# In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 00-358V
February 7, 2011
To be Published

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| ELIZABETH HAYNES, by her Mother and Next Friend, ANN HAYNES, | * | |
| Petitioner, | * | |
| v. | * | DTaP and infantile spasms; vaccinee with epileptogenic potential |
| SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, | * | |
| Respondent. | * | |
| * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * | | |

Ronald C. Homer, Sylvia Chin-Caplan, Boston, MA, for petitioner.
Ryan D. Pyles, Washington, DC, for respondent.

**MILLMAN, Special Master**

## RULING ON ENTITLEMENT[1]

Petitioner filed a petition on June 23, 2000 under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 *et seq.*, alleging that her daughter Elizabeth Haynes (hereinafter, "Elizabeth") had a pre-existing condition significantly aggravated by hepatitis B,

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision is filed, petitioner has 14 days to identify and move to delete such information prior to the document's disclosure. If the special

diphtheria/tetanus (DT), and haemophilus B influenza (HiB) vaccinations she received on October 20. 1997. The case was assigned to then-Chief Special Master Gary J. Golkiewicz.

On April 23, 2001, petitioner filed an Amended Petition for Vaccine Compensation, alleging that hepatitis B, DT, and HiB vaccines significantly aggravated an existing condition resulting in residual seizure disorder, encephalopathy, mental and physical developmental delay, and neurological sequelae.

On September 12, 2003, the case was reassigned to then-Special Master Margaret M. Sweeney as part of a mercury-toxicity/developmental delay group of cases petitioner's counsel was pursuing. Petitioner's counsel asked for a stay in proceedings pending the outcome of discovery in the Autism Omnibus Proceeding. Respondent had no objection to a stay.

On October 27, 2005, the case was reassigned to then-Special Master John F. Edwards.

On February 12, 2007, petitioner filed a Supplemental Amended Petition for Vaccine Compensation. Petitioner alleges that DPaT vaccine, administered on August 1, 1997, caused Elizabeth infantile spasms, and that she suffered significant aggravation of her underlying seizure disorder from the administration of DT, HiB, and hepatitis B vaccines on October 20, 1997.

On July 22, 2008, the case was reassigned to the undersigned.

On November 12, 2008, in response to the undersigned's Order of October 28, 2008 inquiring whether petitioner was still alleging significant aggravation in light of petitioner's expert Dr. Kinsbourne's report stating he did not support significant aggravation in this case, petitioner stated she is not alleging significant aggravation of Elizabeth's infantile spasms.

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master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall delete such material from public access.

On March 5, 2009, a hearing was held. Testifying for petitioner was Dr. Marcel Kinsbourne. Testifying for respondent was Dr. Mary Anne Guggenheim.

On May 4, 2009, petitioner filed a posthearing brief.

On June 10, 2009, respondent filed a posthearing brief.

On June 18, 2009, the Federal Circuit issued a decision in Andreu v. Sec'y of HHS, 569 F.3d 1367 (Fed. Cir. 2009), holding that whole-cell DPT caused Enrique Andreu's seizures which may have been febrile or afebrile. In Andreu, the Federal Circuit was impressed with "the striking temporal connection between the vaccine and Enrique's initial seizure." 569 F.3d at 1375. The onset of Enrique's seizure was one day after vaccination. 569 F.3d at 1370. The Federal Circuit emphasized the importance of the treating doctors' opinions. 569 F.3d at 1375.

On June 24, 2009, Petitioner filed a response to respondent's posthearing brief.

On July 16, 2009, the undersigned issued an Order to the parties to address seriatim the question whether the Federal Circuit's recent decision in Andreu affected "the legal evaluation of this case in light of the Federal Circuit's not distinguishing between febrile and afebrile seizures caused by DPT vaccine. Even though infantile spasms are a distinctive type of afebrile seizure, they are still afebrile seizures." Order of July 16, 2009.

On September 4, 2009, petitioner responded to the undersigned's Order of July 16, 2009, saying Andreu applied to the instant action.

On October 2, 2009, respondent responded to the undersigned's Order of July 16, 2009, saying Andreu did not apply to the instant action.

On October 30, 2009, petitioner replied to respondent's response to the undersigned's Order of July 16, 2009.

On January 13, 2010, the Federal Circuit issued a decision in Moberly v. Sec'y of HHS, 592 F.3d 1315 (Fed. Cir. 2010), a case with the same issue as Andreu and practically identical facts, only Molly Moberly's seizures occurred two days after whole-cell DPT vaccination, while Enrique Andreu's seizures occurred one day post-vaccination. The Federal Circuit in Moberly held that DPT did not cause Molly's afebrile seizures. During oral argument in Moberly, petitioner's counsel (the same counsel as in the instant action) stated that the Federal Circuit had to rule for petitioner because of its decision in Andreu. The Federal Circuit rejected petitioner's counsel's statement, explaining in the Moberly decision that the only reason it had ruled for petitioners in Andreu was that respondent's expert in Andreu had not disputed the biological plausibility of petitioners' expert's breaching of the blood-brain barrier theory, and that Enrique's treating physicians in Andreu stated that DPT caused his seizures, whereas, in Moberly, respondent's expert did not concede the biological plausibility of petitioner's expert's blood-brain barrier theory, and no treating physician opined that DPT caused Molly's seizures. 592 F.3d at 1325.

On January 25, 2010, the undersigned issued an Order to the parties to address seriatim the questions posed by the Moberly decision as to whether respondent's expert in the instant action agreed with petitioner's expert Dr. Kinsbourne's medical theory connecting DTaP and afebrile seizures and whether Elizabeth's treating doctors opined that DTaP had caused her seizures. The undersigned asked in addition, in light of the Federal Circuit's emphasis in Moberly on whether respondent's expert agreed with petitioner's expert's medical theory of causation and of the denigration of petitioner's expert Dr. Kinsbourne (the same expert as in the instant action) by quoting in Moberly former-Special Master Edwards' description of Dr. Kinsbourne's testimony

as "contradictory and confusing" and "shockingly poor," whether either party or both parties would like to retry the instant action with different experts.

On February 26, 2010, petitioner responded to the undersigned's Order of January 25, 2010, saying Moberly did not apply and declining to retry the case with a different expert.

On March 26, 2010, respondent responded to the undersigned's Order of January 25, 2010, saying Moberly did apply and declining to retry the case.

On April 16, 2010, petitioner replied to respondent's response to the undersigned's Order of January 25, 2010.

**FACTS**

On March 16, 1997, Elizabeth and her fraternal twin brother were born. Med. recs. at Ex. 1, p. 2.

On April 2, 1997, Elizabeth received her first hepatitis B vaccination. Med. recs. at Ex. 3, p. 2.

On May 19, 1997, at the age of two months, Elizabeth received her first DTaP, IPV, and HiB vaccinations. Med. recs. at Ex. 3, p. 2.

On August 1, 1997, at the age of four and one-half months, Elizabeth received her second DTaP, IPV, and HiB vaccinations. Med. recs. at Ex. 3, p. 2.

On September 5, 1997, Elizabeth was brought to the emergency department of Westchester County Medical Center with a one-month history of infantile spasms. Med. recs. at Ex. 11, p. 142. Elizabeth responded to ACTH anti-convulsant therapy. Med. recs. at Ex. 3, p. 5.

On September 25, 1997, her pediatric neurologist, Dr. Ronald Jacobson, noted that about one week prior to the onset of Elizabeth's infantile spasms, she had her second DPT shot. He recommended withholding further pertussis vaccination as a precaution. Med. recs. at Ex. 5, p. 3.

On October 1, 1997, Elizabeth went to the emergency department of Westchester Medical Center with an extremely low white blood cell count due to a bacterial infection. The records note that she had been seizure-free for the prior two weeks. Med. recs. at Ex. 11, p. 5.

On October 11, 1997, Elizabeth had an EEG. Med. recs. at Ex. 5, p. 6. The EEG showed simplified background, no seizure activity, and further improvement. She had been already weaned off ACTH. Med. recs. at Ex. 5, p. 7.

On October 20, 1997, Elizabeth received DT, her third HiB, and her second hepatitis B vaccinations. Med. recs. at Ex. 3, p. 2. The vaccinations were given at approximately 9:15 a.m. Dr. Mary Versfelt notes that between 1:30 to 2:00 p.m., Elizabeth had a seizure for approximately two minutes where her eyes rolled back and she was limp. There were no tonic-clonic movements or fever. Med. recs. at Ex. 3, p. 6.

On October 27, 1997, Dr. Versfelt noted that over the prior week, Elizabeth had three more spasms. Med. recs. at Ex. 3, p. 7.

On April 14, 1998, Dr. Versfelt observed Elizabeth having a seizure-like episode and noted that she should defer immunizations. Med. recs. at Ex. 3, pp. 9, 10.

On November 29, 1999, Elizabeth was admitted to Children's Hospital in Boston where the attending physician noted that her onset of infantile spasms occurred after DPT and that a second immunization appeared to have made her worse. Med. recs. at Ex. 8, p. 7.

On January 4, 2000, Dr. Mary Zupanc at The Neurological Institute noted:

> Elizabeth is an almost three year old young girl with a longstanding history of infantile spasms, which have been medically refractory to multiple anti-epileptic medications. Her best response was to ACTH, but this resulted in immunosuppression and secondary E. Coli sepsis. At the present time, she is globally developmentally delayed. Her neurological examination is significant for severe cognitive impairments, lack of expressive and receptive language, diffuse hypotonia, inability to walk independently, and delayed fine motor skills.
>
> On the basis of the history, physical examination, and diagnostic studies performed to date, Elizabeth has an encephalopathy of undetermined etiology. The relationship of her seizure recurrence to her immunizations at six months is intriguing and may indicate dysfunction of her immune system. In addition, the mother does report unusual body odors, including a "vinegar like smell" to the urine, despite the fact that she drinks multiple fluids per day. This may indicate an underlying neurometabolic disorder that has yet to be identified. Elizabeth has certainly had an extensive evaluation, including MRI scan of the brain, PET scan, SPECT scan, and metabolic screening. … In addition, given her mild dysmorphic features, she should also have a chromosomal analysis.
>
> Undoubtedly, Elizabeth's epileptic encephalopathy is also contributing to her global developmental delays. She may have an underlying mild encephalopathy with the epileptic encephalopathy contributing significantly to her developmental delays, especially her lack of expressive and receptive language.

Med. recs. at Ex. 6, p. 13.

## Other Submitted Material

Petitioner filed her affidavit as Exhibit 13. She states that Elizabeth received DTaP, OPV/IPV, and HiB immunizations on August 1, 1997. At some point after this, Elizabeth's father, the babysitter, and petitioner began to notice Elizabeth would occasionally crunch forward as if she were trying to do a sit-up. *Id.* at 1. Her eyes would tear during these episodes. *Id.* Elizabeth's mother described these episodes to the pediatrician on the phone. The pediatrician

attributed the crunching forward to gas pains or constipation. *Id.* at 2. On September 5, 1997, she brought Elizabeth to the pediatrician who saw the crunches and diagnosed seizures. *Id.* On ACTH, Elizabeth stopped seizing by September 22, 1997. *Id.* at 2-3. On October 20, 1997, Elizabeth received DT, HiB, and hepatitis B vaccinations at 9:15 a.m. At about 1:30 p.m. that day, Elizabeth's eyes rolled back and she became limp and non-responsive for about two minutes. The regular babysitter saw this and told Elizabeth's father and petitioner. *Id.* at 3. Elizabeth's seizures returned and became more frequent. *Id.*

On July 30, 2007, petitioner filed Exhibits 32 and 33, consisting respectively of Dr. Marcel Kinsbourne's expert report and his CV. On August 6, 2007, petitioner filed medical literature to which Dr. Kinsbourne referred, marked as Exhibits 34-38. (On October 12, 2007, petitioner filed Exhibit 39, Dr. Kinsbourne's supplemental report. On April 11, 2008, petitioner filed Exhibit 47, the Kivity article. On May 16, 2008, petitioner filed Exhibit 48, Dr. Kinsbourne's second supplemental report, with Tabs A-N, consisting of the literature to which Dr. Kinsbourne referred.)

In Dr. Kinsbourne's first expert report, he describes Elizabeth as having the onset of infantile spasms during the week following her receipt of vaccinations, including DTaP. Ex. 32, p. 2. He states that Elizabeth had cryptogenic (as distinguished from symptomatic) infantile spasms, which describes children with no evidence of antecedent brain injury or dysfunction and who developed normally up until the onset of their infantile spasms. *Id.* Infantile spasms are a severe form of epilepsy usually beginning between the ages of three and eight months of age. *Id.* Dr. Kinsbourne states:

An extensive medical literature deals with the possible role of pertussis vaccine in causing or triggering some cases of cryptogenic infantile spasms. The most comprehensive examination of the issue was that which was incorporated into the National Childhood Encephalopathy Study (Alderslade et al., 1981). The 1,182 children with acute severe neurological illness who were followed prospectively between 1976 and 1979 included 269 cases of infantile spasms. Among these were 163 children who, like Elizabeth, had no antecedent history of brain injury and were developing normally prior to the seizure onset.

In a case-control epidemiological design, children with cryptogenic infantile spasms who had received DPT within four weeks of the seizure onset were classified into four groups, depending on whether the onset was in the first, second, third or fourth week. Across all four weeks, the incidence of DPT vaccination did not differ significantly between the patients and the controls. However, there was a significant clustering of onsets within the first week after the vaccination, such that there were relatively more onsets in the first week, and relatively fewer in the other three weeks. Bellman, Ross and Miller (1983, Table 2), NCES investigators, concluded, "pertussis immunisation—may precipitate the onset of spasms in those children in whom the disorder is already destined to develop" (page 1033).

Goodman, Lamb and Bellman [(]1998) further examined the time relationship between DPT immunization and infantile spasm onset. They found that "the cases are more likely to be reported as having been exposed during the week immediately preceding infantile spasms onset than during the other 3 weeks of that preceding month" (P=0.02) (page 229). They call this evidence of triggering a "temporal shift."

The studies by Bellman et al. (1983) and by Goodman et al. (1998) were with respect to the whole cell pertussis vaccine. The substitution in 1996 of the acellular for the whole cell formulation of pertussis vaccine has been beneficial in reducing the incidence of neurological adverse effects due to pertussis vaccination, ranging from mild to severe. However, the acellular vaccine still includes a full complement of pertussis toxin, a well-known potent neurotoxin. This is because the pertussis toxin is required for the process by which the vaccine generates immunity to whooping cough. Pertussis toxin has the demonstrated ability to increase the

> permeability of the blood brain barrier, and thereby to gain access to the cells of the brain (Bruckener et al. 2003).
>
> The mechanism by which pertussis toxin can precipitate seizures relates to its propensity to bind to neuronal membrane receptors (Legido et al., 2006), and "modify the adenylate cyclase system so that the action of inhibitory neurotransmitters is impaired and the action of excitatory neurotransmitter is enhanced" (page 633). Specifically, pertussis toxin binds to and inactivates G-proteins that mediate the activity of the GABAb metabotropic GABAergic neuronal receptors. GABAergic receptors mediate inhibitory influences on the CNS [central nervous system], and are in dynamic counterbalance with the excitatory glutamatergic system. Depressing the GABA inhibitory system is apt to lead to net CNS overactivation and thus to convulsions. Anticonvulsant drugs typically enhance GABAergic inhibition. Thus pertussis toxin can cause seizures.

Ex. 32, pp. 2-3.

Petitioner filed "The National Childhood Encephalopathy Study. Whooping Cough" by R. Alderslade, M.H. Bellman, N.S.B. Rawson, E.M. Ross, and D.L. Miller (London: Her Majesty's Stationery Office, 1981), also known as the NCES. Ex. 34.

Petitioner filed "Infantile Spasms and Pertussis Immunisation" by M.H. Bellman, E.M. Ross, and D.L. Miller (three of the five authors of the NCES), The Lancet 1031-34 (1983). Ex. 35 (and previously filed as Ex. 25). In the 269 cases of infantile spasms reported to the NCES, 34% had an antecedent factor which could have caused them, the most common being perinatal hypoxia (34 cases) and tuberous sclerosis (16 cases). *Id.* at 1031. There was no significant association between infantile spasms and pertussis immunization within 28 days, but there was a clustering of cases immunized with either DPT or DT within seven days. The authors suggest that these vaccines do not cause infantile spasms but may trigger their onset in those children who are destined to develop infantile spasms. *Id.* All doctors in England, Scotland, and Wales were

asked to notify the NCES of all patients aged two to 35 months admitted to hospital with a defined group of acute severe neurological disorders, including infantile spasms, during 1976-79. *Id.* More specifically, there was an excess of children with infantile spasms who were immunized in the seven days before onset compared with controls, while in the following three weeks, there was a deficit of cases of infantile spasms compared with controls. These differences were not statistically significant. *Id.* at 1032. There were quite pronounced differences between the excess of children whose onset of infantile spasms occurred within seven days of either DPT or DT. *Id.* at 1032-33. The authors state:

> Pertussis immunisation has been cited as a cause of infantile spasms in many published reports. In most of the 71 cases in these reports, the time between immunisation and spasms was less than 7 days. In most quoted cases the vaccine used included diphtheria and tetanus toxoids as well as pertussis antigen. ... [In the NCES] the small excess in the number of cases over that expected by comparison with controls in 7 days after immunisation with both DTP and DT vaccines followed by a corresponding deficit in the next 3 weeks suggests that, in some cases, immunisation may trigger the onset of spasms or attract attention to symptoms in children destined to show the condition overtly within a short time. ... Since this effect was seen after DT as well as after DTP vaccine it is, presumably, a non-specific response. [M]ost of the DTP-associated cases were cryptogenic, whereas most of the DT-associated cases were in the symptomatic group. ... We conclude from the NCES results that pertussis immunisation is not a direct causal factor for infantile spasms in children with structurally normal brains, but that it may precipitate the onset of spasms in those children in whom the disorder is already destined to develop.

*Id.* at 1033.

Petitioner filed "Temporal relationship modeling: DTP or DT immunizations and infantile spasms" by M. Goodman, S.H. Lamm, and M.H. Bellman, 16 Vaccine 2/3:225-31 (1998). Ex. 36. The authors took the NCES data and determined that DPT vaccine did not affect

symptomatic infantile spasms cases due to such causes as tuberous sclerosis, but children who were previously normal had a shortening of time to onset of cryptogenic infantile spasms after receiving DPT vaccine. *Id.* at 225. They describe a temporal shift in cases meaning that the onset of infantile spasms clustered in the early part of the one-month period, i.e., within one week, and equate temporal shift with triggering. *Id.* at 228. However, since the Institute of Medicine (IOM) used the term triggering to mean "a biological susceptibility" rather than a temporal shift, Goodman et al. opted to use the term temporal shift. *Id.* at 228-29. The pattern for DPT or DT exposure for previously normal cases "demonstrates a significant fit to the temporal shift model" because cases were clustered in the first week after vaccination more so than in the three subsequent weeks. *Id.* at 229. The authors caution that "the precise date of onset for an insidious disease such as infantile spasms is difficult to determine." *Id.* The authors state they do not disagree with the IOM 1991 report that evidence does not suggest a causal relation between DPT vaccine and infantile spasms. They cite a 1989 article in which the author (J.D. Cherry) published a similar analysis of the NCES data for all neurologic events. Dr. Cherry also noted an increase in onset during the first week after immunization with a lowered incidence in the subsequent three weeks, interpreting "these findings as showing that 'immunization brings out a neurologic event that would have occurred anyway or calls attention to an event that is already occurring.' This interpretation precisely fits our temporal shift model." *Id.* at 230.

Petitioner filed an article entitled "Permeabilization in a cerebral endothelial barrier model by pertussis toxin involves the PKC effector pathway and is abolished by elevated levels of cAMP" by K.E. Brückener, et al., 116 Journal of Cell Science 9:1837-46 (2003). Ex. 37. The authors experimented with pertussis toxin in pig brains to determine if the pertussis toxin

penetrated the blood-brain barrier. *Id.* at 1837-38. The authors did not use pertussis vaccine, but in discussing the disease pertussis, they queried whether pertussis toxin "might be instrumental in the development of neurological complications that are occasionally observed as a sequelae of pertussis disease." *Id.* at 1837. They comment that pertussis toxin is frequently used in immunological studies to enhance the onset of autoimmune disease in experimental animals. *Id.* at 1837-38. Pertussis toxin might enhance the development of EAE or experimental allergic encephalomyelitis, an animal model of multiple sclerosis, by increasing the vascular permeability of the blood-brain barrier. *Id.* at 1838. Their "study implies a potential mechanism for the onset of neurological disorders associated with pertussis disease due to the effect of PT [pertussis toxin] on the integrity of the blood-brain-barrier." *Id.* The authors found that pertussis toxin compromised cerebral barrier function only in endothelial cell monolayers. *Id.* at 1843. Their study provides a molecular explanation for the frequently performed enhancement of EAE sometimes with pertussis toxin alone. *Id.* at 1845.

Petitioner filed a chapter entitled "Autoimmune and Postinfectious Diseases" by A. Legido, et al., from the text Child Neurology, 7th ed., ed. J.H. Menkes, et al. (2006), ch. 8, pp. 557-667. Ex. 38. The authors state: "Experimental data indicate that pertussis toxin can attach itself to neuronal membrane receptors and, by ADP-ribosylation, modify the adenylate cyclase system so that the action of inhibitory neurotransmitters is impaired and the action of excitatory neurotransmitters is enhanced...." (Citations omitted.) *Id.* at 633. They note that major neurologic reactions to acellular pertussis vaccine have been reported significantly less frequently than after whole-cell vaccination. *Id.*

Petitioner filed Dr. Kinsbourne's supplemental expert report, dated October 12, 2007, as Exhibit 39. He addressed the undersigned's question of why he stated that Elizabeth's onset of infantile spasms was within one week of her August 1st DTaP vaccination in an Order dated September 17, 2007. Dr. Kinsbourne stated the basis of his conclusion was an entry dated September 6, 1997 in the Westchester County Medical Center ER records (Ex. 11, p. 142), stating that one month previously, Elizabeth was noticed to have an upward movement of her upper extremities with her head moving forward, stiffening of legs, with redness of face, which appeared to her parents like a swan dive, occurring in two to three episodes lasting for one minute, in addition to an entry in the hospital's Progress Notes of the same date (Ex. 11, p. 145), stating that, one month previously, Elizabeth had eight per minute episodes of arching and may have had about two to three a day, sometimes none in a day, with eyes tearing spontaneously but not crying, and her face turning red. *Id.* Dr. Kinsbourne states that both descriptions are classic for infantile spasms, and the diagnosis was subsequently confirmed. The one-month history dates back to onset in the week following the August 1, 1997 DTaP vaccination, or August 6th, five days post-vaccination. *Id.* As for the assertion that Elizabeth's October 20, 1997 vaccination significantly aggravated Elizabeth's condition, Dr. Kinsbourne stated that was not his opinion and he does not believe that a significant aggravation occurred. *Id.*

Petitioner filed Dr. Kinsbourne's second supplemental report, on May 16, 2008, as Exhibit 48 with attachments marked Tabs A through N. Dr. Kinsbourne states that although his opinion is that DTaP vaccine triggered Elizabeth's infantile spasms, she might possibly have had the onset of infantile spasms at some later time absent the vaccination. *Id.* at 1. Citing to the Bellman study based on the data accumulated for the National Childhood Encephalopathy Study (NCES),

Dr. Kinsbourne notes that although DPT vaccine can trigger infantile spasms, this does not result in a statistically significant increase in the total incidence of infantile spasms. *Id.* DPT vaccine did however appear to accelerate the onset of infantile spasms in cryptogenic cases while triggering infantile spasms in symptomatic cases (children who had tuberous sclerosis or Down syndrome). *Id.* Dr. Kinsbourne referred to the Melchior study showing that when Danish children had not yet received DPT, 12 percent had onset of infantile spasms before the age of two months. But after the vaccine schedule was changed and DPT was given at five weeks, 23 percent had onset of infantile spasms before the age of two months. *Id.*

Dr. Kinsbourne then explains the difference between symptomatic infantile spasms, where there is a structural abnormality of the brain, and cryptogenic infantile spasms, where there is no abnormality except the disorder itself. *Id.* at 2. There is no pre-existing brain damage to Elizabeth's brain. Therefore, she should have had a good outcome if her infantile spasms have an unknown cause, i.e., are cryptogenic. But Elizabeth had a terrible outcome which Dr. Kinsbourne attributes to the effect of pertussis toxin from the DTaP on Elizabeth's brain due to the inhibition of neuronal cells that would prevent hyperexcitability in her brain. *Id.* at 4-5. The damage of DTaP to Elizabeth's brain would therefore change the category of her infantile spasms from cryptogenic to symptomatic, according to Dr. Kinsbourne. *Id.* at 5.

Tab A to Dr. Kinsbourne's report of May 16, 2008 (Ex. 48) is an article entitled "Epileptic disorders with onset in the first year of life: neurological and cognitive outcome" by D. Battaglia, et al., 3 European J of Paediatric Neur 95-103 (1999). The authors followed 135 patients for four years who had onset of epilepsy in their first year of life to determine long-term prognosis for neurological and cognitive development. *Id.* at 95. They initially began with 150 children, but 15

died in the first year. *Id.* Fifty-nine of the study children had West syndrome.[2] Of these 59 children with West syndrome, 16 had cryptogenic West syndrome, and 43 had symptomatic West syndrome. *Id.* at 96. Children with West syndrome had more abnormal results. *Id.*

Tab B to Ex. 48 is an article entitled "Infantile spasms and pertussis vaccination" by M.J. Bellman, E.M. Ross, and D.L. Miller, 8332 Lancet 1031-34 (May 7, 1983). These co-authors were also co-authors in the NCES epidemiological analysis of whole-cell pertussis vaccine and encephalopathy and prolonged seizures. *Id.* at 1033. Part of the data in the NCES was for children who had infantile spasms. *Id.* at 1031. The authors state that 269 cases of infantile spasms were reported to the NCES among 1182 cases of severe neurological illnesses reported to the authors. By examining the occurrence of infantile spasms cases within 28 days of vaccination with whole-cell DPT, the NCES authors found no significant association between the illness and the vaccine. *Id.* However, they did notice a clustering of infantile spasms onsets within seven days of vaccination with either DPT or DT. *Id.* and 1032. Correspondingly, this excess of onsets was matched by a deficit in occurrence during the remainder of the 28 days. *Id.* The authors of the Bellman paper suggest that although these vaccines do not cause infantile spasms, they may trigger their onset in children who would have developed infantile spasms at some point. *Id.*

The authors in the Bellman paper state that the disorder of infantile spasms "appears to be a response of the infant brain to various severe neurological insults." *Id.* Of those who had onset of infantile spasms within seven days of DPT vaccination, one third had cryptogenic infantile spasms, which means the cause of the disorder was not known (unlike symptomatic cases which could be in the context of tuberous sclerosis). *Id.* at 1033. The authors note that the age when

[2] West syndrome is infantile spasms. Dorland's, at 1876.

children receive their infant vaccinations is also the age at which they may manifest infantile spasms, raising the question of temporal coincidence. *Id.* Because the clustering of onsets of infantile spasms within seven days occurred after vaccination with both DTP and DT (no pertussis) vaccines, the authors conclude that the effect was presumably a non-specific response. *Id.* The number of patients involved was only a small proportion of the total group of infantile spasms patients, or less than 10%. *Id.* The authors were not surprised that children with symptomatic infantile spasms who generally had either tuberous sclerosis or Down syndrome had more cases of onset of infantile spasms in association with vaccination with DT vaccine, suggesting a triggering effect rather than causation. Normally, children with a known contraindication to DPT vaccine would have received vaccine without pertussis. *Id.* The authors conclude that pertussis immunization is not a direct causal factor for infantile spasms in children with structurally normal brains, i.e., cryptogenic spasms, rather than symptomatic (those with tuberous sclerosis or Down syndrome), "but that it may precipitate the onset of spasms in those children in whom the disorder is already destined to develop." *Id.*

Tab C to Ex. 48 is an article entitled "Predicting favorable outcome in idiopathic West Syndrome" by O. Dulac, et al., 34 Epilepsia 747-56 (1993). Out of 45 patients, 15 had a poor outcome because of abnormal mental development and/or persistence or relapse of epilepsy while 30 had disappearance of seizures and complete mental recovery. *Id.* at 749.

Tab D to Ex. 48 is an excerpt from a textbook's 12th chapter entitled "Long-Term Outcome" in Infantile Spasms. Diagnosis, Management and Prognosis by J.D. Frost and R.A. Hrachovy (2002) at 203-06. The authors state that the prognosis in West syndrome is mostly poor

although a few individuals recover with resolution of seizures and achievement of normal mental development. *Id.* at 203.

Tab E to Ex. 48 is an article entitled "Cognitive deficits after cryptogenic infantile spasms with benign seizure evolution" by E. Gaily, et al., 41 Developmental Med & Child Neur 660-64 (1999). Of 18 children with cryptogenic infantile spasms treated with various drugs, 12 had normal intelligence. *Id.* at 660. However, if epilepsy and hypsarrhythmia occur during a vulnerable period of brain development, even in the absence of structural brain abnormality, the child may have cognitive deficits. *Id.* Three children whose spasms continued for 12 weeks or longer had cognitive deficits while a shorter duration of up to eight weeks had variable developmental outcomes. *Id.* at 664.

Tab F to Ex. 48 (filed on May 22, 2008) is a chapter from the text Epilepsy, Infantile Spasms, and Developmental Encephalopathy by P.A. Schwartzkroin and J.M. Rho, vol. 49 of "International Review of Neurobiology" eds. R.J. Bradley, R.A. Harris, and P. Jenner (2002), entitled "Relationship between Encephalopathy and Abnormal Neuronal Activity in the Developing Brain" by F.E. Jensen, pp. 23 - 35. The author states that infantile spasms "originate from a highly age-specific hyperexcitable network." *Id.* at 23. She states that "the majority of patients suffering infantile spasms have severe neurodevelopmental delay and/or seizures, but up to 10% have spontaneous remission and normal intellectual development...." *Id.* at 24-25. The author discusses glutamate receptors in the brain, stating that glutamate "is the major excitatory neurotransmitter in the brain" with several subtypes of glutamate receptors. *Id.* at 26. She opines that infant brain receptors may favor hyperexcitability and could lower the threshold for excitotoxic encephalopathies and seizures, unlike the adult brain where receptor activation tends

to depress excitatory synaptic transmission by inhibiting glutamate release, thus inhibiting seizure activity. *Id.* at 26-27. The author states that infantile spasms might "worsen an underlying encephalopathy if one exists and lead to later neuronal injury via mechanisms such as excitotoxicity mediated by glutamate receptors." *Id.* at 29. She notes that infantile spasms present with similar behavioral and EEG characteristics independent of their etiology. *Id.* She concludes:

> Normal infancy appears to represent a hyperexcitable state.... Compared to the adult, encephalopathy in the immature brain may be characterized by less neuronal injury but more subtle molecular and cellular changes that can produce neuronal hyperexcitability. The fact that infantile spasms present as such a stereotypical syndrome, despite multiple etiologies, strongly suggests the involvement of a unique and highly age-specific cluster of factors. However, the observation that the long-term outcome can range from normal intelligence to severe mental retardation raises questions about the role of a coexistent or consequent encephalopathy in modifying the long-term function of neuronal networks.

*Id.* at 31.

Tab G of Ex. 48 (also filed as Ex. 47) is an article entitled "Long-term Cognitive Outcomes of a Cohort of Children with Cryptogenic Infantile Spasms Treated with High-dose Adrenocorticotropic Hormone" by S. Kivity, et al., 45 Epilepsia 3:255-62 (2004). The authors compared long-term cognitive and seizure outcomes for 37 children with cryptogenic infantile spasms, 22 of whom were treated with ACTH (adrenocorticotropic hormone) within one month of onset, and 15 of whom were treated from one month up to six and one-half months after onset of infantile spasms. All patients treated in the early treatment group had normal cognitive outcome, whereas 40% of those in the late-treatment group had normal cognitive outcome. The authors

conclude that infants with cryptogenic infantile spasms who receive early treatment have a favorable long-term outcome cognitively as long as the treatment extends to age one year or older. However, if major developmental regression lasts for a month or more before treatment is begun, the prognosis for normal cognitive outcome is poor. *Id.* at 255, 257-61. The authors note that with the advent of modern neuroimaging methods, the causes of infantile spasms have been detected in more cases, thus rendering the number of symptomatic cases (where the cause is known) to be from 60% to 90% of patients. *Id.* at 255. They caution that the late-treatment group data must be interpreted with caution because of the possibility that children with hidden symptomatic etiology were present in that group. *Id.* at 261.

Tab H of Ex. 48 is an article entitled "Infantile spasms: Outcome and prognostic factors of cryptogenic and symptomatic groups" by B. Koo, et al., 43 Neurology 2322-27 (1993). Comparing 17 cryptogenic and 40 symptomatic cases of infantile spasms, the authors found that the developmental score of the cryptogenic group was significantly higher than that of the symptomatic group. *Id.* at 2322. Symptomatic cases of infantile spasms can be due to hypoxic-ischemic encephalopathy, vascular causes, infection, tuberous sclerosis, chromosomal causes, dysmorphic syndromes, dysgenesis/brain malformations, metabolic disorders, and delayed development whose cause is unknown. *Id.* at 2323. The authors state, "Seizures alone may affect cognitive outcome but are also associated with an increased frequency of neurologic deficit." *Id.* at 2326-27. They state that the outcome in infantile spasms "depends more on the effect of infantile spasms per se in cryptogenic cases, and more on the underlying cause in symptomatic cases." *Id.* at 2327.

Tab I of Ex. 48 is an article entitled "Epidemiological Features of Infantile Spasms in Iceland" by P. Lúðvígsson, et al., 35 Epilepsia 802-05 (1994). In their study group of six children with cryptogenic infantile spasms and seven children with symptomatic infantile spasms studied for 10 years, all the children with cryptogenic infantile spasms had a normal or satisfactory outcome with normal intelligence. All the children with symptomatic infantile spasms were either moderately or severely retarded and five of them continued to seize. *Id.* at 804.

Tab J of Ex. 48 is an article entitled "Infantile spasms and early immunization against whooping cough. Danish survey from 1970 to 1975" by J.C. Melchior, 52 Arch Dis Child 134-37 (1977). A change in the age at which infants received their childhood immunizations in Denmark did not result in a change in the onset of infantile spasms, leading the author to conclude that, although there may be an occasional connection between immunization and infantile spasms, the most important factor is a "time-coincidence" between vaccination and onsets natural for the age. *Id.* at 134. Out of a group of 113 children, 60 had symptomatic infantile spasms, 40 had cryptogenic infantile spasms, and 13 cases had no obvious etiology. *Id.* at 135. Thirty-six of the children were never vaccinated and 61 were vaccinated but there was no time relation between their vaccination and the onset of their infantile spasms. *Id.* The author states that vaccination could be considered a triggering mechanism in three cases. *Id.* Those three children had symptomatic infantile spasms. *Id.* The author concludes "that a causal connection between whooping cough immunization and infantile spasms is very unlikely except in a few cases...." *Id.* at 136.

Tab K of Ex. 48 is an article entitled "Workshop on Neurologic Complications of Pertussis and Pertussis Vaccination" by J.H. Menkes and M. Kinsbourne, 21 Neuropediatrics 171-

76 (1990). This article describes a workshop of neurologists meeting to discuss pertussis vaccine and neurologic illness. The difficulty in linking the vaccine to infantile spasms is the problem in determining onset of the spasms. *Id.* at 171.

Tab L of Ex. 48 is an article entitled "Occurrence, Outcome, and Prognostic Factors of Infantile Spasms and Lennox-Gastaut Syndrome" by H. Rantala, et al., 40 Epilepsia 3:286-89 (1999). The authors state that infantile spasms and Lennox-Gastaut syndrome are severe epilepsies of early childhood. *Id.* at 286. All children with infantile spasms and Lennox-Gastaut syndrome had an underlying brain disease, while none of the cryptogenic infantile spasms cases evolved to Lennox-Gastaut syndrome. *Id.* at 289. Six of the seven children or 86% of the children with cryptogenic infantile spasms in the study recovered from their epilepsy. Because in all but four cases, ACTH treatment had begun within one month of onset of symptoms, that may have contributed to the favorable outcome. *Id.* The authors conclude that the underlying brain disease, not the epilepsy, determines the outcome of infantile spasms children and the relation of infantile spasms to Lennox-Gastaut syndrome. *Id.*

Tab M to Ex. 48 (filed on May 22, 2008) is an article entitled "Long-term outcome of patients with West syndrome" by R. Riikonen, 23 Brain & Development 683-87 (2001). The author followed 214 children with West syndrome for 20-30 years or until death. *Id.* at 683. Of the 214, 162 were treated with ACTH (adrenocorticotropic hormone). *Id.* Factors associated with a good prognosis were cryptogenic (25 patients) rather than symptomatic (137 patients) etiology, normal development before onset of infantile spasms, treatment within one month of onset, good response to ACTH therapy, and few relapses. *Id.* at 686, 687. The outcome was worst in those with severe brain malformations, postinfectious etiology, and tuberous sclerosis. *Id.* at 686.

Seventy percent of cryptogenic patients who responded favorably to ACTH had a favorable outcome, whereas 20% of cryptogenic patients who did not respond favorably to ACTH had a favorable outcome. *Id.* Twenty-three percent of symptomatic patients who responded favorably to ACTH had a favorable outcome, whereas none of the symptomatic patients who did not respond favorably to ACTH had a favorable outcome. *Id.* Interestingly, the long-term intellectual outcome was significantly better in those patients who received smaller rather than larger doses of ACTH. *Id.*

Tab N of Ex. 48 is an article entitled "The value of neuroradiology in infantile spasms" by W.D. Singer, et al., 100 J Pediatrics 47-50 (1982). The authors state that more than 60% of patients with infantile spasms who have no other clinically determined central nervous system disorder fail to develop normally. *Id.* at 47. In trying to predict which patients would have an unsatisfactory outcome, the authors performed neuroradiologic studies to assess gross brain structure. *Id.* They examined the records of 100 patients with infantile spasms and performed neuroradiology on 71 of them. *Id.* at 47, 48. They divided the group into two: those with early treatment with ACTH (treatment within one month of onset) and those with late treatment with ACTH (treatment after one month after onset). *Id.* at 48. Of the patients studied neuroradiologically, 27% had normal studies and 73% had abnormal studies. *Id.* The most common abnormality found was cerebral atrophy. *Id.* The authors discovered that of 20 patients presumed to have cryptogenic infantile spasms, upon neuroradiologic testing, 12 of them were found to have symptomatic infantile spasms because of brain abnormalities not detected clinically. *Id.* at 49. Thus only 10% of the patients in the study had cryptogenic spasms. *Id.* The authors suggest early treatment of children with infantile spasms who seem developmentally

normal before onset of spasms and have normal neuroradiologic studies in order to prevent development of mental retardation. *Id.* However, in order to have a favorable outcome, all three factors (early treatment, normal pre-onset development, and normal on neuroradiology) must be present. *Id.*

Respondent filed an expert report from Dr. Mary Anne Guggenheim as Exhibit A, dated December 21, 2007, together with her CV as Exhibit B. Attached to her report are Exhibits C to H which consist of medical literature. She states that Elizabeth was diagnosed with cryptogenic infantile spasms whose onset was sometime in the month prior to the office visit of September 5, 1997. *Id.* at 1. She rejects that DTaP caused the infantile spasms. The three bases for her opinion are: (1) epidemiologic studies do not show DT or DPT vaccine causes infantile spasms; (2) outcome studies of infantile spasms refute the idea that an earlier onset due to a vaccine trigger has any adverse effects; and (3) whenever a post-natal brain injury causes infantile spasms, the onset of the spasms takes weeks to months after the injury. *Id.* at 2.

Referring to the analysis of the NCES data by the Bellman study (1983) and Goodman study (1988), Dr. Guggenheim states there was no difference in occurrence of infantile spasms within one month of receiving either DPT or DT vaccine. *Id.* There was a small clustering of cases in the first week post-vaccination with either DPT or DT followed by a slight decrease in the rest of the month, but these numbers were not statistically significant and constituted a "temporal shift." *Id.* at 3. Moreover, the Institute of Medicine (IOM) in 1991 analyzed the NCES data and other epidemiologic analyses and concluded there was no evidence that vaccines cause infantile spasms. *Id.*

As for the outcome studies, Dr. Guggenheim restricts her analysis to studies reviewing outcome in symptomatic cases, that is, cases of infantile spasms where an underlying brain disorder is known. In those studies, time of onset was unrelated to outcome. She uses this analysis to state that an earlier onset of infantile spasms does not lead to a worse outcome. *Id.*

Also in her analysis of temporal interval between post-natal brain injury and onset of infantile spasms, Dr. Guggenheim restricts her analysis to symptomatic cases. *Id.* She is a co-author of one of those studies. The temporal interval that she and her co-authors discovered between brain damage and onset of infantile spasms ranged from six weeks to 11 months with a mean of 5.1 months. *Id.*

As for Dr. Kinsbourne's medical theory that relates the onset of infantile spasms to pertussis by way of cellular adenycyclase, phosphorylation, and G proteins, Dr. Guggenheim states that no one understands at present the underlying mechanisms of infantile spasms and there is no animal model for them. She calls Dr. Kinsbourne's theory a hypothesis which "does not meet scientific standards to support petitioner's claim." *Id.* at 3.

Dr. Guggenheim notes that Dr. Jacobson mentioned in several of his reports metabolic studies showing that, on two occasions, Elizabeth had an elevated level of 4-hydroxybutyric acid (4-OHBA), which is elevated in a condition called succinic semialdehyde dehydrogenase deficiency (SSADH) and is a breakdown product of GABA, a potent neurotransmitter. *Id.* This is a rare autosomal recessive disease resulting in a variety of severe neurologic abnormalities in children, including seizures and developmental impairment. *Id.* Dr. Guggenheim notes that, since SSADH is a rare condition, "it is likely not the cause of Elizabeth's disease. It does seem to me an important issue to resolve." *Id.*

She concludes that DTaP on August 1, 1997 did not cause Elizabeth's infantile spasms because scientific medical studies have established that immunizations do not cause infantile spasms, the age of the child at onset of infantile spasms does not determine outcome, and there is an average of five months between an external brain injury and onset of infantile spasms. *Id.* at 4.

Exhibit C attached to Dr. Guggenheim's report is an article entitled "Epileptic disorders with onset in the first year of life: neurological and cognitive outcome" by D. Battaglia, et al., 3 Eur J Paediatric Neurology 3:95-103 (1999). (This is also Tab A of petitioner's Ex. 48.) The authors analyzed 135 cases of children with epilepsy, including West syndrome (infantile spasms). The 43 children with symptomatic infantile spasms showed a very poor neurological and cognitive outcome. Only the 16 children with cryptogenic infantile spasms had a benign prognosis. *Id.* at 95, 96. The authors analyzed the role of seizures in mental deterioration in all infants who had normal development before the onset of epilepsy and found the persistence of seizures was significantly associated with poor developmental outcome, stating, "This trend seems stronger in the cryptogenic forms of West syndrome." *Id.* at 98. In their series of cases, only a few cryptogenic cases had a poor outcome. This was generally associated with frequently recurrent seizures and supported evidence of the effect of recurrent seizures on cognitive outcome. *Id.* at 101. The authors comment:

> Cryptogenicity is still a vague definition, comprising a group of doubtful aetiology; normal MRI at an early onset of symptoms could be insufficient to exclude symptomaticity and MRI at any time will be unable to detect microscopic cortical dysplasias.

*Id.* at 102. The authors suggest finding a better early identification of signs predictive of neurological and developmental outcome to provide useful information for the timing of surgery

in treating refractory epilepsy in order to prevent mental deterioration caused by frequently recurring seizures. *Id.*

Exhibit D attached to Dr. Guggenheim's report is the Bellman article that is Tab B to petitioner's Exhibit 48.

Exhibit E attached to Dr. Guggenheim's report is an article entitled "The Clinical Phenotype of Succinic Semialdehyde Dehydrogenase Deficiency (4-Hydroxybutyric Aciduria): Case Reports of 23 New Patients" by K.M. Gibson, et al., 99 Pediatrics 4:567-74 (1997). The authors' goal was to persuade pediatricians and pediatric neurologists to consider SSADH deficiency in the differential diagnosis of children with idiopathic mental retardation. *Id.* at 567. The authors note there is a lack of a clear-cut presenting phenotype and the significant variability in overall presentation underscores the variable nature of SSADH deficiency. *Id.* at 573. SSADH deficiency seems to be primarily a disorder of the Eurasian region. *Id.* Their review of 23 new SSADH-deficient patients clearly showed that the clinical phenotype is extremely nonspecific, suggesting the disorder is significantly underdiagnosed. *Id.* The detection of seizures in half the patients was surprising because seizures were not previously thought to be prevalent in SSADH deficiency. *Id.* at 574.

Exhibit F attached to Dr. Guggenheim's report is an article entitled "Temporal Relationship Modeling: DTP or DT Immunizations and Infantile Spasms" by M. Goodman, S.H. Lamm, and M.H. Bellman, 16 Vaccine 2/3:225-31 (1997). (Bellman was a co-author of the NCES and the 1983 analysis of the data on infantile spasms. See respondent's Exhibit D and petitioner's Exhibit 36.) The authors analyze whether children who had symptomatic or cryptogenic infantile spasms had a shortening of time to onset of seizure after either DPT or DT

vaccination based on the case-control data from the National Childhood Encephalopathy Study (NCES) which was discussed and provided in analytic tables in the 1983 Bellman paper. *Id.* at 225.

Infantile spasms represented 23% of the cases in the NCES of acute neurological illnesses resulting in hospitalization of children under the age of three. *Id.* at 226. The most common cause congenitally is tuberous sclerosis complex and the most common perinatal antecedent cause is perinatal hypoxia. *Id.* Of 1182 cases of severe neurological illness from 1976-79 reported to the NCES, 269 (23%) were diagnosed as infantile spasms. Of the 269 cases, 262 had sufficient records for inclusion in the analysis. Two control subjects were selected for each case, matched for age, gender, and area of residence. *Id.* Infantile spasms cases were identified as either previously normal or previously abnormal. *Id.*

For cases exposed to either DPT or DT vaccination, vaccination was more likely during the week prior to the onset of infantile spasms than in the other three weeks during the month following vaccination, although this occurrence was not statistically significant. *Id.* at 226-27. The authors note the pattern of onset for cryptogenic infantile spasms during the month following vaccination differed from those with symptomatic infantile spasms after vaccination in that the cryptogenic cases had "an increased immunization odds ratio" for the week after vaccination "with reduced odds ratios for the remaining weeks of the month" while the symptomatic cases had a reduced odds ratio for each of the weeks of the month following seizure onset. *Id.* at 227. This comparison of odds ratio was a comparison with the controls.

The authors proposed to analyze the data according to three models: (1) "association" where there is a significant increase in frequency of infantile spasms after vaccination; (2)

"temporal shift" in which "there is a shift in the timing of the infantile spasm onset so that there is a clustering in the early part of the period followed by a subsequent deficit in cases" although the overall frequency of infantile spasms onset during the month after vaccination was not significantly increased; and (3) "no effect" in which the cases that occurred were expected and they occurred no sooner or later than expected. *Id.* at 228. The authors state:

> Our temporal shift model is synonymous with what was called 'triggering' in the original NCES infantile spasms publication [referring to Bellman's 1983 article]; however, since that time the term 'triggering' has come to be used with a broader meaning similar to our 'association' model.

*Id.* at 228. The authors proceed to explain that they do not use the term "triggering" to mean "association" but rather "temporal shift." *Id.* at 229.

Both the total infantile spasms grouping (including both cryptogenic and symptomatic cases) and the symptomatic infantile spasms group alone showed no effect, with the symptomatic group best fitting the no effect model. *Id.* Although the cryptogenic infantile spasms group when looked at for one month after vaccination with DPT or DT shows no association, within that month period, the cases are more likely to be reported as having been vaccinated during the week immediately preceding infantile spasms onset than during the other three weeks of that month. *Id.* The authors found this observation statistically significant and demonstrating "a significant fit to the temporal shift model." *Id.* They caution that the precise date of onset of infantile spasms is difficult to determine because of the insidious nature of the illness. Since the earliest manifestations of infantile spasms are subtle and easy to miss, precise onset is difficult to identify. *Id.*

The authors state that their conclusion is consistent with that of the IOM that no causal association exists between DPT vaccination and infantile spasms. *Id.* at 229-30. They also refer to another analysis by J.D. Cherry of the same NCES data which demonstrated an odds ratio increase during the first week after immunization of all neurologic events rather than just infantile spasms with a decrease in occurrence during the subsequent three weeks. Cherry interpreted his findings as showing that "'immunization brings out a neurologic event that would have occurred anyway or calls attention to an event that is already occurring." *Id.* at 230. The authors of the Goodman paper (Ex. F) state, "This interpretation precisely fits our temporal shift model." *Id.*

Exhibit G attached to Dr. Guggenheim's report is her own article entitled "Time Interval From a Brain Insult to the Onset of Infantile Spasms" by M.A. Guggenheim, et al., 38 Ped Neur 1:34-37 (2008). The authors discuss the onset of symptomatic infantile spasms after a brain insult such as postnatal encephalopathy or perinatal stroke. The onset of infantile spasms occurred from six weeks to 11 months after the brain insult. *Id.* at 34-35. The number of symptomatic infantile spasms now constitutes 90% of all infantile spasms. *Id.* at 34. The authors expect that eventually the category of cryptogenic or idiopathic infantile spasms will disappear due to the increase in effectiveness of diagnosis. *Id.* The authors assume that the underlying brain pathology in all infants who develop infantile spasms is the same.

One of the purposes of the article is to attack the idea that there is a causal relationship between vaccinations and infantile spasms whose temporal latency is close because the authors found that in brain-injured children where the cause of the infantile spasms is known (i.e., post-natal as in encephalopathy or stroke), the temporal latency to infantile spasms was six weeks to 11 months. *Id.* The authors did their analysis by a literature search, omitting all infantile spasms

cases related to an identified metabolic disease, cerebral malformation, genetic syndrome, or other established disease because they could not establish a time when these conditions initiated an epileptogenic process resulting in infantile spasms. *Id.* Similarly, they eliminated all infants who showed serious perinatal distress, especially when related to prematurity, because the infants may have had intrauterine brain insults whose timing was also unknown to the authors. *Id.*

The post-natal events that the authors used to start the clock in timing the latency interval for 19 cases of infantile spasms involved hypernatremia/cerebral infarction; meningitis; near-drowning; intracranial hemorrhage; rotovirus encephalitis; acute disseminated encephalomyelitis; encephalopathy/epilepsy; measles encephalitis; TB meningitis; bacterial meningitis; and head injury. *Id.* at 35.

The authors' review of other studies showed a "wide range of latencies (i.e., time from initial brain insult to onset of infantile spasms)" suggesting that many variables contributed to the underlying pathogenesis: the type and severity of brain injury, and the postconceptional age at which the injury occurred. *Id.* at 36. In cases involving a developmental brain disorder such as tuberous sclerosis, Aicardi syndrome, or homeobox gene disorder, the timing of the onset of infantile spasms likely reflects many aspects of synaptic and neurochemical neuronal interactions that current science does not understand. They conclude that infantile spasms do not occur acutely after a defined postnatal brain perturbation. *Id.* The information suggests a latent period of at least several weeks and usually many months between an event or condition that alters brain function and the onset of infantile spasms. *Id.*

In attempting to understand how the infant brain manifests infantile spasms in light of so many etiologic factors, the authors state that "the crucial element might be an insult resulting in

an unbalanced maturational pattern, in which at least two brain systems become dysfunctional owing to divergent developmental rates, eventually resulting in an inability of the systems to interact normally." *Id.* The authors state that an "important aspect of this model is the idea that the dysfunction responsible for infantile spasms does not occur immediately after the insult, but only becomes manifest when the unequal maturational rates finally result in a critical degree of functional imbalance between the two systems." *Id.* The authors conclude:

> Finally, the results of our analysis preclude claims that the onset of infantile spasms within hours or days of immunization indicates a causal relationship, because such claims are based on the assumption that the brain is injured by a toxin present in the product, or by some unspecified aberrant immunologic process. Consequently, the observation that infantile spasms occur with an average latency of 5.1 months after postnatal injury is supportive of the already existing strong evidence that vaccine administration is not a causative factor in this disorder, and reinforces the generally held view that a close temporal association in occasional cases is only coincidental.

*Id.*

Exhibit H attached to Dr. Guggenheim's report is an article entitled "Clinical spectrum of succinic semialdehyde dehydrogenase deficiency" by P.L. Pearl, et al., 60 Neurology 1413-17 (2003). The authors state that SSADH deficiency presents during childhood with psychomotor retardation, seizures, hypotonia, and nonprogressive ataxia. *Id.* at 1413. Absence and tonic-clonic seizures are observed clinically in nearly half of SSADH-deficient patients. *Id.* at 1414.

On January 4, 2008, respondent filed Exhibit I consisting of chapter 12, "Long-Term Outcome" from J.D. Frost and R.A. Hrachovy's textbook entitled Infantile Spasms. Diagnosis, Management and Prognosis (2003), pp. 203-23. Drs. Frost and Hrachovy were Dr. Guggenheim's co-authors in the article marked as Exhibit G supra. They state the prognosis in

West syndrome (infantile spasms) is poor over all although a small number of children recover. *Id.* at 203. Children with cryptogenic infantile spasms died at a significantly lower rate than children with symptomatic infantile spasms. *Id.* at 206.

The authors found studies that varied in size and other factors made determining the efficacy of ACTH and corticosteroids in treatment difficult to prove. *Id.* at 210. Surgery might have a better result. *Id.* at 210-11. As with all the other factors the authors examined, early treatment was also confusing in results. *Id.* at 211. If early treatment has any effect, it may be restricted primarily to cryptogenic infantile spasms. *Id.* at 212. A much more predictive factor of favorable outcome was classification of a child's infantile spasms as cryptogenic, rather than symptomatic, at the time of initial diagnosis. *Id.* In addition, those children classified as normal developmentally at the first examination were more likely to have a favorable long-term outcome. *Id.* at 213. The authors contrast the study outcomes of a number of other factors which contradict each other in conclusions. *Id.* at 214-15.

The authors note that infantile spasms patients frequently develop other types of seizures which often persist indefinitely. *Id.* at 217. Children with cryptogenic infantile spasms are much less likely to have uncontrolled seizures of any type. *Id.* at 218. They have half the percentage (23%) of uncontrolled seizures as compared to children with symptomatic infantile spasms (54%). *Id.* One study found that a normal MRI was associated with a later onset of infantile spasms, an earlier cessation of spasms, and a lower incidence of subsequent seizures of any type. *Id.* at 219. The earlier the onset of infantile spasms, the higher the probability of uncontrolled seizures. *Id.*

On January 4, 2008, respondent filed Exhibit J which consists of two excerpts from chapter 4 of the Institute of Medicine's Adverse Effects of Pertussis and Rubella Vaccines (1991),

eds. C.P. Howson, et al., 65-77, 118-24. Sixty-five percent of children with infantile spasms go on to have other types of seizures. *Id.* at 65. "Approximately 8 to 14 percent of infantile spasms are attributed to postnatal factors, including central nervous system (CNS) infections, trauma, immunizations, and intracranial hemorrhage [citing articles]. Few of these factors have been subjected to systematic investigation, however...." *Id.* at 66. They describe numerous case reports in the medical literature associating DPT vaccine and infantile spasms with an onset reported between one and five days; other intervals have been from minutes to weeks. *Id.* at 67. The authors of one study considered DPT to be the cause of infantile spasms if there were no other identifiable cause, the child was normal prior to onset of spasms, and the onset of spasms occurred within 48 hours for pertussis-containing vaccines and within 18 days for smallpox, polio, and Japanese encephalitis vaccines. *Id.* at 68. Using these criteria, the authors determined that five out of 110 cases were vaccine-caused. *Id.* In another study, 13 out of 98 cases of infantile spasms were attributed to vaccination. *Id.* at 69. Between 1978 and 1990, 58 cases of infantile spasms occurring within 28 days of DPT immunization were reported through the Centers for Disease Control's Monitoring System for Adverse Events Following Immunization, during which period about 80.1 million DPT vaccines were administered. *Id.*

The authors describe the NCES data that Bellman later described in his article, including the clustering of infantile spasms onsets within the first six days after immunization for both DPT and DT. "Whether the apparent clustering of cases that was observed within the first 6 days after immunization for both DPT and DT represents a triggering phenomenon, bias in assigning date of onset of spasms, or simply a chance observation cannot be determined from these data." *Id.* at 73.

[This IOM book was published seven years before the publication of the Goodman article analyzing the same NCES data.]

The authors describe the Study of Neurological Illness in Children (SONIC) done from 1987-88 concerning children in Washington and Oregon. The authors found a sixfold increased risk of infantile spasms among children who received DPT within 28 days of onset. The IOM considered the number of cases small since only 10 children with infantile spasms after vaccination were involved, creating a wide confidence interval, meaning the estimated risk was very imprecise. *Id.* at 74, 75. The IOM authors state there are no data bearing on mechanisms or biologic plausibility and conclude that the evidence does not indicate a causal relation between DPT vaccine or its pertussis component and infantile spasms. *Id.* at 77.

Filed on January 4, 2008 is respondent's Exhibit K, an article entitled "Infantile Spasms in Children with Down Syndrome" by C.E. Stafstrom, et al., 36 Developmental Med & Child Neurology 576-85 (1994). The authors note that certain inherited disorders and inborn errors of metabolism, e.g. tuberous sclerosis, Aicardi syndrome, and untreated phenylketonuria, are significantly associated with infantile spasms. *Id.* at 576. Another disorder associated with infantile spasms is Down syndrome. *Id.* These are symptomatic infantile spasms. *Id.* at 581. They note that symptomatic infantile spasms have a worse prognosis than cryptogenic spasms, with severity of impairment related to etiology. *Id.* In trying to understand how children with Down syndrome manifest infantile spasms, the authors state that anomalous glutamate receptor function may play a role since the level of this transmitter is elevated in both Down syndrome and infantile spasms. *Id.* at 583.

Exhibit L is Dr. Guggenheim's supplemental report in response to Dr. Kinsbourne's supplemental report, in particular the role of vaccinations as a trigger for infantile spasms and the age of onset of infantile spasms. Dr. Kinsbourne implies that there is a vaccine trigger or temporal shift causing an earlier age of onset of infantile spasms and resulting in a worse outcome for a child than a later onset. *Id.* at 1. Dr. Kinsbourne also raised this point in his first report to which Dr. Guggenheim stated what she reiterates, i.e., there is no evidence that the age of onset is related to a favorable or unfavorable outcome. *Id.* What does affect outcome in terms of mental development and intractable seizures is the underlying brain disorder. *Id.* In the Battaglia study, only two children with symptomatic infantile spasms had normal development whereas 16 children or 63% of children with cryptogenic infantile spasms had normal development. *Id.* However, one-third or more of individuals with cryptogenic infantile spasms had ongoing significant neurodevelopmental problems. *Id.* at 2. She concludes that there is no experimental model for infantile spasms and Dr. Kinsbourne's explanation of vaccine neurotoxicity is hypothetical. *Id.* at 3.

## TESTIMONY[3]

Dr. Marcel Kinsbourne testified first for petitioner. Tr. at 4. He is trained as a pediatric neurologist. Tr. at 6. He phased out his private practice in the 1990s. Tr. at 8. He described the National Childhood Encephalopathy Study or NCES, which was created to determine epidemiologically whether pertussis vaccine causes seizures and encephalopathies. Tr. at 17. Among the category of seizures the authors of the NCES studied was infantile spasms. *Id.* The

[3] This case was simultaneously tried with a companion case, Fowler v. Sec'y of HHS, No. 03-1974V, because of the identical issues, experts, and counsel.

authors found that DPT triggered the onset of infantile spasms, but, in the long term, pertussis did not increase the total number of children with infantile spasms. *Id.* What pertussis vaccine did was affect the brain so as to accelerate the onset of infantile spasms. *Id.*

Dr. Goodman and his colleagues wrote an article on the NCES findings, reanalyzing the data, and concluded that pertussis vaccine caused a temporal shift, meaning the vaccine seemed to precipitate the clinical presentation of infantile spasms. Tr. at 18. This applies to cryptogenic infantile spasms, but not to symptomatic infantile spasms. *Id.*

Bellman was one of Goodman's co-authors and wrote an earlier study (1983) than Goodman's (1998) in which Bellman was a co-author as well. Tr. at 19. Dr. Kinsbourne noted that Goodman's study was more recent and was a well-conducted analysis, but the conclusions of the Bellman study and the Goodman study are consistent. *Id.*

The Goodman authors distinguished between "trigger" and "cause" in concluding that they agreed with the Institute of Medicine (IOM) 1991 report that the evidence does not indicate a causal relation between DPT vaccine and infantile spasms. Tr. at 24, 25. In other words, although DPT can occasionally trigger the onset of infantile spasms, it is not the primary cause of infantile spasms. Tr. at 25. In cryptogenic infantile spasms, we do not know the cause. Tr. at 26. There must be a powerful predisposition in certain children to react to DPT in such an unusual way. Tr. at 27. The prognosis of cryptogenic infantile spasms depends on whether the seizures are ongoing, whether they continue for a long time, whether treatment was given early, and whether they are responsive to antiepileptic drugs. Tr. at 27-28.

In the Bellman study, if one looks at the four weeks after vaccination, there is no level of significant increase because their sample size is quite small. Tr. at 30. If, however, one looks at

the distribution of the cases over the four weeks, there is an interesting curve with a higher incidence of infantile spasms in the first week post-vaccination, and then a reciprocally lower incidence of infantile spasms in weeks two, three, and four. Tr. at 31.

Dr. Kinsbourne finds that the Melchior paper examining onset of infantile spasms over four weeks notes no change in the rate overall post-vaccination, but does show that the vaccine accelerates the onset of infantile spasms just as the Goodman article says. Tr. at 32, 33. Melchior failed to find statistical significance in his data. Tr. at 36. Melchior did not look at the relationship of onset of infantile spasms to the very first vaccination. If he had, he would have found that twice the percentage of children had an onset of infantile spasms in the first period of two months if they had been vaccinated than if they had not. Tr. at 37.

Bellman says in his article that compared with controls during the seven days after immunization with both DPT and DT vaccines, there was a small excess in the number of cases with a corresponding deficit in the next three weeks, suggesting that in some cases, immunization may trigger the onset of infantile spasms or attract attention to symptoms in children destined to have infantile spasms. Tr. at 37-38. That description is the same as Dr. Goodman's temporal shift. Tr. at 38. Unexpectedly, the curve showing excess in the first week applied to both DPT and DT vaccines. *Id.*

In symptomatic infantile spasms, as an article that Dr. Guggenheim wrote makes clear, the brain damage might be prenatal and yet the infantile spasms might not begin until two, three, or four months of age. Tr. at 43-44. There is a period of high susceptibility in the first year of life, between two or three months to about eight months, where the underlying tendency to infantile

spasms, set up by structural brain damage, is most easily transformed by factors largely unknown. Tr. at 44.

In cryptogenic infantile spasms, there are no signs of a brain structural defect, the child has been developing normally, neuroimaging reveals no brain abnormalities, and clinical examination reveals no neurological problems. *Id.* The large majority of infantile spasms are in the symptomatic, not the cryptogenic, category. Tr. at 45. The prognosis for children with cryptogenic infantile spasms is better than for those with symptomatic infantile spasms. *Id.*; tr. at 63.

West syndrome is another name for infantile spasms. Tr. at 47. The Battaglia article shows that only one in 10 children with cryptogenic seizures or West syndrome had an IQ below 50 which is severe impairment. Elizabeth has an IQ far below 50. Tr. at 48. In the Dulac article, only three children out of 35 with cryptogenic infantile spasms had an IQ below 50. Tr. at 49. Dr. Kinsbourne's opinion is that DTaP vaccine caused Elizabeth's cryptogenic infantile spasms, making them far worse than the standard cryptogenic infantile spasms. *Id.* His basis focuses on pertussis toxin. Tr. at 50.

Neurons have a surface membrane composed of G-proteins. *Id.* Pertussis toxin can bind those proteins and inactivate them. *Id.* G-proteins are particularly necessary to transmit inhibitor influences. Tr. at 51. If the G-proteins are inactivated, the brain will experience a greater excitation of neurons than otherwise. *Id.* Normally, there is a balance between neuron transmitters which cause neurons to fire more and other which cause them to fire less. This is called the excitation/inhibition balance in the brain. *Id.*

If there is a shift in this ratio such that the excitation greatly outweighs the inhibition, then the seizure threshold gets lower and seizures are apt to occur. *Id.* Many antiepileptic agents directly correct the balance between excitation and inhibition by strengthening inhibition through the GABA system. *Id.* Pertussis toxin renders a child more liable to have an overexcited network which promotes the occurrence and continuation of seizures. *Id.* When someone has seizures, the seizures tend to cause neuroinflammation which then facilitates further seizures. Tr. at 52.

Infantile spasms "very often, if not typically, begin in a very subtle evanescent manner." Tr. at 70. A parent might notice something out of the corner of his or her eye which came and went in a second or two. *Id.* The illness typically gathers momentum so that a time comes when someone cannot really miss it. *Id.* Although in the beginning, the event could be solitary, infantile spasms tend to cluster over time so that you have a whole series of similar jerklike movements over numerous seconds. *Id.*

Dr. Kinsbourne stated that Elizabeth had a really unremarkable background until she was four and one-half months old and received her second set of childhood vaccines, including DTaP, HiB, and IPV on August 1, 1997. Tr. at 75-76. The notation for that visit was well baby. After those vaccinations, her parents noticed crunching movements which were actually the beginning of infantile spasms. Tr. at 76. The medical records indicate the onset was within the first week after her second set of vaccinations although they were not immediately recognized as being infantile spasms. *Id.* Her pediatrician thought they were gas pains by description, but when she saw one, she knew they were infantile spasms and referred Elizabeth to the ER on September 5, 1997. *Id.* She was admitted to the hospital and started treatment with ACTH. Tr. at 76-77. The seizures stopped on September 22, 1997. On October 20, 1997, Elizabeth received her third set of

immunizations which omitted pertussis but included DT. Tr. at 77. Four hours after vaccination, Elizabeth's seizures began again. *Id.*

Dr. Kinsbourne's opinion is that the second set of vaccinations on August 1, 1997 caused Elizabeth's infantile spasms and there was no alternative cause. Tr. at 79. He believes it was not coincidence that Elizabeth's recurrence of seizures occurred four hours after her third set of vaccinations on October 20, 1997. Tr. at 80. It is unexpected that DT would trigger a recurrence of seizures. *Id.* The treating physicians omitted pertussis from this set of vaccinations so as to prevent a recurrence. *Id.* Dr. Kinsbourne wonders whether tetanus toxoid was "an instrument of heightening the excitability of an already overexcitable neuron or circuit, and in fact precipitat[ed] the relapse." *Id.*

Tetanus toxoid has been associated with seizures which have not been more specifically described so that he does not know if they were infantile spasms. *Id.* However, Dr. Kinsbourne could not say more likely than not that DT significantly aggravated Elizabeth's infantile spasms. Tr. at 81. However, his opinion is that the DTaP administered August 1, 1997 triggered Elizabeth's infantile spasms. Tr. at 83. He prefers the word "triggered" to "caused" because there is some abnormality in the child which made her vulnerable to the effects of pertussis in the DTaP so as to have infantile spasms. *Id.*

Dr. Kinsbourne also believes that the DTaP contains pertussis toxin, which is a neurotoxin, that causes a seizure disorder that is more serious and resistant to control than the infantile spasms would otherwise have been. Tr. at 85. What the vaccine caused was the more severe nature of the infantile spasms. Tr. at 86.

Dr. Kinsbourne stated there is no evidence that Elizabeth had an acute encephalopathy following vaccincation. Tr. at 88. Elizabeth did not have an acute encephalopathy after her DT vaccination either. Tr. at 89.

The blood-brain barrier in a two- to four-month old is incomplete. *Id.* If a child's blood-brain barrier were breached, one might see symptoms of an acute encephalopathy, depending on the properties of the toxin, the amount of the toxin, and other factors. *Id.* The Institute of Medicine stated in 1991 that there are no scientifically certain data bearing on mechanisms or biologic plausibility in relating pertussis vaccine and infantile spasms. Tr. at 91-92, 94. Dr. Kinsbourne is positing a biologically plausible medical theory connecting pertussis vaccine and infantile spasms 18 years after the IOM report. Tr. at 92, 94.

For Dr. Kinsbourne's theory of the effect of pertussis toxin on G-proteins, breach of the blood-brain barrier is not a necessary part. Tr. at 96. The reason is that pertussis can enter a baby's brain without breaching the blood-brain barrier because it is incomplete in infants. Tr. at 97. The Bellman article and the Goodman article were both looking at the same group of cases of infantile spasms from the NCES. Tr. at 107. Nothing in Tables 2 and 3 was statistically significant. Tr. at 108. What was analyzed was the pattern of onset over four weeks. *Id.* Comparing week one after vaccination with week one of control children did not produce a significantly significant result. Tr. at 109. However, the pattern as a whole was not expected by chance. *Id.* The authors concluded that the pattern indicated a triggering effect which they called a temporal shift. *Id.*

Elizabeth's onset of seizures occurred within a week of vaccination. Tr. at 117.

Dr. Mary Anne Guggenheim, a pediatric neurologist, testified next for respondent. Tr. at 128, 129. She will be receiving the Lifetime Achievement Award from the Child Neurology Society. Tr. at 131. She has seen 100 to 200 infantile spasms patients in her practice. *Id.* Her opinion is that there are no data implicating DPT or DTaP as a cause or trigger of infantile spasms. Tr. at 132. She thinks the temporal proximity of onset to vaccination is a chance occurrence of their age at that time. *Id.*

Elizabeth started at the lowest percentile of head growth. At two months of age, she was at the 50$^{th}$ percentile. Over the next year, her head circumference jumped to the top of the normal range, the 95$^{th}$ percentile, and the last measurement at three years of age was at the 80$^{th}$ percentile. She did not become microcephalic. Tr. at 134.

Elizabeth made pretty good developmental progress, even though she had a relapse of seizures. Tr. at 34. At 11 months of age, she began to fall further and further behind. Tr. at 135. Literature does not conclude that the age of the child at onset of infantile spasms determines the outcome. Tr. at 135.

Elizabeth had cryptogenic spasms, meaning that the cause cannot be identified. Tr. at 137. Children with cryptogenic infantile spasms generally do better than those with symptomatic infantile spasms. Tr. at 138. Although Elizabeth's infantile spasms were brought under control, on EEG she still had an abnormal brain due to slow background rate. Tr. at 141. She began to seize once again four hours after she received DT on October 20, 1997, but the seizure was a convulsion without jerking, which was not a cluster of infantile spasms. Tr. at 45. Regarding Elizabeth's nonconvulsing seizure on the day she had a DT immunization, Dr. Guggenheim testified that this was not surprising because it is well-known to pediatric neurologists that

children with a lower seizure threshold have more epileptogenic potential and will seize when challenged by either an intercurrent illness or an immunization. Tr. at 143. Dr. Guggenheim stated:

> THE WITNESS: The thought that she had the overt recurrence of infantile spasms–not of infantile spasms, but of what I think was a nonconvulsing seizure on the day that she had that DT immunization, just–it is not surprising.
>
> It is well known to all of us who have practiced child neurology and taken care of hundreds and thousands of kids with epilepsy that children who have this potential for seizures have a lower seizure threshold, have a more [epi]leptogenic potential, whatever term you want to use, that it is very common that when intercurrent illness occurs in those children with or without a fever that they have breakthrough seizures.
>
> And so with an intercurrent illness you have in a sense the natural occurrence of an immunization and affected with an outside virus, your body reacts to it. And Dr. Kinsbourne has already talked about some of those reactions, and it's very common that we see breakthrough seizures with an intercurrent event with or without fever, and that to me doesn't mean that there was something dramatically different.
>
> I mean, I do not attribute the significance that Dr. Kinsbourne does to that relapse of seizures on the day of the immunization. It happened to be an immunization rather than a recurring illness or nothing at all that we can identify. But that pattern of initial response to treatment, a period of time without overt seizures, and then a recurrence of seizures often of a different type with a very refractory treatment is a very common pattern in infantile spasms in general, including the cryptogenic group.
>
> THE COURT: So, Dr. Guggenheim, are you saying that it is your opinion that the vaccinations, particularly the acellular DPT on August 1, 1997, did not cause Elizabeth Haynes' onset of infantile spasms five days later, but that the vaccination[ ] ... [of] diphtheria/tetanus on October 20, 1997, acted just like an intercurrent illness to cause her resumption of seizures?
>
> THE WITNESS: That would be my position, and I, we know from the EEGs that her brain was still sick.
>
> THE COURT: That her brain was what?
>
> THE WITNESS: Was still sick. It was abnormal because of the background slowing.

Tr. at 143-44.

The earlier infantile spasms are treated, the better. Tr. at 152. Dr. Guggenheim disagrees with Dr. Kinsbourne's opinion that DTaP makes the outlook for infantile spasms worse. Tr. at 153. Most children with infantile spasms have either a genetic determinant or a prenatal/perinatal injury. Tr. at 155. Dr. Guggenheim has never seen a case of infantile spasms occurring within a few days of a cause. *Id.* She examined 19 cases of infantile spasms and found the onset interval between an encephalopathic event and infantile spasms to be six weeks to 11 months. Tr. at 157. She would not rule out a vaccine injury if the infantile spasms occurred six weeks to 11 months post-vaccination. *Id.* A close temporal proximity led to the assumption that there was a cause and effect relationship in the Bellman paper and the Goodman reanalysis. *Id.* The injury of a DPT vaccination is still a hypothesis and not proven, but with events like meningitis, near drowning, and encephalitis, there was a distinct interval between the event that damaged the brain and the child's onset of infantile spasms. Tr. at 158. Infantile spasms is a different type of seizure than other types of epileptic seizures. Tr. at 159.

The children Dr. Guggenheim studied for her article all had some kind of disease or accident. Her goal was to find the time interval between event and onset of infantile spasms. Tr. at 160. She assumes that these diseases or accidents caused the infantile spasms six weeks to 11 months later. *Id.* The hypothesis in the cases asserting that vaccinations caused infantile spasms relies on a time interval that is different from the much later one she discovered in her paper because it occurs much later. Tr. at 161-62. These cases involved symptomatic infantile spasms

because the cause (brain injury) was known. Tr. at 180. Pathologic findings are of post-traumatic epilepsy. Tr. at 182.

Dr. Kinsbourne responded that in cryptogenic infantile spasms, there is no evidence of a brain injury. Tr. at 166. Therefore, we cannot calculate a time between the injury and onset of the seizures. What we have is a susceptibility to starting infantile spasms between two to eight months maybe under provocation such as DPT. Tr. at 166-67. Dr. Guggenheim's article presents brain injury as the cause, whereas Dr. Kinsbourne is not presenting vaccination as the primary cause. Tr. at 167. Triggering an already susceptible individual to have cryptogenic infantile spasms is the issue. *Id.*

Dr. Guggenheim stated that Goodman did a more sophisticated analysis than Bellman did of the same data. Tr. at 168-69. When you look at the raw data plotted out on a graph, there are a few more children in the first week after vaccination with onset of infantile spasms than there are in weeks two, three and four compared to controls. Tr. at 169-70. The numbers are small. In the cryptogenic group, there were only 15 children. It is not surprising then that the results were not statistically significant. Tr. at 170. When you look at the overall occurrence of infantile spasms, there is no difference whether the children had a vaccination or not. *Id.*

Dr. Guggenheim also stated that an earlier onset of infantile spasms would not make a difference in the outcome. Tr. at 171. If the DPT vaccine does have a triggering effect, it will cause infantile spasms to occur only two to three weeks earlier than they otherwise would have and that does not appear to affect outcome. *Id.* Dr. Kinsbourne absolutely agreed that the age of onset of infantile spasms does not affect the outcome. *Id.*

Dr. Guggenheim stated that in the vast majority of cases, about 95 percent, infantile spasms occur within the first year of life, and well over half occur between four and eight months of age. Tr. at 172. Since children are receiving their vaccinations during this time period, onset of infantile spasms is a coincidence. Tr. at 175. If you treat a child with infantile spasms very soon after onset, they do not seem as sick as if you wait until six weeks after onset to treat them. Tr. at 191.

Dr. Guggenheim stated that the G-protein theory does not mean much to her. Tr. at 199. There are processes embodied within cell membrane that trigger intercellular biochemical reactions. *Id.* One of the proteins in the cell membrane that seems linked to the adenylate cyclase system that is intercellular but extends into the biochemical processes in the cells is triggered by a structural protein called the G-protein. Tr. at 199-200. These are complex biochemical processes of the cell that can be modified by numerous agents. Tr. at 200. The first type of neurotransmitter action occurs when neurotransmitters like acetone chlorine and GABA alter the sodium, potassium, and calcium channels in the cell membrane for a microsecond of action potential before reverting to normal. Tr. at 200-01. There is a whole second effect of subneural transmitters involved with G-protein, adenylate cyclase, etc. causing changes within the cell, proteins, RNA, and maybe even DNA. Tr. at 201. The first is very rapid and reversible. The second is slower and able to cause permanent changes within the cell's metabolism. *Id.*

In vitro studies done in petri dishes show an excitatory neurotransmitter enhancement and an inhibitory neurotransmitter impairment from the action of pertussis toxin. Tr. at 201-02. An enhancement of excitatory neurotransmitters certainly predisposes the brain to have seizures. Tr. at 202. The whole neuro network is in balance between excitatory and inhibitory stages. *Id.*

When the excitatory neurotransmitters become excessive enough to have an action potential occurring with neurons, which gets synchronized with millions of neurons, that can trigger a seizure. *Id.* There are neither epidemiologic studies nor animal models establishing that pertussis immunization causes infantile spasms. Tr. at 204.

Dr. Guggenheim stated that she could not say either way based on a 50 percent probability whether what Bellman and Goodman described in their articles was a true phenomenon. Tr. at 211. In Elizabeth's case, she did not have a viral disease, a fever, or exposure to endotoxin to explain any breach of her blood-brain barrier. Tr. at 212. Relating the clinical event of infantile spasms to in vitro studies that underlie Dr. Kinsbourne's G-protein hypothesis is too big a jump for Dr. Guggenheim to make. Tr. at 213. She does not think it is plausible. *Id.* She does not think it is 100 percent impossible, but she considers that mechanism of infantile spasms to be unlikely. *Id.*

## DISCUSSION

To satisfy her burden of proving causation in fact, petitioner must prove by preponderant evidence "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Sec'y of HHS, 418 F.3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Sec'y of HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992):

> A persuasive medical theory is demonstrated by "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" the logical sequence being supported by "reputable medical or scientific explanation[,]" *i.e.*, "evidence in the form of scientific studies or expert medical testimony[.]"

In Capizzano v. Sec'y of HHS, 440 F.3d 1317, 1325 (Fed. Cir. 2006), the Federal Circuit said "we conclude that requiring either epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect is contrary to what we said in Althen . . . ." Such an approach is inconsistent with the use of circumstantial evidence. *Id*. The Federal Circuit stated in Althen, 418 F.3d at 1280, that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body."

Close calls are to be resolved in favor of petitioners. Capizzano, 1440 F.3d at 1327; Althen, 418 F.3d at 1280.

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, 956 F.2d at 1149. Mere temporal association is not sufficient to prove causation in fact. *Id*. at 1148.

"Petitioner need not show that the vaccine was the sole or predominant cause of her injury," just that the vaccine was a substantial factor in causing her injury. De Bazan v. Sec'y of HHS, 539 F.3d, 1347, 1351 (Fed. Cir. 2008).

In essence, the special master is looking for a medical explanation of a logical sequence of cause and effect (Althen, 418 F.3d at 1278; Grant, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen v. Sec'y of HHS, 35 F.3d 543, 548-49 (Fed. Cir. 1994)). To the undersigned, medical probability means biologic credibility rather than specification of an exact biologic mechanism. As the Federal Circuit stated in Knudsen:

> Furthermore, to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program. The Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal "compensation program" under which awards are to be "made to vaccine-injured persons quickly, easily, and with certainty and generosity." House Report 99-908, *supra*, at 3, 1986 U.S.C.C.A.N. at 6344.
>
> The Court of Federal Claims is therefore not to be seen as a vehicle for ascertaining precisely how and why DTP and other vaccines sometimes destroy the health and lives of certain children while safely immunizing most others.

35 F.3d at 549.

The Federal Circuit in Capizzano emphasized that the special masters are to evaluate seriously the opinions of the vaccinee's treating doctors since "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury." 440 F.3d at 1326. See also Andreu v. Sec'y of HHS, 569 F.3d 1367, 1375 (Fed. Cir. 2009).

As the Federal Circuit stated in Knudsen, 35 F.3d at 548, "Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or medical rules." The undersigned's task is to determine medical probability based on the evidence before the undersigned in this particular case. Althen, 418 F.3d at1281 ("judging the merits of individual claims on a case-by-case basis").

The Federal Circuit in Knudsen, 35 F.3d at 549, also stated: "The special masters are not 'diagnosing' vaccine-related injuries."

As for epidemiological support for causation, the Federal Circuit in Knudsen, 35 F.3d at 551, ruled for petitioners even when epidemiological evidence directly opposed causation from DPT vaccine. The case concerned the cause of a baby's encephalopathy after a vaccination.

Respondent provided evidence that more encephalopathies are caused by viruses than by vaccines, convincing the special master to rule against petitioners. But the Federal Circuit thought the epidemiologic evidence should not bar petitioners from prevailing. Even though epidemiological evidence supported respondent's view that viruses are more likely to cause encephalopathy than vaccines, the Federal Circuit held that that fact alone was not an impediment to recovery of damages. In Knudsen, the Federal Circuit stated:

> The bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies is not evidence that in a particular case an encephalopathy following a DTP vaccination was in fact caused by a viral infection present in the child and not caused by the DTP vaccine.

35 F.3d at 550.

The special masters "are entitled–indeed, expected–to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence." Moberly v. Sec'y of HHS, 592 F.3d 1315, 1325 (Fed. Cir. 2010) (special master found petitioner's expert neurologist Dr. Kinsbourne not credible).

The Federal Circuit in Moberly stated that, in addition to satisfying the three Althen prongs, whether petitioner prevails depends on whether respondent's expert agrees with the medical theory petitioner's expert propounds and whether the treating doctors opined that the vaccination caused the injury. In both Andreu and Moberly, the fact patterns were the same--DPT vaccination followed shortly by seizures in the vaccinee. Petitioners in Andreu prevailed because respondent's expert agreed with the blood-brain barrier theory of petitioners' expert (Althen prong one), and the vaccinee's treating doctors thought the vaccination caused the seizures.

Petitioner in Moberly did not prevail because respondent's expert disagreed with the blood-brain barrier theory of petitioner's expert, and the vaccinee's treating doctors did not opine the vaccine caused the seizures. Moberly, 592 F.3d at 1324-25.

The undersigned ordered the parties in the instant action to analyze Andreu and its relevancy to the instant action. After the Federal Circuit issued Moberly. the undersigned similarly ordered the parties in the instant action to analyze Moberly and its relevancy to the instant action.

Petitioner states in her response regarding Andreu that the fact patterns for both Enrique Andreu and Elizabeth were the same. P. Resp. at 2. Moreover, Elizabeth's treating pediatric neurologist, Dr. Mary Zupanc, noted that Elizabeth's seizure recurrence after her DT vaccination was intriguing and may indicate dysfunction of her immune system. P. Resp. at 4, n.5. The Federal Circuit in both Capizzano and Andreu emphasized the importance of treating doctors' opinions. Elizabeth's treating physicians recommended that she receive no further vaccinations, which the Federal Circuit in Andreu found significant in proving causation. *Id.*; 569 F.3d at 1376.

Respondent states in her response regarding Andreu that the facts in that case differ from the facts in the instant action because Enrique Andreu received whole-cell DPT while Elizabeth received acellular DPT, and Enrique had focal seizures while Elizabeth had infantile spasms. R. Resp. at 2. Respondent also dates the onset of Elizabeth's spasms to some time before September 5, 1997 in the month after vaccination, not within the week of vaccination. *Id.* Since DTaP contains very little endotoxin unlike DPT, there is no way for DTaP to breach the blood-brain barrier. R. Resp. at 3. Whereas in Andreu, respondent's expert agreed that petitioner's causal theory was plausible, in the instant action, respondent's expert Dr. Guggenheim disagreed with

the plausibility of Dr. Kinsbourne's theory. *Id.* Unlike in Andreu, none of Elizabeth's treating physicians testified in the case. R. Resp. at 5, n.5.

Petitioner states in her reply to respondent's response regarding Andreu that the Federal Circuit ruled that the absence of fever during seizures does not bar petitioner from prevailing. P. Reply at 10.

Petitioner states in her response regarding Moberly that Elizabeth's treating doctors causally linked her infantile spasms to her DTaP by allusions in the medical records to Elizabeth's onset being after her receipt of DTaP. P. Resp. at 2-3. The doctors recommended no further vaccinations. P. Resp. at 4-5. Petitioner states, "The respondent says Elizabeth's pre-existing damaged brain, or a delay in treatment, may have contributed to her present condition. Elizabeth agrees." P. Resp. at 14-15. Petitioner states that the vaccine, Elizabeth's genetic predisposition, and the delay in treatment are all substantial factors in causing Elizabeth's infantile spasms and subsequent brain injuries. P. Resp. at 15.

Respondent states in her response regarding Moberly that Elizabeth's doctors did not causally connect her DTaP with her infantile spasms. R. Resp. at 2-3. Respondent's expert Dr. Guggenheim did not think petitioner's expert Dr. Kinsbourne's theory plausible. R. Resp. at 5.

Petitioner states in her reply to respondent's response regarding Moberly that Elizabeth's physicians directed that she no longer receive immunizations. P. Reply at 3-5.

As to the issue of onset, the undersigned accepts petitioner's assertion that Elizabeth's first infantile spasm occurred within one week of her August 1, 1997 DTaP vaccination because this is reflected in the notes of her treating pediatric neurologist Dr. Jacobson on September 25, 1997 and is consistent with the initial history given at the emergency department at Westchester County

Medical Center on September 5, 1997 that onset occurred within the past month. Respondent's view that the onset occurred some time before September 5, 1997 is not persuasive since this position ignores Dr. Jacobson's notation and the history given at the emergency department both of which are the earliest medical records of onset, and both of which are consistent with a one-week onset after the August 1, 1997 DTaP.

The NCES data, upon which Bellman and later Goodman relied in determining whether DPT was a trigger or caused a temporal shift in onset of infantile spasms, relied on a week by week analysis. The authors found more cases of cryptogenic infantile spasms occurring in the first week post-vaccination, than in the second, third, and fourth weeks. Bellman called the vaccine a "trigger" during the first week. Goodman termed this anomaly a "temporal shift." However, Dr. Guggenheim, using symptomatic (not cryptogenic) infantile spasms cases where the causes of the infantile spasms were post-natal, i.e., not tuberous sclerosis or Down syndrome but a near-drowning or stroke, wrote in an article and testified that the onset interval between vaccination and infantile spasms was weeks to months, purportedly proving that vaccines cannot cause infantile spasms because onset is too soon. The undersigned does not regard as persuasive Dr. Guggenheim's testimony based on the article in which she is lead author concerning the appropriate interval between vaccination and onset of infantile spasms because the article and her testimony involve only symptomatic infantile spasms which Elizabeth did not have. She had cryptogenic or idiopathic infantile spasms. Moreover, Dr. Guggenheim's testimony and article make conclusions that directly conflict with the Bellman and Goodman papers' analyses which relied on onset beginning within one week of vaccination. Based on Dr. Jacobson's medical record, and the emergency room record that precedes it, the undersigned holds that Elizabeth's

onset of infantile spasms was within one week of her receipt of DTaP on August 1, 1997, and that this onset interval is medically appropriate for a trigger effect or a temporal shift in producing infantile spasms.

Dr. Guggenheim and her article are persuasive on another point, however. The percentage of children with infantile spasms compared to symptomatic infantile spasms has declined to 10% due to the advances in medicine that have discovered various causes for the infantile spasms. This makes sense. At some point in the future, there will be no cryptogenic or idiopathic infantile spasms because science will have discovered all the causes. Medical science is not quite there yet.

The medical records confirm that Elizabeth was not normal even before she received her four-month vaccinations. According to Dr. Mary Zupanc, a treating pediatric neurologist at The Neurological Institute, Elizabeth had mild dysmorphic features, reflective of some congenital problem, and may have a neurometabolic disorder that has yet to be identified. Because of Elizabeth's seizure recurrence at six months, Dr. Zupanc said that Elizabeth might have dysfunction of her immune system.

Dr. Zupanc recognized that there was something abnormal about Elizabeth's brain from birth, i.e., before she received her August 1, 1997 DTaP. This reflection on the nature of Elizabeth's vulnerabilities leading to seizures is what occasioned the caution from Dr. Jacobson and other treaters that Elizabeth no longer be vaccinated and even that caution was not sufficient because, on October 20, 1997, when her doctor intentionally omitted giving Elizabeth pertussis and she received DT, she seized again when, until that point, her seizures had been brought under

control. Dr. Guggenheim recognized in her testimony that DT triggered Elizabeth's recurrent seizures.

Since modern science cannot explain in many cases why vaccinees suffer reactions to vaccines, circumstantial evidence is sufficient for petitioners to prevail. Althen; Capizzano. Petitioners do not need to show a specific biological mechanism in order to prevail. Knudsen. Dr. Guggenheim's criticism of Dr. Kinsbourne's opinion that DTaP may cause infantile spasms and did so in this case within an appropriate time interval is based on what she terms its failure to satisfy scientific standards of causation (i.e., no epidemiologic or animal studies). But this criticism is not apposite in this Program under Althen and Capizzano because the Federal Circuit specifically stated petitioners do not need to provide epidemiologic or animal studies in order to prove their cases.

Something was wrong with Elizabeth's brain before she received DTaP vaccination, but in a way that doctors have not categorized yet. It makes sense that a child who develops cryptogenic infantile spasms does not have a normal brain. Were this not so, then every child who receives DTaP or even DT vaccine would have infantile spasms after vaccination. Although something is wrong with the brain of a child with infantile spasms, in the minority of cases called cryptogenic, doctors do not know yet what that abnormality is.

What the undersigned finds most striking in this case is Dr. Guggenheim's testimony in which she accepted that Elizabeth had a recurrence of seizures four hours after DT vaccination because of the vaccine's effect on her as someone with epileptogenic potential, i.e., a lowered seizure threshold. To Dr. Guggenheim, the vaccine's effect was the same as if Elizabeth had had an intercurrent illness (which Dr. Guggenheim called "a natural occurrence of an immunization")

which could also cause someone with epileptogenic potential to have a recurrence of previously-controlled seizures. Dr. Guggenheim said this effect is well-known to pediatric neurologists. Anti-convulsants had successfully stopped Elizabeth's seizures before her DT vaccination, although, on EEG, her brain was still abnormal with background slowing. Then, four hours after the DT vaccination, when her seizures recurred, she was never able to have control of the seizures again, resulting in serious damage.

Dr. Guggenheim testified:

> THE WITNESS: The thought that she [Elizabeth] had the overt recurrence of infantile spasms–not of infantile spasms, but of what I think was a nonconvulsing seizure on the day that she had that DT immunization, just–it is not surprising.
>
> It is well known to all of us who have practiced child neurology and taken care of hundreds and thousands of kids with epilepsy that children who have this potential for seizures have a lower seizure threshold, have a more [epi]leptogenic potential, whatever term you want to use, that it is very common that when intercurrent illness occurs in those children with or without a fever that they have breakthrough seizures.
>
> And so with an intercurrent illness you have in a sense the natural occurrence of an immunization and affected with an outside virus, your body reacts to it. And Dr. Kinsbourne has already talked about some of those reactions, and it's very common that we see breakthrough seizures with an intercurrent event with or without fever, and that to me doesn't mean that there was something dramatically different.
>
> I mean, I do not attribute the significance that Dr. Kinsbourne does to that relapse of seizures on the day of the immunization. It happened to be an immunization rather than a recurring illness or nothing at all that we can identify. But that pattern of initial response to treatment, a period of time without overt seizures, and then a recurrence of seizures often of a different type with a very refractory treatment is a very common pattern in infantile spasms in general, including the cryptogenic group.
>
> THE COURT: So, Dr. Guggenheim, are you saying that it is your opinion that the vaccinations, particularly the acellular DPT on August 1, 1997, did not cause Elizabeth Haynes' onset

> of infantile spasms five days later, but that the vaccination[ ] ... [of] diphtheria/tetanus on October 20, 1997, acted just like an intercurrent illness to cause her resumption of seizures?
> THE WITNESS: That would be my position, and I, we know from the EEGs that her brain was still sick.
> THE COURT: That her brain was what?
> THE WITNESS: Was still sick. It was abnormal because of the background slowing.

Tr. at 143-44.

According to Bellman, Goodman, and Cherry, the vaccine causes a temporal shift (or as Bellman earlier termed it, acts as a trigger) so that a child who might eventually have had infantile spasms would get them earlier. Melchior noted causation in a few cases of infantile spasms. Dr. Guggenheim has given the rationale for how this happens: the vaccine acts just like an intercurrent illness in a child with epileptogenic potential because of a lowered seizure threshold. The vaccine is a trigger or creates a temporal shift in a vulnerable child, causing the illness together with whatever brain process it is that makes the child's brain abnormal.

Because anti-epileptic drugs did not stop Elizabeth's seizures after their recurrence post-DT vaccination, Elizabeth is now severely retarded. Unlike symptomatic infantile spasms where the medical literature ascribes the severity of outcome to the underlying illness, here the severity is due to uncontrolled seizures. In the literature petitioner and respondent provided, unless someone with cryptogenic infantile spasms not only had anti-seizure medication within one month of onset, but also had medication that successfully stopped the seizures, the outcome for the child would be unfavorable. The undersigned does not accept Dr. Guggenheim's testimony that early onset has no damaging effect because it contradicts the literature she herself provided as Ex. C, the article by D. Battaglia, et al., in which the authors analyzed 135 cases of children with

epilepsy, including infantile spasms. In the few cases of cryptogenic infantile spasms with a poor outcome, the outcome was associated with frequently recurrent seizures. Dr. Guggenheim's opinion is also contrary to the conclusion of a chapter she provided as Ex. I, the Frost and Hrachovy textbook on infantile spasms, in which the authors state that the earlier the onset of infantile spasms, the higher the probability of uncontrolled seizures.

The fact that Elizabeth's brain abnormality, although never identified, may have made it inevitable that, at some point, she would have started seizing does not vitiate petitioner's prevailing in this case. In Zatuchni v. Sec'y of HHS, 69 Fed. Cl. 612 (2006), Barbara Snyder's estate's representative appealed a denial of compensation for Ms. Snyder's prior allegation that the rubella component of MMR vaccine caused her fibromyalgia. The appeal was successful and her fibromyalgia was deemed a vaccine injury. 69 Fed. Cl. at 624. The case was remanded to determine if her death were caused by her vaccine injury. Her treating doctor testified that Ms. Snyder died from smoking-induced chronic obstructive pulmonary disease (COPD). 2006 WL 1499982 (Fed. Cl. Spec. Mstr. 2006), *adopted in part, vacated in part on other grounds*, 73 Fed. Cl. 451 (2006), *aff'd on other grounds*, 516 F.3d 1312 (Fed. Cir. 2008). Ms. Snyder would have died in any event from her primary illness COPD. But her fibromyalgia made it impossible for her to exercise for 13 years. Had she been able to exercise, her doctor said, she would not have died at the time she did from COPD, but later on. 2006 WL 1499982, at *4.

Without her having received DTaP at four months, Elizabeth would not have started having infantile spasms at that time. Without her receiving DT at six months, she would not have had the recurrence of seizures which turned out through the failure of multiple anti-convulsants to be intractable. Her condition is due to those early, intractable seizures as well as her underlying

brain condition. Elizabeth had an abnormal brain with a lowered seizure threshold and thus epileptogenic potential for whom the vaccine, functioning just like an intercurrent illness, prompted her seizures.

The undersigned holds, based on Dr. Guggenheim's testimony, that DPaT or DT vaccine can affect a brain that has epileptogenic potential because of a lowered seizure threshold (Althen prong one) and trigger seizures, and, based on Dr. Kinsbourne's testimony, did cause Elizabeth's onset of infantile spasms in this case (Althen prong two) within a medically appropriate time interval (within one week) to signify causation (Althen prong three), and that without having received DTaP, Elizabeth's current condition would not be as grievous as it is.

Petitioner has proven causation in fact.[4]

[4] Respondent may wonder whether the undersigned can base a decision partly on the testimony of respondent's expert. The answer is yes. In Sword v. Sec'y of HHS, No. 90-1491V, 1998 WL 957201 (Fed. Cl. Spec. Mstr. 1998), aff'd, 44 Fed. Cl. 183 (1999), the undersigned ruled in favor of petitioners in a case in which their daughter Natalie died four hours after receiving DPT vaccine. The undersigned held that a combined effect of DPT and the child's congenital cystic adenomatoid malformation (CCAM), a lung condition, was the most plausible explanation for Natalie's sudden death. Respondent's pathologist agreed that the child's immediate somnolence after vaccination was a reaction to the vaccination but said it was the CCAM that killed her. The undersigned ruled for petitioners based on their theory of a Table encephalopathy, but also on the theories of causation in fact (DPT caused the child to become drowsy and, because of her underlying condition, she could not recover from that drowsiness), and significant aggravation of the CCAM. The Honorable Lawrence M. Baskir affirmed the undersigned's merging of each side's testimony, stating: "The Special Master's explanation, and only her explanation, incorporates all the facts, including the medical facts offered by the doctors, surrounding Natalie's death. The Special Master's conclusion is more than simply supported by the evidence. It is the most intellectually satisfactory explanation of the entire factual record." 44 Fed. Cl. at 188. In the instant action, the undersigned has incorporated both Dr. Kinsbourne's and Dr. Guggenheim's testimony, together with the articles and textbook chapters they provided, to come to an explanation for what happened to Elizabeth in this case. As Dr. Guggenheim testified, it is not surprising to pediatric neurologists that a vaccine just like an intercurrent illness can start children with epileptogenic potential seizing. Elizabeth, having an abnormal brain in ways not yet understood, was vulnerable to seizing.

## CONCLUSION

Petitioner has prevailed in this case. The undersigned will schedule a telephonic status conference soon to discuss damages.

**IT IS SO ORDERED.**

February 7, 2011
DATE

s/Laura D. Millman
Laura D. Millman
Special Master