Respondent’s Exhibit DD
Max Wiznitzer, M.D.

April 19, 2007

Associate Director, Programs Operations Branch
Division of Vaccine Injury Compensation
5600 Fishers Lane, Room 16C-17
Rockville, MD 20857

RE: Cedillo
No. 98-916V

Dear Sir:

I have reviewed additional records in the above named case. These include the records and other materials in Medical Exhibits 1-54 and the reports of Drs. Kinsbourne, Byers, Aposhian and Krigsman. This report represents a supplement to my report of 7/8/01, which contains history of the events immediately following the MMR immunization of 12/20/95 and the diagnosis of autism. On the basis of this review and in response to Dr. Kinsbourne's report, I have reached the following conclusions (using the template in Dr. Kinsbourne's report):

The Diagnosis of Autism

The diagnosis of an autistic spectrum disorder (ASD), including autistic disorder, is clinical in nature and based on established diagnostic criteria in the areas of socialization, communication and restricted interests and activities. However, even before a definitive diagnosis is established, the child manifests clinical features that, in retrospect, are clearly associated with and part of the diagnostic criteria. With increasing awareness of and education about this disorder and because of changes in diagnostic criteria, the diagnosis is being made more often and at an earlier age. While the diagnosis is becoming more common, in my clinical practice I have not seen evidence of an "epidemic."

While ASD is a clinical diagnosis, an identifiable biologic underpinning is identifiable in a minority of cases. This includes disorders such as marker chromosome 15 syndrome, fragile X syndrome, tuberous sclerosis and certain inborn errors of metabolism. In the
presence of additional clinical features (either in history or on examination), certain in utero exposures (such as thalidomide, rubella or cytomegalovirus) can be identified.

In approximately 1/4 - 1/3 of children with ASD, a history of autistic regression is elicited. This occurs in those with apparently normal developmental progress (including functional communication, play and social skills) until the second or third year of life, at which time there is a clear loss of skills in communication (predominantly pragmatics), representational and pretend play and socialization that cannot be explained by another medical or neuropsychiatric condition. In retrospective evaluation, clinicians frequently identify developmental abnormalities occurring before the frank appearance of apparent regression (Rogers 2004).

In his report, Dr. Kinsbourne discusses causes of developmental regression in children (page 9, last paragraph) and makes some factual errors. Girls with Rett syndrome have a regression in development that plateaus after a period of time, unlike his statement that they have a “relentless deterioration without plateau” (Hagberg 2002). Children with Landau-Kleffner syndrome (also known as epileptic aphasia) usually present with an evolving inability to understand spoken language that leads to loss of speech with relatively few, if any seizures, at onset. Furthermore, they do not have a global mental regression but, rather, an acquired “word deafness” (Pearl et al 2001).

Measles as a Cause of Autistic Spectrum Disorder

Dr. Kinsbourne states that Michelle Cedillo has regressive autism due to brain infection by measles virus from her MMR immunization that was able to enter the central nervous system due to a compromised immune system caused by thimerosal in her immunizations prior to the MMR. However, that conclusion is speculative and without support.

1. There is no biologic model of measles virus – induced autism (let alone autistic regression). Natural measles infection is not recognized as a cause of ASD. Measles virus can affect the brain in 2 proven ways – direct infection (measles inclusion body encephalitis and subacute sclerosing panencephalitis) or post-infectious inflammation (acute disseminated encephalomyelitis). Clinically, ASD features are not a component of the central nervous system dysfunction described in proven measles-related infection. Furthermore, there is an abrupt change in functioning that results in hospital admission and identifiable abnormalities on neuroimaging studies (Norrby & Kristensson, 1997). Michelle Cedillo did not meet diagnostic criteria for either mechanism of measles-related brain involvement.

2. Dr. Kinsbourne states that when “measles virus invades the brain it is known to cause inflammation” (page 16, paragraph 2). However, Michelle Cedillo did not show any evidence of inflammation or of injury to the brain on any medical testing (including neuroimaging, EEG and CSF analysis). He quotes de la Torre et al (1996) that “viruses can also persist in the CNS and, in the absence of cell destruction or inflammation, cause defects in goal-directed behavior as the main or sole manifestation of infection”. However, this was an infection of newborn mouse brain by lymphocytic choriomeningitis
virus (LCMV), which is a virus in a different family from measles, has a different pathology in animals of this age and cannot be compared to the proven pathology changes of measles infection. Furthermore, LCMV infection of the human can cause meningitis and encephalitis and birth defects of the brain in the fetus. This difference in the manifestations of LCMV infection in the human and newborn mouse (with the former clearly showing neuropathologic changes) shows how one cannot cite animal research as supportive data without a direct human correlate (Barton & Hyndman 2000, Quinn 2005).

3. Dr. Kinsbourne cites studies of the neuropathology of autism as support for his speculation about inflammatory changes in the ASD brain. He writes that Bailey et al “found gliosis, a sequel of inflammation, in the autopsied cerebra of autistic individuals” (page 17 last paragraph). A closer examination of Bailey et al’s paper finds that this change, when present, was minor in degree and very limited in location except for the changes in Case 3 that were “consistent with an old head injury” and not with inflammation. Bailey et al (1998) identified the main pathologic findings as “developmental abnormalities” and not an acquired insult due to an inflammatory process. Review of other neuropathology papers cited by Dr. Kinsbourne also shows no evidence of an inflammatory disorder as the cause for ASD (Bauman & Kemper 2005, Kemper & Bauman 1998). Therefore, Dr. Kinsbourne’s statement “Chronic inflammation has been found in the cerebrum and the cerebellum of children with ASD that is consistent with the effect of chronic virus infection” is not supported by this medical literature.

4. References are made to “plausible mechanisms in the virus causation of autism”. However, in my clinical experience, this usually represents prenatal exposure (rubella and CMV) or atypical presentations with additional deficits, older age of occurrence, presence of an acute encephalitic illness, or identifiable brain pathology. Animal models of viral infection only describe certain behaviors and do not have the full phenotype of ASD. Epidemiological studies do not support a causal relationship between MMR vaccine and autism. The purported biological model of bowel disease and ASD has limitations in the purported relationship between onset and MMR immunization and in the diagnosis of ASD. Therefore, prenatal viral exposure can be a cause of ASD, but there is poor support for postnatal causation (except for atypical cases with well identified brain abnormalities).

5. Articles are cited to support the claim that children with autism have more gastrointestinal problems than the general pediatric population and that these occur more often in children with regressive autism. A careful reading of the articles finds complaints of vomiting, bulky stools or chronic constipation in Valicenti-McDermott et al (2006)’s report, which can be explained by the children’s eating habits or excessive anxiety, and significant differences in the frequency of GI symptoms (some of which would have been non-significant with correction for the effect of multiple comparison) and no difference in the rates of GI disorders such as inflammatory bowel disease in Richler et al (2006)’s paper. There are many dietary and behavioral reasons for the increased GI problems in children with ASD but no evidence of an increased rate of inflammatory bowel disease, suggesting that these publications do not support the
speculative claim of ASD secondary to MMR immunization and thimerosal exposure. In my clinical experience, children with ASD have GI problems that are either directly related to their ASD features or comorbidities or are caused by conditions that are independent of their ASD diagnosis. While some have inflammatory bowel disease, none have a history that relates their medical problems to immunizations.

Dr. Kinsbourne states that Michelle Cedillo had autistic regression after her MMR immunization (Rogers 2004). However, the medical records suggest that she may have had features indicative of dysfunction prior to the MMR immunization. These features include description of a good baby who “cried little” and word use that was mostly imitative in nature and an acceleration of head circumference growth in the first year of life followed by a relative deceleration in the second year of life. The latter has been well described as a manifestation of abnormal brain development in children with ASD (Dawson et al 2007, Redclay & Courchesne 2005). In his report, Dr. Kriksman states “development proceeded in an age appropriate manner during the first year as evident from pediatrician notes and home videos”. Review of these home videos (in total and with no editing) would be useful to better define the nature of her functioning in the first year of life.

In summary, Dr. Kinsbourne’s report, which contains much speculation, does not add to the information already available and does not alter my 7/8/01 opinion that there is no history to support the claim of causation in fact and no medical literature to show that immunization is a cause or contributing factor to autism/ASD.

If you have any questions or if more information becomes available, please feel free to contact me.

Sincerely,

Max Wiznitzer, M.D.
Pediatric Neurology
REFERENCES


