

Respondent's Exhibit DD

Max Wiznitzer, M.D.
2686 Belvoir Blvd.
Shaker Heights, Ohio 44122

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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 Dr. Kinsbourne's post-hearing report on Colton Snyder (3/6/08) and his critique of my testimony. In response to his comments, I offer the following analysis of the core features of his critique:

Page 1

Dr. Kinsbourne cites Anderson, Hooker & Herbert (2008) as "close in parts of their text to my account of the role of microglial and astroglial activation during an innate immune responses"(Attachment 1). While these authors propose a hypothetical model, their observations do not support Dr. Kinsbourne's entire hypothesis, as suggested on page 1 of his report. For example, the authors state that the damage pattern to dendrites due to excitotoxicity (Kinsbourne, page 5-6) "has not yet been described in the autism neuropathology literature (page 171). Additionally, unlike Dr. Kinsbourne, they do not speculate about elevated glutamate levels as the cause of neural circuit dysfunction, despite comments about GABAergic neurons (page 171) and central neuromodulatory systems (page 172). Therefore, Anderson et al's hypothetical model is not supportive of stages 2 and 3 of Dr. Kinsbourne's report.

Page 2, stage 1

Dr. Kinsbourne quotes from Bezzi et al (2001) about activated glia amplifying glutamate release from astrocytes. This paper deals with the induction of neurotoxicity by a component of HIV-1 (human immunodeficiency virus-1). Upon review of this paper, which I was not allowed to do during my cross examination, the authors describe increased glutamate release when activated microglia are present (in this case due to HIV coat glycoprotein stimulation). Therefore, upon review of the paper, I agree that this glutamate release occurs. However, Dr. Kinsbourne ignores a key message of this paper

– the altered communication “has direct neuropathological consequences” and results in neuronal death (apoptosis). This supports my statement during cross examination (page 698) that “you’re going to get too much glutamate building up, and there is going to be cell death period”.

Page 3 – Stage 2a

Dr. Kinsbourne’s statement from Rubenstein and Merzenich about the glutamate potentiation by chemicals in the PCB family does not contradict my testimony since, if one actually reads the cited reference in Rubenstein & Merzenich, one discovers that this potentiation does not occur by a sustained and significantly increased amount of glutamate in the synapse but by potentiation of the electrical function of the neuron through effects on intracellular messengers (Fischer et al, 1998) (Attachment 2).

Goodwin et al (2006) is cited to show that children with autism had chronically elevated heart rates. Dr. Kinsbourne then concludes that this is due to increased sympathetic tone. However, this conclusion ignores that, in part, heart rate is modulated by the effects of the sympathetic and parasympathetic autonomic systems and is not supported by his other references. Toichi and Kamio (2003) state that, in individuals with autism, “parasympathetic activities under resting conditions were lower than those of controls” (page 424). Ming et al (2005b) title their paper “Reduced Cardiac Parasympathetic Activity in Children with Autism”. Therefore, the dysfunction appears to be an underfunctioning parasympathetic nervous system rather than an overactive sympathetic nervous system. Dr. Kinsbourne’s own references contradict his conclusion that chronic arousal is due to “glutamate levels...activating the sympathetic nervous system”. Furthermore, his citation of Deuchars et al (1995) to support the role of glutamate in stimulation of an area of the brainstem of the rat to trigger sympathetic neurons in the region of the spinal cord ignores that this is not a real life model, but rather an in vitro model using isolated brainstem and spinal cord in a nutrient bath with limited application of glutamate to the brainstem (not the prolonged exposure postulated by Dr. Kinsbourne).

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Dr. Kinsbourne concludes that “Much of EEG abnormality in regressive autism is epileptiform” and cites as a reference Lewine et al (1999). However, this paper described a highly selected population. EEG epileptiform abnormalities have been reported in 10-40% and nonepileptiform abnormalities in 11-30% of individuals with autistic spectrum disorders. A bias towards referral for children with paroxysmal events and regression makes it impossible to adequately analyze this data or to make definitive conclusions about the frequency of epileptiform discharges.

Page 4 – Stage 2c

During my cross examination, I was asked a question about pyramidal cells. I answered that I was aware of no evidence that pyramidal cells are more or less vulnerable than any other neuron (Transcript, p. 694A). The pyramidal cell is a specific neuron that is located

in the cerebral cortex. Dr. Kinsbourne's attempt to portray the Purkinje cell (which is located in the cerebellum) as a pyramidal cell because of its shape is a misrepresentation of a well known neuroanatomic fact. In fact, one of his references (Hamann et al 2005) states "loss of Purkinje cells and pyramidal cells" (Ex. 223, p. 1), clearly differentiating between these 2 cell types.

Furthermore, Dr. Kinsbourne then explores the issue of decreased number of Purkinje cells in neuropathologic studies of autism. While this was not the question that I was asked (which pertained to pyramidal cells), his comments can be addressed. Specifically, he refers to Palmen et al's citation of Harding and Copp (1997). While it is clear that Palmen et al considered the Harding and Copp hypothesis, they conclude that "there is evidence from neuropathological data for an evolving pathological process in the autistic brain that extends from the fetal period of brain development into adulthood" (Ex. 229, p. 9), supporting the theory of autism as a prenatally determined disorder. Furthermore, Palmen et al, cite Blatt et al (2001), who investigated 4 neurotransmitter systems (including glutaminergic) in the hippocampus and found that "GABAergic system was the only neurotransmitter system found to be significantly reduced in autism" (Ex. 229, p. 7). Neither conclusion by Palmen et al is supportive of Dr. Kinsbourne's hypothesis of excess glutamate as a consequence of an acquired insult to the brain (measles infection) in the second year of life.

Page 5

Dr. Kinsbourne states that there is a "depletion of synapses and dendrites in the hippocampus...due to excitotoxicity" and questions my statement that "if you get enough cytotoxicity you are going to kill the cell. It's not going to change the number of synaptic connections". He cites Monnerie et al (2003) that "an early consequence of glutamate toxicity is dendrite injury, which often precedes cell death" and that "alterations in dendritic morphology are one of the earliest signs of excitotoxic injury" with the rest of the sentence being "that occurs in several acute neurologic and chronic neurodegenerative diseases". What Dr. Kinsbourne doesn't include is the basis for Monnerie et al's statements and whether it is applicable to autism. First, the paper involved in vitro embryonic mouse cortical neurons, which are relatively resistant to the amount of glutamate used in the experiment (which lead to cell death in mature neuronal cell culture), and clearly are not representative of the more mature state of the human brain at age 1-2 years. Secondly, the exposure to glutamate was for a period of 1 or 2 days, which is a much shorter time period than the years of exposure that Dr. Kinsbourne hypothesizes for Colten Snyder. Thirdly, the glutamate exposure in the in vitro experiment resulted in a loss of dendrites manifested as decrease in number, length and branching with dendritic beading that was reversible after cessation of glutamate exposure. This pathological finding is not that of the hippocampus in autism, in which one finds increased cell packing density, reduced cell size and a simplified dendritic pattern with no evidence of beading (Ex. 229, p. 2). Monnerie et al state that "These alterations in dendritic structure can occur without cell death provided glutamate concentration is low and the exposure brief", implying the more prolonged exposure (which, according to Dr. Kinsbourne's hypothesis, is Colten Snyder's circumstance) will

result in a situation in which “dendritic injury may precede or be a step toward cell death” and “glutamate-induced alteration in dendrites may be an early event in a pathway leading to neuron death” (Ex. 228, p. 8). Similarly, Bellizi et al (2005) created in vitro hippocampal cell cultures from embryonic rats and exposed them to platelet activating factor, which releases glutamate from the cells, for 60 hours. This produced dendritic injury (beading and spine loss). The comments about the Monneric et al paper also apply to Belliz et al’s publication (Ex. 217).

Stage 3

Dr. Kinsbourne then discusses his overactivation model and critiques my testimony. It is obvious that brain “overexcitation” as manifested by abnormal synchronous brain epileptiform discharges will result in seizures (Tuchman et al (1997), Attachment 3). Therefore, my statement is valid. While Dr. Kinsbourne hypothesizes that overarousal in autism is caused by excessive glutamate mediated brain overexcitation, his own references (see page 2) do not support his conclusions. While I agree that children with autism can be more easily stressed by their “environments” and by unexpected changes in routine (the ‘desire for sameness’ in the diagnostic criteria), I do not find support for Dr. Kinsbourne’s hypothesis as the reason for this behavior. His attempt to compare the behaviors in children with Fragile X syndrome to those with autism is like comparing ‘apples and oranges’. Children with Fragile X syndrome manifest social avoidance/social anxiety rather than the significant qualitative impairment in socialization.

Dr. Kinsbourne states that my testimony that “in autism, it appears that they have little to no interest in social interaction” does not “square with the relevant literature. The American Academy of Pediatrics, in their guidance for the clinician on “Identification and Evaluation of Children with Autism Spectrum Disorder” (Johnson et al 2007, Attachment 4) states that ‘lack of gaze’, not gaze avoidance, is an early deficit in these children (page 1192) and that the children “often do not appear to seek connectedness; they are content being alone, ignore their parents’ bids for attention and seldom make eye contact or bid for others’ attention with gestures or vocalizations”. These behaviors are a manifestation of their deficits in social relatedness defined as “the inherent drive to connect with others and share complementary feeling states” (page 1190). Similarly, Dalton et al (2005), who are cited by Dr. Kinsbourne in support of his hypothesis, state that “inattention to faces is an early developmental sign of autism” (not gaze avoidance) and propose a model for the “diminished gaze fixation” (Ex. 220, p. 1). These support my statement “that the social issue in autism is not avoidance of contact” (Transcript, p. 710).

Similarly, Dr. Kinsbourne’s overexcitation (due to excessive brain glutamate) model is not applicable as an explanation for the stereotypies and repetitive behaviors in children with autism. Baumann (1999) is quoted by Dr. Kinsbourne that the “stereotypies appeared to be associated with concentration, arousal, frustration, boredom, and distraction and seemed to stabilize the child’s level of arousal in monotonous, frustrating, or overwhelming situations”. A closer reading of the reference (Troster 1994) finds that the children, while in residential care, were not handicapped and that the described

behaviors were those typically seen in children of that age range (e.g., nail biting in school aged children and thumb sucking and rocking in infants and toddlers). Boredom/monotony was one situation. Clinically, parents of children with autism in my practice will report that stereotypies occur in several circumstances, including apparent boredom and excitement. The fact that the movements stop when one engages the child is not consistent with Dr. Kinsbourne's premise that stereotypies occur under circumstances of high arousal (since, according to his hypothesis, social contact should lead to more overarousal and increased movements).

In addition to these responses, my review of Dr. Kinsbourne's comments/critique does not alter my opinion and testimony that Colton Snyder did not have sufficient information in the contemporaneous records to support a diagnosis of regressive autism and that Dr. Kinsbourne's hypothesis of measles infection of the brain with resultant triggering of neuroinflammation, excessive glutamate flow, brain overactivation and autistic behavior is purely speculative, does not have a logical sequence of cause and effect, and does not reflect the known consequences and natural history of the central nervous system complications of measles infection.

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

Sincerely,

A handwritten signature in cursive script, appearing to read "Max Wiznitzer". The signature is written in dark ink and is positioned above the typed name.

Max Wiznitzer, M.D.
Pediatric Neurology

References

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Fischer LJ, Seegal RF, Gancy P, et al. Symposium overview: toxicity of non-coplanar PCBs. *Toxicol Sci* 1998;41:49-61.

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Tuchman R, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. *Pediatrics* 1997;99:560-566.