Respondent's Exhibit Y

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

RE: Snyder
No. 01-0162

Dear Sir:

I have reviewed additional records in the above named case. These include medical records and videos on DVD and the reports of Drs. Kinsbourne, Kennedy, and Bradstreet. This report represents a supplement to my report of 7/8/01, which contains history of the events immediately following the MMR immunization of 4/23/98 and the later diagnosis of pervasive developmental disorder. 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 5, 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).

In his report, Dr. Kinsbourne repeatedly states that Colten Snyder has autistic disorder (including the terms "autistic regression" and "autistic spectrum disorder"). This appears to differ from Dr. Bradstreet's determination that Colten Snyder has an autoimmune encephalopathy (also used by Dr. Ronald Kennedy is his opinion). In addition, information in the records raises questions about the appropriate diagnosis.

Dr. Bradstreet's records list the use of treatments for Colten Snyder's condition that include chelation therapy, gluten and casein free diet, nutritional supplements, secretin and oral and intravenous immunoglobulin. None of these treatments have been shown to successfully treat the central nervous system manifestations of "measles virus persistence" or the core features of autistic disorder or autistic regression (using terminology from the petitioner's experts' reports). Furthermore, chelation therapy has potential adverse/harmful effects.

Measles as a Cause of Autistic Spectrum Disorder

Dr. Kinsbourne states that Colten Snyder has regressive autism due to brain infection by measles virus from his MMR immunization that was able to enter the central nervous system due to "a failure of immune response and long term persistence of the measles virus". 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 & Kristennson, 1997). The clinical course of "persistent measles infection" of the central nervous system is progressive deterioration of neurological function. None of the treatments that Colten Snyder received are known to alter this deterioration. Therefore, the finding of measles RNA in CSF in 2002 is not compatible with the expected clinical course of this type of infection and suggests the finding of a false positive result.

2. Dr. Kinsbourne states that when "measles virus invades the brain it is known to cause inflammation" (page 14, last paragraph). However, Colten Snyder did not show any evidence of inflammation or of injury to the brain on any medical testing (including neuroimaging 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 pathologic 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 16 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).

4. On pages 15-16, Dr. Kinsbourne argues that "a potentially injurious agent with affinity for the cerebrum, hippocampus, amygdala and/or cerebellum...could trigger regression into an autisitic disorder, especially if the child is genetically predisposed". There are several problems with this statement. First, the anatomic locations that he identifies are the majority of the brain tissue and too general in location. Secondly, in my clinical experience, "virus infections that cause autism"(to use Dr. Kinsbourne's words) 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 speculative 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 Vallicenti-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.

6. Dr. Kinbourne speculates on the mechanism by which measles vaccine virus can cause autistic regression (pg18-19). He states that excessive glutamate is harmful to brain and will result in cell death or overexcitation of brain cells (with consequences that include seizures and deterioration in the quality of sensory information). His conclusions are not supported by the available evidence. A close reading of his reference (Rubenstein & Merzenich (2003)) finds that these authors offer several mechanisms for this imbalance in excitation/inhibition via the glutamate and GABA systems. While they mention "mutations...that increase the amount of glutamate in the synapse" as one of many hypothetical causes of this imbalance, they provide no support for this portion of the model. In fact, when these authors discuss the loss of cerebellar Purkinje cells in autism, they propose that a disruption in synapse formation or survival related to the need for neurotrophic molecule effect is a conceivable mechanism (pg 262). However, the authors are careful to conclude that this postulated concept concerning the ratio of excitation/inhibition is a "hypothesis" (pg 263). Furthermore, in clinical disorders with overexcitation of neurons due to excessive glutamate, there are identifiable structural brain changes and atrophy on neuroimaging. This was not present in this case.

A review of the home videos that were provided finds information up to February 1998 (age 13 months) and, then, the appearance of a much older child (appearing to be at least 2 years old). While the timing of the February 1998 portion of the video is supported by a statement by one of the Snyder children, there is no information on the DVD that allows one to accurately time the other segments (leading to an estimation of Colten Snyder's age in the latter portion of the DVD). The videos up to February 1998 show that Colten Snyder has little vocalization (only a few monosyllabic sounds). This implies

that there may have been a pre-existing problem with expressive language development. There is no identifiable video of birthday parties in the first 3 years of life (with the exception of a few seconds of a cake in one of the last segments). No significant tantrums are noted. I understand that a chronology of events was recently filed by the petitioners, but I have not had an opportunity to review the video again with the chronology in hand.

In summary, Dr. Kinsbourne's report, which contains much speculation, does not add to the information already available and does not alter my 7/14/01 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/PDD

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

Bailey A, Luthert P, Dean A, et al. A clinicopathological study of autism. Brain 1998;121:889-905.

Barton LL, Hyndman NJ. Lymphocytic choriomeningitis virus: reemerging central nervous system pathogen. Pediatrics 2000;105. URL: http://www.pediatrics.org/cgi/content/full/105/3/e35.

Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. Int J Dev Neurosci 2005;23:183-187.

de la Torre JC, Mallory M, Brot M, et al. Viral persistence in neurons alters synaptic plasticity and cognitive functions without destruction of brain cells. Virology 1996;220:508-515.

Hagberg B. Clinical manifestations and stages of Rett syndrome. Ment Retard Dev Disabil Res Rev 2002;8:61-65.

Kemper TL, Bauman ML. Neuropathology of infantile autism. J Neuropath Exper Neurol 1998;57:645-652.

Norrby E, Kristensson K. Measles virus in the brain. Brain Res Bull 1997;44:213-220.

Pearl PL, Carrazana EJ, Holmes GL. The Landau-Kleffner syndrome. Epilepsy Curr 2001;1:39-45.

Quinn R. Comparing rat's to human's age: How old is my rat in people years? Nutrition 2005;21:775-777.

Richler J, Luyster R, Risi S, et al. Is there a 'regressive phenotype' of autism spectrum disorder associated with the measles-mumps-rubella vaccine? A CPEA study. J Autism Dev Disord 2006;299-316.

Rogers SJ. Developmental regression in autism spectrum disorders. Ment Retard Dev Disabil Res Rev 2004;10:139-143.

Rubenstein JLR, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2003;2:255-267.

Tordjman S, Drapier D, Bonnot O, et al. Animal models relevant to schizophrenia and autism: validity and limitations. Behav Genet 2007;37:61-78.

Vallicenti-McDermott M, McVicar K, Rapin I et al. Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. J Dev Behav Pediatr 2006;27:128-136.