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August 31, 2007

VIA UPS DELIVERY

Clerk
United States Court of Federal Claims
717 Madison Place, NW
Washington, D.C. 20005

Re: In Re: Claims for Vaccine Injuries Resulting in Autism Spectrum Disorder, or a Similar Neurodevelopmental Disorder v. Secretary of Health And Human Services
Autism Master File
Our File No. 054500 - Omnibus Autism Proceeding

Dear Clerk of Court:

Enclosed for filing in the Autism Master File is the original and two copies of the report of petitioners' expert Dr. H. Vasken Aposhian, PhD, including his current curriculum vitae and a bibliography of literature in support of his expert opinion. This report is submitted in support of petitioners' theory that exposure to the mercury contained in certain pediatric vaccines was a substantial contributing cause of some or all of the injuries at issue in the Omnibus Autism Proceeding. Petitioners' anticipate relying on this testimony in hearings on "test cases" currently scheduled for May 2008.

Very truly yours,

Thomas B. Powers
Attorney at Law

Enclosures

cc: John Fabry, Esq., Williams Bailey Law Firm, LLP (via e-mail)
Vincent J. Matanoski, Esq., U.S. Department of Justice (via UPS delivery)

CERTIFICATE OF SERVICE

I hereby certify that on August 31, 2007, I served the foregoing **Expert Report from Dr. H. Vasken Aposhian, PhD** on the following individual(s):

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By United Parcel Service, next 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.

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Thimerosal and its biotransformant ethylmercury cause injury to the developing brains of human embryos and young children.

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Outline

1. Introduction

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4. There are specific windows for brain development in the human embryo, fetus and infant.

    a. The specific developmental windows of thalidomide for the human embryo and the lessons learned from thalidomide are guides for understanding such effects of other agents.

    b. Recent evidence demonstrates that terbutaline (a drug used to treat premature labor) is a developmental neurotoxicant and may cause brain damage in the infant.

5. Thimerosal containing vaccines will result in toxic levels of mercury in the brain.

6. Conclusion: Thimerosal and its biotransformant ethylmercury cause injury to the developing brains of human embryos and young children by interfering with brain development during highly specific windows of brain development. These windows of susceptibility may occur during the prenatal and/or postnatal periods. These windows are vulnerable and open at very specific times. Thus, thimerosal induces symptoms of autism spectrum disorders in some subsets of children.

There is growing importance of neuroinflammatory events in the development of autism. All of this indicates the need for closer examination and better correlations of past research on the genetics and environmental factors causing autism. One of these environmental factors is surely thimerosal..

Professional Qualifications and Experience

My curriculum vitae is appended hereto as Appendix "A". As it shows, I am Professor of Molecular and Cellular Biology, Faculty of Science, and Professor of Pharmacology, College of Medicine, at The University of Arizona, Tucson, Arizona. I received my undergraduate education (Sc. B. in Chemistry) at Brown University and was awarded a Ph.D. in Physiological Chemistry from The University of Rochester. I have been a member of the basic science departments of a number of medical schools, including Vanderbilt, Stanford, and Tufts. Early in my professional education and training, I spent three years doing research as a National Institute of Health Senior Postdoctoral Fellow under the tutelage of Nobel Laureate Dr. Arthur Kornberg, Professor of Biological Chemistry, College of Medicine, Stanford University. I was brought to The University of Arizona in 1975 as Department Head to modernize the biology departments. I have been elected to a number of professional societies such as the Society of Toxicology, The American Society of Biological Chemistry and Molecular Biology, The American Association for the Advancement of Science, The American Society of Microbiology and others.

I have published numerous peer-reviewed research papers in first-class international scientific journals dealing with my research on DNA, gene transfer, treatments for and mechanisms of the toxicology of lead, arsenic and mercury and other heavy metals. My laboratory is still active in research dealing with mercury, arsenic as well as chelating agents. A recent article (Aposhian and Aposhian, 2006) from my laboratory was the most downloaded article in 2006 of the preeminent toxicology journal Chemical Research in Toxicology.

I have been on numerous scientific committees of the federal government including the White House Conference on Mercury; the National Academy of Science/National Research Committees that wrote the critical monograph Toxicological *Effects of Methyl Mercury* and the

monograph on *Arsenic in Drinking Water*. I wrote the toxicology chapter of the former monograph. I have been a member of numerous Committees of the National Institutes of Health, the Environmental Protection Agency, the National Science Foundation and a number of Foundations. I have studied mercury and/or arsenic in people in Chile, Inner Mongolia, Mexico, China, and Romania. The visits to these foreign countries to do the studies for research purposes required scientific knowledge, tact, and unusual communication skills. I am still active in teaching undergraduate human toxicology.

My research has been supported since 1955 by one or more grants from the National Institute of Health, the U. S. Army, the National Science Foundation, The Wallace Research Foundation, The Autism Research Institute and other foundations. I have been a consultant to a number of multi-national pharmaceutical firms. I have given, by invitation, innumerable presentations on the results of my scientific research at many universities, pharmaceutical companies, and national and international government organizations. I have been a National Academy of Science Visiting Fellow to the former USSR and an official guest in the Soviet Union, China and Mexico to deal with mercury and arsenic health problems. I have been very fortunate in life being paid to do what I enjoy doing.

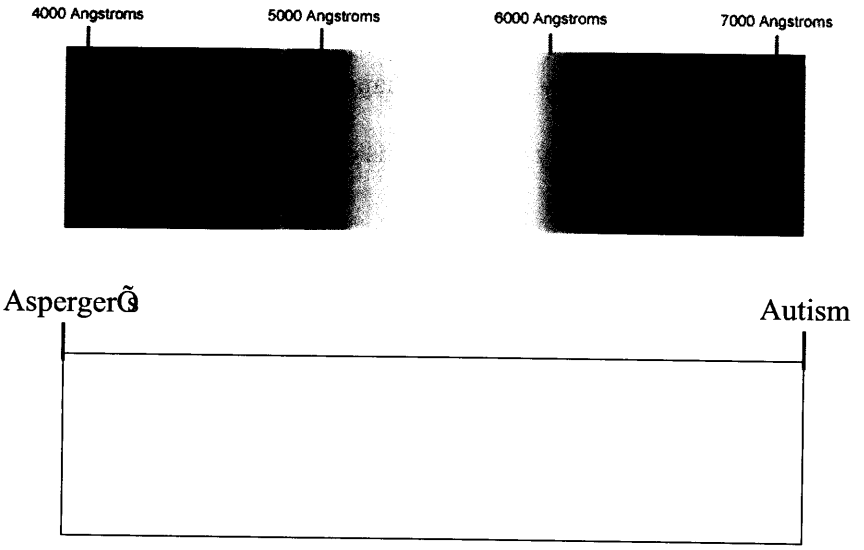
1- Introduction

The purpose of this report is to give the Court information as to the possibility that some cases of autism are caused by a direct action of thimerosal and/or its metabolite ethyl mercury on the developing brain/central nervous system. This happens during certain vulnerable windows of the developmental processes of the very young brains of embryos and/ or children.

Autism spectrum disorders (ASD) are composed of a broad spectrum of neurodevelopmental disorders known as pervasive developmental disorders. They occur in childhood and are characterized by impairments in social interaction, verbal and nonverbal communication and restricted and repetitive stereotyped behaviors. The etiology of ASD is largely unknown. However, genetic, environmental, immunological, and neurological factors are believed to have a role in its development of this disorder. The onset of ASD usually occurs in the first 36 months of childhood. The CDC has recently stated that the prevalence of ASD is as high as 1 per 150 children.

One of the problems of trying to understand the etiology of ASD is that at one end of the spectrum is severe autism at the other end is Asperger's Disorder (Figure 1) . When a chemist looks at or studies a spectrum, he looks at the individual defined bands. Unfortunately, this has not been done with ASD. It appears that very little has been done to characterize each of the individual disorders or each band that characterize ASD.

Figure 1. The visible spectrum and autism spectrum disorders



Where are the bands of ASD?

Another point that is pertinent to make in this introduction is that one needs to realize that until recently the once accepted toxicology axiom that the dose determines the poison is no longer 100% correct. Many other factors are involved in vulnerability of a person to poisons. Some of them are listed below

i) Antibiotics being used when mercury exposure occurs can inhibit mercury excretion and thus potentially increase its toxicity. (Rowland et al., 1984)

ii) A combination of a genetic predisposition and a stress (e.g. a fever) may increase the impact of the stress-causing agent. (Morton et al., 1991)

iii) The environment is of course important: The more mercury in the air the greater the incidence of autism. (Palmer et al., 2006)

iv) Diet can make a child more vulnerable to autism. Glutamine is low in autistic children. Glutamine is a precursor of glutathione. Glutathione is a major factor and is necessary for metal transport in the body and detoxification processes. (Nordberg et al., 2007).

2. Brief overview of the chemical forms of mercury

Although the toxicology of the various chemical forms (sometimes called species) have been presented in the Federal Vaccine Court Cedillo proceedings it is pertinent to extend the previously submitted information.

Mercuric mercury (Hg^{+2}) is known to bind strongly to sulfhydryl groups, for example those of proteins and glutathione (GSH). The ultimate toxin for organic mercury compounds such as methyl mercury (MeHg) or ethyl mercury (EtHg), however, is still unknown. It could be MeHg (EtHg), per se, mercuric mercury (Hg++) or a combination of both Hg++ and the organic mercury compound. In addition it is not clear as to whether MeHg or EtHg causes cell death by binding to sulfhydryl groups as does mercuric mercury. MeHg, for example, causes many different deviations from the usual cause of cell death. These include impaired glycolysis, impaired nucleic acid biosynthesis, impaired aerobic respiration, impaired protein synthesis (Cheung and Verity, 1985), and impaired neurotransmitter release (Atchinson and Hare, 1994).

3. There is evidence for genetic differences (hypersusceptibility) in response to mercury exposure.

The brain and central nervous system (CNS) not only develop in utero but continue to develop until at least puberty. The stages of CNS development are often described as windows of development and the windows of many toxic chemicals are known.

It has been known for some time that heavy metals disrupt the normal metabolism for example, heme metabolism (Heyer et al. 2006). This is usually expressed by a change in the urinary porphyrin profile. Urinary porphyrins of dentists with low-level mercury exposure were analyzed. The expected urinary porphyrin profile was found in 85% of the dentists. But 15% had an atypical porphyrinogenic response. The latter was due to polymorphism in the human gene that modifies the effect of Hg on a biological process. This human gene is the coproporphyrinogen oxidase gene. (Woods et al., 2005). The result of the polymorphism is the inhibition of an enzyme and the occurrence of a new porphyrin in the urine. Although this work was published over two years ago, many toxicologists do not cite it in their published review articles because they are not cognizant or familiar with the importance of genetics and genetic toxicology as an important area of human toxicology. Research into the genetics of mercury toxicity is just beginning.

The Woods et al., (2005) work has been followed by a paper from France (Nataf et al., 2006) involving 115 autistic and 119 control children. They showed that urine coproporphyrin levels were elevated in autistic children. Urinary precoproporphyrin, an indicator of heavy metal toxicity was also elevated in autism. When subgroups of these children were given the chelating agent DMSA, there was a reduction in the mean urinary levels of precoproporphyrin and coproporphyrin for the autistic children.

Another example of hypersusceptibility to mercury is Pink Disease. During the years 1850 through 1955, a devastating syndrome called Pink Disease or acrodynia affected many

infant children (see Dally, 1997, for an excellent review). It is now believed that a teething powder that contained mercurous salts caused this illness.

While review articles exist about "Mercury-the metal of mystery" (e.g. Clarkson, 2002; Clarkson et al., 2003; Clarkson and Magos, 2006; and Counter and Buchanan, 2004), they must be viewed cautiously as current scientific investigations may render some of their conclusions false, inaccurate or outdated. After all, one definition of science is the search for the truth. Scientific investigation is always ongoing and cannot be stagnant. Science always progresses and the resultant knowledge changes with time. This concern about inaccurate and outdated conclusions has also been voiced by Mutter et al., (2007)

It is appropriate to distinguish between two very similar concepts, heritability and genetic causation. Heritability involves similar traits seen between parents and offspring. For example among Europeans the wearing of skirts is a very strong heritability (it occurs only among women, except for an occasional Scot). The wearing of a skirt thus is related to having two X chromosomes but the trait is not genetically determined. On the other hand the number of fingers on a human hand is completely determined by genetics. When there is a deviation from the normal five-fingered hand it is caused by defects in development. Thalidomide, a potent teratogen, causing severe birth defects is an example of this and is not heritable. A better discussion of this can be found in Vineis and Kriebal (2006).

4. **There are specific windows for brain development in the human embryo, fetus and infant.**

a. The specific developmental windows of thalidomide for the human embryo and the lessons learned from thalidomide are guides for understanding such effects of other agents.

The concept that the toxicity of a chemical depends on when the exposure to that toxin occurred is well demonstrated by thalidomide. This agent was developed and used in Germany and many other countries as a sedative. In the late 1950 to early 1960's a large number of malformed children were born in Germany and Austria. Some were born with phocomelia (a developmental anomaly in which the proximal portion of a limb or the complete limb is absent, - the hands or feet are attached directly to the trunk of the body), some with amelia (the absence of hands and limbs), and/or other developmental defects. There were at least 6000 cases of thalidomide-caused live births with birth defects. By excellent medical investigations, it was demonstrated that these birth defects were caused by women using thalidomide as a sedative at some time during their pregnancy. What soon became apparent was that the type of defect depended on when during the gestation period the thalidomide had been taken. See figures taken from Miller and Stromland (1999) below. Thalidomide was found to be teratogenic between 20 to 36 days after fertilization (34-50 days after the last menstrual cyclic). The windows for phocomelia and amelia have been narrowed down to specific periods of 1 to 2 days. Other windows for other thalidomide-caused developmental defects were also discovered.

Since then developmental windows in which other drugs and chemicals exert their effects have been discovered. Thalidomide was the initial reason for the development of a new area of

scientific investigation known as teratogens that is medically defined as agents causing monster formation.

Not all children whose mothers took thalidomide during their pregnancies were born with deformities. For teratogenicity to occur, the mother must be predisposed to having the drug act in that manner and the embryo must be predisposed (genetic!) to its action. In addition, thalidomide differs from some other teratogens in that the **time of administration of the drug appears to be more important a factor than the dosage** (Miller and Stromland, 1999)

Figure 2. Miller and Stromland (1999) *Image unavailable at time of filing*

Figure 3. Miller and Stromland (1999)

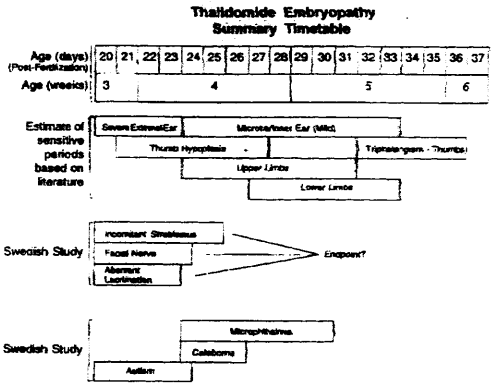


Fig. 7. Summary estimates of sensitive periods for ophthalmic malformations based on associated anomalies manifested by most patients (see Fig. 6 for Duane syndrome, the most frequent incomitant strabismus). The other clinical forms of incomitant strabismus had similar associated anomalies. These sensitive time blocks for the development of eye anomalies and autism are estimations and they may be shorter or slightly longer than indicated. The thalidomide timetable for the ear, thumb, and limb anomalies was derived from the literature (Nowack, '65; Lenz, '66, Kida, '87).

Thus, it is very reasonable and likely that thimerosal/ethylmercury (like thalidomide and many other agents) have specific windows of brain toxicity. Mercury (thimerosal/ethylmercury) containing vaccines (MCV's) given on typical US schedules in the 1990's (which called for 187.5 micrograms of mercury to be injected into virtually every child by six months of age and

which started on the day of birth) likely contributed to the development of Autism Spectrum Disorders in a susceptible small subset of those children. Also it must be remembered that windows of vulnerability vary within a very small time period because everything biological has a certain degree of variability. Thus the reason why some children got autism while other did not was they were not all vaccinated at precisely the same time. For example some received their 2 month vaccination precisely on the 60th day of their life; others maybe on their 57 th day of life; others on their 64^{th} day of life and so on. The perturbations would be worthy of a mathematician. It is also very important to realize that the effects of thalidomide teratogenicity are delayed. For example

A		B		C		D
Gene expression for arm development	→	**armbuds develop**	→	**growth of arms**	→	**arms developed.**

Another way of looking at this pathway is A>B>C>D.

The arm develops along the A to D pathway. Thalidomide acts during A, B or C not at D.

So most agents acting on such windows have a delayed response. Thalidomide causes phocomelia but it acts before the actual arms have developed. In other words there is a **delay** in the manifestations to its exposure. This is true of most developmental toxins.

b. Recent evidence indicates that terbutaline (a drug used for premature labor) is a developmental neurotoxicant and may cause brain damage in the infant (Rhodes et al, 2004).

Terbutaline is a $ß_2$-adenoceptor agonist that crosses the placenta and enters the fetal brain to stimulate fetal $ß_2$-adenoceptors that control neural cell development. This drug causes

biochemical changes and structural damage in the immature brain during critical times of such development (Rhodes et al., 2004). These effects strongly indicate that fetal terbutaline exposure causes a higher incidence of cognitive and neuropsychiatric disorders for the children born of women given terbutaline treatment for preterm labor.

These two drugs, thalidomide and terbutaline, demonstrate in the former case a well established and long-accepted developmental toxicity of a drug given during the time and windows of fetal brain development. For the latter drug, such information is more recent but just as important. All this information is relevant as to how thimerosal/ethylmercury can act to damage the development of the brain in embryos and young children. Furthermore, Zerrate et al. (2007) have developed a rat model in which terbutaline given at very specific times in the window of brain development causes overstimulation of $ß_2$-adrenoceptor resulting in microglial activation associated with innate neuroinflammatory pathways and behavioral abnormalities similar to those seen for autism.

5- The Brain and Mercury

How much mercury gets into an infant's brain after an injection of thimerosal containing vaccine? We can make calculations as follows based on the papers of Burbacher et al., (2005) and Pichichero et al., (2002).

Burbacher et al., (2005) demonstrated that the brain to blood concentration ratio was 3.5 ± 0.5 in infant monkeys receiving thimerosal.

Pichichero et al., (2002) using **nonautistic** children showed that

	2-month-old children	6-month-old children
Blood Hg concentration range	**4.50 to 20.6 nanoMolar**	**2.85 to 6.9 nanoMolar**
Mean	**8.20 nanoMolar ± 4.85 SD**	**5.15 nanoMolar ± 1.20 SD**

From the above and the Burbacher derived brain to blood mercury ratio in infant monkeys, the following can be calculated for human infants after receiving a thimerosal-vaccine injection

	2-month-old children	6-month-old children
Brain Hg range	**15.75 to 72.1 nanoMolar**	**9.98 to 24.15 nanoMolar**
Mean	**28.7 nanoMolar**	**18.0 nanoMolar**

Controls with no thimerosal had no quantifiable Hg except for one of 15 control infants.

It is reasonable than that 2-month-old infants have as much as 72.1 nanoMolar brain Hg. It needs to be remembered, however, that the above data are based on investigations of normal, not autistic children. If there is a subset of autistic children with a mercury efflux disorder, they would be expected to have even greater concentrations of mercury in their tissues. Also when we are able to calculate back to the time of the peak of the bolus injections of thimerosal containing vaccines, the concentration of brain mercury would be expected to be even greater.

Neuroinflammation and autism. There is increasing evidence for neuroinflammatory events being involved in the development of autism. It should be kept in mind that the term "neuroinflammation" was not even found in the scientific literature before 1995. This thinking is very recent and is just the "tip of the iceberg" as to what we expect to learn about immunity, neuroglia and neuroinflammation in autism. The presence of neuroglial and innate neuroimmune system activation in brain tissue and cerebrospinal fluid of autistics supports the theory that neuroimmune abnormalities occur in their brain (Pardo et al. (2005).

Connors et al. (2005) from Johns Hopkins Medical Center have investigated certain activities and genetic polymorphisms in autism using dizygotic twins. They concluded that prenatal overstimulation of the $ß_2$-adrenergic receptor by terbutaline or by the increased signaling caused by polymophisms in the genes of this receptor having diminished desensitization can influence the cellular responses sand developmental programs of the fetal brain leading to autism.

Courchesne et al., (2005) from the University of California, San Diego have argued that in autism, higher order functions appear to fail to develop normally because frontal, cerebellar and temporal cellular and growth pathologies occur prior to and during the critical period, much of it immediately after birth, when these higher order brain areas first begin to form their neurological circuitry. They go on to state that "this altered circuitry impairs the essential role of frontal cortex in integrating information from diverse functional systems (emotional, sensory, autonomic, memory, etc) and providing context-based and goal-directed feedback to lower level systems."

With the above in mind it is not difficult to hypothesize the effects of thimerosal and/or ethylmercury on the developing brain. However, although the purpose of this report is to examine the likelihood that thimerosal and/or ethylmercury causes damage to the developing brain of a subpopulation of hypersusceptible children, we must realize that such a child would not only have been exposed to thimerosal mercury from being vaccinated but the child would be expected to have also prenatal and postnatal exposure to the following: methylmercury, dental amalgam mercury, and thimerosal/ ethyl-mercury . It would be reasonable to believe that the vaccination mercury could trigger an autism response.

Thus, it is of interest to review these possible exposures to mercury.

i) **Methyl mercury** from the fish that the mother consumed during pregnancy.

ii) **Methyl mercury** from the chicken that the mother consumed during pregnancy, since chicken feed often contains fish bones and fish remains.

In a 2003 examination of the National Health and Nutrition Examination Survey, a cross-sectional survey of the non-institutionalized U. S. population, it was found that approximately 8% of women had blood mercury concentrations higher than the U. S. EPA recommended reference dose of 5.8 μg/L (CDC 2003). Thus, mercury exposure continues to be a public health concern. While the greatest mercury exposure to the general population is through mercury contained in dental amalgams (NRC, 2000), the evidence to date indicates that exposure to methyl mercury causes the most toxic responses

Methyl mercury (MeHg), a form of organic mercury, is found almost exclusively in fish. Approximately 95% to 99% of ingested methyl mercury is absorbed by the gastrointestinal tract, after which much of it combines with the amino acid cysteine and is rapidly transported to the blood-brain barrier. The cysteinyl methyl mercury structure is believed to be analogous in chemical structure to that of the amino acid methionine. Thus, methyl mercury is transported across the blood-brain barrier by the protein that transports methionine. Once methyl mercury is deposited in the brain, it is slowly demethylated to mercuric mercury (Vahter et al., 1994) that **strongly binds** to brain proteins.

iii) **Elemental mercury** from amalgams that the mother had present or had been installed during pregnancy.

Dental amalgams, so called "silver" fillings, emit elemental mercury vapor. (Skare and Engqvist, 1994). This dental restoration material can contain up to about 50% mercury. The average person with the average number of amalgam surfaces emits and retains about 10 μg

mercury per day from such amalgams. The elemental mercury vapor is rapidly moved from the mouth cavity to the lungs where it is rapidly absorbed, enters the blood and transported to the tissues and brain. Because elemental mercury is fat-soluble, it is able to pass through the blood-brain barrier. Once it gets into the brain, it is rapidly oxidized to inorganic mercury (Hg^{+2}), which binds strongly and tenaciously to brain protein and thus remains in the brain. The health effects of dental amalgams include increases in antibiotic resistance (Rowland et al. 1984; Summers et al., 1993), the in vitro destruction of snail brain neurons (Leong et al., 2001), and hypersensitivity problems in approximately 0.5 to 15% of the population. Sweden, Britain, and Germany have prohibited dental amalgams restorations for pregnant woman and young children. These two vulnerable groups have also been cautioned to limit their ingestion of seafood.

iv.) **Ethyl mercury** from the thimerosal of vaccines that the mother may have been given during her pregnancy. Thimerosal from vaccines is metabolized to ethyl mercury. While ethyl mercury is analogous in chemical structure to methyl mercury, its toxicokinetic properties are quite different. Most importantly, thimerosal is metabolized very quickly to ethyl mercury which is transported in the blood to the tissues, crosses the blood-brain barrier, and is converted to mercuric mercury in the brain at a far faster rate than methyl mercury (Burbacher et al., 2005).

Once any form of mercury enters the brain and is converted to mercuric mercury, it is not easily eliminated from the brain, despite estimates of brain mercury half-life data appearing in scientific literature. In fact, inorganic mercury, the mercuric species, formed in the brain cannot easily leave and therefore it will be trapped and accumulate in the brain (Magos et al., 1985, NRC, 2000). Mercuric mercury has been used for over 60 years as an in vitro and in vivo enzyme inhibitor, as every first year biochemistry student soon learns. It is not innocuous even when formed in vivo.

An example of methylmercury demethylation and the powerful retention of the resulting mercuric mercury in the brain is as follows: During August of 1969, a New Mexico farmer fed his hogs grain seeds treated with a fungicide containing methyl mercury. A month later, a hog was killed and the family ate it for three months. In December, several of the children became ill with neurological disorders. Deaths occurred. However, one daughter, eight years old at the time of exposure, lived until the age of 29. An autopsy determined that 100% of the mercury in her brain was inorganic. In her cerebellum, the total mercury concentration was 100 times greater than controls, even though it was about 21 years after the original exposure (Davis et al., 1994). In another study, exceedingly high levels of mercury were demonstrated in the human brain and other organs 17 years after metallic mercury exposure (Opitz et al., 1996). In summary, once mercury converts to mercuric mercury in the brain, elimination of the mercury from the brain is extremely slow if it occurs at all. It is pertinent to remember that mercuric mercury has a very high affinity for sulfhydryl groups and it is used extensively in vitro as a potent, powerful inhibitor of enzyme activity and other protein functions. Mercuric mercury, although unable to pass through the blood brain barrier, does accumulate in large amounts in the brain as the metabolic end product of the other forms of mercury that do pass through the blood brain barrier (Vahter et al., 1994). It is noteworthy that the developing brains of young children are particularly vulnerable to damage by organic (ethyl mercury and methyl mercury) and elemental mercury. In this regard, it must be emphasized; that children are not little adults. They are physically immature developing human beings with substantial metabolic differences as compared to adults. A good example of this is that at birth the blood brain-barrier is not completely developed.

One of the most common forms of mercury exposure for humans is methyl mercury by the ingestion of fish. It occurs as a result of mercury vapor and mercuric mercury becoming airborne when emitted from soil, mountains, chimneys of fossil fuel-burning utility plants and incinerators. The mercury in the air then enters rivers, bays, and oceans by means of rain and other phenomena, including leaching from the soil. Bacteria methylate the Hg^0 and Hg^{+2} in the water and in the sediment of oceans, rivers, and lakes. Unicellular organisms take up the MeHg. Then, larger organisms take up the unicellular organisms. Through a process called biomagnification, small fish containing small amounts of MeHg are eaten by larger predators, such as swordfish, tuna, shark, and tilefish which then will contain large amounts of methyl mercury. Humans then consume these larger predator fish with substantial concentrations of methyl mercury. In this regard, it is noteworthy that methyl mercury is a proven human teratogen and is particularly hazardous to pregnant women and the developing brains of young children. (The medical definition of teratogen is "monster forming".) Two methyl mercury public health disasters have been well documented. These two public health disasters occurred in Japan and Iraq and demonstrated that methyl mercury can cross the placenta and be detrimental to the developing brains of embryos and young children.

Pink Disease- The fact that not all children who were exposed to mercurous mercury-containing teething powder came down with Pink disease and the fact that the mortality of the children was not 100% demonstrated that the genetic hypersusceptibility of some children to mercury played a significant role with respect to the nature and extent of the injury.

Between 1850 and 1950, a common syndrome, known as Pink Disease, acrodynia, erythredema, or Feer-Swift Disease (Dally, 1997), affected young children. As noted earlier, a teething powder containing mercurous salts caused this condition. Affected babies and toddlers

were unsightly and miserable. Their skin was bright pink or red in color. They were photophobic with "raw beef" hands and feet. They had peeling skin and gangrene in their extremities. The mortality was 5.5% to 33.3%. At the time, the symptoms were thought to be due to a viral disease or a nutritional deficiency. In 1920, when Pink Disease was discovered in three areas of the United States, investigators identified a mercurous mercury compound in a teething powder (as the cause. ***Curiously, established, conservative medicine for years denied that Pink Disease was caused by mercury. In the mid 1950's, however, the federal government finally banned the use of mercurous mercury in teething powder and new cases of Pink Disease disappeared.*** As a final note, the fact that neither morbitity nor mortality of the children was 100% demonstrates that the genetic hypersusceptibility of some children to mercury plays a significant role with respect to the nature and extent of the injury.

Thimerosal and childhood vaccines- Thimerosal is an organic mercurial metabolized quickly to ethyl mercury (Takeda and Ukita, 1969; Magos et al., 1985; Suzuki et al., 1963). It has been used as a preservative in numerous childhood vaccines. The Thimerosal molecule contains approximately 50% mercury and 54% ethyl mercury. Some children received 187.5 mcg ethyl mercury from Thimerosal-containing vaccines during the first 14 weeks of life (Clements et al., 2001). Thimerosal is given as repeated doses equivalent to 5-20 mcg ethyl mercury over the first six months of life (Halsey, 1999). In pre-term infants, blood mercury levels after only one hepatitis B vaccination increased more than 10-fold to levels above U.S. EPA guideline of 5 mcg per liter of blood (Stajich et al., 2000). Mercury contained within the vaccines is administered as a bolus injection resulting in an exceedingly high mercury compound being injected at one time. The half time of such injected mercury in the serum of *normal* human infants was estimated to be seven days (Pichichero et al., 2002). However, recent evidence obtained from primates seems

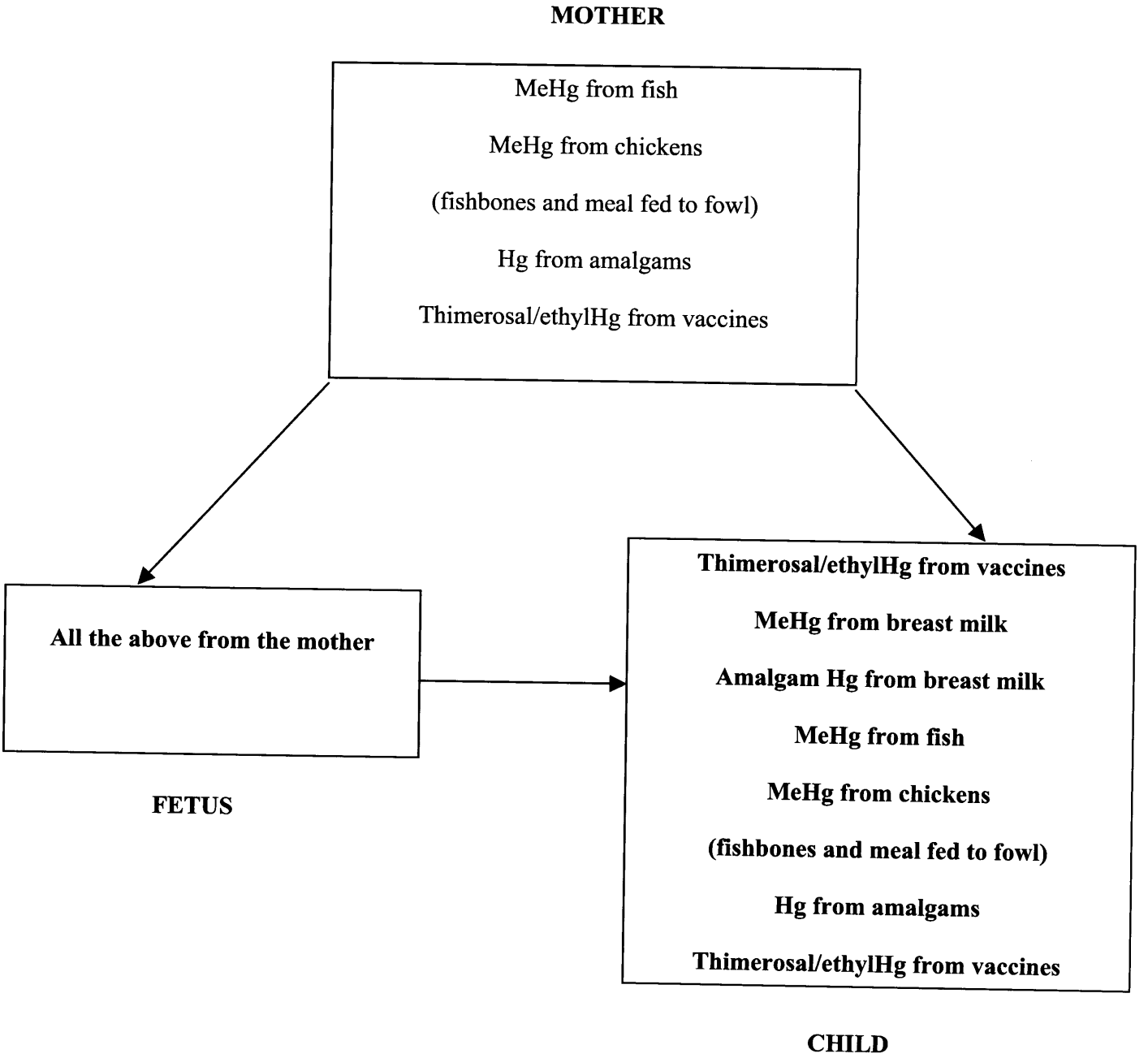
to indicate that a disproportionate amount of mercury from ethylmercury finds its way to the brain when compared to oral ingestion of methyl mercury (Burbacher et al., 2005).

Because of Burbacher's and other papers, it is often incorrectly stated that the toxicities of methylmercury and ethylmercury are very different. This statement is incorrect. Based on the data of Burbacher et al. (2005) and others, the toxicokinetics, not the toxicities, of methyl and ethyl mercury differ. There is not sufficient evidence to say that in the human the toxicities of methylmercury and ethylmercury are different.

While the chemical structure of ethyl mercury, CH_3CH_2Hg+, is similar to methyl mercury, CH_3Hg+, its toxicokinetics are markedly different. In Burbacher et al. (2005), the authors demonstrated that when infant monkeys were given Thimerosal, the ethyl mercury in the brain was converted to inorganic mercury at a rate seven times faster than occurred for methyl mercury. Once formed in the brain, inorganic mercury, as noted above, is bound and held firmly by brain proteins because of its great affinity for thiol groups of proteins. The initial $t_{1/2}$ (half time) of ethyl mercury in the blood of the infant monkeys was 2.1 days. The terminal $t_{1/2}$ in blood was 8.6 days. For methyl mercury the $t_{1/2}$ was 21.5 days. While methyl mercury kinetics indicated a one-compartment model, the kinetics for ethyl mercury indicated a two-compartment model (Burbacher et al., 2005). For this reason, the disposition kinetics and demethylation rates differ. Because of these reasons, the toxicokinetics of methylmercury and ethylmercury differ. However, this does not mean the toxicity differs.

The maternal and other sources of mercury exposure for an infant is shown in Fig 4.

Figure 4. Influence of the mother and other sources for mercury exposure of infants



The mercury public health disasters- In Japan, a chemical factory dumped mercury wastes into a river that emptied into Minamata Bay. Mercury concentrations were found to be high in the water of the Bay and large amounts of methyl mercury were found in the fish. Unfortunately, by the time of this discovery, many people living near the Bay had suffered central nervous system disorders (Tsubaki and Irukayama, 1977). In fact, the word "minamata" is now used in Japan as a word synonymous with idiot.

Beginning in the 1960s, over 6,500 individuals were hospitalized with methyl mercury poisoning and numerous deaths occurred in the Iraqi mercury disaster (Bakir et al., 1973). These two public health disasters in Japan and Iraq demonstrate that methyl mercury can cross the placenta and be detrimental to the developing brains of embryos and young children. The disasters stimulated the U.S. government to sponsor two studies to investigate the effects of low-level exposure of methyl mercury. Specifically, the studies focused on the impact of the exposure with respect to the intelligence of children born to mothers from populations eating fish as their primary source of protein. The two studies, the Seychelles Island study (Myers et al., 2000; Myers et al., 2003) and the Faeroe Island study (Grandjean et al., 1997a, 1997b; Grandjean, 1999) had contrasting results. The Faeroe Island study showed cognitive deficits in seven-year-old children who had prenatal exposure to methyl mercury (Grandjean et al., 1997a). The Seychelles Island study, on the other hand, initially showed no harmful effects of methyl mercury (Myers et al., 2000).

A White House conference was called to evaluate the discrepancies in the two studies. (The writer of this report was invited and participated in this conference). Once some method changes were made, intelligence deficits were also found subsequently in some Seychelle Island children (Myers et al., 2003). The New Zealand study (Kjellstrom et al., 1986, 1989), has now

confirmed the Faeroe Island study. In these circumstances, it is clear that low level methyl mercury exposure can be detrimental to the developing brain of young children. See also Trasande et al. (2006), wherein the authors forcefully warn of the adverse public health and economic consequences of methyl mercury toxicity.

In another study, Hightower and Moore (2003), the authors reported a group of wealthy persons (CEOs, attorneys, and physicians) who presented to their physicians with central nervous system complaints. Their histories disclosed that they could afford and ate expensive fish, such as shark, swordfish, and tuna, almost exclusively as their protein source. These fish are predators and contain high concentrations of methyl mercury. After six months on a seafood-free diet, the patients returned to normal health.

6. **A highly plausible theory is that thimerosal and its biotransformant ethylmercury cause injury to the developing brains of human embryos and young children.**

Evidence for thimerosal/ethylmercury being implicated in the etiology of autism is summarized below. Each piece of evidence alone leaves some doubt but taken all together the evidence implicates thimerosal/ethylmercury in the etiology of some of the autism spectrum disorders. Another way of saying this is that in some specifically susceptible subset of infants who received mercury-containing vaccines on the US vaccination schedule in place from roughly 1991 to 2003, the ethylmercury probably caused the symptoms of autism in many of them.

First, Adams et al. (2007) demonstrated that teeth from autistic children contain more mercury than those from non-autistic children.

Second, Holmes et al (2003) demonstrated that the hair from the first haircut of autistic children contained statistically significant less mercury than that of control children. This would be expected if autistic children had a mercury efflux disorder; that is they could not move

mercury out of their cells. This would result in decreased blood and hair mercury (but not tooth mercury). This work has been criticized unjustly. Some of the reasons for this criticism has been the mercury analyses were performed by a commercial lab (this lab is certified by the FDA and probably performs more mercury analysis each year than any other lab including academic labs in the world. Another criticism was that the research was performed by individuals not having research experience and not recognized for their research expertise. Yet, one of them was and is funded by NIH grants and was the head of a university chemistry department. The hair analysis of controls was higher than the normal American population. The Holmes et al., study has been confirmed by the MIT group. (Hu et al. 2003)

Third, Bradstreet et al. (2003) demonstrated that autistic children given the chelating agent DMSA excreted more mercury in their urine than did control children.

The Nataf et al., (2006) study confirmed the Bradstreet et al results. In addition Nataf et al., found that the mercury-specific porphryinuria increased in autistic children and that there was a marked decrease in the mercury-specific porphryinuria of autistic children after chelation of mercury using DMSA.

Fourth, the most beneficial treatment for autism as reported by the parents of autistic children was chelation therapy using DMSA (meso-2,3-dimercaptosuccinic acid) as reported in a study by the Autism Research Institute in San Diego, CA (2006). Although this study has been criticized, such a clinical trial is being planned or has begun at the NIH.

Fifth, autoimmune disease sensitive mice exposed to mercury after birth develop enlarged brains and autistic-like symptoms. (Hornig et al., 2004).

Sixth, there is evidence for postnatal loss of brain cells in autism, particularly in the cerebellum. Courchesne (2005) at p. 584 and references cited there.

To repeat, each piece of evidence alone leaves some doubt but taken all together the evidence implicates thimerosal/ethylmercury as the likely precipitating agent in the etiology of some of the autism spectral disorders.

6- Conclusions

Thimerosal and its biotransformant ethylmercury cause injury to the developing brains of human embryos and young children by interfering with brain development during highly specific windows of brain development. These windows of susceptibility may occur during the prenatal and/or postnatal periods. These windows are vulnerable and open at very specific times.

Thus, thimerosal induces symptoms of autism spectrum disorders in some subsets of children. There is growing importance of neuroinflammatory events in the development of autism. All of this indicates the need for closer examination and better correlations of past research on the genetics and environmental factores causing autism. One of these environmental factors is surely thimerosal.

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August 30, 2007

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Education

B.S. Brown University, 1948 (Chemistry)
M.S. University of Rochester, 1950 (Physiological Chemistry)
Ph.D. University of Rochester, 1953 (Physiological Chemistry)
Advanced Training:

Department of Biochemistry, Stanford University School of Medicine (with Nobel Laureate Dr. Arthur Kornberg), 1959-1962

Department of Biology, Massachusetts Institute of Technology (with Dr. Paul Schimmel) -- six-month sabbatical, January 1-June 30, 1983

Department of Biology, University of California, San Diego -- six-month sabbatical as Visiting Scholar, June 1-December 30, 1990

Positions Held

1954-56	Instructor, Department of Pharmacology, Vanderbilt University School of Medicine
1956-59	Assistant Professor, Department of Pharmacology, Vanderbilt University School of Medicine
1959-62	USPHS Senior Research Fellow, Department of Biochemistry, Stanford University School of Medicine
1962-67	Associate Professor, Department of Microbiology, Tufts University School of Medicine
1966-75	Professor, Department of Cell Biology and Pharmacology, University of Maryland School of Medicine. (As Head of Department, 1966-72)
1975-present	**Professor, Department of Pharmacology, College of Medicine, University of Arizona**
1975-83	Professor, Department of Cellular and Developmental Biology, College of Liberal Arts, University of Arizona. (Head of Department, 1975-79)
1983	Visiting Professor, Department of Biology, Massachusetts Institute of Technology (January 1, 1983-June 30, 1983)
1983-present	**Professor, Department of Molecular and Cellular Biology, Faculty of Science, University of Arizona**

Research Interests

1. Metal toxicity and mechanisms of intoxication of arsenic, mercury, lead, and manganese, polymorphisms involved.
2. Biological chelation: Use of DMPS as a challenge test for mercury, arsenic and lead.
3. Arsenic detoxification and intoxication: molecular mechanisms.
4. DNA and gene delivery systems for mammalian cells and intact animals.
5. Pseudovirions.
6. Autism

Professional Societies

Society for Toxicology
American College of Toxicology
American Society of Biological Chemistry and Molecular Biology
American Society of Microbiology
American Society for the Advancement of Science, Fellow
New York Academy of Sciences
American Society for Pharmacology and Experimental Therapeutics (resigned 1976)
American Academy of Microbiology
American Association of University Professors

Awards or Honors

1959-64	USPHS Senior Research Fellowship (resigned 1962)
1959	Jane Coffin Child Fellowship (declined)
1972	Sigma Xi Annual Award for Scientific Achievement, Maryland Chapter
1974	Student Council Award for Excellence in Teaching, University of Maryland School of Medicine
1977	Invited Guest, Soviet Academy of Science, June, 1977
1977	Invited Lecturer, Al-Hazen Research Institute, Baghdad, Iraq, May, 1977
1981	Invited Speaker, Korean Biochemical Society
1985	National Academy of Science (U.S.) - Soviet Union Academy of Science Exchange Fellow for September, 1985, in Soviet Union
1985	Official Guest of Peoples' Republic of China, Academy of Science, Lecture Tour, October, 1985
1996	Official Guest of Peoples' Republic of China, Academy of Science, Evaluation of arsenic problem in Guizhou Province, November, 1996
1998	Official Guest of Peoples' Republic of China, Academy of Science, Evaluation of arsenic problem Autonomous Region of Inner Mongolia, November, 1996
1999	Official Guest of Peoples' Republic of China, Academy of Science, Treatment of Arsenic problem in Guizhou Province.

National Service (only a few are listed)

1970-78	Member of ad hoc committees for cancer programs and cancer construction programs of the National Cancer Institute.
1971	Consultant to National Cancer Institute Planning Session, Airlie Conference Center.
1972	Advisor on gene technology to U.S. Senator J.V. Tunney. U.S. Environmental Protection Agency, Mercury Advisory Committee.
1971-73	American Cancer Society, Maryland Division - Member, Board of Directors.
1971-72	American Cancer Society, Maryland Division -Chairman Grants Committee.
1989-	Consultant For Various Multinational Pharmaceutical, Consumer-Goods And Life Science Companies – Confidential.
1990	Lecturer - Continuing Education Committee, Society of Toxicology.
1990-94	Member of various ad hoc study sections, National Institutes of Health especially for the National Institute for Environmental Health Sciences.
1993	Councilor - Metal Section, Society of Toxicology.
1993	Super Fund - Agenda Workshop for Biodiversity Toxicology of Children, for the National Institute for Environmental Health Sciences.
1995	WAARF Arsenic Research Priority Planning Meeting,-- Mechanisms Section Chairman.
1995	WAARF Arsenic Grant Application Study Section.
1997-98	National Research Council, Committee on Toxicology, Subcommittee on Arsenic in Drinking Water, member.
1997	EPA Working Committee on Arsenic Carcinogenesis.
1998	NIEHS Methylmercury evaluation group.
1998	Mercury toxicity. Presentation to Committee On Government Reform, House of Representatives, Congress of the United States
1998	Cure Autism Now, Research Grant Committee
1999-2000	National Research Council, Committee on Toxicology, Committee on Mercury Toxicity, member.
2004	Presentation to Vaccine Committee of IOM entitled: *A Toxicologist's View of Autism and Thimerosal*
2005-2006	EPA, Arsenic Study Committee

International Service

Present	Research and Scientific Evaluations of Arsenic, Mercury and Other Toxic Chemicals for National Governments.
1992	Metal Toxicology Workshop for Physicians, Taipei Veterans Hospital Center, Taiwan.
1993	Superfund Workshop, Campaigne de Madonna, Italy.
1993	Mercury Levels in Mexican Dental and Tampico Factory workers.

1994	German Government Metal Toxicology Workshop.
1994	Arsenic Toxicity in Chile.
1994	Hg Toxicity in Denmark.
1996	Arsenic toxicity in China.
1998	Arsenic toxicity in Inner Mongolia.
1999	Arsenic toxicity in China.
1999	Arsenic toxicity in Romania
2000	Lead, cadmium and arsenic toxicity in children in Torreon, Mexico
2003	WHO workshop on Child Health in Southeast Asia (Bangladesh)
2003	US-Japan meeting on arsenic (by invitation only)
2004	Arsenic toxicity in rural elevated Argentina
2006	International Conference of Chelating Agents, Advisory Board

University of Arizona Service

1976-79	University Advisory Committee on Promotion and Tenure.
1975-79	Biomedical Support Research Grants Committee.
1975-77	Executive Committee, Cancer Center.
1976-77; 1979	Search Committee, Biochemistry Head.
1977-85	University Committee to review DNA recombinant research.
1978	Toxicology Program - Member of Executive Committee.
1979-85	Graduate Council - Chairman, Student Affairs Subcommittee; Petitions Subcommittee.
1987	Toxicology Faculty Search Committee, College of Pharmacy.
1988	Molecular and Cellular Biology Faculty Search Committee, College of Arts and Sciences.
1991-95	Chairman, Biomedical Group for Superfund Center.
1992	Member of committee to review College of Medicine Molecular and Cellular Biology course.
1993	Chairman of committee for five-year review of Department Head.
1994	Environmental Quality Committee.
1995	Medical School Neurosciences Review Committee.
1995	Chairman, Departmental Promotion and Tenure Committee.
1998	College of Science, Promotion and Tenure Committee.

State of Arizona Service

1989-92	Commissioner, Structural Pest Control Commission, State of Arizona.

Present Grant Support

NIEHS Superfund Project, $181,000 per year. *In vivo* and *in vitro* metabolism of arsenic.
Autism Research Institute, $40,000 per year. Autism Biomarkers.

Other

Paid consultant at various times for various multinational pharmaceutical or consumer product companies.

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(Does not include abstracts of papers presented at international or national meetings or seminars and lectures given at various institutions.)

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