gradually lapse into autism in the second year of life, a triggering event presumably launched a disease process that is active at least during the course of the autistic regression. Different triggers may be involved in different cases. Since autistic regression does not necessarily follow a viral infection, vaccination, or toxic exposure, it must also have other causes. In many cases, however, there is no viable alternative diagnostic option other than the involvement of a post-natal environmental insult or exposure.

3. Exposure to Thimerosal as Causing Inorganic Mercury (Hg++) to Accumulate in the Brain

Dr. Aposhian's report describes how the ethylmercury constituent of thimerosal is broken down into inorganic mercury (Hg++), and how the Hg++ enters the brain. I rely on his expertise and opinions as regards those issues. The potential neurological significance of Hg++ in the developing brain is its role in triggering a neuroinflammatory process that leads to the appearance of regressive autism symptoms in some children. It is this neuroinflammatory process, rather than an acute, cytotoxic mercury poisoning or "intoxication," that is the subject of this report and of my opinion.

In the mid-1990s Burbacher and his colleagues based a series of studies on controlled-dose methylmercury exposures in a group of adult monkeys. They performed multiple analyses of the post-mortem brains that were designed to examine any changes to brain pathology associated with the mercury exposures. The project sought information regarding low-dose, sub-clinical, sub-acute exposures to mercury, as distinct from focal damage caused by high dose exposures. It was designed to examine the speciation of mercury in the brain following such exposures, and to observe cell damage across different areas of the brain and between different cell types (Charleston et al. 1996 PMRL# 0116, pages 127-128). A key finding was that Hg++ is very poorly eliminated from the brain; in fact, the half-life of Hg++ in the brain is measured in years (Vahter et al. 1994 PMRL# 0060, page 221). This is distinct from the very much shorter half-life of the organic methylmercury species, which is measured in days. Because Hg++ accumulates in the brain and is sequestered in cells for many years, a series of low-dose, subacute exposures to organic forms of mercury can lead to increasing levels of Hg++ in the brain. Within the brain itself, Hg++ preferentially accumulates in astrocytes and microglia as compared to other cell types. These cells accumulate increasingly larger deposits of Hg++ as exposures to the organic species of mercury continue (Charleston et al. 1995 PMRL# 0032, page 326).

Not only was Hg++ preferentially found in microglia and astrocytes, but also the astrocyte population in the brain decreased significantly after 6 months of MeHg exposure, while

microglial cells proliferated (Charleston et al. 1996 PMRL# 0116, pages 133-134). The proliferation of microglia and the decline in astrocytes are consistent with the inflammatory response that the innate immune system of the brain would mobilize during a toxic exposure. Since low-dose, episodic exposures to the organic mercury component of thimerosal cause Hg++ to accumulate in the brain, it is medically reasonable to conclude that the accumulation of Hg++ in the developing brain, and particularly the preferential deposition of Hg++ in cells of the brain's innate immune system, could result in neuroinflammation, the mechanism of injury in some children with regressive autism:

> "Further loss of astrocytes would be expected to have deleterious effects on the neuron population (e.g. through an excitotoxic mechanism (see Beal, 1992). The continued accumulation of IHg [inorganic mercury] over time within the brain following low level exposure to MeHg may prove to be the proximate toxic form associated with this type of exposure scenario. This form of long-term toxic response may be mechanistically different from the focal damage associated with acute high level exposures to MeHg." (Charleston et al. 1996 PMRL# 0116, page 135).

While the research cited above focused on low-level methylmercury exposures in adult primates, a later experiment by Burbacher et al. (2005 PMRL# 0026) involving low-level ethylmercury exposures in infant primates further observed the deposition of Hg++ in the brain after ethylmercury exposure. One group of monkeys was exposed to ethylmercury via intramuscular injection of thimerosal in a weight-equivalent dose designed to correspond to the dose/weight exposure of human infants receiving TCVs. Another group of monkeys was given oral doses of methylmercury (page 1016). While ethylmercury was cleared from the blood more rapidly than methylmercury, the absolute concentrations of Hg++ (the inorganic breakdown product of both EtHg and MeHg) were twice as high in the brains of EtHg-exposed monkeys as compared to MeHg-exposed monkeys, and much more of the total brain Hg in EtHg-exposed monkeys was in the inorganic, Hg++ form (Burbacher et al. 2005 PMRL# 0026, page 1020): "... although little accumulation of Hg in the blood occurs over time with repeated vaccinations, accumulations of Hg in the brain of infants will occur ... There was a much higher proportion of inorganic Hg in the brain of thimerosal monkeys than in the brains of MeHg monkeys (up to 71% vs. 10%)" (page 1021).

These findings indicate that conclusions about the safety of thimerosal based on how quickly EtHg is cleared from a child's *blood* may not be valid (Burbacher et al. 2005 PMRL# 0026, page 1020); that is, the potential mechanism of injury is more accurately described, not by post-injection levels of EtHg in blood, but by the levels of Hg++ in the *brain,* which accumulated following multiple exposures. The experiment also calls into question the validity of earlier studies indicating that the breakdown of Hg is a detoxification process that protects the brain. Instead, the dealkylation process, particularly as it involves EtHg, actually leads to the accumulation of Hg++ in the brain. Since Hg++ is associated with microglial activation and proliferation and the decline of astrocyte cell populations, it is reasonable to conclude that EtHg exposures via TCVs may disrupt brain function by a process that is mediated by the brain's innate immune system and the resulting neuroinflammation, as detailed later in this report.

In overview, low-level exposures to EtHg can lead to the accumulation of inorganic Hg++ in the brain; Hg++ is preferentially deposited in microglia and astrocytes; EtHg exposure leads to more Hg++ accumulation in the brain than does MeHg exposure. Because of these findings, the investigators found that, with reference to thimerosal, a "compound that has been (and will continue to be) injected in millions of newborns and infants" it is "difficult to understand" why the 2004 Institute of Medicine review of thimerosal safety felt able to conclude that there was no evidence that TCV exposures are associated with developmental disorders (page 1021).

4. A Neuroinflammatory Response within the Brain due to Accumulated H++

ASD has traditionally been regarded as a static neuropathology, or encephalopathy, that originates from before birth. If that were so, it would be unclear how autistic regression can occur as late as the second year of life (and even later, in childhood disintegrative disorder). To the contrary, a current view holds that ASD can be due to active inflammation involving specific territories of the brain over many years. One potential cause of such chronic inflammation would be a series of low-dose exposures to organic mercury, doses too small to cause substantial acute or focal neuronal damage and death, but doses sufficient to lead to the accumulation of Hg++ in astrocytes and microglia.

Neuroinflammation is the brain's innate immune system's response to invading organisms and foreign proteins and toxins. It is characterized by edema, activation of microglia (which are the equivalents in the nervous system of macrophages), and local invasion of immune cells from the circulation. Microglia release proinflammatory cytokines, free radicals and other potential neurotoxins (Vezzani and Granata 2005 PMRL# 0569). Neuroinflammation is often associated with the activation, proliferation and ultimate disintegration of astrocytes, as well as increase in neural excitability. An early study of individuals with autism had discovered breakdown products of astrocytes in the CSF, implicating them in the neuropathology of autism (Ahlsen, Rosengren, Belfrage et al. 1993 PMRL# 0545). Activated microglia and astrocytes produce proinflammatory cytokines and free radicals, which are agents of oxidative stress. Inflammation in the central nervous system can be a reaction to protein aggregates such as viruses, either inside or outside the cell membranes, heavy metals and also to the breakdown products of the cells themselves. If the provocative substances persist in the brain despite the immune reaction, then inflammation can become chronic and itself damaging to bystanding neighboring tissues.

The view that relates autism to neuroinflammation has recently found dramatic support. Bailey et al. (1998b PMRL# 0090) found gliosis, a sequel of the death of astrocytes in inflammation, in the autopsied cerebral hemispheres of autistic individuals. Lopez-Hurtado and Prieto (2008 PMRL# 0446) studied language related areas in autistic brains postmortem. They found a striking degree of decreased density of neurons and increased density of glial cells, indicating accelerated neuronal death with gliosis (findings consistent with the impairment in language

function that is prominent in most individuals with autistic disorder). Friedman et al. (2006 PMRL# 0323) found chemical evidence of ongoing active disease in cerebral gray matter of individuals with autism, and the same group found neuroimaging evidence of neuroinflammation in their cerebral gray matter (Petropoulos, Friedman, Shaw et al. 2006 PMRL# 0320). Vargas et al. (2005 PMRL# 0069) examined autopsied brains of ASD children and adults, and found evidence of chronic inflammation, with microglial activation and cytokine production, in sampled cerebral territories, as well as in cerebellar areas, which were depleted of Purkinje cells (a classical finding in ASD autopsies). This inflammation can be of very long standing, since it was present even in older people who had been autistic since early in life. Vargas and colleagues (2005 PMRL# 0069) also examined the CSF of living children with autism, and found a suite of elevated proinflammatory cytokine levels, consistent with an active ongoing neuroinflammatory process in the brain (Pardo, Vargas and Zimmerman 2005 PMRL# 0072). Proinflammatory cytokines in the CSF of autistic children are markers for inflammation in these children's brains.

Microglial activation is also a source of oxidative stress, to which autistic children may be particularly vulnerable (James et al. 2006 PMRL# 0049). Microglial activation and the overproduction of proinflammatory cytokines are related to environmental toxins (Block 2005 PMRL# 0559, page 8). Since Hg++ is sequestered in glial cells, and since it cannot be mobilized across the blood-brain barrier, the provocative stimulus for inflammation persists, and the immune reaction attacks adjacent cells, notably astrocytes. Microglial activation and inflammation are implicated in a diverse range of neurological diseases, particularly neurodegenerative diseases (Block 2005 PMRL# 0559, page 15). Neuroinflammation thus represents a medically reasonable mechanism by which an environmental toxicant such as Hg++ can cause neurological dysfunctions.

Pardo et al. (2005 PMRL# 0072) write: "We hypothesize that environmental factors (e.g., neurotoxins, infections, maternal infections) in presence of genetic susceptibility and the immune genetic background of the host, influence the development of abnormalities in cortical organization and neuronal circuitry and neuroinflammatory changes responsible for the generation of the autistic syndrome" (page 493). The late onset of the regressive subtype, and subsequent remission or relapses, become more understandable if autism is due to disease than if it is the aftermath of congenital maldevelopment.

Dr. Carlos Pardo's research group at Johns Hopkins University School of Medicine have taken inflammation in autism seriously. They have undertaken to treat people with regressive ASD with an anti-inflammatory agent. They were awarded an NIMH research grant to determine whether minocycline is specifically beneficial for the behavior of children with regressive autism (ClinicalTrials.gov PMRL# 0369). Minocycline is a tetracycline derivative and also an antibiotic (e.g., Levkovitz et al. 2007 PMRL# 0372). The investigators selected it because it down-regulates microglial activation.

The association of neuroinflammation with autistic symptoms finds additional support in observations of brain pathology in autism. The infant brain develops dramatically in the first two years of life. The pattern of neuronal growth and differentiation becomes increasingly complex, with synapse formation, and axonal growth and progressive myelination. This "unique period of neural differentiation and circuit formation is also a time when the brain is particularly vulnerable to abnormal events that disrupt" the brain maturation process (Courchesne 2005 PMRL# 0104, page 582). It is during this vulnerable period that infants are exposed to a series of EtHg exposures via TCVs, with the risk of resulting deposition of Hg++ in the developing brain. Postmortem brain studies indicate abnormal increases in cerebral neurons that may be associated with "a compensatory neural genesis during perinatal or postnatal life that is triggered by adverse events such as those that ignite the neuroinflammatory reaction reported by Vargas" (pages 584-585). Further, since both astrocytes and microglia are associated with neuronal differentiation and migration, as well as axonal myelination, it is reasonable to conclude that Hg++-induced disruptions of glial cell function would lead to abnormalities in brain development and maturation.

5. <u>Neuroinflammation as Engendering a Brain State that can cause Autistic Symptoms</u>

I discussed at length the implications of neurotropic viral infections, particularly the measles virus component of the MMR, in my reports and testimony in the Cedillo and Snyder proceedings. However, I pointed out that persisting viruses in brain are not the only targets for attack by the innate immune system. It is generally acknowledged that heavy metals elicit an immune attack, which has the same properties as that which is caused by viruses in the brain.

Does the inflammation caused by an immune attack on low levels of mercury-containing compounds resemble that unleashed by viruses in setting the scene for neurotoxicity and for over activation of brain circuitry? I now cite evidence that the persistence of Hg++ in the developing brain, accumulating after multiple exposures to TCVs and preferentially deposited in the cells regulating the brain's innate immune response, is also a medically reasonable cause of neuroinflammation and its sequelae in some children. The manner in which Hg++-induced neuroinflammation can cause the symptoms of regressive autism is closely analogous to the manner in which a virally induced inflammatory process in the brain can cause such symptoms.

Aschner et al. (2007 PMRL# 0570) reviewed the mechanism of methylmercury (MeHg)-induced neurotoxicity. They summarized evidence that compounds of mercury, such as MeHg and mercuric chloride preferentially accumulate in the astrocytes, and inhibit their uptake of glutamate (e.g., Mutkus et al. 2006 PMRL# 0571). The adverse effect of mercury on neurons is mediated by glutamine (Aschner et al. 2000 PMRL# 0568). They write: "In the absence of glutamate, neurons are unaffected by acute exposure to mercury, suggesting that neural dysfunction is secondary to disturbances in astrocytes (Brookes 1992). Co-application of nontoxic concentrations of MeHg (methyl mercury) and glutamate leads to the typical appearance of neuronal lesions associated with excitotoxic stimulation (Matyja and Albrecht 1993)". Although neural dysfunction due to MeHg is primarily due to disturbances in astrocytes, mercury compounds can also inhibit glutamate transporters on neurons (Fonfria et al. 2005 PMRL# 0573). In a study of the effects of mercuric chloride (HgCl2) on astrocyte cultures, Brookes (1988 PMRL# 0574) found that mercury "can impair glial glutamate transport reversibly at exposure levels that do not compromise some other vital cell functions" (page 1117). These findings are all significant for the mechanism of brain injury to be outlined below, in which glutamate excess due to failed astrocyte reuptake will be shown not only to be potentially neurotoxic, but also to set up a state of brain overarousal which could generate the clinical appearances of ASD.

The mitochondria have a neuroprotective role, in that they moderate the accumulation of glutamate (Castilho et al. 1998 PMRL# 0575). Mercury compounds such as MeHg also generate reactive oxygen species, and the resulting oxidative stress can impair the functioning of mitochondria, which lose control of glutamate flow. Reciprocally, persisting glutamate excess is

apt to impair mitochondrial function (Singh et al. 2003 PMRL# 0516). In a study of 120 autistic children, about 7% were found to have mitochondrial dysfunction that was related to autism (Oliveira et al. 2005 PMRL# 0548). Poling et al. (2006 PMRL# 0071) reported a child with vaccine-related autism of the regressive type attributable to mitochondrial dysfunction.

In summary, micromolecular (trace) amounts of mercury derived from the breakdown of several different mercury compounds can damage astrocytes, releasing glutamate flow from control, damage the glutamate transporters on neurons, with similar consequences, compromise the function of mitochondria in the energy metabolism of cells, and lead not only to "an unimpeded cytotoxic cycle" (Aschner et al. 2007 PMRL# 0570, page 286), but also an overactivated brain state. Aschner et al. (2007) summarize: "a large body of literature suggests that neuronal damage in response to MeHg most likely represents aberrant control of the extracellular milieu by astrocytes" (page 288).

Vargas et al. (2005 PMRL# 0069) found that in the brains of deceased individuals with autistic disorders, the brain's innate immune system had reacted with microglial and astrocytic activation. There was accompanying release of proinflammatory cytokines, and these were also found in high levels in the CSF of a different, living, group of children with autism. Activated microglia release proinflammatory cytokines in response to the presence of foreign and unrecognized proteins, such as viruses and heavy metals. If the target (e.g., Hg++) cannot be eliminated, for instance if it is so chemically bound that it cannot be transported out of the brain (as Dr. Aposhian describes), the inflammation becomes chronic, and the immune attack spreads to neighboring cells, which become the bystanding victims of "friendly fire". At first, astrocytes become activated, and also themselves express proinflammatory cytokines. However, under maintained immune attack, some will die, leaving gliotic residues.

The present state of knowledge does not permit conclusions at a level of scientific certainty to be drawn about the neurological processes that are capable of causing autistic encephalopathies. The following is a viable candidate mechanism of injury, and is medically reasonable.

Glutamate is the predominant excitatory neurotransmitter in the brain. The chief inhibitory neurotransmitter is GABA. The balance between the levels of these two neurotransmitters is the

main factor in determining the level of the excitation/inhibition balance in the brain. Because excess glutamate is harmful, its levels are normally tightly controlled at the synapse. Excessive glutamate flow leads to an overexcitation which at the local level can be excitotoxic, causing brain cells, including neurons, to become more excitable, release spontaneous nerve impulses, and as the toxic effects increase, to die (Vezzani and Granata 2005 PMRL# 0569). Pyramidal cells are particularly vulnerable targets for excitotoxic damage due to glutamate (Hamann et al. 2005 PMRL# 0494). The depletion in the number of Purkinje cells in the cerebellum and frontal cortex that has been demonstrated in the brains of individuals with autism may in some cases represent the cytotoxic effect. Lesser degrees of cytotoxicity may apply to the loss of synaptic connections and diminished dendritic growth in the hippocampus in autism. At a somewhat lower level of activation imbalance, few if any cells may actually die, but the overexcitation will have predictable effects on the functioning of the brain. The most obvious effect is to render the brain more apt to generate epileptic discharges. Epilepsy, as well as subclinical disturbances of the EEG, is very common in ASD. There are also predictable effects of overexcitation on behavior.

Astrocytes regulate levels of glutamate at the synapse. Glutamate transporters are expressed on astrocytes. These receptor sites are instrumental in the reabsorption of "spare" glutamate. The astrocytes form a sheath around the glutamatergic synapse, and the glutamate transporter intercepts and mops up spare glutamate, blocking its extrasynaptic spread to neighboring synapses. In this way the astroglia help protect the brain from glutamate excess. Proinflammatory cytokines produced by activated microglia attenuate the astrocytic clearance of extracellular glutamate. When the astrocytes malfunction or die, they lose control over glutamate flow, which may become excessive, shifting the excitation-inhibition balance in the direction of overexcitation. In addition, astrocytes can release glutamate themselves, and "the interaction with activated microglia can substantially amplify glutamate release from astrocytes, thus conferring pathological relevance to the process" (Bezzi, Domerq, Brambilla et al. 2001 PMRL# 0367). Due to glutamate excess, adjacent circuitry becomes activated in a manner that escalates over time. In their postmortem study of brains of autistic individuals, Purcell, Jeon, Zimmerman et al. (2001 PMRL# 0567) concluded that: "Subjects with autism may have specific abnormalities in the AMPA-type glutamate receptors and glutamate transporters in the cerebellum. These abnormalities may be directly involved in the pathogenesis of the disorder".

The neuroinflammation/glutamate excess model provides a final common pathway by means of which numerous and highly diverse prenatal and postnatal agents can cause autistic disorders in genetically susceptible children. It remains to consider how such an apparently general mechanism of injury can result in as distinctive a pattern of disabilities and abnormal behaviors as is found in the autistic spectrum disorders. How could such disparate factors as viruses and heavy metals, via neuroinflammation, cause autism?

6. The Overarousal Model: Its Explanatory Value for Autistic Behavior

Mercury has long been known to be a potent neurotoxin, and it might not be considered surprising that it is capable of causing serious brain damage. It is well known to do so at high doses, particularly with exposures that were prenatal. The consequences of such acute severe brain injury have not been reported to include autism. However, this report deals with low dose mercury exposures, and as has been explained, this can cause neuroinflammation. Why would neuroinflammation result in brain dysfunction that presents as autism, rather than in any of the very numerous other ways in which injury to the brain might present? Short of brain injuries due to widespread excitotoxic necrosis of neurons, can an excess of glutamate, causing chronic overarousal, account for the features of ASD?

Rubenstein and Merzenich (2003 PMRL# 0530) utilized the construct of increased excitatory tone due to increased glutamate signaling which raises the level of brain activation. "Mutations (or potentially, environmental factors) that increase glutamate signaling increase excitatory tone. Thus, mutations that increase the activity or number of glutamate receptors, that increase the amount of glutamate in the synapse, or that amplify glutamate-mediated synaptic potentiation can increase the excitatory state of the brain." (page 260). On the same page, Rubenstein and Merzenich offer an instance of an environmental factor that can increase the level of glutamate-induced increase in excitatory tone. They write "Among environmental factors that could amplify glutamate-based potentiation are chemicals in the PCB family, which have been demonstrated to generate up to five-fold increases in induced LTP amplitudes in cortical slice preparations."

The mechanism of injury outlined above has been shown capable of causing overactivation of the brain, resulting in behavioral overarousal and its consequences for the individual. The overactivation/overarousal model is one of three main explanatory theories for the neuropathophysiology of autism (the others being executive dysfunction and weak coherence/underconnectivity; these three theories are not mutually exclusive). Autistic behavior is precisely what one would expect if the brain's excitation/inhibition ratio were skewed in favor of excitation (as occurs in hyperglutamatergic states).

Baron et al. (2006 PMRL# 0550) review the evidence for overarousal in autistic spectrum disorder. A possible distinction exists within the ASD population. While the higher functioning majority was overaroused, a substantial minority of patients seems lethargic and underaroused. They were generally those patients who were most intellectually handicapped. Liss et al. (2006) formed a similar conclusion based on the results of factor analysis of responses to parental questionnaires (page 167). Therefore the overarousal model may apply to most, but not all people with ASD. Baron et al. (2006) cited Goodwin et al. (2006 PMRL# 0496) who documented a high basal heart rate in an ASD group, 20 beats per minute higher on average than controls. "The high basal heart rate was interpreted as increased general arousal, and the reduced responsivity to the potential stressors was taken to be evidence for autonomic defensiveness (Lacey 1967 PMRL# 0576) or sensory rejection in an attempt to escape threatening stimuli" (page 53).

"Autistic symptomatology can be classified into that which exemplifies the effects of hyperarousal and that which represents an attempt to escape from such effects or fend them off." (Kinsbourne 1987 PMRL# 0460). Echolalia (verbatim repetition of speech without comprehension) and hyperselective attention would arise as consequences of overarousal. Autistic children's preference for working with limited sets rather than open-ended situations implies that they are "more comfortable when the range of cues is limited"..."Gaze avoidance, isolation and need for sameness obviously could be, and have often been, interpreted as being defensive, minimizing the possibility of encountering a novel and therefore arousing input (page 117).

Ultimately, the inflamed brain becomes precipitated into episodes of seizure activity (Vezzani and Granata 2005 PMRL# 0569). Overactivated, the brain suffers deterioration in the quality of sensory information, due to the failure to suppress competing "neural noise". The individual would readily become overwhelmed by sensory stimulation. Overexcitation tends to minimize differences in patterned activation of cerebral gray matter, collapsing multiple distinct representations into one that is dominant, and that represents the sometimes very minute local target of the child's attention. Thus the child will "overfocus" (Liss et al. 2006 PMRL# 0373). The signal to noise ratio is reduced, obscuring distinctions that need to be made in perception and reasoning. Rubenstein and Merzenich (2003 PMRL# 0530) point out that "higher-than-normal noise in cortical processes also frustrates the development of normally differentiated representations. (These) would result in larger (less selective) and more strongly engaged neural populations. Such over-representation by non-differentiated systems could plausibly account, for example, for the strong aversive reactions to auditory, tactile and visual stimuli that are commonly recorded in autistic individuals" (pages 260-261). Rubenstein and Merzenich (2003 PMRL# 0530) also state: "These children have noisy and unstable cortical networks. This type of cortex will lead to broad ranging abnormalities in perception, memory and cognition and motor control. Moreover, "noisy" (hyperexcitable, poorly functionally differentiated) cortex is inherently unstable and susceptible to epilepsy" (page 256). "Higher-than normal noise in cortical processes ... could plausibly account, for example, for the strong aversive reactions to auditory, tactile and visual stimuli that are commonly recorded in autistic individuals (page 260). They explicitly endorse the relevance of the overactivation theory to treatment: "Intensive perceptual and movement training therapies could also be expected to improve functional signal-to-noise conditions in a noisy forebrain" (page 264). The overactivation/overarousal model has explanatory value for autistic behavior. Specifically, it explains why autistic children actively do avoid social interactions, rather than simply finding them uninteresting.

Do autistic children fail to interact because they have no interest in doing so, rather than on account of avoidance? This does not square with the relevant literature. An example is Dalton et al.'s (2005 PMRL# 0577) functional imaging study of "gaze fixation." Impaired gaze fixation refers to the well-known failure of individuals with autism to make and maintain eye contact. Dalton et al. (2005 PMRL# 0577) found that unlike neurotypical individuals, their autistic group exhibited strong activation in the amygdala while fixating gaze on others. "Amygdala

hyperactivation in the autistic group...is specific to the amount of eye fixation" (page 524). They conclude: "On the basis of these findings we suggest that within the autistic group, eye fixation is associated with negatively valenced arousal, mediated by activation in limbic regions such as the amygdala. We propose that diminished gaze fixation within the autistic group may facilitate reduction of overarousal to social stimuli" (page 524). So avoiding eye contact is a compensatory strategy.

When the brain is overexcited, the individual feels subjectively dysphoric and anxious. This state leads to a tendency for him/her to compensate by restricting sensory input, turning attention inward and as a result, being oblivious of external events. The internalizing of attention also leads to egocentricity, which is tapped by failures in tests of "theory of mind". The child will avoid sources of stimulation, and protect himself against the arousing effects of unexpected motion and change. The child will tend to engage in solitary occupations and become engrossed in unusual topics of interest, seek to isolate, and minimize eye contact and other human interaction until the brain activation level has subsided. To make this happen, the child engages in stereotypical and manneristic behavior, which are to be understood as being dearousing maneuvers, analogous to displacement behaviors in animals (Kinsbourne, 1980 PMRL# 0460). Over time, stereotypies lower neural excitation levels. Remote consequences of the flight from human interaction are difficulties in social understanding, at least in part due to inexperience.

Describing stereotypic and repetitive movements in children with autism, Baumann (1999 PMRL# 0578) noted "They appear most often among autistic children that are mentally retarded, and are progressively less apparent with increased IQ. It has been noted, however, that among normally intelligent autistic children stereotypies may be exacerbated during periods of stress on into adulthood". Referring to a discussion of stereotypies in children in residential care, Baumann (1999 PMRL# 0578) remarked: "These stereotypies appear to be associated with concentration, arousal, frustration, boredom and distraction and seem to stabilize the child's level of arousal in monotonous, frustrating or overwhelming situations." Given these observations, "it is possible that stereotypic behavior may be playing a similar role for autistic children" (page 602).

Do autistic children make abnormal movements only when they are overaroused? One does see autistic children apparently at rest making repetitive movements, perhaps for purposes of self-stimulation. Under quieter circumstances, movements often called "stimming" are observed. That is a different movement category, which is thought to be a voluntary behavior that increases the individual's well being. Stimming may reflect inner overarousal in a quiet environment, and be performed for its calming effect. Toichi and Kamio (2003 PMRL# 0528) reported a paradoxical autonomic response of autistic children. The finding "suggests that some autistic subjects were more stressed under "resting" conditions than while performing mechanical or repetitive mental tasks'. Ming et al. (2004 PMRL# 0434) also reported behavior (absent) and mental effort (present) in an autistic patient. Ming et al. (2004b PMRL# 0579) reported raised sympathetic tone in autistic children although they were at rest ("baseline"). Children with autism are perhaps more comfortable doing something repetitively than doing nothing. I conclude that there is evidence that stereotypic movements occur under circumstances of high arousal, and are compensatory.

Concluding Comments

The state of the science in autism has shifted radically in recent years. Long assumed to be the static aftermath of early brain damage or genetically induced dysgenesis, many investigators now regard autism as often caused by an active ongoing disease process. Gene-environment interaction, on account of which genetically predisposed individuals react to specific environmental factors, such as infections and toxins, by becoming autistic, is coming into favor as a mechanism of causation. The mechanism of injury offered in this report, of causation by a hyperglutamatergic state, is not specific to any one provocative agent, but can result from a range of virus and of heavy metal exposures (and is also found in neurodegenerative diseases, which however are not at issue in the causation of regressive autism). The proposed causation involving exposure to the mercury in TCVs is presented in the light of these advances in the science of autism.

TVCs are sources of inorganic mercury, which is the breakdown product when TCVs are deposited and accumulate in the brain. Reacting to the presence of the mercury, the brain's innate immune system launches an ongoing neuroinflammatory process. (The autistic brain

itself has been found to be the site of innate immune activation and neuroinflammation, and corresponding inflammatory markers have been found in the cerebrospinal fluid of autistic children). The neuroinflammation results in a hyperglutaminergic state. Mitochondria, which are neuroprotective in that they moderate glutamate excess, are themselves compromised by the oxidative stress generated by the inflammation. Furthermore, if for genetic reasons a particular child's mitochondria are abnormally vulnerable to stress, then the glutamate levels will be particularly apt to swing out of control. The overactivation of cerebral neuronal systems that results from the hyperglutamatergic state causes behavioral overarousal. Many, if not all, of the symptoms that collectively lead to the diagnosis of autistic spectrum disorder are explained by overarousal.

For reasons summarized in this report, it is my opinion, to a reasonable degree of medical probability that a series of TCVs can result in or contribute to an accumulation of Hg++ in the brain. The mercury in the brain may trigger an inflammatory response in some children. The inflammation results in a hyperglutamatergic state. This state is characterized by overactivation (increased excitatory tone). Overactivation gives rise to behavioral arousal, which accounts for the child's regression into particular patterns of deficits and abnormal behaviors that characterizes autism. This process and the resulting symptoms may occur even if there is no clinical or pathological evidence of acute mercury poisoning or toxicity.

It is therefore medically reasonable to consider the involvement of a TCV-induced encephalopathy when one engages in the differential diagnosis of a case of regressive autism, particularly when the other known medical causative factors in the differential diagnosis have been ruled out, or are not supported by reliable evidence.

Marcel Kinsbourne, M.D.

(On April 22, 2008, the Petitioners' Steering Committee filed a compact disc containing a scientific articles referenced in the expert report of Dr. Marcel Kinsbourne. This disc has been placed into the record of the Omnibus Autism Proceeding, but its contents, except for the list of titles that follows this page, are not being placed on the website at this time. This is due to the fact that most of the scientific articles published in professional journals are copyrighted material.)

[LIST OF SCIENTIFIC ARTICLES FOLLOWS]

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CERTIFICATE OF SERVICE

I hereby certify that on April 21, 2008, I served the foregoing **NOTICE OF FILING EXPERT REPORT OF MARCEL KINSBOURNE, M.D.** on the following individual(s):

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By DHL, next business day delivery.

Petitioners specifically authorize the Court and the Office of Special Masters to post this document, and any attachments or exhibits thereto, on the Court/OSM website, expressly waiving any confidentiality as to the contents of these materials. Petitioners expressly wish to publicly disclose this filing in any other forum designated by the Court or the OSM.

WILLIAMS LOVE O'LEARY & POWERS, P.C.

Thomas B. Powers
Of Attorneys for Petitioners' Steering Committee