In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 03-1974V
January 31, 2011
To be Published

MINAH FOWLER, by her Mother and Next Friend, HOPE FOWLER,	*	
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 August 22, 2003 under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 *et seq.*, alleging that her daughter Minah Fowler (hereinafter, "Minah") had mercury toxicity seizures from thimerosal-containing vaccines (TCVs) that she

[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 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.

received on September 19, 2000 at the age of 19 months. Those vaccines were DTaP, HiB (haemophilus B influenza), and hepatitis B. The case was assigned to then-Chief Special Master Gary J. Golkiewicz.

On September 4, 2003, the case was reassigned to Special Master George L. Hastings.

On November 12, 2003, petitioner filed an amended petition with the same allegations.

On August 12, 2004, the case was reassigned to then-Special Master Margaret M. Sweeney.

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

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

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 Minah'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 July 20, 2000, Minah was born. Her mother is a registered nurse. Med. recs. at Ex. 3, p. 1. Minah has two older siblings, one five years older and the other two years older than Minah. *Id.*

In July 31, 2000, Minah was seen at Children's Community Care because she had been spitting up for two days. Med. recs, at Ex, 3, p. 3.

On August 2, 2000, Minah returned with her parents after hospitalization. She was on Reglan and Zantac for her feeding disorder. She continued to reflux but had improved. *Id.*

On August 7, 2000, Minah returned to her pediatrician Dr. Kiran Bhat. She was still on Zantac and Reglan. Dr. Bhat spoke with a gastroenterologist who recommended eliminating all dairy products from Minah's mother's diet. Dr. Bhat was considering testing Minah's stool and obtaining RAST tests for allergies. Med. recs. at Ex. 3, p. 4. Minah received her first hepatitis B vaccination. Med. recs. at Ex. 24, p. 1.

On August 10, 2000, Minah returned to Dr. Bhat for a check-up on her weight. Minah's mother was still breastfeeding. Minah was eating without difficulty now. Dr. Bhat's impression was gastroesophageal reflux (GER).[2] She was still on Reglan and Zantac. Med. recs. at Ex. 3, p. 5.

On August 16, 2000, Minah returned to Dr. Bhat for a check-up on her weight. She was doing well and Dr. Bhat increased her dose of Reglan and Zantac. Med. recs. at Ex. 3, p. 6.

On August 25, 2000, Minah's mother telephoned Dr. Bhat's office to get a Reglan prescription refill. *Id.*

On September 19, 2000, at the age of two months, Minah returned to Dr. Bhat with a rash on her face and chest. She could fix and follow, respond to sound, lift her head, vocalize and coo,

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[2] Gastroesophageal reflux is "reflux of the stomach and duodenal contents into the esophagus, which sometimes occurs normally, particularly in the distended stomach postprandially, or as a chronic pathological condition...." Dorland's Illustrated Medical Dictionary, 31st ed. (2007) at 1640. (Hereinafter, Dorland's.)

and had a social smile. Minah received DTaP, HiB, inactivated polio, and hepatitis B vaccines. Med. recs. at Ex. 3, p. 7.

On October 9, 2000, Minah returned to see Dr. Bhat. His note reads as follows:

> Recheck of weight. Patient is a 2 and 1/2 month old female who has history of GER, on Zantac and Reglan who presents for recheck. The child had a dystonic[3] reaction to Reglan two weeks prior to visit. The dose was decreased to 0.25 cc. She has been doing very well. The child has not vomited and has been eating well. Doing well. Will discontinue Reglan and will monitor. Mother will call if child begins to vomit again. Continue Zantac.

Med. recs. at Ex. 3, p. 8.

On October 17, 2000, Dr. Bhat's office received a telephone call from Minah's mother saying that Minah had been doing some odd posturing, hunching her back, and pulling her arms in. Minah's mother wanted to speak with Dr. Bhat and was concerned that Minah's postures were related to her medicines. Med. recs. at Ex. 3, p. 9. This is the first notation in the contemporaneous medical records of Minah's mother telephoning Dr. Bhat after the September 19th vaccinations..

On October 19, 2000, Minah's mother brought Minah to see Dr. Bhat, telling him that she thought Minah's belly hurt because Minah seemed to grunt and curl up. Minah seemed jittery. Med. recs. at Ex. 3, p. 9. Dr. Bhat notes that Minah presented with a two-day history of jerking movements, putting onset at October 17, 2000. Minah's mother told him Minah jerked three times a day, but did not vomit with these episodes. Whether or not Minah was feeding made no

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[3] Dystonia is "dyskinetic movements due to disordered tonicity of muscle." Dorland's, at 590.

difference to the occurrence of the episodes. Minah's mother also told Dr. Bhat that Minah was not smiling and not fixing and following anyone. He diagnosed infantile spasms. *Id.*

On October 19, 2000, Minah's mother brought Minah to Children's Hospital of Pittsburgh. The history of present illness (HPI) that Minah's mother gave to the outpatient clinic was that Minah had a four-day history of clustered spasms. Med. recs. at Ex. 8, p. 46. The spasms lasted about two to three seconds and usually occurred in clusters when Minah was nursing. Minah thrust her head and arms forward and made a small grunting noise. Minah's parents were also concerned that Minah had stopped smiling. This started about two to three weeks earlier. *Id.* Minah had a history of hiatal hernia, weight loss, and excessive vomiting. *Id.*

On October 19, 2000, Minah saw Dr. Ira Bergman, a pediatric neurologist, at Children's Hospital of Pittsburgh. Med. recs. at Ex. 5, p. 37. Minah's mother gave a history that, for the past four days, Minah had developed spells of flexion spasms recurring in clusters. Over the past week, Minah seemed less interested and less social. "However, overall she has never learned to fix and follow well and only has a little smile." Med. recs. at Ex. 5, p. 37. Her immunizations occurred one month previously. *Id.* The grandmother has a niece with seizures. Med. recs. at Ex. 5, p. 38. Dr. Bergman diagnosed Minah with developmental delay, tremor, questionable microcephaly, and probable infantile spasms. He admitted Minah to the hospital. *Id.*

A history of present illness taken on October 19, 2000 at 7:30 p.m. notes that Minah had a four-day history of spasms. Med. recs. at Ex. 8, p. 48. The mother, "an excellent historian," reported that the spasms, which she described as grunting, flexing of the abdomen and legs, and widening of the eyes, started four days previously while Minah was nursing. *Id.* Episodes were two to three seconds in nature, occurring 15 to 20 times. The amount of episodes varied during

the day and night. There were no eye rolling, loss of urine or bowel control, nausea, or vomiting. Minah's mother phoned her primary medical doctor on Tuesday and saw him on Thursday at Children's. Minah's mother denied Minah had fever and chills, change in appetite, diarrhea, or constipation. There was tremor. *Id.* Minah's mother noted a recent change in the quality of Minah's cry; it was louder and increased in pitch. *Id.* Minah had a history of hiatal hernia and jaundice. *Id.*

There is a second record reflecting an October 19, 2000 visit with Dr. Bergman detailing Minah's mother's history that Minah developed infantile spasms after her DPT vaccination. She saw Dr. Gabriel M. Ronen in Canada who started Minah on Vigabatrin from which she did not benefit. Med. recs. at Ex. 5, p. 17. This record was dictated on January 4, 2001. Med. recs. at Ex. 5, p. 18.

No record of a visit to Dr. Ronen prior to October 19, 2000 was ever filed. It is conceivable that the second record with a date of service of October 19, 2000 for Dr. Bergman at Ex. 5, p. 17 was actually a later record with the earlier visit transposed to the beginning of the later record or else dictated from the earlier record and affixed to the later record.

On October 20, 2000, Minah had a brain MRI which was normal. Med. recs. at Ex. 5, p. 24.

On August 23, 2003, at the Thumb Butte Clinic, Minah was diagnosed with seizures and symptomatic dystonia. Med. recs. at Ex. 14, p. 9.

On November 3, 2000, Minah's mother brought Minah to see Dr. Ronen, a pediatric neurologist at McMaster University, where Minah's mother gave a history that the onset of Minah's spasms was two to three weeks earlier, in other words, from early to mid-October 2000.

There were a few suggestions of potential problems from early on, including significant delay in Minah's ability to fixate which was best at two months just prior to her immunization, repeated episodes of throwing her head back, and poor head control. She had hiatal hernia with reflux and tracheomalacia.[4] Med. recs. at Ex. 7, p. 1. A second cousin had seizures early on. *Id.* Dr. Ronen told the family that "there was some suggestion that Minah had shown symptoms of abnormal development prior to the notorious immunization." Med. recs. at Ex. 7, p. 2.

On November 16, 2000, Minah returned to Dr. Bergman. Med. recs. at Ex. 9, p. 30. He noted that Minah presented on October 19, 2000 with a history of infantile spasms for four days. "Apparently, the spasms began after a DPT immunization." *Id.*

On January 11, 2001, Minah saw Dr. Inna Vaislieb, a pediatric neurologist, to whom Minah's mother recounted that the onset of Minah's infantile spasms was October 7, 2000. Med. recs. at Ex. 5, p. 21. On October 16, 2000, Minah developed her first cluster of five seizures and, shortly after, numerous seizures up to 35 daily in clusters usually upon awakening in the morning or after naps. Shortly thereafter, her parents noted regression of her development as Minah stopped smiling and cooing and her seizures became more intense with rolling up and fluttering of the eyelids and grunting noises. *Id.* Her diagnosis was idiopathic infantile spasms. *Id.*

On March 8, 2001, Dr. Vaislieb saw Minah again. Med. recs. at Ex. 5, p. 1. Minah's head circumference was just below two standard deviations on the growth chart. Med. recs. at Ex. 5, p.

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[4] Tracheomalacia is "softening of the tracheal cartilages, often as a congenital condition in infants ..., and usually accompanied by a barking cough and expiratory stridor or wheezing...." Dorland's, at 1971.

2. She had significant hypotonia[5] throughout and bilateral fisting. *Id.* Minah failed therapy with Vigabatrin,[6] ACTH,[7] Zonegran,[8] Topamax,[9] and vitamin B6. *Id.* Her PET scan was suggestive of possible structural abnormality in the left frontal lobe, but Minah's parents were not interested at that time in a pre-surgical evaluation. *Id.* They were also not interested in a ketogenic diet, but were willing to try therapy with Felbamate.[10] *Id.*

On December 6, 2001, Minah saw Dr. Stephanie F. Cave of Integrative Family Medicine. Med. recs. at Ex. 9, p. 26. The history Minah's mother gave was that, after she was born, Minah did not nurse well and threw up for the first two weeks. *Id.* She had a hiatal hernia and reflux, arched her head back, and was more jittery. She was on Zantac and Reglan. She received hepatitis B vaccine at two weeks. Her ears had a bad smell. On September 19, 2000, she received her two-month vaccines. She had a stiff neck reaction and her head turned to the right. Minah's mother gave her Benadryl. Minah lost her smile and stopped cooing. She grunted and had clustered tics. She was hospitalized with infantile spasms. Minah's mother stopped

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[5] Hypotonia is "a condition of diminished tone of the skeletal muscles, so that they have diminished resistance to passive stretching and are flaccid; this usually means the nerve supply is compromised." Dorland's, at 920.

[6] Vigabatrin is "an anticonvulsant used as an adjunct in the treatment of epilepsy refractory to conventional treatment and to control infantile spasms; administered orally." Dorland's, at 2084.

[7] ACTH is "adrenocorticotropic hormone...." Dorland's, at 22.

[8] Zonegran is "trademark for a preparation of zonisamide." Zonisamide is "a sulfonamide that acts as an anticonvulsant...." Dorland's, at 2122.

[9] Topamax is "trademark for a preparation of topiramate." Dorland's, at 1965. Topiramate is "a substituted monosaccharide used as an anticonvulsant ...." *Id.* at 1966.

[10] Felbamate is "an anticonvulsant used ... as an adjunct in the treatment of seizures associated with Lennox-Gastaut syndrome in children; administered orally." Dorland's, at 695.

vaccinating all her children after this. *Id.* Minah was moderately deaf with her eyes deviated to one side. The hospital wanted to remove 70% of Minah's brain for seizures. Minah's mother changed her diet to vegetables and fruit and Minah got better. Before the two-month vaccinations, Minah had normal milestones. Then she regressed. She saw a chiropractor for cranial and sacral therapy. *Id.* On April 1, 2002, Dr. Kiran Bhat, Minah's pediatrician, wrote a "To Whom It May Concern" letter addressed to Minah's mother stating:

> This letter is a letter describing an incident that occurred on September 19, 2000. On that day, Minah was in my office and had a routine 2 month well child check. Minah had a history of gastroesophageal reflux and was on Reglan and Zantac. She had received her shots on that day. Minah was doing well with the Reglan and Zantac and on the evening of the 19th, Minah began to have spasms. Minah's mother, Hope, called me that evening describing the spasms and with the child being on Reglan it was believed these were dystonic reactions. Therefore, I prescribed Benadryl over the phone for Minah. The spasms did not improve with the Reglan and currently Minah is diagnosed with infantile spasms.

Ex. 26.

On September 26, 2005, Minah saw Dr. Shyam Kishan, an orthopedist at Shriners Hospitals for Children. Med. recs. at Ex. 23, p. 1. Minah's parents gave a history that Minah suffered an adverse reaction to her vaccination at about a year or so of age, after which she developed a seizure disorder and a static encephalopathy. She was last seen by physicians about three years previously at Pittsburgh Children's Hospital which recommended ablative surgery for Minah's seizures. At that point, Minah's parents stopped going back to see her neurologist and she had not been on any medications or was seen by any specialist since then. *Id.* Minah was profoundly developmentally delayed although her parents said she did understand spoken language and could relax when instructed. On physical examination, Minah was small for her age

and appeared slightly malnourished. She had a scoliotic deformity of her spine. Her right femur was slightly longer than her left. She had hamstring spasms with popliteal angles about 90 degrees bilaterally. Dr. Kishan's diagnosis was total body involvement cerebral palsy with scoliosis, multiple joint contractures, and bilateral clubfoot deformities. *Id.* Dr. Kishan suggested serial casting for Minah's feet and possible Botox injection. Med. recs. at Ex. 23, pp. 1-2. He also suggested surgery for her hips and spine, recommended that the family get Minah's nutrition repleted, possibly with a G-tube, and that she see a neurologist for anti-seizure medications and possible use of Baclofen to decrease muscle tone. That in itself could help correct her scoliosis. Med. recs. at Ex. 23, p. 2.

Other Submitted Material

On November 1, 2003, Minah's mother signed an affidavit stating that after Minah's two-month vaccinations on September 19, 2000, she "had a muscle spasm reaction. She couldn't pick up her head." Ex. 15, p. 2. She phoned Dr. Bhat who returned her call at 10:00 p.m. and told Minah's mother to give Minah some Benadryl. *Id.* Over the next few days, she would see a jerking movement. Minah's parents also noted Minah having startling/crying out episodes while asleep. *Id.* Minah began to lose her smiles and cooing. On October 16, 2000, around 5:00 a.m., while nursing, Minah had crunch-like spasms five times in a row. She continued these spasms for the next two days. *Id.* A March 8, 2001 PET scan showed that Minah's spasms originated from the left frontal and right temporal regions of her brain. Ex. 15, p. 4.

On March 22, 2007, petitioner wrote a supplemental affidavit, stating Minah's behavior after her two-month vaccinations was not the same as her behavior from birth when she had GER. Ex. 28.

On July 30, 2007, petitioner filed Exhibits 29 and 30, consisting respectively of Dr. Marcel Kinsbourne's expert report and his CV, with medical literature to which Dr. Kinsbourne referred, marked as Exhibits 31-35. (On October 12, 2007, petitioner filed Exhibit 36, Dr. Kinsbourne's supplemental report. On April 11, 2008, petitioner filed Exhibit 37, the Kivity article. On May 16, 2008, petitioner filed Exhibit 38, Dr. Kinsbourne's second supplemental report, with Tabs A-L, consisting of the literature to which Dr. Kinsbourne referred.)

In Dr. Kinsbourne's first expert report, he describes Minah as having the onset of infantile spasms on the day of her receipt of vaccinations, including DTaP. Ex. 29, p. 2. He states that Minah 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 Minah, had no antecedent history of brain injury and were developing normally prior to the seizure onset.
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> 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. 29, 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. 31.

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. 32. 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 Td 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. These 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. 33. 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. 34. 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. 35. 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 9, 2007, as Exhibit 36. He addressed the undersigned's question of why he stated that Minah's onset of infantile spasms was September 19, 2000 in an Order dated September 17, 2007. Dr. Kinsbourne stated the basis of his conclusion was a telephone interview he had with Minah's mother on October 4, 2007. Minah's mother stated that, while she was giving Minah a bath, Minah suddenly turned her head sideways and maintained that position stiffly for three to five minutes. *Id.* at 1. On the next day or so, Minah's mother noticed Minah experiencing brief bodily jerks, sometimes occurring during sleep with a brief cry. On October 15, 2000, Minah had five crunching spasms in rapid succession. Those crunches continued. *Id.* Minah's pediatrician, Dr. Bhat, corroborated Minah's mother's account of a seizure the evening of the vaccinations. *Id.* at p. 2. Initially, Dr. Bhat thought Minah had a dystonic reaction to Reglan (metoclopramide), a

medication prescribed for gastroesophageal reflux, but jerking is not part of a dystonic reaction. Previously, Minah had never had a spasm from Reglan. *Id.* When Minah had classic spasms on October 19, 2000, they were occurring in clusters and no one would have marked "less salient preceding motor episodes." *Id.* Infantile spasms have been called "lightning spasms" because they are fleeting. *Id.* at 3. They occur subtly and are often mistaken for colic. *Id.* The typical developmental decline of infantile spasms was not noted until after Minah's vaccinations. *Id.*

Petitioner filed 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 studied the long-term cognitive outcome of children with cryptogenic infantile spasms treated within a month of onset compared to those treated after a month and found that those treated earlier had a more favorable outcome. *Id.* at 261.

Petitioner filed Dr. Kinsbourne's second supplemental report, dated May 9, 2008, as Exhibit 38 with attachments marked Tabs A through M. Dr. Kinsbourne states that although his opinion is that DTaP vaccine triggered Minah'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 Minah's brain. Therefore, she should have had a good outcome if her infantile spasms have an unknown cause, i.e., are cryptogenic. But Minah had a terrible outcome which Dr. Kinsbourne attributes to the effect of pertussis toxin from the DTaP on Minah's brain due to the inhibition of neuronal cells that would prevent hyperexcitability in her brain. *Id.* at 2-3. The damage of DTaP to Minah's brain would therefore change the category of her infantile spasms from cryptogenic to symptomatic, according to Dr. Kinsbourne. *Id.* at 3.

Tab A to Dr. Kinsbourne's report of May 9, 2008 (Ex. 38) 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.[11] 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.*

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

Tab B to Ex. 38 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 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. 38 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. 38 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. 38 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. 38 (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. 38 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. 38 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. 38 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. 38 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. 38 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. 38 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. 38 (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. 38 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 January 8, 2008. Attached to her report are Exhibits C to I which consist of medical literature. She states that Minah was diagnosed with cryptogenic infantile spasms, but unfortunately they did not respond to many anti-epileptic drugs. By the age of five years, Minah was severely neurologically and developmentally impaired. Ex. A, p. 2. Dr. Guggenheim disagrees with petitioner's expert Dr. Kinsbourne's opinion that Minah's DTaP vaccination on September 19, 2000 caused her infantile spasms whose onset was the same day. 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.*

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, in the Bellman study's terms 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 minimum scientific standards to establish a mechanism of injury for infantile spasms." *Id.* at 4. She concludes that Minah developed cryptogenic infantile spasms sometime between two and three months of age and that Dr. Kinsbourne's opinion that DTaP caused them is "not credible when examined in light of current scientifically based medical knowledge." *Id.*

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). 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 38.

Exhibit E attached to Dr. Guggenheim's report is 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 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 38, Tab B.) 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 ratios 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 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 them. *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 (Part I) attached to Dr. Guggenheim's report is part of a chapter from J.D. Frost and R.A. Hrachovy's textbook entitled Infantile Spasms. Diagnosis, Management and Prognosis

(2003), ch. 12, "Long-Term Outcome," pp. 203-06. 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.

Exhibit H (Part II) attached to Dr. Guggenheim's report is a continuation of chapter 12 from Frost and Hrachovy's textbook on infantile spasms, pp. 207-15. They 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.

Exhibit H (Part III) attached to Dr. Guggenheim's report is a continuation of chapter 12 from Frost and Hrachovy's textbook on infantile spasms, pp. 216-23. They 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.*

Exhibit I attached to Dr. Guggenheim's report are 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.

Exhibit J 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. 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.

TESTIMONY[12]

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 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.*

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[12] This case was simultaneously tried with a companion case, Haynes v. Sec'y of HHS, No. 00-358V, because of the identical issues, experts, and counsel. The child's name in Haynes is Elizabeth. Elizabeth received DTaP on August 1, 1997 and had infantile spasms five days later. Her seizures were controlled with treatment until she received DT on October 20, 1997 and, four hours later, resumed seizing.

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 Italia article shows that only one in 10 children with cryptogenic seizures or West syndrome had an IQ below 50 which is severe impairment. Both Minah and Elizabeth have 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 Minah's and 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 fie 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.

Prior to her two-month checkup, Minah was normal except for reflux. Tr. at 67. After her two-month vaccinations, Minah's mother reported a spasm occurring the evening of the vaccination. Tr. at 68. Although the medical records do not reflect that, on October 9, 2000, the

records do reflect a dystonic reaction two weeks earlier which can be reinterpreted as an infantile spasm. Tr. at 68-69. Two weeks earlier would place it on September 25, 2000, within the first week after vaccination. Tr. at 69. A dystonic reaction means abnormal posturing. *Id.* What Minah's mother was describing turned out later to be infantile spasms. *Id.*

Minah was diagnosed with infantile spasms on October 19, 2000. *Id.* The history was that Minah had four days of flexion spasms. Tr. at 70. It appears that the seizure pattern had become very clear now so that nobody could miss it. *Id.* "That's relevant because infantile spasms very often, if not typically, begin in a very subtle evanescent manner." *Id.* 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.* Minah's current condition is in the lowest category of mental functioning. Tr. at 72.

Dr. Kinsbourne's opinion is that DTaP triggered the onset of Minah's infantile spasms. Tr. at 73. Her long term outcome is extremely severe which is quite atypical for cryptogenic infantile spasms. *Id.* He thinks that severity is due to DTaP triggering the onset of the infantile spasms. *Id.* The onset of Minah's infantile spasms falls within the time frame of the Bellman article, perhaps six days. *Id.* The onset could have been the evening of the vaccination although that source comes only from Minah's mother. Tr. at 74. Whether the onset was the same day or five or six days, it falls within the Bellman article time frame. *Id.* There have been no other causes identified for Minah's infantile spasms. Tr. at 75.

Referring to the other child, Elizabeth Haynes, whose case the parties were discussing, 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 treating her 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 infantile spasms 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 infantile spasms 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 infantile spasms. *Id.* The treating physicians had 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 Minah or 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. Minah's onset was insidious which can generally occur with infantile spasms. Tr. at 125.

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.*

Minah's head circumference was at the lower range of normal until she was between four and 12 months of age when her brain growth stopped fairly abruptly and she became very microcephalic. Tr. at 133. Elizabeth started at the lowest percentile of head growth. At two months of age, she was at the 50th percentile. Over the next year, her head circumference jumped

to the top of the normal range, the 95th percentile, and the last measurement at three years of age was at the 80th percentile. She did not become microcephalic. Tr. at 134.

When Minah developed infantile spasms, her developmental regression was quite soon and quite severe. Tr. at 134. Elizabeth made pretty good developmental progress, even though she had a relapse of seizures. *Id.* 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. Since the course of these children's infantile spasms was different, perhaps the cause of them was different as well. Tr. at 136.

Both Minah and 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 that children with epilepsy have a potential for seizures because they have a lower seizure threshold, a more epileptogenic potential. 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 presenting vaccination as the primary cause. Tr. at 167.

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 the two cases under discussion here, neither girl had a viral disease, a fever, or exposure to endotoxin to explain any breach of their 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 petitioner'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 Minah were the same. Moreover, Minah's treating doctor, Dr. Shyam Kishan noted that Minah suffered an adverse reaction to a vaccination. P. Resp. at 4, n.5. The Federal Circuit in both Capizzano and Andreu emphasized the importance of treating doctors' opinions. Minah's

treating physicians recommended that she receive no further vaccinations, which the Federal Circuit in Andreu found significant in proving causation. 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 and Minah received acellular DPT and Enrique had focal seizures while Minah had infantile spasms. Respondent also dates the onset of Minah's spasms to 26 days after vaccination, not the same day as vaccination. R. Resp. at 2. 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. Unlike in Andreu, none of Minah's treating physicians testified in the case. R. Resp. at 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 Minah's treating doctors causally linked her infantile spasms to her DTaP by allusions in the medical records to Minah's onset being after her receipt of DTaP. P. Resp. at 2. Dr. Shyam Kishan writes she suffered an adverse reaction to her vaccination. P. Resp. at 4. The doctors recommended no further vaccinations. *Id.* Petitioner states "The respondent says pre-existing damaged brain, or a delay in treatment, may have contributed to Minah's present condition. Minah agrees." P. Resp. at 13-14. Petitioner states that the vaccine, Minah's pre-existing brain, and the delay in treatment are all substantial

factors in causing either Minah's infantile spasms or her current damaged condition. P. Resp. at 14.

Respondent states in her response regarding Moberly that Minah's doctors did not causally connect her DTaP with her infantile spasms. R. Resp. at 2. Rather, any record notation of causality is merely a recitation of provided history. *Id.* Dr. Shyam Kishan who notes causality saw Minah for an orthopedic examination five years after vaccination and after the filing of this petition. R. Resp. at 3. Any directive to avoid future immunizations came from the parents. *Id.* 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 Minah's physicians themselves directed that she no longer receive immunizations and that the records do not just reflect the parents' directives. P. Resp. at 10.

As to the issue of onset, the undersigned accepts petitioner's assertion that Minah's first infantile spasm occurred on the evening of her two-month vaccinations. Dr. Bhat, Minah's pediatrician, noted that Minah had an abnormal movement (dystonia) a couple of weeks before he saw her in October. In retrospect, according to his letter to Minah's mother, since he knew by mid-October that Minah had infantile spasms, he attributed Minah's dystonia not to a reaction to Reglan which she was taking to treat GER, but to infantile spasms.

Respondent views the onset of Minah's infantile spasms as occurring 26 days post-vaccination. The confusion is understandable for two reasons: (1) Minah's mother gave various onset dates that were weeks after vaccination; and (2) infantile spasms have a subtle or insidious onset and the beginning is easily not recognized. However, respondent also takes the position

through respondent's expert Dr. Guggenheim that DTaP could not possibly cause infantile spasms the same day as the vaccination because, as in incidents to infants like near drowning or stroke that cause symptomatic infantile spasms, the onset interval is weeks if not months after the incident. By taking the view that Minah's onset of infantile spasms occurred 26 days post-vaccination, respondent is essentially providing the third prong of Althen that this is a medically appropriate time interval to show causation. The undersigned does not regard as persuasive for the purposes of this case both Dr. Guggenheim's testimony and the article in which she is lead author on the issue of appropriate interval because Minah did not have symptomatic infantile spasms. She had cryptogenic or idiopathic 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. 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. Science is not there yet. The medical records confirm that Minah was never normal even before she received her two-month vaccinations. She had a very little smile and was not totally normal in development.

The NCES data show that over the 28 days after vaccination, there was an increase in onset of infantile spasms among vaccinees in the first week, with a correlative decrease in onset in the following three weeks post-vaccination compared to controls. Bellman, a co-author of the NCES, termed the vaccine a "trigger" because of this increased incidence in the first week after vaccination in his analysis of the data in an article published in 1983 after the NCES was published. To Goodman in 1988, together with Bellman, this increased incidence was a

"temporal shift. " Goodman also analyzed the same NCES data. Goodman cites Cherry who also analyzed the NCES data and came to the same conclusion about temporal shift. The vaccine precipitates earlier onset of infantile spasms than if the child had not received the vaccine. Melchior, who had his own data in Denmark, noted causation of infantile spasms from pertussis vaccination is very unlikely except in a few cases. That statement is impressive in an epidemiologic study.

Since contemporary science cannot explain in many cases why vaccinees suffer reactions to vaccine, circumstantial evidence is sufficient to prevail. Althen; Capizzano. Petitioners do not need to show specific biological mechanisms. Knudsen. Dr. Guggenheim's criticism of Dr. Kinsbourne's opinion that DTaP may cause infantile spasms based on its failure to satisfy scientific standards of causation (i.e., no epidemiologic or animal studies) is not apposite in this Program under Althen and Capizzano. .

The experts in this case went back and forth over the infantile spasms that Minah had. Although she was diagnosed with cryptogenic spasms, Dr. Kinsbourne opined that Minah actually had symptomatic infantile spasms, instead of cryptogenic, because DTaP caused her infantile spasms. This is not persuasive. As Dr. Guggenheim has written and testified, there is an increasingly small percentage of infantile spasms categorized as cryptogenic or idiopathic because as modern medicine advances, more diagnoses are made of the causes of infantile spasms. Eventually, no one will be diagnosed with cryptogenic infantile spasms. Were this not so, then every "normal" child who receives DTaP vaccine or even DT would have infantile spasms after vaccination. Something is clearly wrong with the brain of a child with infantile spasms but, in a minority of cases, doctors do not know yet what that abnormality is.

Something was wrong with Minah's brain before she received her DTaP vaccination, but it is not known how to categorize it. Dr. Ira Bergman noted on October 19, 2000 that Minah's mother, a registered nurse whom the undersigned assumes therefore is a reliable historian, stated that, in addition to Minah's recent history of spells, "overall she has never learned to fix and follow well and only has a little smile." Dr. Gabriel M. Ronen noted on November 3, 2000 that Minah's mother gave a history of potential problems early on, including significant delay in Minah's ability to fixate which was best just prior to her immunizations at two months, plus a history of repeated episodes of throwing her head back and poor head control. He told Minah's family that there was some suggestion that Minah had shown symptoms of abnormal development prior to her immunizations.

What the undersigned finds most striking in this case is Dr. Guggenheim's testimony in which she accepted that Elizabeth Haynes, whose case the undersigned tried simultaneously with Minah's, had a recurrence of seizures four hours after DT vaccination because of the vaccine's effect on her as a child with epileptogenic potential, i.e., a lowered seizure threshold. Elizabeth had previously had infantile spasms onset five days after receiving DTaP. Anti-convulsants had successfully stopped her seizures although, on EEG, her brain was still abnormal with background slowing. Dr. Guggenheim testified that she was not surprised that DT vaccine would start Elizabeth seizing all over again (and it is well known to child neurologists) because, just like an intercurrent illness, a vaccination has an effect on someone with an epileptogenic potential, i.e., vulnerability to seizing. That means, if someone is susceptible to seizing because her brain is abnormal, a vaccination or an intercurrent illness can cause seizures. 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 along with whatever brain process it is that makes the child abnormal.

Because anti-epileptic drugs did not stop Minah's seizures and she had no relevant medical therapy for years, Minah 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 Exhibit 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. Her opinion is also contrary to the conclusion of a portion of a chapter she provided as Exhibit H (Part III) of 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 Minah's brain abnormality, although never identified, may have made it inevitable that, at some point, she would have started seizing does not vitiate petitioners' 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 two months, Minah would not have started having infantile spasms at that time, 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. Just like Elizabeth Haynes, she 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, based on Dr. Kinsbourne's testimony, did cause Minah's onset of infantile spasms in this case (Althen prong two) within a medically appropriate time interval (within one day) to signify causation (Althen prong three), and that without having received DTaP, Minah's current condition would not be as grievous as it is.

Petitioners have proven causation in fact.[13]

CONCLUSION

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

IT IS SO ORDERED.

January 31, 2011
DATE

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

[13] 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 Minah 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. Minah, having an abnormal brain in ways not yet understood, was vulnerable to seizing.