In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 05-1133V
Filed: September 20, 2012
Re-Filed: October 4, 2012

WILLIAM TAYLOR, parent of J.T., a minor,	)	
	)	TO BE PUBLISHED
Petitioner,	)	
	)	Tetanus-diphtheria-acellular
v.	)	pertussis (DTaP) vaccine;
	)	epilepsy; neurological disorder;
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	West Syndrome; Infantile Spasms
	)	
Respondent.	)	

Ronald C. Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for Petitioner; Ryan D. Pyles, United States Dep't of Justice, Washington, D.C., for Respondent.

DECISION ON ENTITLEMENT [1]

LORD, Special Master.

I. INTRODUCTION AND SUMMARY

On October 19, 2005, Petitioner William Taylor ("Petitioner"), on behalf of his son, J.T., filed a Petition maintaining that J.T. suffered a neurological disorder as a result of receiving the Tetanus-diphtheria-acellular pertussis ("DTaP") vaccination on December 5, 2003. Petitioner sought compensation under the National Childhood Vaccine Injury Act of 1986 (the "Act"), 42 U.S.C. § 300aa-10 et seq. (2006).[2] The Secretary declined to compensate the claim.

[1] This Decision was originally filed on September 20, 2012. On September 25, 2012, this case was reassigned to Special Master Vowell. On October 4, 2012, petitioner requested redactions. Thereafter, Special Master Vowell granted in part and denied in part petitioner's request in an Order, filed on October 4, 2012. In this reissued version, the minor child's name is redacted to initials, the minor's birth date is omitted and this footnote is changed to reflect the redaction. The remainder of the Decision is unchanged.

[2] The National Vaccine Injury Compensation Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 et seq. (2006). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Vaccine Act.

J.T. was diagnosed with infantile spasms, also known as West Syndrome, a form of epilepsy. West Syndrome may prove refractory to treatment and lead to further neurological dysfunction, as in J.T.'s case.

Petitioner's expert, Dr. Griesemer, presented evidence gleaned from reports of scientific experiments, some using pertussis toxin, to study the impairment of signaling processes in the brain. Such impairment could lead to seizures, according to Dr. Griesemer. The evidence he presented, however, did not link the scientific experiments with possible vaccine causation or with the discrete epileptic syndrome from which J.T. suffers.[3] The gap between Dr. Griesemer's general presentation and possible vaccine injury in J.T.'s case was too wide to be breached solely by his opinion, without other reliable evidence. See Moberly ex rel. Moberly v. Sec'y of Dep't of Health & Human Servs., 592 F.3d 1315, 1325 (Fed. Cir. 2010) (special master, as fact finder in Vaccine Act cases, may make "credibility determinations regarding expert testimony"); see also Snyder ex rel. Snyder v. Sec'y of Dep't of Health & Human Servs., 88 Fed. Cl. 706, 742-43 (special master is not required to accept the ipse dixit of an expert) (citing Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)).

In addition, decades of epidemiological research into the issue presented in this case—whether pertussis vaccination causes West Syndrome—has not yielded reliable evidence of a causal link. The possibility exists that J.T. had some unique susceptibility that caused him to develop West Syndrome within hours of his vaccination, but there is no indication of such a unique condition in the record, and Dr. Griesemer identified none.

Petitioner has not shown by preponderant evidence a reliable theory of vaccine causation or a logical cause and effect between J.T.'s vaccination and his epilepsy. Accordingly, entitlement to compensation is denied. Althen v. Sec'y of Dep't of Health & Human Servs., 418 F.3d 1274 (Fed. Cir. 2005).

[3] One publication did link pertussis vaccine with "brain damage." That article was not peer-reviewed. See Pet'r's Ex. 26, J.H. Menkes et al., Workshop on Neurologic Complications of Pertussis and Pertussis Vaccination, 21 Neuropediatrics 171 (1990). See Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 573, 593-94 (1993) (noting peer review as an indication of reliability); Terran ex rel. Terran v. Sec'y of Dep't of Health & Human Servs., 195 F.3d 1302, 1316 (1999) (special master may apply Daubert).

II. PROCEDURAL HISTORY [4]

This matter originally was assigned to former Special Master John Edwards, who held an entitlement hearing on March 16, 2007, in which Dr. David A. Griesemer testified for Petitioner and Dr. Mary Anne Guggenheim testified for Respondent. More than a year after that hearing, on April 23, 2008, Petitioner filed a motion to stay the case because of the discovery of "new" medical information, viz., an article by Sara Kivity et al. Pet'r's Ex. 28, Sara Kivity et al., Long-term Cognitive Outcomes of a Cohort of Children with Cryptogenic Infantile Spasms Treated with High-dose Adrenocorticotropic Hormone, 45 (3) Epilepsia 255 (2004). Petitioners asked at that time that the matter be joined with two other cases, Fowler v. Sec'y of Dep't of Health & Human Servs., No. 03-1974V, 2011 WL 693746 (Fed. Cl. Spec. Mstr. Jan. 31, 2011), and Haynes v. Sec'y of Dep't of Health & Human Servs., No. 00-358V, 2011 WL 681066 (Fed. Cl. Spec. Mstr. Feb. 7 2011), which were then pending before Special Master Laura Millman. Following Special Master Edwards's departure, the case was reassigned to Special Master Millman. Petitioner again requested that the instant case be consolidated with Fowler and Haynes. Pet'r's Resp. to Ct's Order at 4, Oct. 28, 2008, ECF No. 71. On November 24, 2009, the motion was denied. Order Denying Mot. to Consolidate, ECF No. 79.

On June 22, 2009, the case was reassigned to my docket. On April 9, 2010, Petitioner filed a motion to reassign the case back to Special Master Millman. Petitioner argued that Special Master Millman had heard pertinent testimony regarding the Kivity article in Haynes and Fowler and that, if it were reassigned to Special Master Millman, there would be no need to conduct further hearings in this case. Pet'r's Mot. to Transfer at 7-10, ECF No. 80. On April 13, 2010, the motion to reassign was denied. Order Denying Mot. to Reassign, ECF No. 81. Petitioner was ordered to file an expert report to permit his expert to comment on the Kivity article. Respondent was ordered to file a responsive expert report within 30 days thereafter. Id.

On July 12, 2010, Petitioner filed a post-hearing brief and an expert report. On September 10, 2010, Respondent filed a post-hearing brief and supplemental expert report.

On February 25, 2011, I asked for additional information and testimony from the parties. Order, ECF No. 97. I discussed with the parties the need to conduct another hearing, in light of the newly presented evidence. Id. I ordered a status conference set for March 23, 2011, to discuss scheduling a hearing. Id. I asked Petitioner to file a status report and to file any updated medical records that had not yet been filed into the record by April 26, 2011. Id. Following the submission of additional medical records,

[4] Following the hearing in this case, which was the second hearing following re-assignment from a previous special master, the parties were ordered to file a "memorandum setting forth all undisputed facts and discussing in detail, with appropriate references to the record, the significant procedural history of the case." Order, Oct. 28, 2011, ECF No. 124. The discussion of the procedural history and the undisputed facts herein relies for some facts on the parties' Joint Post-Hearing Memorandum, filed January 26, 2012. Certain statements are taken verbatim from the parties' Joint Post-Hearing Memorandum.

supplemental expert reports, and additional medical literature, a second hearing on entitlement was held on October 25, 2011, in Washington, D.C.[5] Petitioner submitted a post-hearing brief on April 9, 2012. Respondent submitted a post-hearing brief on June 8, 2012. Petitioner submitted a response on June 25, 2012. The case now is ready for decision.

III. FACTUAL BACKGROUND

A. Undisputed Facts

J.T. was born in the spring of 2003, and appeared healthy for the first six months of his life. See Pet'r's Ex. 3 at 14; Pet'r's Exs. 4, 5, 15. On October 22, 2003, he received his initial DTaP, inactivated polio ("IPV"), hepatitis B ("hep B"), and haemophilus influenza type b ("Hib") vaccines. Pet'r's Ex. 11 at 2. No adverse reaction was noted to the first set of vaccinations. See Pet'r's Ex. 6 at 265 (Dr. Amaio).

On December 5, 2003, J.T. was seen for his six-month checkup. During the visit, he received DTaP, IPV, Hib, and hep B vaccines. Pet'r's Ex. 15 at 2. Later that day, he was taken to the Palomar Medical Center Emergency Room ("ER") with "a possible seizure episode." Pet'r's Ex. 7 at 3. It was noted that he had received vaccinations earlier in the day. Id.[6] He had a temperature of 100.1 degrees. Id. at 4. Before arriving at the ER, his mother "noticed that he appeared to be stiffening his body for seconds at a time. He appeared to be awake and alert, between episodes." Id. at 3. He had a normal chest x-ray, complete blood count, urinalysis and cultures. Id. at 6-10. J.T. was discharged with instructions to follow up with his pediatrician in 24 hours. Id. at 4.

On December 6, 2003, J.T. was taken to the emergency room at Children's Hospital, San Diego, with the chief complaint of seizures, "multiple times since yesterday at 4 pm." Pet'r's Ex. 6 at 258, 264-68. It was noted that J.T. "had 4 month vaccines yesterday." Id. at 258. J.T. continued to have seizures while at the hospital and was admitted for a full evaluation. Id. at 264-67. He had a "markedly abnormal electroencephalogram ["EEG"] due to a pattern of electrical activity consistent with hypsarrhythmia. Such findings may be associated with infantile spasm." Id. at 252. J.T. had a normal MRI and echocardiogram, and his other tests were negative. Id. at 220-21.

J.T. continued to experience seizures and was started on adrenocorticotropic hormone ("ACTH"). He was discharged on December 12, 2003, with decreased seizures. Pet'r's Ex. 6 at 138. On January 6, 2004, Dr. William J. Lewis, M.D., J.T.'s

[5] It is regrettable that, as a result of Special Master Edwards's departure, this case had to be heard twice. On the other hand, the passage of time permitted Petitioner the opportunity to supplement the record with additional evidence.

[6] J.T. received his four month vaccinations two months after they were due. Pet'r Ex. 6 at 264 (on December 5, 2003, J.T. "received his 4-month immunizations as he was 2 months behind").

treating neurologist, stated that J.T. had a diagnosis of infantile spasms ("IS") and had been seizure-free within one or two days after discharge. Id. at 294-95. A Vaccine Adverse Event Reporting System ("VAERS") report by Julia Woodshank, M.A., a staff member in the office of J.T.'s pediatrician, was completed on March 22, 2004. Pet'r's Ex. 12 at 1.

On April 20, 2004, J.T. had a physical therapy evaluation for his developmental and gross motor delays. Pet'r's Ex. 6 at 91.

A repeated EEG on December 3, 2004 was "abnormal due to . . . high amplitude, disorganized background with intermixed multifocal sharp waves, perhaps with more predominant epileptiform discharges at times . . . [F]indings would support a clinical diagnosis of seizures." Pet'r's Ex. 6 at 51.

J.T. had a Speech/Language Pathology Evaluation on April 6, 2005, which showed "a severe expressive language disorder secondary to seizure disorder and recently diagnosed hearing loss . . . ." Pet'r's Ex. 6 at 28-32.

On September 15, 2005, Dr. Lewis noted, "This boy has a past history of infantile spasms that initially responded to ACTH therapy, but several months after discontinuing the ACTH, began to have recurrent seizures." Pet'r's Ex. 15 at 111.

J.T. was hospitalized repeatedly in 2006 for seizures. His diagnosis was a complex partial seizure disorder. Pet'r's Ex. 29 at 22.

J.T. has been seizure free since February 2007, although he still has an abnormal EEG and a diagnosis of pervasive developmental delay. Pet'r's Ex. 30 at 53, 56. He continues to take medication, although his last EEG (in February 2010), was "less abnormal" than the previous results. Pet'r's Ex. 30 at 32. "He still has a lot of repetitive behaviors and he likes to open and close doors," as noted by Dr. Elizabeth A. Thiele, J.T.'s referring doctor. Id. at 31-32.

B. Petitioner's Case [7]

1. The Amended Petition

Petitioner alleged that J.T. was a healthy child until his December 5, 2003 vaccinations. Am. Pet. at 1. He was "fussy and uncomfortable" afterwards, slept for a short time and then started to cry "like he was in pain." Id. at 3. He started having seizures and was taken by his parents to the ER. Id. In his history, it was noted that he had received his six-month vaccinations earlier in the day "and was discharged from the clinic without complications." Id. The Petition states that "It was suspected that [J.T.]

[7] I discuss below the parties' allegations and contentions, as well as their supporting documentation, in some detail. I do so in part to provide the reader with context in which to evaluate and understand the parties' arguments and this decision. In part, I do so to document my review and consideration of the pertinent evidence and arguments.

had a seizure related to a low-grade fever, as a result of vaccinations he received earlier that day." Id. at 4.

The following day J.T. again had seizures. Am. Pet. at 4. He was taken to Children's Hospital and evaluated. It was noted that he had had vaccinations the day before. Id. at 4-5. The Emergency Room Evaluation record stated, "Concern was initially for either an atypical febrile seizure or an immunization reaction to the vaccines that he received yesterday as this began several hours [after] administration of his vaccines . . . ." Id. at 5-6.

J.T. was admitted to the hospital for observation and an EEG exam revealed a markedly abnormal pattern of brain waves "consistent with hypsarrhythmia." Am. Pet. at 6. The possible association with infantile spasms was noted. Id.

Dr. William Lewis, chief of the Neurology Clinic at Children's, diagnosed J.T. with West syndrome "within seconds" of reviewing J.T.'s EEG. Am. Pet. at 6. When questioned about the cause of J.T.'s condition, Dr. Lewis allegedly "explained the relationship between the 'old' pertussis vaccine and seizures and said it shouldn't be happening now with the newer acellular pertussis vaccine." Id. The Amended Petition also alleged that Dr. Lewis told J.T.'s parents "never to give J.T. another pertussis shot." Am. Pet. at 10 (quoting Pet'r's Ex. 17 at 4).[8]

J.T. continued to have clusters of seizures over the next week. Id. at 6-7. J.T.'s seizures did not respond to pyridoxine but decreased while he was on ACTH. He was discharged on medication. Id. at 7-8.

Dr. Lewis's records indicated the diagnosis of infantile spasms and the persistence of seizures, as well as slow development. Am. Pet. at 8. J.T. continued to have an abnormal EEG but "with much reduced epileptiform activity." Id. at 9. An attempt to wean J.T. from ACTH was unsuccessful. Id.

[8] Petitioner has not cited to any document supporting the assertion that Dr. Lewis made these statements. It may well be that Dr. Lewis made these comments, but he did not include them in his notes. To the contrary, Dr. Lewis's records reflected only the diagnosis of an "underlying epilepsy" and "infantile spasms." See Pet'r's Ex.6 at 4; Pet'r's Ex. 6 at 56 ("My impression remains one of an underlying epilepsy with a previous history of infantile spasms"); Pet'r's Ex. at 101; Pet'r's Ex. 6 at 252 ("This is a markedly abnormal EEG due to a pattern of electrical activity consistent with hypsarrhythmia. Such findings may be associated with infantile spasms."); Pet'r's Ex. 6 at 294. Under these circumstances, I follow the black letter law favoring acceptance of contemporary, documentary evidence over later oral testimony. See Curcuras v. Sec'y of Dep't of Health and Human Servs, 993 F.2d 1525, 1528 (Fed. Cir. 1993) ("Medical records . . . warrant consideration as trustworthy evidence."). I recognize that the Curcuras doctrine is not to be applied rigidly, especially when the controversy involves omissions from medical records, and I have given the matter careful consideration in light of all the pertinent circumstances. See Murphy v. Sec'y of Dep't of Health & Human Servs., No. 90-882V, 1991 WL 74931, at *6 (Cl. Ct. Spec. Mstr. Apr. 25, 1991), aff'd, 23 Cl. Ct. 726 (1991), aff'd 968 F.2d 1226 (Fed. Cir. 1992).

On March 23, 2004, a VAERS report was completed. Am. Pet. at 9. The report stated, "[p]atient received DTaP, IPV, Comvz and 6 hours after developed fever to 103° and seizures . . . EKG =infantile spasms." Id. at 9-10 (quoting Pet'r's Ex. 12 at 1).[9]

J.T. had many physical therapy evaluations and treatment for the physical effects of the ACTH and the seizures. Am. Pet. at 10.

In June 2004, J.T. had an episode of tongue smacking, difficulty breathing, and episodes of vomiting. Am. Pet. at 10. He was seen by Dr. Lewis, who suspected that this occurred after missing a dose of Phenobarbital, "due to a viral illness." Id. at 11.

On August 23, 2004, J.T. received his third DT vaccine, administered without pertussis. Am. Pet. at 11. His EEG results continued to be abnormal. Id. at 11-12.

J.T. also was evaluated and treated for delayed speech and language milestones. Id. at 12.

J.T. continued to suffer from poorly controlled seizures. Id. at 13. Various other medications were prescribed, but J.T.'s seizures continued. Id. at 13-14.

2. Petitioner's expert's reports

Petitioner submitted four expert reports:

February 2, 2006

In his first report, dated February 2, 2006, Dr. Griesemer reviewed the medical record. He noted that J.T.'s "mother elected to delay his Hep B vaccine and initial OPV/DPT, which he received without complication." Pet'r's Ex. 14 at 1. He described J.T.'s vaccinations on the morning of December 5, 2003, and his initial seizures, which began that same afternoon and continued the next day. Id.

Dr. Griesemer noted that an EEG performed on December 7, 2003, "confirmed the diagnosis of infantile spasms." Pet'r's Ex. 14 at 1-2. Dr. Griesemer explained that the "EEG diagnosis was 'hypsarrhythmia,' which is a pattern diagnostic of infantile spasms, or West syndrome." Id. at 2 n. 3. Alternative diagnoses of vitamin B6 deficiency or tuberous sclerosis were ruled out. Dr. Griesemer described J.T.'s course

[9] It has been noted often that the information submitted in VAERs reports is not reliable evidence of causation. Manville v. Sec'y of Dep't of Health & Human Servs., 63 Fed. Cl. 482, 494 (2004) (noting that a VAERS report "can be filed by anyone, thereby bringing into question the quantity and quality of the information gathered"); Ryman v. Sec'y of Dep't of Health & Human Servs., 65 Fed. Cl. 35, 40, 43 (2005) (noting that VAERS reports "can be filed by anyone," provide insufficient information to make an assessment, and they "show a bias toward prevailing concepts of adverse events"). Resp't's Ex. H, Michael Goodman et al., Vaccine Adverse Event Reporting System Reporting Source: A Possible Source of Bias in Longitudinal Studies, 117 Pediatrics 387 (2006).

of treatment and hospitalization. Id. at 2. Despite medication, J.T. was noted to have refractory seizures, five to 15 per day. Id.

According to Dr. Griesemer, a "minority of children with infantile spasms have continuing epilepsy and developmental problems." Pet'r's Ex. 14 at 2. "[J.T.] has developed a severe expressive language delay." Id. at 2-3.

Dr. Griesemer stated that J.T.'s clinical presentation was "somewhat unique in that he has also developed 'high tone' of his muscles, requiring regular Physical Therapy." Pet'r's Ex. 14 at 3. Dr. Griesemer opined that this is not typical of children with "idiopathic" infantile spasms, and suggested the likelihood that "mild spasticity, as well as the seizure disorder, was the consequence of the brain injury that occurred following vaccination." Id.

Dr. Griesemer stated that, "The development of infantile spasms in a child at 6 months of age is not diagnostically specific for a vaccine injury." Pet'r's Ex. 14 at 3. He pointed to several factors that in his opinion indicated vaccine injury in this case:

(1) "[N]o indication of gradual or insidious onset of infantile spasms, which is typically the case;"

(2) J.T.'s seizures "have proven refractory to control, which is not the case in most children with infantile spasms." According to Dr. Griesemer, the refractory nature of J.T.'s seizures "are not the result of an age-specific developmental abnormality but the result of an insult to the brain." Id.

(3) the presence of "mild spasticity or 'high tone;'" and

(4) the "temporal correlation" of vaccination with the onset of seizures. Id. at 3. J.T.'s spasticity offers "additional evidence . . . of brain dysfunction." Id. Dr. Griesemer stated that [i]Increased tone related to prenatal or birth-related injuries is clinically manifest by 4-5 months of age." Id.

October 26, 2006

In a supplemental report filed in response to Dr. Guggenheim's initial report, Dr. Griesemer alluded to a study conducted in the late 1970s in the U.K. by the National Childhood Encephalopathy Study concerning pertussis immunization (the "NCES"). Resp't's Ex. G, M.H Bellman et al., Infantile Spasms and Pertussis Immunisation, 8332 Lancet 1031 (1983). [10] The data in the NCES study on incidence of infantile spasms "peaking at approximately 6 months of age" suggested to Dr. Griesemer that there "may be a need to differentiate between infantile spasms occurring after 12 months of age. Pet'r's Ex. 19 at 1.

[10] Michael Goodman et al., revisited the NCES data in a 1998 report. See Resp't's Ex. N, Michael Goodman et al., Temporal relationship modeling: DTP or DT immunizations and infantile spasms, 16 Vaccine 225 (1998).

Dr. Griesemer noted an article cited by Dr. Guggenheim, in which the authors suggested that infantile spasms "may derive from an interruption" of the process of synaptic development. Pet'r's Ex. 19 at 2. He stated, however, that "[t]his mechanism may have on[ly] limited applicability to [J.T.] Taylor." Id.

Dr. Griesemer opined that J.T.'s "outcome more closely resembles" that of a child with symptomatic rather than cryptogenic infantile spasms. Pet'r's Ex. 19 at 2. Since up to 38 percent of children with cryptogenic infantile spasms "may display normal development," Dr. Griesemer hypothesized that J.T.'s poor outcome made his spasms more likely to be symptomatic, with the cause being "his response to vaccination." Id. Dr. Griesemer said Dr. Guggenheim's statement that "children with infantile spasms overall have a poor prognosis," exaggerated the unfavorable outcome in such cases by combining the data for children with both symptomatic and cryptogenic IS. Id.

Dr. Griesemer then reviewed the "legal elements" of his opinion, offering several comments in that respect. With regard to Prong 3 of the Althen test, Dr. Griesemer conceded that J.T.'s injury occurred too fast following vaccination to be caused by an immunologic response; instead, "the timing is consistent with a direct toxic effect of vaccine or vehicle." Pet'r's Ex. 19 at 2.

Although he did not dispute the diagnosis of infantile spasms, Dr. Griesemer stated that the "distress" J.T. experienced ("screaming in terror and crying") was not consistent with that disorder. Pet'r's Ex. 19 at 3.

Dr. Griesemer relied on the NCES, see supra, but he also stated that "it has limited applicability in [J.T.]'s case." Pet'r's Ex. 19 at 3. He distinguished J.T.'s "dramatic" response to vaccination from "an acceleration, or trigger, of an insidious process" as described in the Bellman article. Id.

In discussing the existence of a logical sequence of cause and effect, Dr. Griesemer again cited the NCES. "Symptoms occurred in tight proximity to the neurologic insult, well within the 7-day period adopted by epidemiologists in the Bellman study." Pet'r's Ex. 19 at 3.[11]

Dr. Griesemer reiterated that, "[t]here is an appropriate temporal relationship between the immunization and [J.T.]'s response." Pet'r's Ex. 19 at 3. He supported this conclusion with the observation that there was no history of IS before immunization and "no indication of normalized behavior or normalized function following immunization. The vaccination just prior to his 6-month birthday was a demarcating event." Id.

[11] As discussed below, if Dr. Griesemer was implying that infantile spasms occurring within seven days were caused by vaccination, that implication would not be consistent with the Bellman study. See Resp't's Ex. N at 230 (Goodman) (interpreting Bellman's findings as "bringing out a neurologic event that would have occurred anyway").

Finally, Dr. Griesemer noted that there was no "credible alternative cause, given [J.T].'s unremarkable medical history and evaluation." Pet'r's Ex. 19 at 3. Dr. Griesemer again attempted to distinguish J.T.'s case from that of a child with cryptogenic infantile spasms. "As noted above, his prognosis is somewhat inconsistent with *cryptogenic* cases of infantile spasms, and the timing of spasms onset is somewhat later than peak synaptogenesis at 3 months of age." Id.

June 24, 2010

In a supplemental report, Dr. Griesemer noted that the International League Against Epilepsy ("ILEA") had proposed a new classification system for infantile spasms, categorizing them as "genetic," "structural/metabolic," and "unknown." Pet'r's Ex. 31 at 1 n. 1. Dr. Griesemer then appeared to advert to the former classifications, stating that J.T.'s infantile spasms should be considered "symptomatic," because they have a known cause—vaccination. Id. at 4 n.5 (". . . [J.T.]'s clinical course was inconsistent with *cryptogenic* infantile spasms and should be considered *symptomatic* infantile spasms secondary to vaccine injury.").

Dr. Griesemer stated that a 2004 article by Kivity et al. provided additional support for his opinion. First, he stated that Dr. Guggenheim's criteria for determining causation were too strict. See Pet'r's Ex. 31 at 2.[12] He then analyzed the Kivity study, concluding that J.T.'s case was like that of the children whose cryptogenic infantile spasms were diagnosed and treated promptly, with excellent results. Id. J.T.'s EEG, in contrast, remained abnormal. Id. at 2-3.

Dr. Griesemer contrasted the cognitive outcome in the group studied by Kivity, which was normal, to J.T.'s condition, which "revealed severely impaired performance." Pet'r's Ex. 31 at 3. Dr. Griesemer noted a study from Iceland "in which the cases of cryptogenic infantile spasms were all seizure free and developmentally normal." Id. (citing Pètur Luovigsson et al., Epidemiologic features of infantile spasms in Iceland, 35 Epilepsia 802 (1994)).

Dr. Griesemer noted that outcomes "for subjects with cryptogenic infantile spasms in Kivity's late-treatment group were not as good." Pet'r's Ex. 31 at 3. According to the Kivity article, quoted by Dr. Griesemer, "'the major impact of early treatment may be to prevent irreversible cognitive decline.'" Id. Since J.T. was treated early but had a poorer outcome, Dr. Griesemer reasoned that his case should be considered symptomatic. Id. at 4. Based on the conclusion in the Kivity report that "'the long-term prognosis of cryptogenic infantile spasms is good to excellent in nearly all of the affected children with a prolonged treatment protocol . . . provided that the treatment is started within a month after the onset of spasms[,]'" Dr. Griesemer stated that it was

[12] Dr. Griesemer pointed to an alleged inconsistency in Dr. Guggenheim's reports. See Pet'r's Ex. 31 at 2 (200 causes of infantile spasms versus 17 causes of infantile spasms). It is clear from her report that Dr. Guggenheim distinguished between "putative" and actual causes of infantile spasms. Id. at 2. The allegation of inconsistency lacks merit.

implausible that J.T. had cryptogenic infantile spasms, "as suggested by Dr. Guggenheim." Id.[13]

July 28, 2011

In a supplemental report dated July 28, 2011, Dr. Griesemer noted that "there has been additional scientific evidence of the relationship between pertussis toxin and its role in disrupting the balance between excitatory and inhibitory neurotransmitters in the brain." Pet'r's Ex. 37 at 2. Dr. Griesemer explained the role of GABA as the "predominant inhibitory neurotransmitter in the brain." Id.[14] He stated that "$GABA_B$ receptors are linked to adenylyl cyclase through G proteins that are sensitive to pertussis toxin." Id. "The ability of pertussis toxin to bind to the $GABA_{B2}$ subunit . . . provides a mechanism for disturbing the balance between excitatory and inhibitory neurotransmission in the brain." Id. at 2-3.

Dr. Griesemer noted that the acellular pertussis vaccine "reduces or mitigates the available pertussis toxin, but the toxin remains central to producing the immunizing effect." Pet'r's Ex. 37 at 3.

3. Petitioner's expert's testimony

Dr. Griesemer is Chief of pediatric neurology at The Floating Hospital of Tufts University and director of the Child Neurology Fellowship Program. Tr. at 7.[15] He is board certified in neurology with special competence in child neurology. Tr. at 8. He has published articles in the area of epilepsy. Id.; see Pet'r's Ex. 13 (CV).

Dr. Griesemer described the course of J.T.'s neurological disorder. Tr. at 13. He testified that "the pertussis component of the DTaP was a contributor to" J.T.'s seizures. Tr. at 14. He described in detail the manner in which pertussis toxin is believed to interfere with normal neurological function so as to cause seizures. Tr. at 15-19. In sum, pertussis "[i]nterferes with transmission of inhibitory neuronal messages" resulting in "increased seizure activity." Tr. at 18. The mechanism by which this occurs is thought to be uncoupling of G proteins from GABA receptors. Id. "[I]n the presence of pertussis, the GABA B receptor cannot . . . perform the things that it needs to do, and as a result, the ongoing seizure activity that may be experienced is less uninhibited." Id. According to Dr. Griesemer, a period of four to six hours following vaccination with pertussis would be sufficient time "to cause this uncoupling effect of the neurotoxin." Tr. at 27.

[13] One of J.T.'s treating physicians, Dr. Boosara Ratanawongsa, noted his diagnosis on December 12, 2003, as "infantile spasms of idiopathic origin." The doctor stated, "Given that the patient has a normal developmental history and no history of birth trauma or anoxia, it was more likely that he had cryptogenic infantile spasms." Pet'r's Ex. 6 at 138.

[14] Gamma-Aminobutyric acid (GABA) is "the principal inhibitory neurotransmitter in the brain." Dorland's Illustrated Medical Dictionary 62 (32nd ed. 2012).

[15] All citations to "Tr." indicate the transcript of the hearing on October 25, 2011.

Dr. Griesemer testified that, in children with IS, "if brain cells are engaged in non-productive seizure activity, then they are not engaged in the kind of useful integration sensory experience that allows them to help the brain mature." Tr. at 21. This explains developmental delays following the onset of seizures. Tr. at 21-23, 29.

Dr. Griesemer alluded to "a variety of metabolic disorders, some of which may be inherited," that can lead to seizure activity. Tr. at 25.

Dr. Griesemer noted that J.T.'s treating physicians had ruled out known causes of IS. Tr. at 26.

In contrast to "specific infectious" processes that are known to lead to IS, which involve "just part of the brain," a neurotoxin like pertussis "would affect, in theory . . . all of the brain cells that will be exposed to this." Tr. at 28. According to Dr. Griesemer, that would account for the rapidity with which seizures could occur following exposure to pertussis. Id.

Dr. Griesemer summarized the reasons for his opinion that pertussis toxin caused J.T.'s IS and developmental problems, citing (1) pertussis toxin alters neuronal excitability by disrupting the GABA (B) G protein complex; (2) J.T.'s physicians looked for alternative causes of IS and found none; (3) sudden, "dramatic" onset of seizures instead of typically "insidious" onset of infantile spasms; (4) temporal proximity to vaccination; and (5) "slightly increased muscle tone that indicated some cerebral irritability that we don't often see with other types of infantile spasms." Tr. at 30-31.

On cross-examination, Dr. Griesemer reiterated that, according to the medical records, "there was a fairly clear 20 minute episode where recurrent two to three second spasms were occurring," which J.T.'s parents readily identified as seizures. Tr. at 34.

Dr. Griesemer testified that he did not know whether, using a "new system of classification" that he described on direct examination, J.T.'s infantile spasms would be classified as genetic, structural, metabolic or unknown. Tr. at 36-37.

Dr. Griesemer testified that it was possible for pertussis toxin to cross the blood brain barrier but that he saw no "clinical evidence" of a breach in the blood brain barrier in J.T.'s case. Tr. at 40-45. He agreed that the acellular pertussis vaccine J.T. received was designed "to reduce the amount of pertussis toxin that the brain is exposed to." Tr. at 43. Nevertheless, he stated, "we don't know with certainty that there is no endotoxin effect." Id.[16]

Dr. Griesemer agreed that the evidence supporting possible causation of IS by pertussis vaccination did not meet "a medical standard, as opposed to a clinical or legal standard." Tr. at 54. He stated that epidemiology cannot detect extremely rare cases of

[16] Endotoxin is "a heat-stable toxin associated with the outer membranes of certain gram-negative bacteria . . . ." Dorland's at 621.

vaccine injury causation. "That's why it's been necessary for me to rely on the basic science evidence that is moving our understanding forward." Tr. at 58.

On questioning by the Court, Dr. Griesemer explained that he would consider vaccination a "substantial cause" of an injury whether it was the sole cause or "a trigger" for an underlying brain disorder. Tr. at 71 ("I would be inclined to consider the trigger a substantial contribution.") He agreed, however, that before attributing causation to a vaccination in the case of an individual with a latent abnormality, he would need to know more about the individual and the condition. Tr. at 72-73.

Although he had testified on direct examination that certain clinical features in J.T.'s case indicated vaccine injury, Dr. Griesemer also stated that he could discern nothing about J.T.'s case in particular that explained why the pertussis vaccination caused infantile spasms. Tr. at 77-78.

Dr. Griesemer testified that J.T.'s subsequent diagnosis of Lennox-Gastaut syndrome (another epileptic disorder) also was caused by his vaccination, as well as his autism spectrum disorder. Tr. at 84-85. He added, "We don't know whether the neurodevelopmental problems are the direct cause of poorly controlled seizures or whether they're a direct cause of improper neuronal function as a direct result of pertussis toxin." Tr. at 85.

Dr. Griesemer laid great emphasis on the fact that pertussis is a known neurotoxin "that has in the past caused enough problems that there have been intense efforts to reformulate it so it's less toxic." Tr. at 87. "Whether [the clinical scenario that occurred in J.T.'s case] is through triggering an adverse event and somebody's predisposed or there is a sole cause, I don't know." Tr. at 88.

Dr. Griesemer agreed that there was a "remote" possibility that the temporal relationship between the vaccination and the onset of J.T.'s seizures could be coincidental. Tr. at 88-89.

He stated that he could identify no "specific literature that links the vaccine or the vaccine product with the GABA B receptor dysfunction." Tr. at 95.

4. Petitioner's medical literature

Petitioner's Exhibit 20 described a 1988 study of children with IS. Daniel Glaze et al., Prospective study of outcome of infants with infantile spasms treated during controlled studies of ACTH and prednisone, 112 J. Pediatr. 389 (1988). The authors followed 64 infants, concluding that their overall prognosis for long-term outcome was poor. Pet'r's Ex. 20 at 389. Eight of the 64 infants had cryptogenic as opposed to symptomatic IS. Id. at 391. In that group of eight patients, three [or 38%] "had a normal outcome or only mild impairment. In contrast, of the 56 patients in the symptomatic group, three (5%) had a normal outcome or only mild impairment." Id. at 391, 392. The

study also found that "early treatment did not ensure a normal outcome or response to therapy, even in the cryptogenic group." Id. at 393.

Petitioner's Exhibit 21 described West syndrome in detail. John Pellock et al., Pediatric Epilepsy: Diagnosis and Therapy, 177- 91 (2d ed. 2000). The text discussed the features of the disorder and noted that "[t]he diagnosis of infantile spasms is often delayed for weeks or months because parents, and even physicians, do not recognize the motor phenomena as seizures." Pet'r's Ex. 21 at 178-79.

Pellock also described the classification of patients "as cryptogenic if there is no abnormality on neurologic examination, no known associated etiological factor, normal development before onset of the spasms, and normal CT and MRI scans before institution of therapy." Pet'r's Ex. 21 at 179. He noted that "[c]lassifying a patient as cryptogenic or symptomatic is crucial when considering long-term outcome." Id. Pellock stated that the pathophysiological mechanism underlying infantile spasms is not known, and described several hypotheses. Id. at 182-83. Pellock noted that statistical studies have indicated that "the apparent association between DPT immunization and infantile spasms is coincidental and that no causal relationship exists." Id. at 180.

Pellock reported that children with cryptogenic spasms have a "significantly better outcome . . .; 38 percent . . . were normal or only mildly impaired, in contrast to 5 percent of the symptomatic patients." Pet'r's Ex. 21 at 185. The authors noted, "We were unable to predict which cryptogenic patients would have normal outcomes and which would not." Id. The authors reported that "[a]pproximately one-third to one-half of cases of infantile spasms reportedly develop the Lennox-Gastaut syndrome." Id. at 187.

Petitioner's Exhibit 22 concerned an article on "epileptic spasms" in older children. Dinesh Talwar et al., Epileptic Spasms in Older Children: Persistence Beyond Infancy, 36 Epilepsia 151 (1995).

Petitioner's Exhibit 26 was a "Special article" resulting from a workshop on neurologic complications of pertussis and pertussis vaccination. J.H. Menkes et al., Workshop on Neurologic Complications of Pertussis and Pertussis Vaccination, 21 Neuropediatrics 171 (1990). The report "was 'clearly not a peer-reviewed article.'" Moberly v. Sec'y of Dep't of Health & Human Servs., 85 Fed. Cl. 571, 586 n.15 (2009) (quoting Borin v. Sec'y of Dep't of Health & Human Servs., No. 99–491V, 2003 WL 21439673, at *11 (Fed. Cl. Spec. Mstr. May 29, 2003)), aff'd, 592 F.3d 1315 (Fed. Cir. 2010). The report stated that a "consensus" of the workshop participants concluded, among other things, that "there was no inherent difficulty in assigning cause and effect to the [DPT] vaccine and subsequent permanent neurologic residua." Pet'r's Ex. 26 at 171. The article suggested a "mechanism for vaccine-induced brain damage." Id. "Pertussis toxin has been shown to alter cellular signaling," the authors stated. "It also affects the catecholaminergic and GABAergic systems in the brain." Id. The article explained that "[a]lthough normally a protein of the size of PT [pertussis toxin] would not

be able to cross the blood-brain barrier . . . a direct, endotoxin-mediated attack on the endothelial cells could create a local defect of the blood-brain barrier." Id.

The report discussed the whole cell pertussis vaccine, identifying it as causative of a variety of "neurological vaccine injuries." Id. at 172-73.[17] The article reported that the "only retrospective case-control study . . . reported that the relative risk of a previously normal infant of the onset of an illness leading to permanent encephalopathy was 4.2 times greater during the first 72 hours following DPT vaccination than in controls." Id. at 173. The article stated that "before two years of age the immature brain cannot react to an autoimmune challenge." Id. at 174. For this reason, according to the authors, examination of infants succumbing to pertussis vaccination cannot be expected to confirm the proposed pathogenetic mechanisms in post-pertussis vaccine encephalopathy. See id.

Petitioner's Exhibit 27 concerned "G Protein Diseases." Zvi Farfel et al., The Expanding Spectrum of G Protein Diseases, 340 New England Journal of Medicine 1012 (1999). The article discussed mutations in the "trimeric guanine nucleotide-binding proteins (G proteins), which . . . cause many diseases." Pet'r's Ex. 27 at 1012. According to the authors, mutations in G proteins, "a ubiquitous family of signaling molecules," can cause, among many other diseases, cholera, night blindness, pertussis, acromegaly, and essential hypertension. Id. at 1013-19. The article described the effect of *Bordetella pertussis,* the organism that causes whooping cough. Id. at 1018. The molecular reaction caused by Bordetella toxin "reduces responsiveness to receptor activation," the authors stated. They observed that "[k]nowledge of the molecular mechanism of the toxin has not yet led to understanding of the cellular pathogenesis of pertussis." Id.

Petitioner's Exhibit 28 reported on a study of children with cryptogenic infantile spasms treated with ACTH. Sara Kivity et al., Long-term Cognitive Outcomes of a Cohort of Children with Cryptogenic Infantile Spasms Treated with High-dose Adrenocorticotropic Hormone, 45 Epilepsia 255 (2004). The study found that 22 infants treated with high-dose ACTH within one month of onset of infantile spasms had a normal cognitive outcome. Those treated later showed normal development in only 40 percent of the cases. The study concluded that early treatment of cryptogenic infantile spasms is associated with favorable long-term cognitive outcomes. "Once major developmental regression lasts for a month or more, the prognosis for normal cognitive outcome is poor," the study noted. Pet'r's Ex. 28 at 255.

The study noted that due to modern neuroimaging, "the proportion of symptomatic" cases of West syndrome has increased to 60-90%. Id. Since the outcome for those in the symptomatic group is predictably poor, the authors "assessed the long-term cognitive outcome in infants with cryptogenic infantile spasms." Id.

[17] In contrast to the whole cell pertussis vaccine discussed in Petitioner's Exhibit 26, the evidence here showed that there was little or no endotoxin in the acellular vaccine received by J.T. Tr. at 168 (Dr. Guggenheim); Tr. at 43 (Dr. Griesemer).

The authors discussed an educational program to help physicians and public health nurses identify infantile spasms. "The mild initial clinical symptoms were stressed . . . which are not always identified by parents as abnormal." Id. at 256. "Parents were closely questioned about the time of onset of spasms to determine the delay in diagnosis and treatment. Patients treated within 1 month of onset of the spasms were categorized as the early treatment group . . . ." Id. The delay in starting treatment for the late-treatment group "was due to lack of recognition of the significance of the movement by the parent . . . failure to diagnose these on the part of the general physicians . . . and misdiagnosis by pediatricians and emergency room physicians." Id. at 257. The study stressed the importance of early treatment in cases of infantile spasms. Id. at 260. "Even with the delayed treatment group, however, outcome was more a function of whether significant regression had already taken place than of delay per se." Id. at 260-61.

Petitioner's Exhibit 31, Tab A, was a "Special Report." Anne Berg et al., Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009, 51(4) Epilepsia 676 (2009). The authors re-classified epilepsies based on "mechanisms" rather than causes. Pet'r's Ex. 31, Tab A at 679. The authors proposed substituting for the terms idiopathic, symptomatic, and cryptogenic the terms genetic, structural, metabolic, and unknown cause. Id. at 690. The authors classified West Syndrome as an "electroclinical syndrome" occurring in infancy. Id. at 682. An "electroclinical syndrome" is a clinical entity that is "reliably identified by a cluster of electroclinical characteristics." Id. at 680.

Petitioner's Exhibit 31, Tab B, reported on a study in Iceland of 13 children with infantile spasms. Pètur Luovigsson et al., Epidemiologic Features of Infantile Spasms in Iceland, 35 Epilepsia 802 (1994). This study, which preceded and was cited by the authors of the Kivity article, see Pet'r's Ex. 28 at 255, found that all six of the children with cryptogenic infantile spasms studied were subsequently "seizure-free and have developed normally intellectually." Pet'r's Ex. 31, Tab B at 802, 805. The authors noted that "The proportion of cases with a favorable outcome was greater than reported in most clinical series." Id. at 802.

Petitioner's Exhibit 37, Tab A, described a scientific experiment. Tomiko Asano, Prevention of the agonist binding to $GABA_B$ receptors by guanine nucleotides and islet-activating protein, pertussis toxin, in bovine cerebral cortex, 260 J. Biol. Chem. 12653 (1985). The islet-activating protein (IAP), pertussis toxin, was used to demonstrate that "the affinity of $GABA_B$ receptor binding decreased upon ADP-ribosylation of the membrane protein by IAP and that the decrease was reversed by the addition of the GTP-binding proteins which were IAP substrates." Pet'r's Ex. 37, Tab A at 12658.[18]

[18] The particular significance of many of the articles described herein was not explained by Dr. Griesemer.

Petitioner's Exhibit 37, Tab B, described another scientific experiment. Ying Chen et al., Differential Modulation by the $GABA_B$ Receptor Allosteric Potentiator 2, 6-Di-tert-butyl-4-(3-hydroxy-2,2-dimethylpropyl)-phenol (CGP7930) of Synaptic Transmission in the Rat Hippocampal CA1 Area, 317 J. Pharmacol. Exp. Ther. 1170 (2006). Using a drug called baclofen, which is prescribed as a muscle relaxant, among other uses, scientists detected modulations of GABA, an inhibitory neurotransmitter in the central nervous system.[19] They examined slices of tissue obtained from the hippocampi of rats sacrificed at 25-30 days of age whose brains were removed and preserved. Id. at 1171. The experiment was intended to elucidate the "underlying molecular mechanisms enabling the $GABA_B$ allosteric modulators to dissociate from [] $GABA_B$ agonistic side effects." Id. at 1170.

The article recited the fact that it is well known that GABA plays a role in synaptic transmission. Id. at 1171, 1175. The article also noted that "Differences between presynaptic auto- and heteroreceptors in the CA3 area of the hippocampus included the finding that $GABA_B$ receptor-mediated synaptic inhibition was more sensitive to baclofen (Lei and McBain, 2003), and to pertussis toxin and barium treatments (Thompson and Gahwiler,1991)." Id. at 1175. Another portion of this article stated, "Several intracellular mechanisms have also been shown to influence the $GABA_B$ function, which include receptor G-protein coupling, type of G-proteins, G-protein effecter coupling, and subunit phosphorylation states (Couve et al., 2002; Bettler et al., 2004)." Id. at 1176. Further with respect to the intracellular mechanisms, the article noted that "the existence of any subtypes of $GABA_B$ is still uncertain." Id.

In the final paragraph, the authors stated:

> Our work has thus revealed a novel pattern of allosteric modulation on native $GABA_B$RS in their modulation of synaptic transmission. The differential potential of $GABA_B$R-mediated functions by CGP7930 provides a synaptic mechanism by which the $GABA_B$ potentiators may exert their in vivo efficacies without [] untoward side effects [providing] an exciting new and better therapeutic alternative to $GABA_B$R agonists.

Id.

Petitioner's Exhibit 37, Tab C, contained a discussion of the potential therapeutic value of developing drugs targeting $GABA_B$ receptor function. S.J. Enna et al., $GABA_B$ receptor alternations as indicators of physiological and pharmacological function, 68 Biochem. Pharmacol. 1541 (2004). The article noted that "[c]linical and preclinical data suggest a wide range of therapeutic possibilities for drugs that influence $GABA_B$

[19] Baclofen, a GABA analog, is used as a "muscle relaxant/antispastic agent." Physicians' Desk Reference, http://www.pdr.net/drugpages/concisemonograph.aspx?concise=1641 (last visited Sept. 20, 2012). The drug's mechanism of action is "not fully known," but it is "capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect." Id. The drug is used in the "[t]reatment of spasticity associated with multiple sclerosis," and "[m]ay be effective in spinal cord injuries and other spinal cord diseases." Id.

receptor function." Pet'r's Ex. 37, Tab C at 1541. The article noted the variety of functions that are modulated by $GABA_B$ receptors, including convulsant and anti-convulsant properties. Id. at 1542. In a discussion of alterations in $GABA_B$ receptors induced by drugs, including antidepressants, the article noted, "These findings indicate that the $GABA_B$ site is subject to homologous receptor up- and down-regulation, which may be responsible for tolerance." Id. at 1543. The article also noted that, "Alterations in $GABA_B$ receptor binding and subunit expression are associated with a variety of neurological and psychiatric disorders." Id. at 1545. The article concluded, "Likewise, a change in $GABA_B$ receptor binding, function or expression in disease tissue could represent an adaptive response important for maintaining homeostasis, or could contribute to symptomatology, making it difficult to conclude whether it would be best to facilitate or inhibit this modification." Id. at 1546.[20]

Petitioner's Exhibit 37, Tab D, concerned neonatal seizures.[21] Joseph Glykys, Differences in Cortical versus Subcortical GABAergic Signaling: A Candidate Mechanism of Electroclinical Uncoupling of Neonatal Seizures, 63 Neuron 657 (2009). This is another extremely technical article with no focus on vaccination or infantile spasms. The study noted differences at the molecular level in epileptiform activity in the neocortex versus the thalamus, and concluded that "maturation determines neuronal responses to GABA" and neuronal function. Id. at 664-66. GABA receptors are inhibitory in some contexts and excitatory in others. Id. at 667. The authors suggested that "selective inhibition of subcortical structure could suppress convulsive activity" and therefore help in the treatment of seizures in neonates. Id. at 667-68.

Petitioner's Exhibit 37, Tab E, is a comprehensive article on $GABA_B$ receptors. D. I. B. Kerr et al., $GABA_B$ Receptors, 67 Pharmaco. Ther. 187 (1995). The abstract explained that $GABA_B$ receptors "are a distinct subclass of receptors for the major inhibitory transmitter 4-aminobutanoic acid (GABA) that mediate depression of synaptic transmission and contribute to the inhibition controlling neuronal excitability." Pet'r's Ex. 37, Tab E at 187. The article stated that $GABA_B$ receptors are sensitive to pertussis toxin, citing the Asano article described above. Id. at 207. The article noted research indicating that "[t]he selective failure to block presynaptic inhibition of excitatory, but not inhibitory, transmission with PTX [pertussis toxin] strongly suggests that different G-proteins are involved." Id. at 212. The article, which covered a vast array of data concerning GABA receptors, noted that they are found not only in the brain, but in the

[20] This citation, like many of those included in Petitioner's medical literature, was highlighted by Petitioner before hearing, in accordance with my standard Pre-Hearing order. I have reviewed these highlighted citations carefully, and in many instances they support Dr. Griesemer's theory of vaccine causation only superficially, if at all. Indeed, the literature indicates the enormous complexity of $GABA_B$ receptor activity and the difficulty in attempting to draw facile conclusions about its effects. See Pet'r's Ex. 37, Tab C, at 1546 ("Thus, it is usually not possible to determine from receptor binding, expression, or even functional data, whether a drug- or disease-induced alteration in a neurotransmitter system is responsible for a beneficial or an adverse effect."); see also Tr. at 109-12 (Dr. Guggenheim).

[21] J.T. was not a neonate when his disorder began, and infantile spasms typically do not occur in neonates. Tr. at 49, 177; see also Pet'r's Ex. 31,Tab A at 683, Table 3 (showing distinct classification for neonatal seizures as opposed to seizures occurring in infancy).

gut, id. at 218-19, the sympathetic ganglia of the autonomic nervous system, and in non-neural tissues, id. at 220. The article discussed the "clinical advances associated with $GABA_B$ receptors as targets for pharmacological intervention." Id.

In a discussion of epilepsy, the authors noted the varying results of baclofen in experimental and clinical studies. Id. at 221. "[T]he multiple effect of baclofen can result in excitation at certain concentrations and inhibition at other concentrations." Id. The study noted "recent findings [that] suggest that absence seizures arise as a consequence of an overactivity of $GABA_B$ receptors." Id. at 222. The authors noted as well the "substantial evidence for a role of GABAergic transmission within the thalamus in the genesis and control of absence seizures." Id. They noted the possibility that $GABA_B$ (n) antagonists may have therapeutic potential in petit mal epilepsy. See id.

It is difficult in a summary fashion to communicate all the bodily functions affected by GABA receptors that were discussed in the Kerr article; suffice it to say that these included cognition, nociception, alcohol actions, affective disorders, feeding and satiety, blood pressure control, respiration, gastric function, and micturition. See id. at 222-26.[22]

Petitioner's Exhibit 37, Tab F, described research conducted on patients with limbic encephalitis. Eric Lancaster et al., Antibodies to the $GABA_B$ receptor in limbic encephalitis with seizures: case series and characterization of the antigen, 9 Lancet Neurol. 67 (2010). This article discussed symptoms of seizures and memory dysfunction in adults with this rare disorder, "suspected to be paraneoplastic or immune mediated." Pet'r's Ex. 37, Tab F at 67. The types of seizures noted were complex partial seizures, status epilepticus, and subclinical seizures. Id. at 73. Evidence of brain damage in these patients was visible on MRI studies. Id. at 71. The article included a discussion of GABA receptors and their activity in the brain and spinal cord. Id. at 74.

Petitioner's Exhibit 37, Tab G, described additional research on GABA receptors. Yuji Odagaki et al., Identification of G_α subtype(s) involved in fix-aminobutyric acidfix receptor-mediated high-affinity guanosine triphosphatase activity in rat cerebral cortical membranes, 297 Neurosci. Letter 137 (2001). The portion of the article highlighted by Petitioner described the authors' attempt "to identify the G_α subtype(s) involved in the $GABA_B$ receptor-mediated signaling in rat cerebral cortical membranes [at] a pivotal site implicated in receptor/G protein functional interaction. . . ." Id. at 139. The authors concluded that "$GABA_B$ receptor-induced high-affinity GTPase activity in rat cerebral cortical membranes is mainly mediated by the AS/7-sensitive G proteins . . . ." Id. at 140.

[22] The scope of the Kerr article indicated that Dr. Griesemer may have oversimplified the scientific evidence. Using his theory, pertussis vaccination could cause depression, obesity, high blood pressure, respiratory ailments and urinary incontinence, among other disorders.

Petitioner's Exhibit 37, Tab H, is another technical article concerning GABA receptors. Claire Padgett et al., $GABA_B$ Receptor Coupling to G-proteins and Ion Channels, 58 Adv. Pharmacol. 123 (2010). The article described the complex role of GABA as "the major inhibitory neurotransmitter in the brain. . . ." Pet'r's Ex. 37, Tab H at 124. One GABA receptor is "a G-protein coupled receptor (GPCR) that associates with a subset of pertussis toxin sensitive G-proteins (Gi/o family).[23] Activation of the receptor . . . in turn, regulate[s] specific ion channels and trigger[s] other secondary messenger cascades that affect neuronal excitability." Id. The diagram below, taken from this article, provides an inkling of the complexity of the material studied by these authors.

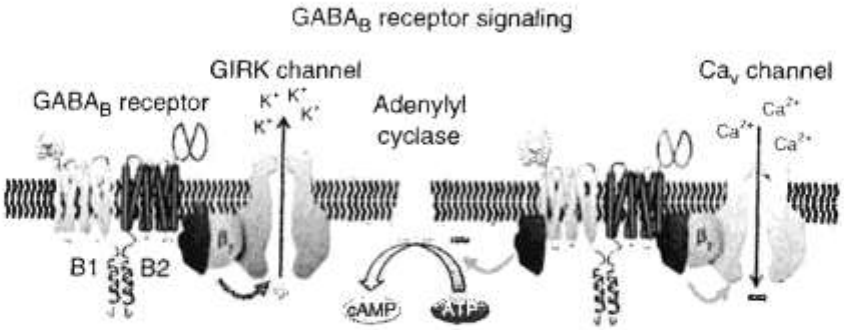

FIGURE 2 The primary $GABA_B$ receptor effectors. Activation of the G-protein coupled $GABA_B$ receptor stimulates GTP-dependent G-protein (Gi/o) dissociation of the Gα and Gβγ dimer. The Gαi/o subunit has been shown to inhibit adenylyl cyclase while the Gβγ dimer is capable of modulating voltage-gated Ca^{2+} (Ca_V) or G protein-gated inwardly rectifying K^+ (GIRK) channels, resulting in potent neuronal inhibition. Effector specificity may be regulated by heterocomplex formation, guided by targeting protein partners and subcellular localization.

The article discussed a wide array of cellular functions mediated by GABA receptors, including the activity of potassium channels, enzymes, G-Proteins, and macromolecular signaling heterocomplexes. Id. at 134. Petitioner did not highlight any portion of this article as being particularly applicable to his case. The diagram above seemed, however, to illustrate at least one aspect of the theory presented by Dr. Griesemer at hearing.

Petitioner's Exhibit 37, Tab I, discussed experiments on GABA-deficient mice. Haydn Prosser et al., Epileptogenesis and enhanced prepulse inhibition in $GABA_B$-deficient mice, 17 Mol. Cell Neurosci. 1059 (2001). In the introduction, the article stated

[23] For context, this appears to be the only mention of pertussis toxin in the entire article.

that "$GABA_B$ receptors are members of the G protein couple receptor (GPCR) superfamily whose modulation is thought to be involved in a number of physiological and disease processes, including nociception, cognitive impairment, epilepsy, spasticity, and also in the aetiology of drug addiction." Id. at 1059. The article noted further that, "$GABA_B$ receptor activation inhibits adenylate cyclase activity and causes prolonged synaptic inhibition through restriction of presynaptic calcium channel activity and activation of postsynaptic potassium channels." Id. The article described the molecular effects in a mouse lacking a subunit of $GABA_B$. Id. at 1060. Among the effects noted were spontaneous generalized seizures that were ultimately fatal. Id. at 1060-61.[24] Petitioner highlighted the observation that $GABA_B$ receptor activity provides "an overall inhibitory tone necessary for normal physiological processing in the postnatal developing brain." Id. at 1066.

Petitioner's Exhibit 37, Tab J, is a "Perspective" on the components of the DTaP vaccine. John B. Robbins et al., The Diphtheria and Pertussis Components of Diphtheria-Tetanus Toxoids—Pertussis Vaccine Should be Genetically Inactivated Mutant Toxins, 191 J. Inf. Diseases 81 (2005). The article noted that "Replacement of cellular with acellular pertussis (aP) vaccine has considerably reduced the systemic reactions observed with diphtheria-tetanus toxoids—pertussis vaccine but has not eliminated the extensive swelling . . . observed after the fifth injection" of the vaccine. Pet'r's Ex. 37, Tab J at 81. The article provided a detailed history of pertussis and pertussis vaccination. Id. at 82-84. The authors stated that "[t]he substitution of DTP vaccine with DTaP vaccine has brought attention to an adverse reaction that is considered to be minor," specifically, swelling after the fifth dose. Id. at 85. The authors suggested that genetic modification of the vaccine could reduce these minor reactions and encourage greater usage of the vaccines by adults, enhancing immunity in the general population. Id.

Petitioner's Exhibit 37, Tab K, is another study of GABA deficient knockout mice. Valerie Schuler et al., Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic $GABA_B$ responses in mice lacking $GABA_{B(1)}$, 31 Neuron 47 (2001). The article stated that "$GABA_B$ receptors . . . activate second messenger systems and modulate potassium and calcium channel activity, thereby controlling presynaptic transmitter release and postsynaptic silencing of excitatory neurotransmission." Pet'r's Ex. 37, Tab K at 47. The article noted that "the $GABA_{B(2)}$ subunit appears important for surface trafficking and G protein coupling." Id. The article noted a multiplicity of effects on the experimental subjects, including seizures. Id. at 48-55. "The lack of presynaptic and postsynaptic $GABA_B$ receptors [] in null mutant mice leads to a loss of control over both excitatory and inhibitory neurotransmission." Id. at 55.

[24] The mice "exhibited spontaneous generalized seizures that could also be provoked by presentation of mild stressors, such as cage movement or gentle handling. Irrespective of the precipitating factor, each seizure generally lasted tens of seconds and was typified by wild running, subsequent forelimb and hind limbclonus and tonus followed by a period of postictal behavioral depression; a pattern of seizure activity most closely resembling human grand mal epilepsy." Pet'r's Ex. 37, Tab I at 1061.

Petitioner's Exhibit 37, Tab L, discussed the role of $GABA_B$ receptors. Andrea Straessle et al., Rapid and long-term alterations of hippocampal $GABA_B$ receptors in a mouse model of temporal lobe epilepsy, 18 Eur. J. Neurosci. 2213 (2008). This article reported on an experiment in which adult mice received injections of kainic acid (KA) into the brain. The result, among other molecular changes, was loss of GABA receptors. "The rapid KA-induced loss of $GABA_B$ receptors might contribute to epileptogenesis because of a reduction in both presynaptic control of transmitter release and postsynaptic inhibition," the authors stated. Pet'r's Ex. 37, Tab L at 2213. The article described the disorder known as temporal lobe epilepsy (TLE). Id. The cause was unknown but the disorder was associated with underlying tissue changes. Id. The article stated that $GABA_B$ receptors "play an important role in the control of neuronal excitability in the CNS." Id.

C. Respondent's Case

1. Respondent's expert's reports

Dr. Guggenheim submitted three reports over the course of this litigation.

March 19, 2006

In her initial report, Dr. Guggenheim described J.T.'s medical history and the onset of his infantile spasms. Resp't's Ex. A at 1. She noted that J.T.'s "neurologic examination was normal" following his initial seizures "and he was alert and responsive without any evidence of an acute encephalopathy." Id. His diagnosis was cryptogenic infantile spasms." Id.

Dr. Guggenheim discussed J.T.'s subsequent treatment and progress, and his mild developmental delays. Resp't's Ex. A at 2. Dr. Guggenheim explained the term cryptogenic infantile spasms and stated that "most pediatric neurologists world-wide" accept that "there is some underlying brain disorder that results in this seizure syndrome in all cases." Id.

Dr. Guggenheim disagreed with the arguments set forth by Dr. Griesemer in support of his conclusion that vaccination caused J.T.'s infantile spasms. With regard to the persistence of J.T.'s seizures, Dr. Guggenheim quoted an article stating that, "The majority of patients with infantile spasms have a poor prognosis with intractable epilepsy, severe developmental delays and/or significant cognitive impairments." Resp't's Ex. A at 3. Dr. Guggenheim opined that hypotonia is not "atypical" in cases of infantile spasms. Id. She added that "neither infantile spasms nor seizures in general are recognized in the vaccine table to be a consequence of immunization with the pertussis antigen," and that "[a]s early as 1983, medical literature concluded that there was no causative relationship between childhood immunization and infantile spasms." Id.

August 25, 2006

Dr. Guggenheim submitted a supplemental report on August 25, 2006, in which she described infantile spasms at some length. Resp't's Ex. I at 1. She discussed the research that has focused on the syndrome, and the "definitive textbook" by Frost and Hrachovy. Id. at 2. She stated that the causes of IS are not known. She noted that more than 200 putative causes of IS have been described, but only 17 have been identified by scientific measures as causally related to West Syndrome. Id.

Dr. Guggenheim explained that concern about childhood immunizations has led to careful study of vaccination as a possible cause of IS. She noted the NCES, which found "no difference in the incidence of prior exposure to a DPT or DT immunization" in children who developed IS compared to a control population. She explained that the "temporal shift" reported in the NCES study did not indicate a causal relationship.

Dr. Guggenheim explained the difference between symptomatic and cryptogenic IS. "[I]f all diagnostic tests and clinical findings in an infant presenting with infantile spasms are normal and the child has been developing in a normal fashion prior to the onset of the seizures, then the diagnosis of cryptogenic infantile spasms is made." Resp't's Ex. I at 3. In the last half-century, as medicine has progressed, fewer cases have been deemed cryptogenic. Dr. Guggenheim stated her belief that in the future "the cryptogenic category of IS will further diminish, and, likely, disappear." Id.

Dr. Guggenheim opined that onset of infantile spasms would not occur within days of an external event such as vaccination. Resp't's Ex. I at 4. This conclusion was based on her clinical practice as well as indirect data. She subsequently published a study in a peer-reviewed journal (with Drs. Frost and Hrachovy)[25] reporting that IS has a latency period of six weeks to 11 months between the causative event and the onset of seizures. See id.; see also Resp't's Ex. C.

August 12, 2010

Dr. Guggenheim responded to the Court's order to both parties to comment on an article published in 2004 by Sara Kivity et al. Order, Apr. 13, 2010, ECF No. 81. In the article, the authors identified 37 infants diagnosed with IS and treated between 1974 and 1993. Resp't's Ex. O at 1. The article reported that children whose treatment with ACTH began four weeks or less after onset of spasms had "an excellent outcome relative to both development and persistent epilepsy," while those treated more than four weeks after onset did not fare as well. Id.

Dr. Guggenheim construed Dr. Griesemer's argument, based on the Kivity article: children with IS who are treated promptly with ACTH do well. J.T. was treated promptly with ACTH and did not do well. Therefore, J.T.'s poor outcome was not

[25] Drs. Frost and Hrachovy are acknowledged leaders in the medical community regarding infantile spasms. See Tr. at 60 (Dr. Griesemer).

caused by IS, but by vaccination, which occurred in a temporally proximate relationship and is the only other "credible" cause for his disorder. Resp't's Ex. O at 1.

In response, Dr. Guggenheim pointed to articles by other experts showing that infants with cryptogenic infantile spasms who were treated "early" had a poor outcome. Resp't's Ex. O at 2. "These authors emphasize that it is the underlying cause, not just a classification of cryptogenic or early treatment that appears to determine outcome," she explained. Id.

She disputed the argument based on "temporal proximity," stating that the onset of IS "following a post-natal brain injury" does not occur within days of the injury. Resp't's Ex. O at 3.

Dr. Guggenheim also commented on the fact that "a serious epileptic encephalopathy can occur in a previously normal infant and the treating physicians conclude that the cause of this serious brain disorder is unknown." Resp't's Ex. O at 3. She referred to a study by Coppola in which three sets of identical twins, all previously developmentally normal, with no evidence of brain abnormalities, suffered the onset of IS on the same day, "within each twin pair." Id. From this evidence, Dr. Guggenheim concluded that "there must be a common underlying genetically determined abnormality that caused this epileptic disorder even though at the present time none of our diagnostic tools can identify it." Id. at 4.

2. Respondent's expert's testimony

Dr. Guggenheim is an expert in child neurology. She practiced for many years and is currently retired, but she maintains her certification in pediatrics as well as psychiatry and neurology, with special competence in child neurology. Tr. at 98-101; see Resp't's Ex. B.

Dr. Guggenheim testified that Dr. Giesemer's hypothesis of a toxic effect on GABA receptors causing infantile spasms was "too big a jump for me." Tr. at 106, 151-52 ("There are experimental models and human events, clinical events in which there seems to be a very short time between a change in the brain and a convulsive response. To jump from that to the very unique disorder of infantile spasms is a very big jump.").

In addition, Dr. Guggenheim questioned whether GABA receptors invariably exert anti-convulsive effects. Tr. at 109. She characterized this as "a sweeping generalization." Id. Extensive examination and cross-examination ensued on this point. See Tr. at 109-113, 119, 130-135, 138-140.

Dr. Guggenheim also questioned whether the animal studies relied upon by Dr. Griesemer actually supported his hypothesis. Tr. at 114-15. She noted that the mice in one study were adults and were not noted to have experienced seizures. Tr. at 137-38.

Dr. Guggenheim questioned whether "a small amount of toxin given int[ra]muscularly crosses the blood brain barrier, when [the toxin], does nothing else to the child." Tr. at 116. She stated that there was no evidence that the blood brain barrier was breached in J.T.'s case or in other instances of vaccination. Tr. at 121, 125. "When I look at what we know about how children react to immunizations, we don't find evidence of disturbance of the blood brain barrier . . . ." Tr. at 154. She conceded on cross-examination that ACTH is effective at decreasing infantile spasms although it does not appear to cross the blood brain barrier. Tr. at 156, 172.

Dr. Guggenheim stated that abnormal muscle tone, noted in J.T.'s case, was not significant in terms of understanding the cause of his infantile spasms. Tr. at 122. In addition, she stated that the first indications of infantile spasms are so subtle that they might not be recognized as seizures. Tr. at 124. "[W]hen we use the word 'insidious' in a case like this, all it means to me is the first time that it was recognized that this was this rare disorder of infantile spasms, is the first time it's presented to somebody who understands what they are." Id.

Dr. Guggenheim identified several conditions for which there was "scientific validation" of an association with infantile spasms, "like apoxic ischemic encephalopathy, tuberous sclerosis, things like that. And then there are . . . rare conditions . . . that . . . cause perturbations of the brain, overt brain injury or significant changes . . . mitochondrial diseases, all kinds of inherited diseases of metabolism." Tr. at 164-65. She confirmed that no such cause was found in J.T.'s case. Tr. at 165.

Dr. Guggenheim described "three boxes" – "the disease pertussis . . . the immunization using whole-cell pertussis . . . and then there's . . . acellular in the disease pertussis . . . ." Tr. at 167-68. She testified that in the acellular pertussis vaccine "there's virtually no endotoxin." Tr. at 168. She testified that "there is still a small amount of pertussis toxin in the acellular vaccine." Tr. at 169 (recognizing that she was beyond her area of expertise).

She distinguished between an epileptic encephalopathy and an acute encephalopathy. Tr. at 170. An epileptic encephalopathy is "seizures in which there's concomitant loss of development." Id. An acute encephalopathy means "there's an acute injury of some kind to the brain and . . . the child's brain function diminishes." Id. "But it's acute," "meaning at the time that the injury has occurred." Id.

Dr. Guggenheim stated that there were no treating physician opinions in J.T.'s record identifying the cause of his infantile spasms as vaccination. Tr. at 173-74. "Although the recognition of temporal proximity is often there, I never saw any conclusion of causation." Id.

Dr. Guggenheim testified that West Syndrome does not develop overnight. Tr. at 175. She also stated that IS, unlike other types of seizures, "does not generally occur in the context of fever." Tr. at 176. Dr. Guggenheim agreed that J.T. had a fever following

his vaccination, but "we don't have any indication that fever brings on or exacerbates infantile spasms." Tr. at 176-77.

Dr. Guggenheim testified that the time frame for the commencement of infantile spasms is mostly between two to twelve months of age, "with the peak being right around six months." Tr. at 177. She noted that children with IS develop "diffuse epileptic encephalopathies" "and that's what sometimes gets called Lennox-Gastaut syndrome," as in J.T.'s case. Tr. at 178.

Dr. Guggenheim could not say whether J.T.'s seizure within hours of his vaccination was the first one related to his IS. Tr. at 179. She indicated that symptoms of IS can be subtle and in some cases go unnoticed for a period of time "before you really recognize if the kid isn't continuing to develop or has lost some development." Tr. at 179-80.

Dr. Guggenheim stated that she knows of no data that convinces her that vaccination is a factor in causing infantile spasms, whether symptomatic or cryptogenic. Tr. at 181. She testified that over the first two or three days following his initial seizure J.T. was treated only with pyroxidine, which did not alleviate his seizures. Tr. at 182. She stated that J.T.'s clinical progression was a common course for children with IS. Tr. at 183-84.

3. Respondent's medical literature

Respondent's Exhibit C described West Syndrome in detail. Richard Hrachovy et al., Infantile Epileptic Encephalopathy with Hypsarrhythmia (Infantile Spasms/West Syndrome), 20 J. Clin. Neurophysiol. 408 (2003). The article stated, "Infantile spasms is a unique disorder that affects individuals during infancy and early childhood." Resp't's Ex. C at 408. The article noted the "interictal EEG pattern, hypsarrhythmia, which is usually associated with infantile spasms" and the typical age of onset within the first year of life. Id. at 409-10. The article described the classifications of patients with IS and stated that, "Patients in the cryptogenic category have the best prognosis for seizure control and favorable developmental outcome." Id. at 418. The study noted that there are various treatment modalities but that "there is no conclusive evidence that such treatment affects the developmental/mental outcome of these patients." Id. at 420. The study reviewed long-term outcome for patients with IS. Id. at 421-22.

Respondent's Exhibit D discussed epilepsy in a set of patients with mitochondrial disorders. L.G. Sadleir et al., Spasms in children with definite and probable mitochondrial disease, 11 Eur. J. Neurology 103 (2004). The study discussed a methodology for identifying children with epilepsy who also have mitochondrial disease. Resp't's Ex. D at 103-04.

Respondent's Exhibit E is an "Expert Opinion" reviewing infantile spasms. Mary L. Zupanc, Infantile spasms, 4 Expert Opin. Pharmacother. 2039 (2003). The author stated that, "[t]he mechanism of infantile spasms is unknown," but research suggests

that seizures "once induced, can produce permanent changes in the brain." Id. at 2040. The article stated that immature brains are more subject to seizures than mature brains, and noted that the "provconvulsant isoform of GABA-A receptor is more prominent" in the immature rat brain. Id.

Respondent's Exhibit F is an article on X-linked myoclonic epilepsy. I.E. Scheffer et al., X-linked myoclonic epilepsy with spasticityand intellectual disability, 50 Neurol. 348 (2002).

Respondent's Exhibit H discussed a possible source of bias in studies of the Vaccine Adverse Event Reporting System ("VAERS"). Michael Goodman et al., Vaccine Adverse Event Reporting System Reporting Source: A Possible Source of Bias in Longitudinal Studies, 117 Pediatrics 387 (2006).

Respondent's Exhibit J discussed the role of hypsarrhythmia in infantile spasms. E.L. Gibbs et al., Diagnosis and Prognosis Of Hypsarrhythmia and Infantile Spasms, 33 Pediatric 66 (1954). According to the authors, the electroencephalographic pattern referred to as hypsarrhythmia "is a strikingly abnormal pattern" that appeared in all 237 cases of infantile spasms reported in the article. Id. at 66.

Respondent's Exhibit K is a chapter from a book by Frost and Hrachovy on infantile spasms. James Frost et al., Infantile Spasms Diagnosis, Management and Prognosis, 129-33 (2003). The authors noted findings from the NCES that detected a "slight excess of infantile spasms cases during the 7 days after vaccination." Id. at 132. The authors noted "the possibility that vaccination may have triggered an earlier onset of spasms who were beginning to develop the disorder, or (as seems more likely) that spasms were detected earlier by heightened vigilance of parents following the immunization procedure." Id.

Respondent's Exhibit L is an excerpt from the IOM discussing the concept of causality.

Respondent's Exhibit M is another article by Frost and Hrachovy on infantile spasms. James Frost et al., Pathogenesis of Infantile Spasms: A Model Based on Developmental Desynchronization, 22 J. Clin. Neurophysiol. 25 (2005). This article explored the possible causes of the disorder.

Respondent's Exhibit N analyzed data gathered in the NCES. Michael Goodman et al., Temporal relationship modeling: DTP or DT immunizations and infantile spasms, 16 Vaccine 225 (1998). The British government commissioned the NCES "to examine the temporal relationship between [whole cell] pertussis vaccine and serious neurologic illness." Resp't's Ex. N at 1.

Goodman and his colleagues re-examined the NCES data in light of "previously reported analyses show[ing] that cases of infantile spasms were not specifically associated with recent diphtheria, tetanus and pertussis immunization." Id. The

analysis showed no effect of vaccination overall on the onset of infantile spasms. Id. The authors noted a "statistically significant" temporal shift in cases of infantile spasms following DPT or DT immunization. Id. at 5. "[T]he 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," they stated. Id.

The authors disclaimed any inference that the data indicated a causative association between vaccination and infantile spasms. Rather, "immunization brings out a neurologic event that would have occurred anyway or calls attention to an event that is already occurring." Id. at 6 (internal quotation marks omitted). The authors also pointed out that reports by parents of vaccination in the days immediately preceding seizures may be unrelated to causation. Id. at 5 (noting that the "precise date of onset for an insidious disease such as infantile spasms is difficult to determine" and the "earliest manifestations" of the disorder "may be easily missed"). Further, "[a] temporal association with immunization may be sought by parents for children who have no other apparent antecedent factor of infantile spasms." Id. at 5.

Respondent's Exhibit P is an article on the Simultaneous Onset of Infantile Spasms in Monozygotic Twins. Giangennaro Coppola et al., Simultaneous Onset of Infantile Spasms in Monozygotic Twins, 43 Ped. Neur. 128 (2010). The findings indicated "that genes other than those currently known likely play a role in genetic predisposition to infantile spasms." Resp't's Ex. P at 130.

Respondent's Ex. Q is an article by Dr. Guggenheim on the time interval from a known brain injury to the onset of infantile spasms. Mary Anne Guggenheim et al., Time Interval From a Brain Insult to the Onset of Infantile Spasms, 38 Ped. Neuro. 34 (2008). The article stated that there is a latency period between injury and onset, "and this process is correlated with a progressive development of underlying pathologic processes such as gliosis, mossy-fiber and other axonal sprouting, and synaptic reorganization." Resp't's Ex. Q at 36. The authors concluded, "the results of our analysis preclude claims that the onset of infantile spasms within hours or days of immunization indicates a causal relationship." Id.

Respondent's Exhibit R is a "Special Report" on a workshop regarding infantile spasms. John Pellock et al., Infantile Spasms: A U.S. Consensus Report, 51(10) Epilepsia 2175, 2175 (2010).[26] The workshop described categories of IS and stated that "[p]rognosis is better in patients with cryptogenic IS who are treated early." Resp't's Ex. R at 2. The study reviewed "two potential mechanisms proposed in the pathogenesis of IS – increased excitability and loss of inhibition." Id. at 3. The study also reviewed the early phases of the disorder, noting that parents underestimate the number of spasms that their children are experiencing and "in some cases the events are subtle and may not even be recognized." Id. The report also noted that outcomes in cases of IS "are most dependent on etiology and may be more favorable in cryptogenic IS." Id. at 10. The report referred to the Kivity study in which normal cognitive development was documented in 22 patients with cryptogenic IS. Id.

[26] This does not appear to be a peer-reviewed publication. See Note 3, supra.

Respondent's Exhibit S is a Finnish study on children with IS. Raili Riikonen, Long-term outcome of patients with West syndrome, 23 Brain & Develop. 683 (2001). The author followed 214 children for 20-30 years or until death. Resp't's Ex. S at 684. The authors noted the relatively favorable prognosis for patients with cryptogenic IS and speculated that "intellectual outcome depends on the location of the abnormalities." Id. at 687. The authors described a variety of factors that seemed to influence outcome. Id.

Respondent's Exhibit T is an excerpt from a report by the Institute of Medicine ("IOM"). IOM, Adverse Effects of Pertussis and Rubella Vaccines 65-77, 118-24 (1991). The IOM stated, "Hypsarrhythmia . . . refers to an EEG pattern that is frequently associated with infantile spasms." Resp't's Ex. T at 77. The authors concluded that evidence does not indicate a causal relation between the DPT vaccine or the pertussis component of DPT and hypsarrhythmia. Id.

Respondent's Exhibit V is an article on GABA and epilepsy. S. Robert Snodgrass, GABA and Epilepsy: Their Complex Relationship and the Evolution of Our Understanding, 7 J. Child Neurol. 77 (1992). The article explored the possible relationship between GABA deficiency or abnormality and epilepsy. The article cautioned against "sweeping generalizations" regarding GABA receptors and convulsions and indicated that the process of epileptogenesis is complex. Resp't's Ex. V at 83-84.

D. Court's exhibits

Court Exhibit 1 was an excerpt from the most recent publication of the Institute of Medicine concerning adverse effects of vaccines. Ct. Ex. 1. The exhibit contained an extended description of the NCES. Id. at 464. The IOM stated, "The epidemiologic evidence is insufficient or absent to assess an association between acellular pertussis vaccine and infantile spasms." Id. The IOM concluded that "The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-. or acellular pertussis-containing vaccine and infantile spasms." Id. at 465.

Court Exhibits 2 and 3 contained additional material from the 2011 IOM publication. The excerpts described and explained the processes behind the IOM's conclusions regarding vaccine safety, and provided guidance on interpreting the IOM's conclusions. Ct. Exs. 2, 3.

IV. DISCUSSION

A. Petitioner's Burden of Proof

Petitioners seeking to establish causation-in-fact must show by a preponderance of the evidence that but for vaccination they would not have been injured, and that vaccination was a substantial factor in bringing about the injury. Cedillo v. Sec'y of

Dep't of Health & Human Servs., 617 F.3d 1328, 1338 (Fed. Cir. 2010); Shyface v. Sec'y of Dep't' of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Proof of actual causation must be supported by a sound and reliable "medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" Moberly, 592 F.3d at 1322 (quoting Knudsen v. Sec'y of Dep't of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994)); see also Grant v. Sec'y of Dep't of Health & Human Servs. 956 F.2d 1144, 1148 (Fed. Cir.1992) (finding a medical theory must support actual causal connection). Evidence should be viewed under the preponderance standard as it is understood in civil courts, "not through the lens of the laboratorian." Andreu v. Sec'y of Dep't of Health & Human Servs., 569 F.3d 1367, 1380 (Fed. Cir. 2009).

Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." Knudsen, 35 F.3d at 548. A petitioner may use circumstantial evidence to prove the case, and "close calls" regarding causation must be resolved in favor of the petitioner. Althen, 418 F.3d at 1280.

Petitioner's burden is to show that the vaccination brought about J.T.'s injury by providing: "(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, 418 F.3d at 1278. If Petitioner succeeds in establishing the case-in-chief, the burden then shifts to Respondent to prove alternative causation by a preponderance of the evidence. Id. If Petitioner fails to establish the case-in-chief, the burden does not shift. Doe 11 v. Sec'y of Dep't of Health & Human Servs., 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); see Cedillo, 617 F.3d at 1335 (citing Walther v. Sec'y of Dep't of Health & Human Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007)).[27]

B. Althen Prong 1

1. Nature of the inquiry

The issue under Prong 1 is whether there is preponderant evidence that vaccination could have caused the injury. In Moberly, the Federal Circuit reiterated that the standard of proof in a vaccine case is the traditional tort standard of preponderance of the evidence; otherwise stated, the matter to be proved must be shown to be more likely than not. Moberly, 592 F.3d at 1321-22. In the past, confusion has arisen as to the correct application of the standard of proof under Prong 1 of the Althen test, which asks whether there is preponderant evidence of a theory of possible vaccine causation. See Pafford v. Sec'y of Dep't of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed.

[27] The Federal Circuit discussed the shifting burdens of proof in some detail in de Bazan v. Secretary of the Department of Health & Human Services, 539 F.3d 1347, 1353-54 (Fed. Cir. 2009). In this case, Petitioner has not presented sufficient evidence to shift the burden of proof to the Secretary to establish causation by an alternative factor. See Doe 11, 601 F.3d at 1358.

Cir. 2006). The confusion arises when the matter to be established is conflated with the amount of evidence that needs to be shown to establish it. Properly understood, what is required under Prong 1 is preponderant evidence of possible vaccine causation. As discussed above, this requires a showing of a reliable theory of causation.

On this record, it has been shown to be not very likely that vaccination with an acellular pertussis vaccine could directly cause the syndrome diagnosed as cryptogenic infantile spasms. Boiled down to the essentials, the only evidence favoring the theory is the ipse dixit of Petitioner's expert. Against the theory, among other factors, are the medical literature finding no causal association, the significant gaps in Petitioner's expert testimony, and the countervailing testimony of Respondent's expert. The evidence weighs against Petitioner, even though under Prong 1, he need only show preponderant evidence of a theory of possible causation. Could the acellular pertussis vaccine have caused J.T.'s infantile spasms by crossing the blood brain barrier and within a matter of hours, resulting only in the discrete disorder of infantile spasms, with no other clinical evidence of a toxic assault on the brain? On this record, there is not preponderant evidence showing that it could.

In deciding these issues, a special master weighs which side has presented more and better evidence, considering all the facts in the record. Whether the special master actually is persuaded that the vaccine could cause the injury is not the issue. Doe 93 v. Sec'y of Dep't of Health & Human Servs., 98 Fed. Cl. 553, 566-67 (2011). The special master is called upon to weigh the evidence, not to weigh in on the science. Thus, "[t]he sole issues for the special master are . . . whether it has been shown by a preponderance of the evidence that a vaccine caused . . . injury." Knudsen, 35 F.3d at 549; see Hodges v. Sec'y of Dep't of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) ("Congress assigned to a group of specialists, the Special Masters . . . , the unenviable job of sorting through these painful cases and, based upon their accumulated expertise in the field, judging the merits of the individual claims.").

It follows that each case must be considered on the record in that case. See Knudsen, 35 F.3d at 548 (stating that "[c]ausation in fact under the Vaccine Act is based on the circumstances of the particular case."); Campbell v. Sec'y of Dep't of Health & Human Servs., 69 Fed. Cl. 775, 784 (Fed. Cl. 2006) (indicating that a "'cookie cutter'" approach to resolving causation issues "remains the antithesis of the individualized determinations required by the Vaccine Program"). This is reflected in the well-established doctrine that special masters' decisions – even their own past decisions – are not precedential. See Hanlon v. Sec'y of Dep't of Health & Human Servs., 40 Fed. Cl. 625, 630 (1998) (indicating decisions are not binding on special masters except in the same case), aff'd, 191 F.3d 1344 (Fed. Cir. 1999); see also Stone v. Sec'y of Dep't of Health & Human Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012) ("[T]he special master is entitled to consider the record as a whole in determining causation."). A special master also is not compelled to accept the same theory of causation in different cases. Rickett v. Sec'y of Dep't of Health & Human Servs., 468 Fed. App'x. 952, 959 (Fed. Cir. 2011) ("A special master's acceptance of a theory in one case does not require him or

her to accept the theory in subsequent cases involving similar facts or the same vaccine. Rather, a different evidentiary record can lead to different outcomes.").

In evaluating whether a petitioner has presented sufficient evidence of a medical theory, "the special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Cedillo, 617 F.3d at 1350 n.3 (quoting Moberly, 592 F.3d at 1324). A special master is not required to rely on a speculative opinion that "is connected to existing data only by the ipse dixit of the expert." Snyder, 88 Fed. Cl. at 743 (quoting Joiner, 522 U.S. at 146).

2. Application of the legal standards

Assessing the reliability of an expert opinion in Vaccine Act cases can be challenging because often there is little supporting evidence. See Althen, 418 F.3d at 1280 (noting that the "field [is] bereft of complete and direct proof of how vaccines affect the human body"). Most expert opinions extrapolate from existing data and knowledge. The weight to be given to an expert's opinion is based in part on the size of the gap between the science and the opinion proffered. Cedillo, 617 F.3d at 1339 (citing Joiner, 522 U.S. at 146).

Of particular significance in this case is that the Petitioner must show a sound and reliable "medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" Moberly, 592 F.3d at 1322 (quoting Knudsen, 35 F.3d at 548-49) (emphasis added); see also Grant 956 F.2d at 1148 (medical theory must support actual cause).

a. Gap between expert's evidence and J.T.'s condition

Dr. Griesemer's evidence of a possible causative link between J.T.'s DTaP vaccination and his West Syndrome does not preponderate for one basic reason: his theory supports the general hypothesis that pertussis toxin can cause seizures by interfering with neuronal signaling; it does not address how pertussis toxin in a DTaP vaccine causes infantile spasms, the condition from which J.T. suffers. Seizures are a symptom of J.T.'s disorder, but his condition is more closely defined than simply "seizures." West Syndrome is defined by particular types of seizures, a typical age of onset and period of duration, a signature abnormality evident on EEG known as hypsarrhythmia, a common response to ACTH, and in many cases further seizures and developmental delay similar to the outcome in J.T.'s case. How pertussis toxin could cause this particular condition is not explained by Dr. Griesemer.

In essence, Dr. Griesemer has presented reliable evidence of a phenomenon—"seizures"—which does not correspond to J.T.'s diagnosis of IS. Tr. at 77-78. J.T.'s symptoms are not those of an individual who suffered a direct, almost immediate, toxic insult to the brain. Id. As Dr. Guggenheim pointed out, direct pertussis poisoning would cause more general effects than appeared in J.T., who showed no clinical signs, even

according to Dr. Griesemer, of such an insult. Tr. at 77-78 (Dr. Griesemer); Tr. at 120-25 (Dr. Guggenheim) (no symptoms of encephalopathy). Had he exhibited clinical evidence of a toxic insult to the brain, J.T.'s diagnosis would not have been infantile spasms. As stated by Dr. Guggenheim, "There are experimental models and human events, clinical events in which there seems to be a very short time between a change in the brain and a convulsive response. To jump from that to the very unique disorder of infantile spasms is a very big jump." Tr. at 151.

I agree with Dr. Guggenheim that the size of the gap between the scientific evidence presented by Dr. Griesemer and the theory of possible vaccine causation he expounded in J.T.'s case is too large. See Cedillo, 617 F.3d at 1339 (citing Joiner, 522 U.S. at 146). Nothing in the medical record, or in any of the considerable body of medical literature concerning the role of GABA receptors in disrupting brain signaling, bridges the gap between the alleged toxic event here and the syndrome known as infantile spasms. See, e.g., Tr. at 95 (Dr. Griesemer: No "specific literature [] links the vaccine or the vaccine product with the GABA B receptor dysfunction.")

The highly technical articles submitted by Petitioner elucidating the function of GABA receptors did not address pertussis vaccination. Principally, these articles reported developments in molecular biology and their possible therapeutic implications. See Tr. at 105 (Dr. Guggenheim: "[Dr. Griesemer's] hypothesis is a very beautifully described one of GABAergic neurologic function" but does not support the hypothesis of vaccine injury.). While medical literature is not necessarily required to establish possible vaccine causation, the evidence Dr. Griesemer presented was connected to infantile spasms only by his ipse dixit, which I am not required to accept.[28]

b. Countervailing evidence of non-causation

(i) Dr. Guggenheim's testimony

Weighing significantly against a finding of preponderance is Dr. Guggenheim's testimony. As she explained, most neurologists believe infantile spasms result from an underlying brain disorder in all cases. Resp't's Ex. I at 2. As medical science advances and the causes of IS are identified, fewer and fewer cases are classified as cryptogenic. Id. at 3. Cryptogenic cases are likely to decline, as medical science advances further.

Dr. Guggenheim's testimony in this respect finds support in the movement to re-classify infantile spasms that is presented in Petitioner's Exhibit 31. The recommended classifications reflect the known structural, genetic, metabolic, as well as unknown, causes of infantile spasms. See Pet'r's Ex. 31, Tab A, (Berg). Such classifications corroborate Dr. Guggenheim's view that West Syndrome is a specific disorder that has identifiable underlying causes, and does not arise simply as the result of seizures. See

[28] The commentary by Menkes and Kinsbourne concerned a theoretical connection between whole cell pertussis vaccine and encephalopathy. Pet'r's Ex. 26. In addition to lacking reliability because the article was not peer reviewed, it was not on point because J.T. received a different vaccine (DTaP) and suffered a different injury (West Syndrome).

Resp't's Ex. K at 129-33 (Frost).

That some of the causes of West Syndrome are as yet undiscovered does not change the fact that it is to a considerable extent a "known quantity." See, e.g., Resp't's Ex. J at 66 (strikingly abnormal electroencephalographic pattern of hypsarrhythmia appeared in all 237 cases of infantile spasms reported). Hypothesizing about a possible mechanism for triggering seizures in general is unlikely to produce a reliable explanation, sufficient to satisfy Althen Prong 1, for the possible cause of this medically distinct disorder.

(ii) Epidemiological studies

Also weighing against Petitioner's theory is the evidence amassed in the scientific community over a period of several decades during which pertussis vaccination has been explored as a possible cause of infantile spasms. Although epidemiological studies do not eliminate the possibility of a unique injury in a particular case, they are evidence to be weighed along with all the other evidence. See Andreu, 569 F.3d at 1379 ("the special master can consider [epidemiological evidence] in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.") In this instance, in which a possible relationship between infantile spasms and pertussis inoculation has been explored in a serious way by scientific investigators over the years, it would be irresponsible to ignore the result of their investigations.

According to the IOM, "Evidence does not indicate a causal relation between DPT vaccine or the pertussis component of DPT and hypsarrhythmia." Resp't's Ex. T at 77. The IOM's most recent report concluded: "The epidemiologic evidence is insufficient or absent to assess an association between acellular pertussis vaccine and infantile spasms." Ct. Ex. 1 at 464. While the IOM has not ruled out a connection, it has not identified any causative association in the epidemiological studies that were reviewed.

The NCES study disclosed no causal association. See Resp't's Ex. N. The only statistically significant finding in the controlled NCES was of a "temporal shift," in which more cases of IS were reported in the seven days following vaccination than in the next three weeks. Id. at 4-6. In light of the finding of no statistically significant causal association between vaccination and IS, two possible explanations for the "temporal shift" were noted in the record: (1) spasms that would have occurred anyway because of the disorder may have been accelerated by vaccination; and (2) cases were more likely to be reported during the week following vaccination because parents were more vigilant. Id.; see Resp't's Ex. K at 132.[29]

[29] Dr. Griesemer's observation that the occurrence of J.T.'s seizure within seven days of his vaccination fits the "temporal shift" noted by Goodman et al., therefore adds nothing to the weight of the evidence favoring causation of his seizures and their neurological sequelae.

Ohtahara, in the chapter from the textbook submitted as evidence by Petitioner, also noted that "the apparent association between DPT immunization and infantile spasms is coincidental and that no causal relationship exists." Pet'r's Ex. 21 at 183.

In light of this evidence that pertussis vaccination, in particular acellular pertussis vaccination, has not been shown to cause infantile spasms, Dr. Griesemer's speculation that J.T. may or may not have been predisposed to suffer the disorder is significant. See, e,g., Tr. at 36 (Dr. Griesemer: The vaccine "could have interacted with some predisposition about which we know nothing as opposed to be[ing] a stand alone trigger or cause."). If pertussis vaccine, without more, could cause the devastating effects on neuronal function that Dr. Griesemer posited in this case, the question arises why such cases do not occur more often. Since they do not occur with any frequency, see Tr. at 36 ("Dr. Griesemer: We're talking about an event that is very rare and doesn't happen very often."), the only explanation would be some particular factor in J.T. that caused the reaction. Dr. Griesemer stated candidly that he did not know what that particular factor might be.[30] His testimony left a huge hole in the proposed explanation of possible vaccine causation.

For all these reasons, I find that Petitioner's evidence of possible vaccine injury does not preponderate under the Althen test. I proceed to analyze the second prong of the Althen test for the sake of judicial economy and to provide additional context for this decision.

C. Althen Prong 2

The second prong of Althen requires a petitioner to prove "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Andreu, 569 F.3d at 1374 (quoting Althen, 418 F.3d at 1278). The sequence of cause and effect must be "'logical' and legally probable, not medically or scientifically certain." Knudsen, 35 F.3d at 548-49. A petitioner is not required to show "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." Capizzano v. Sec'y of Dep't of Health & Human Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, circumstantial evidence and reliable medical opinions may be sufficient to satisfy the second Althen factor. Id. at 1325-26; see Andreu, 569 F.3d at 1375-77. Further, evidence used to satisfy one prong of the Althen test may overlap to satisfy another prong. Capizzano, 440 F.3d at 1326.

Petitioners stated that Dr. Griesemer's opinion "does not depend on whether the vaccine was from a bad lot," but on (1) the temporal onset; (2) the toxicity of the vaccine; (3) the "impressive" onset; and (4) the nature of the IS. Pet'r's Post-Hr'g Br. at 16. See also Tr. at 87. I address each of these items below and conclude that they

[30] See Tr. at 77 (The Court: "I think you testified that pertussis vaccine does not cause infantile spasms in the vast majority of cases and that you have no notion of why, in this particular case, the vaccine, in your view, caused infantile spasms. Nothing about this particular case is special?" Dr. Griesemer: "Not that I can discern.").

do not establish a logical sequence of cause of effect between vaccination and J.T.'s West Syndrome.

1. Factors identified as probative by Petitioner

(a) Temporal onset

Dr. Griesemer testified that the onset of seizures within hours of vaccination was consistent with a direct toxic effect on J.T.'s brain, not with the insidious onset typical of infantile spasms. Tr. at 87. From this fact, Dr. Griesemer drew the conclusion that the cause of J.T.'s seizures was direct injury from the pertussis vaccination. Tr. at 87-90.

Dr. Griesemer's conclusion conflicts, however, with what is known about infantile spasms as reflected in his own testimony, the medical literature of record, and Dr. Guggenheim's evidence. The syndrome develops insidiously, so much so that parents and even pediatricians may miss the diagnosis for some period. See Tr. at 31 (Dr. Griesemer); Pet'r's Ex. 28 at 256 (Kivity) ("The mild initial clinical symptoms were stressed. . . ."). Thus, in many cases, by the time the child exhibits seizures, the neurological process that leads to the disorder has been under way for some time.

This happens so commonly that it is mentioned routinely in medical literature on the subject of West Syndrome. Kivity, for example, reported that in the delay starting therapy in the late-treatment group "was due to lack of recognition of the significance of the movements by the parents . . . failure to diagnose these on the part of the general physician . . . and misdiagnosis by pediatricians and emergency room physicians." Pet'r's Ex. 28 at 257. Failure to recognize the early symptoms of West Syndrome also was used by Goodman to explain what appeared to be a cluster of cases reported in the NCES during the first week following vaccination. See Resp't's Ex. N at 225-31 (Goodman). Since the Bellman study found no statistically significant causal association between vaccination and infantile spasms, Goodman noted the possibility that the "temporal shift" they observed in the onset of IS following vaccination—within the first seven days post vaccination—might simply be the result of increased parental vigilance. Id. at 229.[31]

Dr. Griesemer's conclusion that J.T. was neurologically normal until a few hours following his vaccination is not consistent with the accepted understanding in the medical community of how West Syndrome develops. Dr. Griesemer conceded that the temporal relationship between vaccination and the onset of seizures in this case could be coincidental. See Tr. at 88-89. Dr. Griesemer characterized the possibility of a coincidence as "remote." Id. But there is no logical reason to assume, and no evidence

[31] As noted above, Goodman also speculated that vaccination may have triggered seizures that would have occurred anyway because of the underlying disorder of infantile spasms. Seizures following vaccination would under that scenario be the result, not the cause, of J.T.'s condition. See Deribeaux v. Sec'y of Dep't of Health & Human Servs., No. 05-306V, 2011 WL 6935504, at *46 (Fed. Cl. Spec. Mstr. Dec. 9, 2011), aff'd, -- Fed. Cl. --, 2012 WL 2367037 (2012). Even if one assumed that vaccination triggered J.T.'s seizures, no reliable evidence points to aggravation of West Syndrome due to vaccination.

in the record to support, the idea that the remote possibility of coincidence was more remote than the remote possibility of vaccine causation.

(b) Toxicity of the vaccine

Pertussis is a known neurotoxin. Tr. at 30. If that were sufficient to establish a cause and effect relationship, Prong 2 would be satisfied in every case of neurological injury following pertussis vaccination. In general, however, it is well established that, while pertussis toxin may be capable of causing neurological damage, vaccination, especially modern-day vaccination with the acellular form, is generally safe, as even Dr. Griesemer recognized. See Tr. at 43; Tr. at 36 (Dr. Griesemer: "we're talking about an event that is very rare and doesn't happen very often").

Dr. Griesemer also conceded that in order for the alleged direct toxic injury to have occurred, pertussis toxin would have had to breach the blood brain barrier. Dr. Griesemer and Dr. Guggenheim disagreed concerning the permeability of the blood brain barrier and the likelihood that it could be breached by a large molecule like the pertussis protein. Tr. at 41-45 (Dr. Griesemer); Tr. 111-12, 116, 121, 152-55 (Dr. Guggenheim).

That injury due to DTaP vaccination is so rare weighs against the likelihood that the blood brain barrier can be breached by the pertussis toxin in the DTaP vaccine, absent some additional, unknown factor. More importantly, it is agreed that J.T. showed no signs of a generalized toxic insult to the brain. See Tr. at 40, 120-21 ("toxic encephalopathy . . . is a child who is globally impaired relative to brain function."). There was no objective, clinical evidence that J.T.'s blood brain barrier had been breached. Tr. at 121. According to Dr. Guggenheim, if pertussis toxin had penetrated the blood brain barrier, J.T. would have suffered more generalized effects, not only the onset of symptoms specifically identified as infantile spasms. Id.

Dr. Guggenheim testified, "I find it quite difficult to accept that a small amount of toxin given int[ra]muscularly crosses the blood brain barrier [and] does nothing else to the child. Like, for instance, pertussis toxin was also known as islet activating factor because it has effects on the pancreas and promotes insulin secretion. And so nothing else happened to this child except infantile spasms." Tr. at 116 (Dr. Guggenheim). Dr. Griesemer provided no meaningful refutation of this salient point. Tr. at 40. Dr. Guggenheim's testimony preponderated on this issue.

(c) "Impressive" onset

Among the reasons given by Dr. Griesemer as the basis for his opinion was "the dramatic and acute onset of seizures presenting [as] infantile spasms in [J.T.] which is a bit unique [in] that most times infantile spasms develop very insidiously and the onset is very difficult to recognize." Tr. at 31. J.T.'s seizures after vaccination were readily apparent. He was noted for a period of 20 minutes to be stiffening his body for seconds at time, and was immediately diagnosed with seizures. See Pet'r's Ex. 7 at 3; Tr. at 34.

Dr. Griesemer implied that vaccination somehow changed the onset of IS in J.T.'s case from insidious to "dramatic and acute." No evidence, other than Dr. Griesemer's opinion, lends support to the proposition that the onset of IS varies in severity according to its cause. Similarly, the record does not support the idea that cases of cryptogenic infantile spasms occurring in temporal proximity to vaccination are more damaging than cases that occur because of other causes.

(d) Hypotonia and cerebral irritability

Dr. Griesemer identified as another factor signaling a vaccine injury that J.T. had "slightly increased muscle tone that indicated some cerebral irritability that we don't often see with other types of infantile spasms." Tr. at 31; Pet'r's Post-Hr'g Br. at 14. Dr. Griesemer seemed to suggest that there was some other abnormality, not simply West Syndrome, that was triggered by J.T.'s vaccination. This proposition does not advance the argument that there was a vaccine injury, it simply assumes it. See Pet'r's Ex. 14 at 3 ("[M]ild spasticity, as well as the seizure disorder, was the consequence of the brain injury that occurred following vaccination."). As the record stands, J.T.'s hypotonia and cerebral irritability were not linked reliably to his vaccination, other than by Dr. Griesemer's opinion.

(e) Absence of structural brain abnormality

In his post-hearing brief, Petitioner identified the absence of other causes as indicative of vaccine injury. See Tr. at 87-89; Pet'r's Post-Hr'g Br. at 26.

The absence of a known cause indicates that J.T.'s disorder properly was classified as one of cryptogenic IS, in common with a substantial (but declining) proportion of cases. See Pet'r's Ex. 31, Tab B at 802 ("Children with normal neurologic and developmental history, normal neurologic examination, no known associated etiologic factor, and negative diagnostic evaluation were classified as cryptogenic."); Pet'r's Ex. 28 at 255 ("With the advent of modern neuroimaging methods, the proportion of symptomatic cases has increased, and the syndrome has been found to be symptomatic in 60 to 90% of patients."); Tr. at 106, 142-43 (Guggenheim).

The absence of other causes does not logically implicate vaccination; children suffer from cryptogenic infantile spasms without having had a temporally proximate vaccination. See Pet'r's Ex. 14 at 3 (Dr. Griesemer: "The development of infantile spasms in a child at 6 months of age is not diagnostically specific for a vaccine injury."); see also Althen, 418 F.3d at 1278 ("simplistic elimination" of other potential causes of the injury does not meet the burden of showing actual causation).

(f) Categorization of J.T.'s IS

Petitioners devoted some attention to a new system of categorizing infantile spasms. See, e.g., Tr. at 24-25, 140-43; Pet'r's Ex. 31, Tab A (Berg). This evidence was interesting but its significance was not apparent. Recent changes in the categorization of West Syndrome did not establish a logical connection between vaccination and J.T.'s injury.

At one point, Dr. Griesemer stated that J.T.'s condition should be categorized as "symptomatic" rather than cryptogenic because the cause—vaccination—was known. Tr. at 34-35. Again, Dr. Griesemer's statement assumed a causal connection between vaccination and West Syndrome that has not been demonstrated. Moreover, the idea that, if the label of J.T.'s condition changed, causation would be established, does not make sense. See Tr. at 35. The denial of entitlement to compensation does not turn on the label that was applied to J.T.'s case but on the known characteristics of his disorder and the facts in his medical record.[32]

On the other hand, Petitioners themselves relied on J.T.'s diagnosis of cryptogenic infantile spasms. Petitioners implied that, since J.T. was diagnosed with cryptogenic IS, received prompt treatment and, unlike the children in the Kivity and Luovigsson studies, had a poor outcome, this must mean that vaccination was the cause of his refractory seizures and developmental problems. Tr. at 25-29. See Pet'r's Exs. 28 (Kivity) and 31, Tab B (Luovigsson).

The limited studies submitted in support (Kivity involved 37 children with cryptogenic IS; Luovigsson involved a total of only six) cannot be accepted as conclusive evidence that all children with cryptogenic spasms who are treated early will have a good prognosis (unless they are vaccinated). Even Petitioner's sources undermine that conclusion. See Pet'r's Ex. 20 (of eight patients with cryptogenic IS, three (or 38%) had a normal outcome or only mild impairment). Luoviggson also noted that the results he reported were more favorable than in most clinical series. Pet'r's Ex. 31, Tab B at 802.

The studies did furnish evidence that early treatment with ACTH may be beneficial. In the Kivity article, patients with cryptogenic IS who were "treated within 1 month of onset of the spasms" had a favorable outcome. Pet'r's Ex. 28 at 256. Children with cryptogenic IS who did not receive early treatment did not have a favorable outcome. See Pet'r's Ex. 28 at 260 (referencing a study reporting "that eight of nine children with cryptogenic infantile spasms treated within 1 month of spasm onset achieved normal development, whereas none of the 10 treated later had a normal developmental outcome").

[32] If J.T.'s West Syndrome were properly characterized as symptomatic, because it was caused by vaccination, there would be a timing problem. Dr. Guggenheim pointed out that a period of weeks or months typically elapses between the causative event and the onset of symptomatic infantile spasms. See Tr. at 103-04; Resp't's Ex. I at 4.

Notably, however, "[e]arly treatment depends on early diagnosis, which unfortunately is often delayed because symptoms are so likely to be misinterpreted." Pet'r's Ex. 28 at 261. See Tr. at 124, 179-80 (Dr. Guggenheim describing the subtlety of initial symptoms). If J.T. had initial, mild symptoms that were not recognized as such, J.T. might not fall into the early treatment category. As Dr. Griesemer pointed out, J.T. presented with "dramatic and acute" rather than mild symptoms. Dr. Griesemer agreed that this would be unusual for a child with IS (indeed, it is one of the factors Dr. Griesemer cited in pointing to vaccination as the cause of J.T.'s illness). The unusual presentation casts doubt on the time of onset, which is critical under the Kivity model.

That J.T.'s condition was caused by vaccination is unlikely given everything that medical science knows about the DTaP vaccination and IS. The possibility that J.T.'s early symptoms of infantile spasms may not have been recognized as such for a period of time comports with what has been observed and reported regularly by medical experts and is reflected in the literature and expert testimony.

2. Treating physicians' notations

The record contains a number of notations by treating personnel to the effect that J.T. had been vaccinated on the day before his seizures. These notations are highlighted in Petitioner's post-hearing brief. See Pet'r's Post-Hr'g Br. at 22-25. I have reviewed these notes. None constitutes evidence that treating personnel actually ascribed J.T.'s condition to vaccination. Petitioners conceded as much. "The petitioner does not argue that this emphasized notation, and others like it, imply that the physician believed that the vaccine caused the seizures." Id. at 22 n.13.

The notes identified the history of vaccination in temporal association with J.T.'s seizures as a medical fact. Further, some of the early notes identified J.T.'s spasms as possible "febrile seizure related to a low-grade fever, as a result of vaccinations," Pet'r's Ex. 7 at 4, or, similarly, an "immunization reaction," see Pet'r's Ex. 6 at 264-67. These notations concerning a benign, febrile reaction to vaccination were incorrect, as Dr. Griesemer agreed. Tr. at 10 (these were not febrile seizures). Following his evaluation, J.T.'s treating neurologists diagnosed him with West Syndrome, not a vaccine reaction. See supra.

On the whole, it is less likely than not that there is a logical cause and effect between vaccination and J.T.'s injury.

D. Althen Prong 3

A petitioner must establish that the injury occurred within a time frame that is consistent with the theory of causation set forth. See Pafford, 451 F.3d at 1358. The temporal relationship must be within a "medically acceptable" timeframe. de Bazan v. Sec'y of Dep't of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2009). What constitutes an appropriate temporal association is a question of fact and will vary with the particular theory of causation advanced. See Pafford, 451 F.3d at 1358; de Bazan, 539 F.3d at 1352.

Petitioner conceded that the onset of J.T.'s seizures occurred "too soon to be the result of an antibody or an immune reaction." See Pet'r's Post-Hr'g Br. at 15; Tr. at 48. On the theory that J.T.'s seizures must have been "the sudden onset" of a "direct toxic insult by the pertussis toxin to [J.T.]'s brain," they asserted that the timing of his injury was appropriate. Id. Indeed, Dr. Griesemer testified that J.T.'s condition should be categorized as "symptomatic," because the cause his disorder— vaccination—is known. Tr. at 35; Pet'r's Ex. 19 at 2.

Dr. Guggenheim responded that symptomatic cases of infantile spasms do not manifest in close temporal proximity to the cause of the condition. Rather, there is a latency period of some months. See Tr. at 141-152; Resp't's Ex. I at 4. Even if one accepts the label of "symptomatic" infantile spasms to describe J.T.'s case, the timeframe Dr. Griesemer has identified is inappropriate, according to Dr. Guggenheim's article.

If, on the other hand, Dr. Griesemer's theory of direct toxic injury is correct, it is not seriously disputed that the rapid onset of convulsions due to a toxic assault on the brain would be appropriate. See Tr. at 151 (Dr. Guggenheim: "There are experimental models and human events, clinical events in which there seems to be a very short time between a change in the brain and a convulsive response . . . ."). The circumstances would be more like the timing of an encephalopathy following vaccination. Again, a post-vaccination encephalopathy certainly did not occur in this case. See Tr. at 47. Thus, Petitioner's problem is not inappropriate timing; it is the lack of preponderant evidence that J.T. suffered a direct, toxic injury from his vaccination.

V. CONCLUSION

Petitioner has not presented preponderant evidence to support the claim that vaccination caused J.T.'s injuries. Accordingly, Petitioner is not entitled to compensation under the Vaccine Act, and the Petition must be **DISMISSED**. In the absence of a timely motion for review filed pursuant to Vaccine Rule 23, the Clerk is directed to enter judgment according to this decision.

IT IS SO ORDERED.

s/ Dee Lord
Dee Lord
Special Master