Respondent's Exhibit FF

Kennedy Krieger Institute

A comprehensive resource for children with disabilities

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USDOJ/Civil Torts Branch/OCVL
1425 New York Ave. NW
Room 8119
Washington, D.C. 20005

RE: Cedillo case

At your request I have reviewed the medical records of Michelle Cedillo as well as the expert reports in this case, and have formulated the opinions below based on these materials, my knowledge and experience. My opinions are held to a reasonable degree of medical certainty.

By way of introduction, I am a pediatric neurologist with a special interest in behavioral neurology and autism. I have been practicing for 30 years since I completed my residency training in 1977, in two academic settings for 22 years and private practice for 11 years. During practice in Knoxville, TN, I became interested in autism in the mid-eighties and have concentrated my efforts in this field since returning to Baltimore in 1994, at Kennedy Krieger Institute and Johns Hopkins University, in clinical practice, research and teaching. Over the past 21 years, I have evaluated and followed approximately 4,000 children and adults with autism. My major research interest has been the role of the immune system in autism, and I have published on this and related areas in autism research, as indicated in my curriculum vitae. My interests and collaborations have led to new approaches to the understanding of immunity in families with autism, the role of immune system genes, immune factors in cerebrospinal fluid, and immune activation in the brain in autism, among others. I also have experience in drug studies and am a member of the Drug Therapy Committee and a grant reviewer for Cure Autism Now and Autism Speaks. I was an organizer of the first Autism and Immune System Workshop

held recently in Pasadena, and I am currently editing a book with 20 authors, entitled *Autism: Current Theories and Evidence.*

The case of Michelle Cedillo presents complex questions due to the unusual nature of her findings and clinical course, as well as the etiologies (causes) for autism alleged by the petitioners' experts. Autism itself is a heterogeneous group of neurodevelopmental disorders that present with similar clinical signs, and are diagnosed by observed language, social and behavioral characteristics. About 10% of affected children can have any of a large number of "known," diagnosable conditions by examination and using currently available laboratory tests -- conditions such as fragile X syndrome, Rett syndrome and tuberous sclerosis.[1] The designation of a child as "autistic" is therefore no more specific than saying a patient is "hypertensive" or has "pneumonia," since these conditions require the physician to investigate the underlying causes in order to provide specific treatment. The other 90% of children with autism remain "idiopathic," meaning we still do not know the medical basis for their symptoms (i.e., their causes have not been established based on current scientific evidence). Approximately 30% of children with autism present with signs of regression or loss of previously acquired language and social skills, typically between 16 and 24 months of age, although studies have shown that despite the appearance of prior "normality," most had subtle signs of abnormal development during the first year of life. Gastrointestinal symptoms are associated in about 24%, [2] and epilepsy in up to 40% of children with autism, both of which usually improve over time.

In the immune system, a variety of atypical findings have been reported in children with autism, as measured in the blood.[3] These have been difficult to characterize, because of variability among findings in different studies, most of which cannot be compared due to small numbers of patients and their different techniques and measurements. In spite of these findings, severe immune deficiencies typically do not occur in autism, and there is no evidence that correction of mild immune deficiency states (e.g., with administration of immunoglobulins) provides benefit for autistic symptoms.[4] There is also no evidence for correlations or causal connections between findings in the "systemic" immune system (in

the blood and lymph glands) and immune or other findings in the brain in autism Although antibodies to a variety of brain antigens have been described in the blood from children with autism, they have also been found in normal "control" children and have not been proven to play a role in causing or contributing to autism. [5] Indeed, a current focus of immune research is on the *mother's* immune system, which shows that maternal antibodies directed to the developing human fetal brain may be pathogenic (cause pathology) before birth.[6] The effects of these human maternal antibodies have been demonstrated following placental transfer in animal models, producing abnormal behaviors and changes in the brain of the offspring.[7] This implies that differences in the immune system in autism are likely to be important before birth, acting between the mother and fetus. My colleagues and I have also described signs of immune activation in both the cerebrospinal fluid (CSF) of living children, and in postmortem brain tissue from children and adults with autism.[8] There is no evidence in brain tissue or CSF of infection,[9] and the immune activation we observed contained pro-inflammatory as well as anti-inflammatory elements.[8] Further research is needed to determine if the immune activation in the brain in autism is harmful or beneficial to the brain (it may be either or both), is a residual immature pattern of development from an earlier age, or results from abnormal regulation of brain cells (neurons or astroglia) or a genetic abnormality affecting the immune system, among other possibilities.

Autism is primarily a genetically determined disorder.[10] There is a hypothetical basis, but very limited evidence, for environmental factors (such as stress or the drug terbutaline[11]) that may act together with an individual's genetic susceptibility to increase the risk of autism. There is strong evidence that the origins of autism begin before birth, based on genetic and anatomical studies as well as chemical findings at birth in children who go on to develop autism.[12, 13] The usual time period when autism appears and is diagnosed during the 2nd and 3rd years of life reflects the dynamic nature of the child's developing brain and the appearance of pre-programmed disordered expression of genes and pre-existing cellular abnormalities that result in the child's regression with loss of language and social skills. The best example of such developmental regression occurs in Rett syndrome, a genetic disorder that was otherwise undifferentiated from autistic disorder

until the genetic abnormality was discovered in 1999; it is now considered a well-defined cause of autism, the boundaries of which are continuing to expand as more genetic variants are being discovered.[14]

Based on this background, my opinions in this case cover six areas:

1. There is no scientific basis for a connection between measles, mumps and rubella (MMR) vaccine or mercury (Hg) intoxication and autism. Despite well-intentioned and thoughtful hypotheses and widespread beliefs about apparent connections with autism and regression, there is no sound evidence to support a causative relationship with exposure to both, or either, MMR and/or Hg. Michelle Cedillo had a thorough and normal immunology evaluation by Dr. Sudhir Gupta, showing no signs of immunodeficiency that would have precluded her from receiving or responding normally to MMR vaccine.

2. Michelle Cedillo's developmental regression was likely to have been pre-programmed before birth to emerge, as it does in Rett syndrome, long after birth. Although in rare instances MMR can be associated with an acute encephalopathy, this event did not occur here. While parental description of the emergence of Michelle Cedillo's condition has been inconsistent, no description coincides with an acute encephalopathic insult. Petitioners' experts postulate a chronic brain injury. Again, there is no scientific basis for attributing autism to MMR administration.

3. The pediatric growth records show abnormal growth in height, weight and head circumference during Michelle's first 18 months of life. At birth, her weight was at the 50^{th}, while length was at the 90^{th} percentile. By 6 months of age, all measurements were well above the normal growth curve for age. However, at 11 years her height was at the 75^{th} percentile, although she continued to be overweight. This unusual growth pattern suggests a genetic disorder of growth, a so-called "overgrowth syndrome," such as Sotos syndrome[15], which has been

associated with autism. Although she was said to have had extensive genetic testing, I was unable to locate results of such testing in the records, nor was there a genetic consultation recorded, as recommended by Dr. B. J. Freeman (in 7/00), among others. Rapid acceleration of head growth has been documented during early postnatal development in autism (but not height or weight), the causes for which are still unknown.

4. Although Michelle's early developmental milestones were later said to be normal, they were not. Dr. Karlsson Roth recorded during an early diagnostic evaluation that Michelle did not smile until 4-6 months, roll front to back until 4-5 months, crawl until 9 months, sit until 11 months or walk until 16 months. Such delays suggest subtle abnormalities of development during the first year of life, preceding the administration of MMR vaccine.

5. Associated medical disorders in children with autism may occur commonly or uncommonly, but are not diagnostic of autism, nor do they indicate or imply the etiology of autism. For example, gastroesophageal reflux and lymphoid hyperplasia in the gastrointestinal tract, and epilepsy in the nervous system, both occur together with autism, however neither is diagnostic or definitive with respect to its causes or treatment. The medical treatment of these and other associated medical disorders can alleviate suffering and help a child respond better to autism therapies (such as speech and occupational therapy), but in neither case do the treatments change the underlying autism. Crohn's disease, uveitis and arthritis, conditions attributed to Michelle, have no correlation with autism.

6. Autism, in most cases, begins before birth, and the maternal "environment" in the womb is likely to be important in the process. A number of factors are likely to increase susceptibility to autism, such as autoimmune disorders in the mother, including allergy and asthma (for which Theresa Cedillo was treated and followed). Autoimmune disorders are more common in the mothers and families

with autism than the general population, however such associations have not been found in the children.[16, 17]

In summary, the factors outlined above strongly suggest that Michelle Cedillo had unusual signs and symptoms leading up to the appearance of developmental regression and the recognition of autism. Her medical course has also been unusual and complex but does not imply a relationship to a specific etiology. Furthermore, there is no evidence of an association between autism and the alleged reaction to MMR and Hg, and it is more likely than not, that there is a genetic basis for autism in this child.

Sincerely,

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