In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 07-0058V

Filed: 15 March 2010

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ADAM SUCHER and ELIZABETH SUCHER, parents of EVELYN SUCHER, a minor,	*	
Petitioners,	*	**PUBLISHED**
v.	*	Actual Causation; Trigger; Proximate Cause; Substantial Factor; Superseding Cause; Genetic Susceptibility; Factual Inevitability; *Shyface* and the Restatement of Torts; Pertussis Toxoiding; DTaP; Fever; SCN1A
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	
* * * * * * * * * * * * * * * * * * * *	*	

Ronald Craig Homer, Esq., Conway, Homer & Chin-Caplan, Boston, Massachusetts, for Petitioner; *Michael P. Milmoe, Esq.*, United States Department of Justice, Washington, D.C., for Respondent.

ENTITLEMENT RULING[1]

ABELL, Special Master:

On 24 January 2007, Petitioners filed this Petition for compensation under the National Childhood Vaccine Injury Act of 1986 (Vaccine Act or Act)[2] alleging that, as a result of the Diphtheria-Tetanus-Acellular Pertussis (DTaP) vaccine administered to Evelyn on 11 February 2004,

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[1] Petitioners are reminded that, pursuant to 42 U.S.C. § 300aa-12(d)(4) and Vaccine Rule 18(b), a petitioner has 14 days from the date of this ruling within which to request redaction "of any information furnished by that party (1) that is trade secret or commercial or financial information and is privileged or confidential, or (2) that are medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, "the entire decision" may be made available to the public per the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002).

[2] The statutory provisions governing the Vaccine Act are found in 42 U.S.C. §§300aa-10 et seq. (West 1991 & Supp. 1997). Hereinafter, reference will be to the relevant subsection of 42 U.S.C. §300aa.

Evelyn suffered several seizures and eventually *status epilepticus*,[3] which ushered in a long-term seizure disorder. *See* Amended Petition.

Eventually, two evidentiary hearings on the ultimate issue of vaccine causation were convened by the Court, the first held *in vivo* in Boston, Massachusetts on 6 March 2008, and the second held *in vitro* (telephonically) from the Court's Chambers on 25 July 2008. Hearing Transcripts I and II ("Tr. I" and "Tr. II"). Wherein, the Court heard from medical expert witnesses for both parties, neurologists both: Dr. Marcel Kinsbourne for the Petitioner, and Dr. Max Wiznitzer for the Respondent. Following those hearings, the parties filed closing briefs with the Court, and the case is now ripe for a ruling.

As a preliminary matter, the Court notes that Petitioners have satisfied the pleading requisites found in § 300aa-11(b) and (c) of the statute, by showing that: (1) they are the real party at interest as legal representatives of their daughter Evelyn, the injured party; (2) the vaccine at issue is set forth in the Vaccine Injury Table (42 C.F.R. § 100.3); (3) the vaccine was administered in the United States or one of its territories; (4) no one has previously collected an award or settlement of a civil action for damages arising from the alleged vaccine-related injury; and, (5) no previous civil action has been filed in this matter. Tr. I at 4. Additionally, the § 16 requirement that the Petition be timely filed have been met. Tr. I at 5. On these matters, Respondent tenders no dispute. *Id*.

The Vaccine Act authorizes the Office of Special Masters to make rulings and decisions on petitions for compensation from the Vaccine Program, to include findings of fact and conclusions of law. §12(d)(3)(A)(I). In order to prevail on a petition for compensation under the Vaccine Act, a petitioner must show by preponderant evidence that a vaccination listed on the Vaccine Injury Table either caused an injury specified on that Table within the period designated therein, or else that such a vaccine *actually caused* an injury not so specified. § 11(c)(1)(c).

I. FACTUAL RECORD

Despite their accord on certain factual predicates contained in the filed medical records, there is, unsurprisingly, a pronounced conflict between the parties on certain factual issues of viewing understood scientific mechanisms of vaccine injury within the context of the expert witness testimony and the medical records. Considering these disputes and the Court's commission to resolve them, it behooves the Court to explain the legal standard by which factual findings are made.

It is axiomatic to say that a petitioner bears the burden of proving, by a preponderance of the evidence–which this Court has likened to fifty percent and a feather–that a particular fact occurred or circumstance obtains. Put another way, it is required that a special master, "believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the [special master] of the fact's existence." *In re Winship*, 397

[3] Status epilepticus is "1. a continuous series of generalized tonic-clonic seizures without return to consciousness, a life-threatening emergency... 2. any prolonged series of similar seizures without return to full consciousness between them." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (30th ed. 2003) (SAUNDERS) at 1756.

U.S. 358, 371-72 (1970) (Harlan, J., concurring). Moreover, mere conjecture or speculation does not meet the preponderance standard. *Snowbank Enterprises v. United States*, 6 Cl. Ct. 476, 486 (1984).

This Court may not rule in favor of a petitioner based on his asseverations alone. This Court is authorized by statute to render findings of fact and conclusions of law, and to grant compensation upon petitions that are substantiated by medical records and/or by medical opinion. §§ 12(d)(3)(A)(i) and 13(a)(1).

Contemporaneous medical records are afforded substantial weight, as has been elucidated by this Court and by the Federal Circuit:

> Medical records, in general, warrant consideration as trustworthy evidence. The records contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium. These records are also generally contemporaneous to the medical events.

Cucuras v. Sec'y of HHS, 993 F. 2d 1525, 1528 (Fed. Cir.1993).

Medical records are more useful to the Court's analysis when considered in reference to what they include, rather than what they omit:

> [I]t must be recognized that the absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance. Since medical records typically record only a fraction of all that occurs, the fact that reference to an event is omitted from the medical records may not be very significant.

Murphy v. Sec'y of HHS, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F. 2d 1226 (Fed. Cir. 1992), *cert. denied sub nom. Murphy v. Sullivan*, 113 S. Ct. 263 (1992) (citations omitted), citing *Clark v. Sec'y of HHS*, No. 90-45V, slip op. at 3 (Cl. Ct. Spec. Mstr. March 28, 1991).

A. Medical Records *et al.*

There were no issues of circumstantial fact disputed by the parties, and the medical records reveal those circumstances sufficiently. Tr. I at 4. The Court turns first to the recorded facts drawn from the medical records engendered and maintained by those responding to, and treating, Evelyn's condition. The Court gleaned the following from the most pertinent of the medical records:

Evelyn was born 28 August 2003, and developed normally and relatively healthfully throughout her first six months. Petitioners' Exhibit ("Pet. Ex.") 3 at 9 and 32, 4 at 4-11, 7 at 364. On 11 February 2004, at her six month check-up, Evelyn was administered her third DTaP vaccination. Pet. Ex. 3 at 32. At the visit, it was noted that she was healthy, albeit "just over gastroenteritis" for which she was seen at the emergency room on 6 February 2004. Pet. Ex. 4 at 12. Evelyn was described by her parents as cranky the evening of 11 February, and awoke early the

morning of 12 February hot to the touch, prompting her parents to give her Tylenol. Pet. Ex. 7 at 360.

Around 7:00 AM on the morning of 12 February 2004, while Evelyn had been napping after awaking earlier that morning, Mr. Sucher heard a sound coming from Evelyn's room that to him "didn't sound 'right' or natural," prompting him to rush in. Pet. Ex. 11 at 4 (Affidavit of Adam Sucher). He perceived that something was wrong and intuited that Evelyn was experiencing a seizure, which lasted "roughly five minutes" by his estimation. *Id*. When Petitioners took Evelyn to the hospital, she suffered another seizure there. *Id*. During this time, he recalls Evelyn became cyanotic,[4] and it seemed these symptoms continued regardless of treatment. *Id*. at 5.

The history of these events is summated in the medical records:

> [Evelyn] is a 6-month-old girl who is otherwise healthy. She was just seen yesterday by her primary care doctor for routine immunizations. The child apparently was at Children's Hospital over the weekend because of vomiting and a little bit of diarrhea. [She was orally rehydrated and was sent home.] She was seen yesterday for her immunizations. She was well until this morning when she had a generalized seizure that seemed to last less than five minutes according to her mom. Apparently she had been very cranky through the night and at 7:30 [AM] they had given her some Tylenol and then about 15 minutes later the patient had the generalized seizure. ... The parents drove the child here and shortly after arriving, the patient had another seizure which lasted several minutes but less than five minutes but seemed to have a prolonged post ictal period. The child has no past history of seizures. She has not been febrile over the last few days as far as the parents know. She was not febrile over the weekend when she had her vomiting and diarrhea.

Pet. Ex. 3 at 20. On physical examination, it was noted:

> [The seizure was] a generalized seizure, tonic-clonic, lasting several minutes although less than five minutes. The patient was then post ictal and seemed to have a prolonged post ictal period. Her temp on arrival here was only 100.8 rectally...
>
> After the patient had her generalized seizure on arrival here, she was then noted to have several staring episodes and some twitching of the face at which time she was given 0.05 mg/kg of Ativan.

Id. In giving an impression, the treating Emergency Department physician presciently noted:

> At this time, I feel that the patient should be transferred to a tertiary care center as this does not fit into the category of a simple febrile seizure. In fact, the child may have a seizure disorder and this will need further evaluation. She will need neurology consult.

Id. at 21. Her final diagnosis there was "*status epilepticus*." *Id*.

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[4] Cyanosis is "a bluish discoloration, especially of the skin and mucous membranes due to excessive concentration of deoxyhemoglobin in the blood." DORLAND'S, *supra* at note 3, at 455.

From the emergency room, Evelyn was transferred to New England Medical Center, where the admission noted that Evelyn had been "irritable" the previous evening, which her parents ascribed to the vaccination, and had vomited once. Pet. Ex. 10 at 9. There she was diagnosed with "complex seizures." *Id*. at 14. There was initially some suspicion concerning an infectious cause for the seizures, given Evelyn's prior presence in day care, but given the absence of supporting physical findings, this was of diminished concern. *Id*. at 11. The treating physicians also considered her family history and her recent history of vaccination in relation to the possibility of febrile seizure, noting that even though her temperature when first measured was at 100.8 F, that reading "may be confounded by [the] recent tylenol dose," or may have been elevated due to the physical stress of the seizure. *Id*.

Neurologists at New England Medical Center assessed the seizures as "unprovoked" aside from the slightly elevated temperature and Evelyn's family history, which neurologist Dr. Baron said he would "consider." Pet. Ex. 10 at 13 (emphasis in original).[5] The treating physicians repeatedly noted in describing Evelyn's condition her recent history of DTaP vaccination, but none of them seemed to attribute a causal connection in doing so. Pet. Ex. 10 at 25, 77; Pet. Ex. 4 at 13. She was eventually released from the hospital after another week there. Pet. Ex. 10 at 175. Her discharge summary stated that on the day of her vaccinations she was in "good health" although she had experienced "a brief viral illness consisting of some low grade temperatures, a few episodes of emesis, and diarrhea" about one week prior thereto. Pet. Ex. 10 at 174. It also recounted that Evelyn was irritable and suffered one bout of emesis in the evening following the vaccine administration, which symptoms were attributed to the vaccinations. *Id*.

Unfortunately, Evelyn's seizure activity continued in the months that followed. She was again admitted to the hospital on 28 April 2004 due to "persistent seizure breakthrough" and remained there until 13 May 2004. Pet. Ex. 10 at 201, 616. During that stay, Evelyn was examined by pediatric neurologist Dr. James Riviello, who recorded:

> She was in her usual state of health until February, when she had the onset of her seizures. She had her six month check up, she was fine, had her immunizations, and after that, she seemed fussy that day and [her parents] wondered if she was "sensitive to the shots." When she awakened the next day, she was still irritable, did not want to play, she went back to sleep, her father then heard her have a scream, and when he went into the room, she was having a seizure. Her body was stiff, her eyes were deviated to one side, but they are not sure what side it was and it lasted under two minutes in duration. She had not been eating well that morning. They went to the Emergency Department at the Newton-Wellesley Hospital, she seemed lethargic there, woke up screaming, then had another seizure, she was not febrile at the time, a CT scan and a lumbar puncture were done, these were unremarkable, she was given lorazepam and transferred then to the Boston Floating Hospital....

[5] Evelyn's mother suffered from one or more isolated and benign febrile seizure(s) as a child. Pet. Ex. 10 at 174.

> Other than some rare staring spells, without any associated motor stigmata of seizures, she was well until several weeks ago, when again, she woke up screaming, was having a seizure, they thought that this one seemed more severe, it was longer and the motor movements were more dramatic, this lasted three minutes, she went onto [*sic*] then have recurrent seizures, that subsequently lasted from five to seven minutes in duration, and was also cyanotic.
>
> ...
>
> [Evelyn] has no known allergies, her immunizations are up to date, and she has been relatively healthy from an infectious disease point of view, although has a stomach-flu-like illness on two occasions, one of these occurred just before her recent hospitalization by about one week.
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> ...
>
> The family history is positive for a febrile seizure in her mother, following an immunization, and the maternal grandmother had an uncle with seizures.
>
> ...
>
> Evelyn's examination is essentially unremarkable.
>
> ...
>
> She currently has been seizure free after her second episode of a flurry of seizures. Her seizures clinically sound generalized, although apparently there was some focality on her EEGs, I believe with bicentral spikes.
>
> ...
>
> We also discussed the possibility that this could be a familial tendency to her seizures, since her mother did have a febrile seizure. In addition, the onset was within 24 hours of immunization, but currently, the acellular pertussis is not thought to cause the same neurological consequences that could be seen with the whole-cell pertussis, but even this was rare. I also emphasized the importance of making a specific diagnosis, since this allows us to better answer their questions.

Pet. Ex. 32 at 1-3.

At a follow-up visit with Dr. Riviello in September 2005, following an admission to the hospital for a generalized tonic-clonic seizure lasting 25 minutes that would not stop, notwithstanding medication, at which time her temperature was 104°F. Pet. Ex. 7 at 344. She had suffered another seizure the morning of her visit with Dr. Riviello as well, and he directed significant concern (and most of his notes' discussion) to her blend of medications and her dosage levels. *Id*. at 344-45. He also briefly considered what might be the aetiology of Evelyn's seizures:

> In review of the family history, her mother had febrile seizures, and there was a maternal great uncle, with a generalized tonic clonic seizure. I spent a good deal of time talking to them today about the aetiology of the seizures, and treatment, and wondered whether she has the entity of generalized epilepsy with febrile seizures

> plus, which can be associated with multiple seizure types in the same family. So far, gene testing is available for only one subtype[6] of this, and this is a sodium channel gene, and I shall order this.

Pet. Ex. 7 at 345.

Evelyn's seizures continued, despite nuanced re-combinations of medications. *See*, *e.g.*, Pet. Ex. 6 at 1-3 and 18-20; Pet. Ex. 7 at 54-55 and 65-67. However, the Court concludes its review of the medical records inasmuch as (a) it is apparent that Evelyn's condition of intractable seizures exceeded the six months required by statute, and (b) the Court's purpose here is to determine what initially caused the seizure disorder to express itself.

B. Testimony Bearing on Entitlement

The Court greatly appreciated hearing from two eminent scholars on the question presented in this case. At the conclusion of the first hearing, the Court noted:

> I have great professional respect for both experts, Doctors Kinsbourne and Wiznitzer. I have heard both of you gentlemen frequently over the years. And I once again will thank you accordingly.

Tr. I at 115-116. Both experts' testimony is accepted as admissible *in toto*, and the Court reiterates its gratitude for sharing their credible, professional expertise.

[6] The doctor is here referring to SCN1A. Results from testing for a mutation of the SCN1A gene in Evelyn were negative.

1. Marcel Kinsbourne, MD

At the primary entitlement hearing, Dr. Kinsbourne pinpointed the DTaP[7] vaccination, and specifically the acellular pertussis component[8] therein, which Evelyn received the day before her first seizure, as the cause of her long-term seizure disorder. Tr. I at 8. He explained his theory, representing to the Court that it was a medically and scientifically reasonable explanation for Evelyn's injury to have been caused by the pertussis toxin within the DTaP vaccine:

> [T]he pertussis vaccine is a very well-known potentially [neuro-toxic] agent, because of pertussis toxin contained in the vaccine. Although pertussis toxin is a newer toxin, it cannot be removed from the vaccine because it is the chief agent against which the immunity is developed. For which purpose, the vaccine is given in the first place.

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[7] Regarding the difference between acellular pertussis vaccine and its predecessor, the Court notes:

> Technologic developments have allowed identification and selective extraction of the individual [*Bordetella*] *pertussis* antigenic constituents that induce the immunologic response in the host necessary to prevent infection. The antigens that are important in provoking a host immune response and are components of acellular pertussis vaccines are inactivated pertussis toxin, filamentous hemagglutinin, fimbriae, and pertactin.
>
> Pertussis toxin promotes attachment of the bacterium to ciliated respiratory epithelial cells, provokes lymphocytosis, and sensitizes cells to histamine effects. Development of a host antibody response against pertussis toxin may be crucial to development of protective immunity... All four of the currently approved DTaP vaccines contain pertussis toxin that has been detoxified by chemical inactivation or attenuated by molecular genetic techniques to reduce (compared with whole-cell DTP vaccine) the amount of bacterial endotoxin per dose.

Pet. Ex. 21, Dennis A. Conrad and Hal B. Jensen, *Using acellular pertussis vaccines for childhood immunization*, 105 (7) POSTGRADUATE MEDICINE ONLINE, 1-12 (1999).

[8] The Court recites a brief introduction of the pertussis toxin from one article of medical literature filed in this matter:

> The secreted pertussis toxin (PT) is a decisive virulence factor of Bordetella pertussis, the causative agent of the childhood disease whooping cough. PT is organized according to the AB structural principle which is typical for numerous bacterial toxins. The A-protomer consists of a single polypeptide (S1) that mediates ADP-ribosylation of the a-subunit of several heterotrimeric inhibitory G proteins. This modification blocks the inhibitory effect of G_i proteins on adenylate cyclase and in this way not only interferes with the homeostatic inhibitory regulation of adenylate cyclase stimulation but also results in a modulation of G-protein-mediated signal transduction, a central step in cellular communication. ... The B-oligomer mediates binding and uptake of PT by target cells and the translocation of the S1 subunit.

Pet. Ex. 19 (Kerstin E. Brückener *et al.*, *Permeabilization in a cerebral endothelial barrier model by pertussis toxin involves the PKC effector pathway and is abolished by elevated levels of cAMP*, 116 (9) JOURNAL OF CELL SCIENCE, 1837-1846 (2003)) at 1837 (citations omitted). Dr. Kinsbourne cited this article because it discusses the role of the B oligomer ("branch") in raising the permeability, and therefore penetrability, of and through certain cells of the human blood-brain barrier. The Court notes some similarity between this theory and the one rejected by a now-departed special master in *Moberly v. Sec'y of HHS*, No 98-0910V, 2005 WL 1793416, (Fed. Cl. Spec. Mstr. Jun. 30, 2005), which rejection was upheld by Judge Wolski of the Court of Federal Claims (85 Fed. Cl. 571 (2009)), and a panel of the Federal Circuit (__ F. 3d __, 2010 WL 118661 (Fed. Cir. 2010)), and which is the subject of a motion for *en banc* review of the Federal Circuit.

> Now, pertussis toxin has a mechanism of injury of neurons, which has been well established and has been known about and outlined for many years. It attaches to such structures in the cell walls of certain 13 neurons called G proteins. And the neurons that -- it attaches to neurons that are largely inhibitory in nature. The pertussis toxin attached to those G proteins inactivates these inhibitory neurons, thereby disturbing the balance of excitation versus inhibition in the brain. And thereby, facilitating or causing seizures. And in my report, I give some more chemical details of this cascade of events. And as counsel said, I submitted some literature with respect to that.

Tr. I at 12-13. Dr. Kinsbourne replied to Dr. Wiznitzer's criticism that any such injury from the DTaP vaccine is speculative by referring to medical literature supporting Petitioner's contention:

> There are two ways of addressing that. One is, as a preliminary matter, to point out that, of the articles I reviewed,[9] and on the adverse effects of the acellular vaccine, not a single one of them says, well, they couldn't have happened. This had to have been coincidental because the pertussis toxin is -- toxoided, is inactivated. And, no such claim is made. In fact, none of the articles take the position for any reason that the acellular vaccine is safe. In fact, they warn against making that assumption.
>
> But, more specifically, I have researched the matter. And I am able to provide to the Court, if the Court so wishes, literature to the effect that the toxoiding process in pertussis vaccine manufacture is imperfect, and that, in many cases, substantial pertussis toxin does remain.

Tr. I. at 13-14, referencing Pet. Ex. 39-40.[10]

Dr. Kinsbourne next addressed whether the timing of onset following the vaccination fit within the medically-appropriate time frame:

> [T]he usual time frame, which I adopted, which is generally adopted, is three days. But, case reports show that the great majority of these acute events happen in the first day. And even maybe in the first 12 hours or so. So that, it is very typical of severe reactions to pertussis vaccine to occur very early on as they did in this case.

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[9] One example pointed out by Petitioners in their brief states, in part:

> The adverse events profile of DTaP vaccines is more favorable than that of whole-cell DTP vaccines, in terms of both mild local and systemic reactions and moderate to severe reactions. However, the number of subjects who have received DTaP vaccines to date has been too small to calculate the risk of extremely rare but potentially life-threatening reactions (e.g., immediate anaphylaxis, encephalopathy). Moreover, the moderately severe adverse reactions (e.g., temperature exceeding 104°F (40°C), hypotonic-hyporesponsive episodes, persistent crying, *seizures*) reported with use of whole-cell DTP vaccine *have also been observed with use of DTaP vaccine*.

Pet. Ex. 21, Dennis A. Conrad and Hal B. Jensen, *Using acellular pertussis vaccines for childhood immunization*, 105 (7) POSTGRADUATE MEDICINE ONLINE, 1-12 (1999) (emphasis added).

[10] The Court's review of the medical literature filed in this case is included *infra* at page 30 *et seq*.

Tr. I at 18. Dr. Kinsbourne also noted the absence of any other triggering cause for Evelyn's 12 February 2004 seizures, but conceded that she very likely was genetically susceptible or otherwise vulnerable to a seizure disorder:

> I have no doubt that there is some vulnerability factor, or susceptibility factor in this child. After all, millions get this vaccine and do not react in this way. So, there has to be some -- something is going on. And maybe, there is some genetic susceptibility factor at play. We don't know at this time what that is. But, without reservation, I am not aware of any other alternative potential causation.

Id. Dr. Kinsbourne was unaware of any place in the medical records where treating doctors identified an alternative cause. *Id*. at 19. Later, Dr. Kinsbourne was asked what significance lay in the gastrointestinal symptoms that preceded Evelyn's six-month examination and vaccination, and he noted that no full-blown fever accompanied them, and that they had resolved by the time of her visit to the doctor. Tr. I at 39.

One point that both experts agreed was in the classification of Evelyn's first seizure. When the Court asked if the seizure could be typed a "febrile seizure," Dr. Kinsbourne clarified that Evelyn's first seizure(s) on the morning of 12 February 2004 "would be categorized as a seizure with fever." Tr. I at 20. He explained the distinction:

> [T]here is a semantic issue here which is always good to be very clear about. There is an entity called benign febrile seizures, which are seizures that are defined by an accompanying temperature, but also by the fact that they are short lasting, usually two or three minutes, certainly not more than 15. They do not recur sequentially as in this case. And they have a very, very good prognosis. Now, it is very clear that Evelyn's seizure was not in that category. And in fact, that is specifically stated in the record. So, I would say it is a -- what one sometimes calls a complex febrile seizure, which is a type that is known to be associated with brain damage in some children. It is not a benign febrile seizure.

Tr. I at 20. However, Dr. Kinsbourne did believe that Evelyn suffered "a complex febrile seizure," which he thought overlapped with the description "*status epilepticus*," which he defined as "one or more seizures adding up to a total of half an hour." Tr. I at 28-29. Dr. Kinsbourne noted later that he did not derive the diagnosis of *status epilepticus*, but that such diagnosis was rendered by the treating doctors. Tr. I at 31; *see* Pet. Ex. 3 at 21. He explained that the standard of half an hour is just a reference point, "a definition of convenience." Tr. I at 31. Dr. Kinsbourne continued:

> [W]hat you are really saying is, this is a serious continuing seizure event which needs management, needs to be stopped, or otherwise, the child is going to be in very bad trouble. And that may present as one seizure, that just goes on and on and on until you hopefully stop it. Or, the seizures keep coming. Whatever state in the brain is still generating them is still there. It's going on. And they come again and again and again. And these two patterns are really treated in the same way. They both are serious, ominous, and have to be stopped.... So, I don't think that adding it up is the only way to look at it, although it is a legitimate way to look at it. There is something going on in this child's brain after the vaccination which wasn't going on before.

There was some kind of tendency to abnormal neuronal discharge which wasn't before. And it was going on and on. It needed to be stopped.

Tr. I at 31-32.

Dr. Kinsbourne explained and distinguished into three categories the medical literature Petitioner filed in support of Dr. Kinsbourne's expert opinion: 1. Articles addressing the effects of the DPT (whole-cell) vaccine; 2. Articles explaining that when adverse events followed from the DTaP vaccine, they were of similar if not identical nature as those events following the DTP vaccine, even if events following DTaP were much more infrequent; and 3. Small-power epidemiologic studies of DTaP adverse events. Tr. I at 8-11.

On cross-examination, Dr. Kinsbourne acceded that Evelyn did not suffer a "Table Injury." Tr. I at 23. He also conceded that none of the treaters implicated the DTaP vaccine as a cause of the seizures, but added that the treaters did not much pursue aetiology to conclusion, but primarily considered genetic testing for a genetic source for the seizures. Tr. I at 24-25. Dr. Kinsbourne elaborated on the genetic testing of the SCN1A gene, the results of which demonstrated that Evelyn did not have a mutation of that particular gene which would predispose her to a seizure disorder:

It tests for over 100 variants of one particular gene. The reason it is chosen, of course, is that there are many serious epilepsies of early onset in which that test is positive. It just happened not to be here.

Tr. I at 25. This led to a weighty concession by Dr. Kinsbourne amid cross-examination:

Q And the fact that that test wasn't positive here doesn't mean that this child doesn't have a genetic disorder?

A No. On the contrary, I think she might well have one.

Q What do you mean by that, when you say she might well have a genetic disorder?

A I mean the same that I was saying as a proviso earlier, that when an individual child has such a severe reaction to an agent, which elicits in almost everybody else no reaction at all, there has to be a host factor as well as the environmental factor. And even in SCN1A, the mere fact of having that variant is a necessary, but not a sufficient explanation of why an individual might have a very severe epilepsy. There is a collision between the gene, which renders a person susceptible, and the environment, which has an agent which the person has been rendered susceptible. So, I assume that there is something special about Evelyn's constitution, if you like, that made her react in this way to a medication, if you like, which all seven of my children had no trouble with at all.

Q And so, how do you know that there is a confluence between the environmental factor and the genetic factor? Could you develop epilepsy just on the genetic factor?

A Well, we don't know actually. We are discussing the possibilities. We don't know whether she had a genetic factor. It's conceivable that there are genetic

variations which compel a severe seizure outcome under any circumstances. I just don't know of any where we can really say that....

Q But, genetics can be a cause of epilepsy. And is it fair to assume that the physicians who were running these genetic tests thought that Evelyn might suffer from a genetic abnormality as the cause of her seizure?

A Without purporting to know their state of mind, I would say that they more likely thought -- wanted to know why this child was vulnerable to an agent while others are not.

Tr. I at 25-27.

Returning to Dr. Kinsbourne's description of seizure with fever, Respondent asked what caused the fever, and Dr. Kinsbourne noted that "the pertussis vaccines is known sometimes to cause ... fever." Tr. I at 33. This prompted the Court to ask which came first, the fever or the seizure, to which Dr. Kinsbourne replied that the fever appeared first, "[b]ased on the parents' observation of the child in the morning ... that she was warm, which occasioned them to give Tylenol." *Id*., referencing Pet. Ex. 7 at 360. Regarding the temperature taken after the second seizure, at the hospital, Dr. Kinsbourne agreed that the seizure process itself can elevate body temperature, "[i]f they are prolonged, because of the metabolic demands of the continuing firing. I think, it's less likely to be the case when they are brief. And they stayed relatively brief." Tr. I at 38. Likewise, he agreed that a temperature of 100.8° F would be considered "a low-grade fever." *Id*.

Dr. Kinsbourne was called briefly for rebuttal testimony, where he conceded one of Dr. Wiznitzer's central contentions, while still affirming his opinion of vaccine causation:

Evelyn had a susceptibility or vulnerability to having seizure disorder. ... And there are many different reasons. There are some reasons we know. Some reasons hypothetical. Some reasons might have been uncovered had she had those [additional genetic] tests. None of that makes any difference to my belief that she was, indeed, susceptible. When I say that the pertussis vaccines caused the seizure disorder, I didn't say it was like a blow on the head in an otherwise perfectly normal person. Of course, it caused it in that person, because that person was vulnerable to having it caused in that person. So, I see no contradiction between giving a causational opinion for pertussis vaccine and acknowledging a susceptibility or vulnerability which could be very real.

Tr. I at 112.

At the secondary hearing, Dr. Kinsbourne recapitulated that Evelyn's "prolonged" seizure disorder was caused by the acellular pertussis vaccine, and that the premise that acellular pertussis can cause such an injury is considered plausible within many in the medical community, and that such consensus is represented by that vaccine's inclusion on the Vaccine Injury Table:

It's very generally believed. There have been a number of epidemiological studies that have compared the two types of pertussis vaccines with respect to adverse effects, including neurological adverse effects, and all of them have found that the

spectrum of effects is much the same. Although of course the incidence of those effects is far less when the acellular vaccine is used, nonetheless, those effects still occur. And none of the articles have questioned that the acellular vaccine is fundamentally capable of causing neurological harm.

Furthermore, the vaccine injury table has explicitly bracketed together the DTP vaccine and the DTaP vaccine as causes of the table injury encephalopathy, which of course implies that the acellular pertussis vaccine is indeed capable of damaging the brain. And with respect to the present case, if it's able to cause encephalopathy, it is clearly able to cause the lesser level of injury involved in a severe seizure.

Tr. II at 6-7. He reiterated this point later, emphasizing that "if the Court were to find that the acellular vaccine is incapable of causing neurological harm, that would be in direct conflict with the wording of the vaccine injury table." Tr. II at 16.

He elaborated, as well, the mechanism for this injury at the antigen level:

[P]ertussis toxin is generally believed to be the major agent of adverse effects when they occur, when they infrequently occur, after pertussis vaccination. This toxin has two branches or wings, the A and the B. The A section is thought to be the section which inflicts damage on neurons when such damage occurs by a process called ADP ribosylation, which in fact impairs inhibition and causes neurons to fire excessively and sometimes fuels seizures or even cell death. I will refer to that as ADPR as of now. Now the B component of the toxin has among its functions the attachment of the toxin to the cell. So clearly if the toxin can't attach to the cell because the B component isn't working, then the A component could not inflict damage. Now, because of the known fact that the whole-cell pertussis vaccine does at times cause severe neurological damage, the acellular vaccine, which too contains much the same amount of pertussis toxin because that's really the main source of the immunity which is aimed for by the vaccination, is toxoided. That is an attempt to render it inactive, to render the A branch of the toxin inactive such as it can no longer inflict harm. And it seems that this toxoiding has had a considerable effect because, indeed, the incidence of harm is much less than it was in the whole-cell vaccine.

However, the two articles [Pet. Ex. 39 and 40] show that the efficacy of inactivating the A branch of the pertussis toxin is not invariably 100 percent but rather that in a similar vaccine, it is not infrequently the case that ADPR typically can still be identified to a significant extent. So we cannot reliably say that because the vaccine is toxoided, it couldn't inflict neurological harm. That would depend on whether the particular lot of the particular vaccine was in fact 100 percent protected against ADPR activity. And the literature shows both in the two articles that I've cited and in many others that there is no assurance of that. I might add that there are numerous methods of toxoiding, and there are a variety of formulations of acellular vaccines. And the problem with reliably getting rid of ADPR activity is one that is still ongoing, and there is still an energetic research effort ongoing to try to produce an improved late-generation acellular vaccine which will guarantee that toxicity is completely and permanently abolished.

...

> ADP ribosylation could have been still present in the vaccine lot that Evelyn Sucher received. Of course, we don't know whether it was, and we don't know the relative efficacy of toxoid in that particular vaccine. That's a level of detail which I don't believe the Court necessarily would like to address. In response to this point, Dr. Wiznitzer pointed out in fact even if the A wing of the pertussis toxin were still active, that wouldn't matter if the B wing were inactivated. And he argued that the toxoiding might have inactivated the B wing even if it didn't completely inactivate the A portion. And that's cogent because if the B wing is inactivated, then the toxin can no longer attach to the cells, and therefore, the toxin could not inflict harm. However, although Dr. Wiznitzer filed numerous articles, I didn't perceive in any of them any evidence that toxoiding of a similar vaccine indeed does inactivate the B wing of the toxin, and therefore, I have to retain my previous opinion.

Tr. II at 8-9, 11. Dr. Kinsbourne continued this explanation by discussing an article of medical literature filed by Respondent, noting that the article discussed the *possibility*, as a research goal, not current practice, of making a vaccine with only the "B" aspect of the toxin, which would avoid the imperfections of the current manufacturing methods. Tr. II at 12-13, discussing Resp. Ex. H at 1132. This prompted a question from the Court:

> THE COURT: Dr. Kinsbourne, would inactivation of the B wing of the toxin affect the antibody response/interaction?
>
> THE WITNESS: There is some evidence from submitted articles that the B portion itself can generate significant immunity. Whether it will be as effective as using the whole toxin is an open question.

Tr. II at 13-14.

Dr. Kinsbourne also explained a problem that may arise under the current toxoiding processes, even when the process is completely effective, the problem of "reversion":

> There is a second problem which also hasn't been fully dealt with as yet, which is even if the toxoid has completely utilized ADPR activity, it's been found that on occasion that molecule can revert to the active toxin state. In other words, it again has the same adverse effects that it would have had had it not been toxoided in the first place.

Tr. II at 14. Petitioners prompted Dr. Kinsbourne to point out a portion of literature filed by Respondent which acknowledges this concern:

> "Thus, the major advantage of using the B oligomer as a component in a vaccine would be the inability of this protein to revert to the enzymatically active form of the toxin which has previously been reported with chemically modified toxins." In other words, because the A part has been reported to revert and become toxic again, it would be an advantage if one could use the B part for the vaccine. But this again is projected into the future.

Pet. Ex. II at 15, quoting Resp. Ex. H at 1135. Dr. Kinsbourne's direct examination brought to light that, as compared to this article filed by Respondent, the articles filed supplementally by Petitioners (Pet. Ex. 39 and 40) performed their testing "on actual [toxoided] vaccines manufactured for administration in the United States," and that they were more current, having been published as late as 2007. Tr. II at 15-16.

2. Max Wiznitzer, MD

At the primary hearing, Dr. Wiznitzer clarified the categories of seizures and their relative severity:

> It is rare that we, as child neurologists, will see a child with a simple febrile seizure. Even if they are admitted to the hospital. [Neurologists] get involved if there is recurrent febrile seizure, in other words, if it's happened more than once, or if it's a complex febrile seizure.
>
> By definition of febrile seizure, period, a febrile seizure is a seizure in a child with a rectal temperature at or greater than 102 degrees, which is 39 degrees Centigrade. Simple febrile seizure is basically a generalized convulsion, either stiffening or shaking, but, a seizure[] with no focal features, that probably -- it probably lasts less than about 15 minutes or so. Technically speaking, it should be less than 30 minutes. But, on the average, it's rare that they go beyond 50 minutes.
>
> A complex partial seizure is basically the same temperature criteria for a temperature that is associated with a febrile seizure, but you have other phenomenon that are associated with it. Either, there is recurrent seizures during the day, more than one, or it's a seizure that lasts for more than 30 minutes. It's a seizure that occurs with focal features, which means one side shakes, or you may have head turning to one side with no shaking, or no clonic activity ... of any type.

Tr. I at 47-48. He agreed with Dr. Kinsbourne that Evelyn's case represents "a seizure associated with a low-grade fever," and "not a febrile seizure." Tr. I at 71. According to at least one study's criteria, the standard to be counted a febrile seizure is 102°F, which means that, with Evelyn's measured temperature of 100.8°F, her seizure should be accounted afebrile. Tr. I at 71-72, referencing Pet. Ex. 26. He also agreed with Dr. Kinsbourne that the initial seizures which occurred the day after vaccination were indivisibly related to the seizure disorder that followed, that they are all of a piece. Tr. I at 108.

Dr. Wiznitzer's biggest disagreement with Dr. Kinsbourne regards the medical plausibility of direct injury by pertussis toxin in the acellular pertussis (DTaP) vaccine *via* disruption of G proteins leading to increased neuronal excitability, which Dr. Wiznitzer disputed on three separate grounds: first, he disputes the causal relationship between pertussis toxin and onset of epilepsy; second, he pointed to emergent understanding that epileptic encephalopathies "probably are not related in a causal manner to the pertussis toxin, but are related to an underlying genetic predisposition to seizures that is going to show itself" inevitably; and third, that the treating doctors considered the DTaP vaccine as a cause, but decided to pursue genetic susceptibility instead. Tr. I at 50-56. The first two objections challenge Petitioner's proof on the "can it" prong of causation

(whether the vaccine can cause the injury), the latter concerns the "did it" prong (whether the vaccine caused the injury in the instant case).

Discussing the relative capability of the DTaP vaccine to affect the brain sufficiently to result in a seizure, Dr. Wiznitzer pointed out the *Lovejoy* (or *Loveday*) decision in Britain, which ordered the subjects of an epidemiological study to be contacted and their records examined, as a rebuttal to the DTP and NCES studies[11] which had established the association between pertussis toxin and "acute neurologic events." Tr. I at 50-51. According to Dr. Wiznitzer, there the court's ordered study resulted in a finding "that a few of [the subjects then] had no persisting problems," and "an alternate causation for all the others" could be identified.[12] Tr. I at 51. Dr. Wiznitzer alluded also (without citation) to a more recent analysis that did not support a causal relationship, which excluded several data points, data points which had been included by the IOM in its analysis. *Id*.

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[11] *See* Pet. Ex. 16 (R. Alderslade *et al.*, *Whooping Cough*, THE NATIONAL CHILDHOOD ENCEPHALOPATHY STUDY, 80-83, 101-106, 148-150 (1981)), which concluded there was a statistically significant higher risk for neurologic injury associated with the recent receipt of the DPT vaccine. There was a dispute between the experts that is (at best) tangential to the matter at hand: whether Evelyn's course would have qualified her to participate as a subject in that study if it had been conducted contemporaneously with her condition. Dr. Kinsbourne argued that she would be included because she fit the injuries studied and the onset window following vaccination; Dr. Wiznitzer pointed out that the NCES study studied only vaccinees of the whole-cell pertussis vaccine. Neither expert explained why such dispute was remotely relevant to what caused Evelyn's seizures.

[12] However, the IOM did not rest on one set of data points either, but followed a diachronic approach themselves, as Dr. Kinsbourne mentioned in his expert report:

> Based on a 10-year follow-up of the NCES cohort, the Institute of Medicine further concluded "that the balance of the evidence is consistent with a causal relationship between DPT and the forms of chronic nervous system dysfunction described in the NCES in those children who experience a serious acute neurological illness within 7 days after receiving DPT."

Pet. Ex. 14, citing to Pet. Ex. 31 (Kathleen R. Stratton *et al.*, Editors, Institute of Medicine: DPT VACCINE AND CHRONIC NERVOUS SYSTEM DYSFUNCTION: A NEW ANALYSIS, 15 (1994)), referencing Pet. Ex. 28 (Nicola Madge *et al.*, *The National Childhood Encephalopathy Study: A 10-Year Follow-Up*, 35 (68) DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY, 1-118 (1993)).

In support, Dr. Wiznitzer discussed the findings of a study[13] performed on mice which compared the interleukin-dependent neurological effects of the pertussis toxins in DTP and DTaP vaccines: "[Whole-cell Pertussis toxin] is going to induce pro-inflammatory cytokine production of the brain and associated neurologic changes," whereas "acellular pertussis are devoid of active toxins and therefore do not induce inflammatory cytokines or neurologic reactions." Tr. I at 64, citing Pet. Ex. 17 at 30. He added that, based on this animal model, "in the *in vivo* phenomenon, there is no impact when you've detoxified the toxin. It seems to get rid of the effect." Tr. I at 64. Dr.

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[13] That study compared inflammatory cytokine responses between the DTP and the DTaP vaccines:

> The pro-inflammatory cytokine, interleukin-1 (IL-1) plays a pivotal role in mediating central responses to stress, infection and disease and we have previously shown that infection of mice with B. *pertussis* or parenteral administration with [whole-cell pertussis] leads to an increase in IL-1β centrally. We have already demonstrated that an increase in core body temperature following parenteral administration of [whole-cell pertussis] was associated with increased IL-1β in the hypothalamus. This IL-1β-mediated increase in temperature was identified as a causative factor in the development of convulsive behaviour in [whole-cell pertussis]-immunized mice. The central effects of IL-1β in response to [whole-cell pertussis] immunization, may be dependent on the ratio of this pro-inflammatory cytokine to factors that inhibit its bioactivity.... [I]mmunization with [whole-cell pertussis], but not [acellular pertussis], resulted in an increase in the ratio of IL-1RI to IL-1RII mRNA expression in the murine hypothalamus.... Immunization with [whole-cell pertussis] is associated with increased caspase-1 and IL-1β, whereas [acellular pertussis] increases IL-1ra in the hypothalamus....
>
> The increased incidence of adverse neurological events following immunization with [whole-cell pertussis] compared with [acellular pertussis] is largely unexplained. It has been suggested that residual toxins, including LPS and PT, present in [whole-cell pertussis] preparations may be responsible for the neurological reactions. We have previously demonstrated a role for the pro-inflammatory cytokine, IL-1β, in mediating central events following pertussis infection or immunization with [whole-cell pertussis]. Using a murine seizure model, we demonstrated that [whole-cell pertussis]-induced convulsive behaviour was associated with an increase in IL-1β in the hippocampus.... Furthermore, we have demonstrated that active bacterial toxins, including LPS and PT, at the dose present in [whole-cell pertussis] preparations, could induce pro-inflammatory cytokine production in the brain and associated neurological changes observed following immunization with [whole-cell pertussis]. In contrast, [acellular pertussis] are devoid of active toxins and therefore do not induce inflammatory cytokines or neurological reactions, but one of its components, filamentous haemagglutinin, can induce anti-inflammatory cytokine production by macrophages and dendritic cells....
>
> Our findings demonstrate differential effects on IL-1-associated signalling components following [whole-cell pertussis] and [acellular pertussis] immunization in the murine hypothalamus. Immunization with [whole-cell pertussis] resulted in a concomitant increase in IL-1RI mRNA and a decrease in IL-1RII mRNA expression in the murine hypothalamus. [Whole-cell pertussis]-induced IL-1β protein in the hypothalamus was accompanied by an increase in caspase-1 and IL-1β mRNA expression. Furthermore, [whole-cell pertussis] immunization resulted in increased activity of the stress-activated kinase. In contrast, immunization with [acellular pertussis] failed to activate pro-inflammatory IL-1 responses but resulted in an increased production of IL-1ra. These results provide evidence that suggests that the increased incidence of neurological side-effects associated with [whole-cell pertussis], but not [acellular pertussis], are due to a concomitant increase in IL-1β and IL-1 components centrally which facilitate its reactogenicity.

Pet. Ex. 17 (Michelle E. Armstrong *et al.*, "*IL-1β-dependent neurological effects of the whole cell pertussis vaccine: a role for IL-1-associated signalling components in vaccine reactogenicity*, 136 J. NEUROIMMUNOLOGY, 25-33 (2003)) (citations omitted).

Wiznitzer believed that the pertussis component within the acellular pertussis vaccine follows a different "mode of action" than does the whole-cell vaccine, and pointed to that article in support. Tr. I at 64-65. He believed any comparison between whole-cell and acellular pertussis vaccines was inapt, that in the acellular variety, "pertussis toxin [] clearly has been reduced in its potency, if not -- if not had an evolution in its potency." Tr. I at 66. Indeed, he continued in this vein to state that the difference between the two is not quantitative but qualitative: "the core component, which is pertussis toxin, is it not the same thing in the DTAP as it is in whole cell pertussis." Tr. I at 67. He added that even where studies purported to describe a similarity between adverse events of DTP and DTaP, such studies neglected to mention that the long-term sequelae of those reactions were more benign, adding that among revisited subjects of purported DTaP vaccine injuries, "none of the children ever developed epilepsy." Tr. I at 67-68, citing Pet. Ex. 18. Applying that to the instant case, Dr. Wiznitzer said "you don't see basically the progression here that Dr. Kinsbourne is positing." Tr. I at 68.

Dr. Wiznitzer did not believe the medical literature filed by Petitioner on the adverse events associated with DTP were persuasive in this case, because of the difference between DTP and DTaP vaccines, and because he accounts the trend in emerging research to be discounting the previously-understood link between the DTP vaccine and seizures:

> DTaP is not just [DTP] lite. I mean, DTAP is a very refined vaccine that has an extremely limited number of antigens that are present in there, depending on which vaccine you get, if I'm not mistaken, there's either three or four. And it does not have that whole slew -- that whole soup and slush that you find in the whole cell vaccine where there is a lot of other factors in there that you don't wish to be added. Only because they are more likely to provoke some sort of an adverse event. And since -- if you -- you can't compare the two, that basically breaks the chain of a logical association.

Tr. I at 70.

Another point Dr. Wiznitzer made on the infeasibility of vaccine injury by the acellular pertussis vaccine regards the type of studies written up in the medical literature Petitioner filed: he said they were all (but for Pet. Ex. 17, referred to in footnote 13, *supra*) cell culture (*in vitro*) studies, not animal experiments or human epidemiological studies. Tr. I at 65. To him this was a critical distinction:

> The *in vivo* model is much more complex. The *in vivo* model has many protective mechanisms in place to make sure that things don't bother you. There's other systems in there to make sure that the toxin doesn't do what it's supposed to do, that it doesn't get to where it's supposed to get to. Because you are talking about some blood brain barrier components in a cell culture, it's not -- it's not the same thing as blood brain barrier in the body itself which is a much more dynamic, and it's much more complicated and involved system.

Tr. I at 65-66. To Dr. Wiznitzer, because the effects described in *in vitro* studies are not seen in the *in vivo* mouse models, he concludes that "there is no plausible biologic construct that would support

[Dr. Kinsbourne's] hypothesis." Tr. I at 66. He noted later, *a fortiori*, what the absence of human epidemiological evidence portends:

> [W]e don't have human data that tells that this is the expected outcome, that this is where it is supposed to go. You can have an isolated seizure that can occur in temporal association with it. And if you had a temperature that is high enough, if you have a true febrile seizure, we know that it can provoke febrile seizures. But there is no -- there's no sequence that you can say, yes, I've had a febrile seizure, and because of the vaccine, that will develop into an epilepsy. Because even the research he cites in here does not support that conclusion.

Tr. I at 68.

Discussing the strong role of genetic predisposition vis-à-vis vaccine causation, Dr. Wiznitzer stated, interestingly:

> [F]or things like epileptic encephalopathies, is we now have more data and are able to identify genetic disorders that are associated with epileptic encephalopathies, that these epileptic encephalopathies do have genetic bases that probably are not related in a causal manner to the pertussis toxin, but are related to an underlying genetic predisposition to seizures that is going to show itself at some time. It may be the fever that is present from the immunization that provokes that tendency. But, that was a tendency that was destined[14] to be there and would have occurred anyway.

Tr. I at 52. He reminded the Court that Evelyn's mother had suffered from a period of some seizure activity as a young child, which resolved itself, which to him suggested that "there very well may be some underlying genetics that are present." *Id*.

He did not view as dispositive the fact that Evelyn's SCN1A testing found no genetic link:

> SCN1A is a mutation of one of the sodium channels. When a mutation occurs in that gene, and to my knowledge, there is at least 150 mutations of that gene that have been identified, as well as other problems that can occur besides mutations, that when it doesn't work right, the cells become hyperexcitable and are more prone to seizures. Her clinical picture is not classic for a child with typical SCN1A mutations, simply because, she's continued to have seizures. Her -- believe it or not, her IQ is higher than the typical -- although, -- although, I have seen children with proven SCN1A mutations who have the same level of functioning and the same seizure pattern that she has. So, it's a minority that's there. If she had a mutation, the testing most likely would have identified, but it would not identify what's called a deletion, which means that you are missing bigger chunks of genetic material, which for technical reasons, the mutation testing cannot look for -- cannot look for.

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[14] Of the three Fates (Μοίραι), both Dr. Kinsbourne and Dr. Wiznitzer seem to be in agreement about the role of Klotho (Κλωθώ) in Evelyn's seizures: that a predisposition to seizures at some point had been spun into Evelyn's thread. However, regarding the precisely-measured moment of time when a seizure would necessarily have occurred and its inevitability–the provinces of Lachesis (Λάχεσις) and Atropos (Ἄτροπος) respectively–the experts remain opposed.

> But, there's other -- there's other reasons why you can have epilepsy. It's not just SCN1A, there's SCN1B, there's SCN2A. Both of which are now available for testing. There may be testing in the future for GABR1 and a whole slew of other channelopathies that are known to cause epilepsy. And there's even -- there is variations on a gene that causes autosomal dominant frontal lobe epilepsy, which I don't think she has. Just to say that even that theoretically is something that you have to look for that's genetic [in] nature. And there's a whole slew of other genes that people have now identified have a genetic basis. The reason here is that, it's not -- it's not logical to surmise that an immunization that contains a detoxified pertussis toxin, and even if we accept Dr. Kinsbourne's premise from the article he quoted, that there is not complete detoxification, that there is still some active agent, there is a significant decrease in the amount of active agent, more likely than not leading to a lowering of the amount that's there, you know, below the necessary threshold, for causing any kind of an issue. And I would argue that that is probably true.

Tr. I at 61-62.

On the suspicion of genetic causation Dr. Wiznitzer gleaned from the medical records, he explained that when Evelyn was tested for genetic mutations that could be associated with a predisposition for seizures, there were not then available the plethora of tests that now abound. Tr. I at 53. He pointed to treating neurologist Dr. Thiele in the medical records as agreeing with him, that "there is an underlying genetic predetermined basis to the seizures that needs to be checked." *Id*., citing Pet. Ex. 6 at 4-5. He explained the thought process of the prudent neurologist confronted with Evelyn's presentation, that they would continue genetic testing to look for a genetic link, because "this is the way they think and this is the way that they would approach things." Tr. I at 54-55. On the contrary, he did not believe that any of the treating neurologists believed vaccine causation to be a likely proposition. Tr. I at 55-56, citing Pet. Ex. 4 at 12-13.

Dr. Wiznitzer found significant the examination of family history that was the focus of Dr. Riviello, a treating neurologist:

> That means she had more than one seizure suggesting that there is some predisposition. Her mother has a predisposition to febrile seizures that she outgrew. And it also suggests, there is a strong -- there is a very strong suggestion that there is a genetic basis for that. Especially when you have a daughter with seizures that are ongoing from infancy. And as Dr. Riviello pointed out, the difficulty here is that, when you test for SCN1A gene mutation, that only explains approximately 10 to 15 percent of the familial febrile seizure population...

Tr. I at 82.

However, Dr. Wiznitzer did not believe the opinions of the treating neurologists to be dispositive simply because they witnessed the symptoms firsthand. Instead, he explained that:

> I always come to conclusions on my own irrespective of what other people say. You've got to keep an open mind when you look at things. You have to walk in, look at the records, and pretend that there is a blank slate and ask yourself the

question, there's a problem here, what can be -- what can be the reason for the problem. Because, once you've fixed your mind on one idea, you get stuck and you very well may miss something that can be obvious in that regard. ... I listen to what other people say, but I come to my own conclusions.

Tr. I at 58. Dr. Wiznitzer found the treaters assumption of genetic causation significant, because it demonstrated "that they were thinking that there was an underlying genetic basis, even if they couldn't identify it." Tr. I at 60.

Eventually, Dr. Wiznitzer's opinion took an intriguing turn; the following interchange occurred on direct examination:

Q ...Now, you had mentioned earlier on that vaccines can be associated with fever, can cause fever; is that -- is that correct?

A Oh, yes. Yes. In fact, we know that. That's a given.

Q And does the DTaP cause fever?

A Yes.

Q Okay. Compared to the other vaccines, is it more or less likely to cause fever?

A Compared to the DTP, it is less likely to cause fever. I think, some people believe, compared to the pneumococcal vaccine, it is less likely to cause fever. Compared to the chickenpox vaccine, it's more likely to cause fever.

...

Q So, do we know what caused -- to the extent that Evelyn had a low-grade fever, do we know what caused it?

A We have two possibilities. One is that the medical records tell us that the illness to -- the gastrointestinal illness that she had was associated with a low-grade fever that is documented in the discharge summary from the initial hospital admission in February 2004.

...

You've got two reasons why you can have fever. One is the pre-existing illness that you basically were seeing the last aspects of it provoking fever and causing vomiting the evening before, because she had had a gastrointestinal, and that was associated with vomiting and low-grade fever. Or, she has fever due to the immunization. And this is one of those things where you've got some complications here. And -- and you basically have to just look at it and say, here is the two possible reasons.

Q But, the fever itself is not high enough, in your opinion, to be considered a febrile seizure?

A This is not a classic febrile seizure. This is a fever -- in this case, this was a fever associated with seizure.

Q And why is that important to distinguish that from a febrile seizure?

A As Dr. Kinsbourne had stated beforehand, when the temperature goes up in individuals who are susceptible, whether it is due to a factor such as an intercurrent illness with viruses such as HHV6 or parvovirus, or if you have an underlying genetic tendency, because it runs in the family, when the temp goes high enough, it can provoke a seizure. And we have found that when the temp -- the cutoff -- it is a somewhat arbitrary cutoff, but it has been shown that this is probably a valid cutoff that when it's above --it's 102 and above, then it's most likely to be associated with the entity we've defined as febrile seizure. When it's below that, while you still have a fever, it's really just a fever associated with seizure.

And if I may, for instance, my patients with epilepsy -- with known epilepsy, they may not need 102° temperature to provoke their seizures. Those with known epilepsy, I may just need to have a temp of 100 or 100.5 and that's all they need to set off their seizure. These are kids with a pre-existing tendency towards seizure where this is a sufficient stressor to provoke the seizure in that individual. But, the tendency is already there.

Tr. I at 72-77.

Dr. Wiznitzer reiterated repeatedly that, if the vaccine (or any other challenge) caused a fever, which then stressed Evelyn's system enough to trigger (or "unmask") the first seizure of a seizure disorder to which she was genetically predisposed, that would render the triggering agent irrelevant:

THE COURT: So therefore, hypothetically, you could have a gastroenteritis causing a mild seizure -- I mean, causing a mild fever which causes the seizure. Or, in the alternative, you could have a vaccination causing a mild fever which causes the seizure?

THE WITNESS: In a person who already has a tendency towards --

THE COURT: A genetic predisposition.

THE WITNESS: Who already has -- basically, and in my opinion, this is something that is destined to happen. It's just a ticking time bomb destined to happen. It's going to happen anyway. It doesn't matter what the source of fever is, it's going to happen and it's going to follow that time line.

THE COURT: But, can we say, would that seizure -- that first seizure have occurred when it did, if there had been no vaccination?

THE WITNESS: Can't say that, sir. Can't say that because, -- you're asking me, can seizure provoke fever. The answer is yes. We also know that, after -- that children can develop seizures without fever. And we know that in her that that has happened. That she has seizures without fever. So that you can't state that there is definitely -- that that was the ultimate provocation that -- in the absence of fever, you would not have had the seizure on that day.

THE COURT: Okay.

> THE WITNESS: And the reason I am saying that is, we look at her history later on, noting that you can have -- that she had seizures without fever. And therefore, if she has done it then, she can even do it beforehand.

Tr. I at 78-79. He added that, inasmuch as (he believed) Evelyn's temperature was not taken the day of her vaccination, it was impossible for him to tell whether her preceding gastrointestinal illness sparked her heightened temperature, or if it was brought about by the vaccination. Tr. I at 80. He also raised the possibility, without espousing it, that Evelyn was suffering an active viral infection that could also have given rise to a fever that triggered the seizure. Tr. I at 81.

Dr. Wiznitzer's primary direct testimony concluded with a discussion of the linkage between the her seizure disorder and neurologic deficits:

> Here, she's not having the same frequency of the seizures that are recorded in some of these other populations. She's having some sporadic seizures here and there, little flurries. And then, there is a long time period between them. And it's difficult to ascertain -- or I think, it's difficult to come to the conclusion to say it's definitely because you are having recurrent seizures that is causing -- that is causing the cognitive changes. And the cognitive changes you have are going to get worse over time. Versus just saying, you have some underlying problem with the brain that causes seizures, causes these learning issues, and they become more manifest the older you get. When you're very young, when you are a six-month-old, when you are a year old, when you are a year and a half old or so, there is not enough to sample to really get an idea of where you are going to be cognitively. It's only when you're older that it becomes much more evident.

Tr. I at 85-86.

On cross-examination, Dr. Wiznitzer stated that, in 1984, the evidence would have led him to conclude that whole-cell pertussis toxin could cause seizures, but that his perspective has changed with the rising knowledge of genetics, such that today, his opinion is otherwise:

> But, this is 2008, ma'am. This is not 1984. We now know that there are other reasons that you may have seizures besides -- that you may develop an epilepsy after a vaccination in which the vaccination unmasks the epilepsy, but does not cause it, and does not alter the general history of the disorder.

Tr. I at 90. In addition, he alluded to a study of presumed child sufferers of "presumed pertussis encephalopathy," which found a genetic component in a majority of those children, which led Dr. Wiznitzer to conclude, "In other words, it was not the pertussis vaccine that caused it. It was probably the fever provoked the pertussis vaccine that basically unmasked something that was going to happen anyway." Tr. I at 91. This led to another puissant exchange:

> THE COURT: Would it be fair to say, from that -- from your perspective, that you would say yes, A, pertussis can cause a fever and the fever can cause the seizures?
>
> THE WITNESS: That is a given, Special Master.

THE COURT: And B, if I understand the term you just used, that particularly, the pertussis component can unmask a pre-existing problem?

THE WITNESS: It's not the pertussis. It's the fever.

THE COURT: Okay. So --

THE WITNESS: And I think it's very important, Special Master, to think of it that way. It's the fever. Because, it doesn't matter what causes the fever. There's nothing unique. It's just regular fever. It unmasks something that was going to be unmasked any way at some time or another, either with fever or without fever. It was just that, at that point in time, it brought it out now rather than a week from now, a month from now, or three months from now.

THE COURT: Or it could have been a week prior? Or a week before -- or a month before?

THE WITNESS: Or a week prior. Whatever it would be. But, this was something that was destined to happen. And in those cases that were described in the medical literature, their clinical presentation of those individuals was really no different than the ones that are not pertussis associated. That there was no alteration of the natural history of any kind.

Tr. I at 92. This conversation with the Court continued a little later:

THE COURT: Okay. So therefore, amongst the theories on the table would be that, the seizure was unmasked, to use your term, by a fever which was caused by or unmasked by a gastroenteritis. Or, if you use Dr. Kinsbourne's theorem, then by a vaccination?

THE WITNESS: Well, but not by -- not by pertussis toxin. But, we'll say by -- if you're going to ask me, sure, I agree vaccinations can provoke fever. And I had already answered here in the court that -- that one of the possible reasons for the fever that was present on the morning of the 12th was the vaccination. I would also agree with that statement.

Tr. I at 98-99. And although genetic testing did not specify which gene's mutation predisposed Evelyn's seizure disorder, Dr. Wiznitzer firmly stood by genetic causation as a causal factor unrelated to the vaccine, to a reasonable preponderance:

I can't say that she has those mutations. However, I can say that it is more likely than not that there is something genetic going on because of the family history of febrile seizure.

Q Okay. But you can't -- you can't actually point to anything? At this point, it's just speculation on your part?

A It's not speculation, ma'am. It's a logical sequence of thinking, using data that we have available for us, that's readily available in the medical literature, that we know that -- as Dr. Riviello had written, the history is suggestive of generalized epilepsy with febrile seizure plus, because the mother has history of febrile seizure.

> And there's multiple reasons for GEFS plus, some of which we can test for, many of which we can't, because we don't know what they are. And in this basis, if you were going to ask me the most likely reason why she has her seizures, I would say it's because of a genetic predisposition.

Tr. I at 100.

In a word, it seems the sticking point for Dr. Wiznitzer is what the law refers to as *proximity* of cause, the relative logical connection that a cause in fact has to the eventual result. He seemed to say that what had been thought to be a close relationship (between pertussis vaccine and seizure) was not really that close at all:

> Q So, you're saying that, based upon the knowledge that we have today in 2008, that you would disagree with the conclusions of the NCES as well as the IOM report that looked at the NCES and said that there were -- there were severe consequences to the whole cell DPT vaccine?
>
> A No. There are severe consequences. There are seizures that occur that are provoked by the fever and everything. I agree with all that.... But, the real question is, we're talking about the epileptic encephalopathy, the persistent epilepsies that can occur, where it was ascribed -- a causal relationship was ascribed -- it was actually -- really, what we're talking about here is an association, an association between the vaccine and the ensuing epilepsy.

Tr. I at 94.

Revisiting the earlier discussion of febrile versus afebrile seizure categorization, Dr. Wiznitzer believed that a lower-temperature fever could trigger a seizure in someone with a genetic predisposition to seizures:

> [O]n a theoretical basis, a temperature of 100.8 it may -- may provoke it. And if you have an underlying epilepsy tendency already, let's just -- in fact, let's go back and use a simpler word. If you have an underlying seizure tendency, irrespective of what it is, you don't need a temp of 103.... Low-grade fever is sufficient to provoke -- once it's already there, and the source of the fever is immaterial. It's not because you got damage to the brain. It's not because you are damaging neurons. It's not because you are changing the ratio of excitatory to inhibitory neurons, it's just fever period that can do that. And it's something that was going to happen any way.

Tr. I at 101-102.

On redirect, Dr. Wiznitzer discriminated between mere "unmasking" and full-fledged causation, in the context of this case:

> Dr. Kinsbourne's hypothesis is that pertussis toxin leaks into the brain, damages neurons, causes a change in the excitatory to the inhibitory ratio of neuronal function. And therefore, causes [] seizures to occur and establishes an epilepsy that is there. In other words, something causing means that whatever the substance is, or whatever the event is, or whatever the factor is about which we are speaking, it is the reason

> why the seizures are happening. And in the absence of that factor, the child would never have developed seizures of any type.

Tr. I at 103. The Court notes the similarity between Dr. Wiznitzer's explanation and the "but for" test of legal "cause in fact" analysis. Thereafter, Dr. Wiznitzer provided a few examples of his meaning of *cause*, most of which the law would categorize as "superseding causal factors." Tr. I at 104. To Dr. Wiznitzer, genetic predisposition fits within this category, which is distinct from "unmasking":

> It causes the epilepsy. It's going to happen period, because you've got the problem. There is a difference versus unmasking or bringing out. In some of these conditions, they are going to occur anyway. But, an example -- let's assume you get a fever. And that they are going to occur with or without the fever. It doesn't matter if you get the fever or not. The fever just happens to make -- to lower the seizure threshold. You've already got the tendency that's there. And it brings out the seizure tendency that is going to show itself any way. Whether it is going to show itself at age three months, whether it's going to show itself at age four months, six months, eight months, 10 months, 12 months, it will show itself. That to me is what I mean by unmasking.

Tr. I at 105.

Dr. Wiznitzer's initial testimony was concluded with a brief summation initiated by the Court's restatement and query:

> THE COURT: The Court understands Dr. Wiznitzer's position that there is -- there was an underlying genetic issue.
>
> THE WITNESS: An underlying disorder. We'll just say that sort of --
>
> THE COURT: An underlying disorder.
>
> THE WITNESS: Genetics is an explanation.
>
> THE COURT: And presumably, that was provoked, revealed, unmasked, however one wants to put it, by the mild fever which was 100.8 or less and that it would've happened if it did not happen at that point in time. It would've happened to -- it could've happened antecedent or it could have happened a week or a year or five years later. It would've happened at some point.
>
> THE WITNESS: It wouldn't have been five years though, Special Master. It probably would've happened in the months after. More likely than not, it would've happened in the months after. ... [I]n my opinion, this was something that was destined to occur. Had they not occurred on February 12, 2004, you still would've had the subsequent seizures. The seizures that happened later on would still have happened at points in time.

Tr. I at 107-109.

At the second hearing, Dr. Wiznitzer had much to say about Dr. Kinsbourne's presentation of the toxoiding process used for the acellular pertussis vaccine.

First, he gave a clear explanation of the functions of the so-termed "A" and "B" "branch" of the pertussis toxin:

> [T]here are two steps to toxins. Number one is the toxin has to bind at the site at which it's going to act, and number two is that then the toxin has to do its action. Binding occurs with the B subunit, action occurs with the A subunit, which is the enzymatically active portion. Therefore, I'm going to basically reiterate my position that if you can't show up where you're supposed to, you can't do any harm, which means if you can't bind, you can't do any kind of your enzyme activity and do whatever the toxin is supposed to do.

Tr. II at 20. Later, he defined what he saw to be the disputed issues separating his opinion from Dr. Kinsbourne:

> [P]ertussis toxin not only has to have intact A units, the A unit or the A subunit, which is the enzyme function, but it also has to have intact B subunit, which is the binding to the cell subunit, in order to really function as a toxin. And if you can make that, the B subunit nonfunctional, which means you can't show up where you're supposed to and you can't stay where you're supposed to, if you don't do that, then the toxin basically still doesn't work. And our original argument that it's detoxified holds.
>
> Dr. Kinsbourne then comes back and says wait, you can't inactivate the B subunit because if you do inactivate the B subunit, you destroyed the ability of that pertussis toxin to provoke an immune response. That was my reading of it, and I read it into the record just before. All the rest of the articles that I submitted were basically stating that's not true. You do not have to have intact B subunit function in order to provoke an immune response. If that's not correct, basically his initial hypothesis does not hold.

Tr. II at 40-41.

Dr. Wiznitzer expanded his comments on this topic by commenting that the articles relied upon by Dr. Kinsbourne were *in vitro* studies, instead of *in vivo* studies, which he thought limited its applicability to the question at hand. Tr. II at 22-24. The crux of this criticism is that the mere evidence of ineffective toxoiding or reversion does not require the conclusion that the toxin is therefore just as virulent as whole-cell pertussis toxin that has not undergone toxoiding at all, because the toxoiding process may still have been able to disable the toxin sufficiently to render it harmless, by disabling either the A or B branch of the toxin, both of which are necessary for the toxin effectively to inflict damage akin to the whole-cell form. Tr. II at 24-25. Without *in vivo* data of the effects on live subjects of such toxoided forms, Dr. Wiznitzer would not be persuaded of the medical plausibility of acellular pertussis vaccine injury. Tr. II at 26.

According to Dr. Wiznitzer, the article of medical literature Petitioner filed as Pet. Ex. 41, Tab A stated that the purpose of retaining B branch function intact is to enhance immune response

to the other, active antigens in the vaccine (including, presumably, the A branch of the pertussis toxin), acting more as an adjuvant than as an integral mechanistic portion of the pertussis toxin.[15] Tr. II at 26-27. This argument strikes the Court as orthogonal, since Dr. Kinsbourne did at no time claim the B branch was merely an adjuvant, but agreed that the B branch was an integral, functionally-necessary part of the pertussis toxin.

Dr. Wiznitzer defended the article he had filed, which Dr. Kinsbourne pointed out had been prospective about research possibilities and not descriptive of current industry-wide manufacturing methods at the time it was written, by saying that the paper proved that the B branch did not need to be present to incite immune response leading to immunity:

> It was meant to counter Dr. Kinsbourne's argument that you needed an intact B oligomer or B subunit in order to have the vaccine work properly, because if I can counter that argument, it then supports the point that detoxifying the A subunit or the B subunit or both basically can lead to total dysfunction if you want to call it from a functional standpoint of the toxin but not loss of its immune-provoking property. In other words, the antigen is still there, but the function is gone.

Tr. II at 28-29. However, he later conceded that, inasmuch as the article's authors stated that a manufacturing process of disabling the B branch instead of the A branch "has been successfully developed for acellular pertussis vaccine production," to Dr. Wiznitzer, "that is where we're going nowadays, to use the more uniform genetically modified pertussis toxin." Tr. II at 34, discussing Resp. Ex. G. Nevertheless, what Dr. Wiznitzer viewed as the critical point made by that article was that the B branch is "not essential to provoke antibody and immune response to the pertussis vaccine." *Id*. The Court saw this digression as somewhat tangential, inasmuch as the activity of the B branch in Dr. Kinsbourne's theory is not controversial, and is not central; also, given the state of manufacturing procedures at the time Evelyn's dose was produced, there is better than even odds that her dose of the acellular pertussis vaccine was chemically toxoided. Dr. Wiznitzer did not opine on what could result if the B branch was not deleted, and the A branch was imperfectly disabled, whether the toxin might retain the propensity for adverse effects associated with whole-cell pertussis.

Dr. Wiznitzer also criticized one of the citations in an article filed by Petitioner discussing reversion of the pertussis toxin following the toxoiding process:

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[15] In reality, the article addresses adjuvant function as a secondary function for the B branch of the pertussis toxin, that its primary effect is to attach the toxin to receptor sites:

> The B oligomer component of the toxin has a pentametric structure which mediates the binding of the toxin to glycoprotein receptors on the surface of eukaryotic cells and induces polyclonal T cell activation. It has been reported that [pertussis toxin] possesses adjuvant properties [and] has been shown to potentiate both local and systemic antibody responses... These findings suggest that the adjuvanticity of [pertussis toxin] may be associated with enhanced production of both Th1 and Th2 cytokines....

Pet. Ex. 41, Tab A (Mark Ryan *et al.*, *Pertussis toxin potentiates Th1 and Th2 responses to co-injected antigen: adjuvant action is associated with enhanced regulatory cytokine production and expression of the co-stimulatory molecules B7-1, B7-2 and CD28*, 10(4) INTERNATIONAL IMMUNOLOGY 651-662 (1998)) at 652.

> When we look at the reference for no. 22, it's a reference about cholera toxin and their potential reversion. It's not a reference about pertussis toxin and its reversion. What they were saying is that hypothetically it happens with other toxins, and the concern here is that it also can happen with the pertussis toxin.

Tr. II at 29. He added that "one of the things that manufacturers of vaccines are obligated to do is to continually test vaccine lots after they're produced and before they go out to make sure that reversion doesn't occur." Tr. II at 30. Later on, he stated concerning the same article that "there's no proof in this article itself that it's something that commonly happens with pertussis toxin," while also reiterating that it is a potentiality which vaccine manufacturers monitor to prevent. Tr. II at 36. He reconciled these statements by concluding, "Therefore, while hypothetically Dr. Kinsbourne's statements might be right, practically speaking it did not occur because of what the manufacturers do." Tr. II at 37.

On cross-examination at the second hearing, the conversation once again turned to Dr. Wiznitzer's parsing of causation where a DTaP vaccine caused a fever that triggered a seizure which led to an eventual seizure disorder:

> Q Dr. Wiznitzer, would you agree that the DTaP vaccination can cause seizures?
>
> A I would agree -- well, let's turn it around and say it this way. One, DTaP vaccinations can be associated with seizures, and it has been because that's been reported. In the studies that have been done, the rate of seizures with DTaP is usually no higher than the rate of seizures with DT vaccine. That's number one.
>
> Number two, I would also agree that if DTaP vaccine provokes a fever, then that fever, just like fever of any kind, fever from illness, fever from heat overexposure if I put you in a hot bath, if I put you out in the sun so that I overheat you, in people who are already susceptible towards seizures, in other words, people who are destined to have a seizure anyway because fever provokes it, that that fever just like any other fever can do it. There's nothing special about that fever, and it would not alter the clinical course of that underlying seizure tendency just because the fever came from the vaccine. That's different than saying that the vaccine causes brain -- which was represented to the Court today.

Tr. II at 46. Respondent's redirect examination of Dr. Wiznitzer teased out a nuance to this opinion:

> Q You said that DTaP has been associated with seizures when Ms. Ho asked you is there evidence that DTaP causes seizures. Are you making a distinction between associated and caused, and if so, what is it?
>
> A Yes, I'm making a difference. Cause means that the vaccine itself does something, that the vaccine, something special about the vaccine does something to cause a seizure. Dr. Kinsbourne has already basically proffered his hypothetical argument in that what it does is it causes some event where it gets to the central nervous system, causes damage and therefore provokes something. That is not what I'm claiming.

> What happens is when you look at studies that have been done, that if you give immunizations to kids with DTaP and then you follow them for a period of time afterwards, there's a number of kids who are going to have seizures that occur. And that just means that that's because this happened with a temporal association, but it does not mean causal association.
>
> The situation where we know there is an indirect relationship of that type is when the immunization provokes a fever, and the fever, like any other fever from any other source, nothing special about it, with no alteration of the clinical course of the condition, but that fever provokes a seizure in an individual who is going to have seizures provoked by fever anyway, that's the only one where we clearly have definitive and good data to support it.
>
> ...
>
> And if you already have a tendency towards seizures provoked by fever, that fever like any other fever can cause a seizure, but it does not cause an epilepsy. It just provokes a seizure.

Tr. II at 47-48, 51.

Dr. Wiznitzer concluded his testimony by explaining why he thought DTP and DTaP vaccines were too different to warrant comparison:

> Whole-cell pertussis vaccine has a lot of antigens in it, many, many antigens in it that are not present in the DTaP. DTaP basically only has usually two, maybe three or four antigens just related to pertussis. It's a very clean vaccine in that regard.
>
> But you're going to get reactions to vaccines because there's a limited number of reactions monitored for that you can possibly get. The reasons for those reactions have not necessarily been always well defined, but to state that because the reaction occurs to whole-cell DTP and then the same kind of an event occurs after DTaP they must have the same causal mechanism when there are different components and altered components within the DTaP vaccine I think is basically not supported by the medical literature. It's hypothetical.

Tr. II at 48-49.

C. Medical Literature

In this case, inasmuch as a fundamental dispute between the parties' experts hinges on the "can it" prong of theoretical plausibility of Petitioner's theory of causation, the medical literature filed by the parties seems appropriate to summarize. Some citation and quotation was provided *supra* and will not be reduplicated. Similarly, not all of the medical literature was relevant to the disputed issues at hand, so the Court will sort as best as it can. In almost all of them, the internal citations have been omitted.

The most important article to Petitioner's primary theory of causation is Pet. Ex. 19, Brückener *et al.* (*supra* at note 8). The study is summarized as follows:

> Respiratory tract infections caused by *Bordetella pertussis* are occasionally accompanied by severe neurologic disorders and encephalopathies. For these sequelae to occur the integrity of cerebral barriers needs to be compromised. The influence of pertussis toxin, a decisive virulence factor in the pathogenesis of pertussis disease, on barrier integrity was investigated in model systems for blood-liquor (epithelial) and blood-brain (endothelial) barriers. While pertussis toxin did not influence the barrier function in *Plexus chorioideus*[16] model systems, the integrity of cerebral endothelial monolayers[17] was severely compromised. Cellular intoxication by pertussis toxin proceeds via ADP-ribosylation of α-G_i proteins, which not only interferes with the homeostatic inhibitory regulation of adenylate cyclase stimulation but also results in a modulation of the membrane receptor coupling.

Pet. Ex. 19 at 1837. Pertussis toxin is used to initiate experimental autoimmune encephalomyelitis, a lab-introduced mammalian disease used to study auto-immune disorders in humans. "The mechanism by which [pertussis toxin] might enhance the development of EAE has not been elucidated but it appears to involve an increase of the vascular permeability of the blood-brain-barrier." Id. at 1838. The study took note of, but did not study, the difference in effect between whole-cell and acellular pertussis vaccines: "Recently, it has been reported that whole-cell but not acellular pertussis vaccine induced convulsive activity in mice. This could be also induced by the administration of active [pertussis toxin] and LPS, which is residually present in the whole-cell vaccine but is absent in the acellular vaccine." Id. at 1843. The results of the study led to a conclusion that "[pertussis toxin] permeabilizes cerebral endothelial cells." Id. at 1845.[18]

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[16] The Plexus chorioideus consists of "vascular fringelike folds of the pia mater ... concerned with production of the cerebrospinal fluid;" also called choroid plexi, they are "infoldings of blood vessels of the pia mater covered by a thin coat of ependymal cells that form tufted projections into the third [*tertii*], fourth [*quarti*], and lateral [*lateralis*] ventricles of the brain ... and they secrete the cerebrospinal fluid [CSF]." DORLAND'S, *supra* at note 3, at 1453-54.

[17] Endothelial monolayers are single layer sheets of endothelial cells arranged that way for the study of viruses *et al.* Endothelial cells are epithelial cells that line heart cavity and blood and lymph vessels, as well as some other (serous) body cavities. DORLAND'S, *supra* at note 3, at 616, 1170. That study seemed to equate the endothelial layer of cells with the blood-brain barrier, and to use the terms almost interchangeably.

[18] The authors also contextualized that study within the body of existing literature:

> While the enzymatic activity of the S1 subunit is clearly needed for the induction of the disease conflicting reports implicate the B-oligomer subunits as well as the S1 subunit of PT to be involved in the protective effect of PT against EAE. The dual role of PT observed in vivo might be due to the particular PT concentration available locally as at higher PT concentrations elevated cAMP levels proved to reduce the permeability. Furthermore, as the protective effect of the B-oligomer of PT in EAE might be due to the S2/S3-mediated inhibition of leukocyte adherence to selectins on inflamed endothelial cells, elevated PT concentrations might enhance this effect. Thus, with regard to the induction of encephalopathies as a potential consequence of pertussis infection, ... PT might exert a dual effect in permeabilizing cerebral endothelial barriers mediated by the activity of the ADP-ribosyltransferase and, by contrast, mediating an anti-inflammatory effect by competitively blocking leukocyte adherence and recruitment.

Pet. Ex. 19, *supra* at note 8, at 1845 (citations omitted).

Another source submitted by Petitioners, while heralding the greater safety of acellular pertussis and the decisive benefit of the vaccine vis-à-vis any risks it poses, still acknowledged the basis for adverse events as sequelae of the vaccination:

> The adverse events profile of DTaP vaccines is more favorable than that of whole-cell DTP vaccines, in terms of both mild local and systemic reactions and moderate to severe reactions. However, the number of subjects who have received DTaP vaccines to date has been too small to calculate the risk of extremely rare but potentially life-threatening reactions (*e.g.*, immediate anaphylaxis, encephalopathy). Moreover, the moderately severe adverse reactions (e.g., temperature exceeding 104°F (40°C), hypotonic-hyporesponsive episodes, persistent crying, *seizures*) reported with use of whole-cell DTP vaccine *have also been observed with use of DTaP vaccine*.

Pet. Ex. 21 (Dennis A. Conrad and Hal B. Jensen, *Using acellular pertussis vaccines for childhood immunization*, 105 (7) POSTGRADUATE MEDICINE ONLINE, 1-12 (1999)) at 9 (emphasis added).

Another article submitted by Petitioner tracked children who had reacted to DTaP vaccines, which noted seizures as one of those reaction events:

> Seven children with seizures within 7 days of DTaP vaccination were identified. All were younger than 2 years of age, and none had a prior history of seizures. Six had febrile seizures, three occurred within 2 days of vaccination and one of those required hospitalization. [Of those six, none] had neurologic abnormalities or subsequent afebrile seizures documented. ... One child had an afebrile seizure after the second dose of DTaP vaccine given concurrently with other vaccinations at age 5 months. That child was later diagnosed with a chronic seizure disorder and maintained on anti-convulsants. No seizures or other reactions were noted after the next two doses of DTaP vaccine.

Pet. Ex. 24 (Lisa A. Jackson *et al.*, *Retrospective population-based assessment of medically attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids*, 21(8) PEDIATRIC INFECT. DIS. J., 781-786 (2002)) at 784. Petitioners perhaps sought to draw to attention the similarity between Evelyn and the child who suffered from an afebrile seizure and later developed a chronic seizure disorder.

Petitioners submitted an entire 100-page chapter of the seventh edition of CHILD NEUROLOGY, the textbook edited by John H. Menkes, MD: the chapter on "Autoimmune and Postinfectious Diseases." However, they failed to guide the Court's attention to relevant passages of focus. Nevertheless, the Court noted one relevant passage. After discussing the adverse reactions associated with whole-cell pertussis vaccines,[19] the section concludes with, "Major neurologic

[19] That text stated, in the context of DTP, the following quotations, which the Court includes as a general consideration:

> None of the numerous epidemiologic studies has exonerated or implicated pertussis vaccine in these more serious adverse responses. All are confounded by the relatively low incidence of these complications and by the differences in whole-cell pertussis vaccines as used at different times and

reactions to acellular pertussis vaccine have been reported significantly less frequently than those following whole-cell vaccine." Pet. Ex. 25 (CHILD NEUROLOGY, 7th Ed. (2006)) at 633.

Another study filed by Petitioners tracked the decline of seizures associated with pertussis vaccination, as between the DTP and DTaP versions thereof. The study revealed a 79% decrease in febrile seizures following pertussis vaccination, but did not report the absolute cessation of seizures so associated. Pet. Ex. 26 (Nicole Le Saux et al., *Decrease in Hospital Admissions for Febrile Seizures and Reports of Hypotonic-Hyporesponsive Episodes Presenting to Hospital Emergency Departments Since Switching to Acellular Pertussis Vaccine in Canada: A Report from IMPACT*, 112(5) PEDIATRICS (2003)).

Petitioners filed an article for which the findings suggested that:

> [T]he adverse neurological side effects of [whole-cell pertussis] may be mediated through the induction of IL-1β and modulation in neurotransmitter release. The ability of the residual toxins, [pertussis toxin] and [lipopolysaccharide], to exert similar effects, suggests a role for these toxins in the adverse neurological effects associated with [whole-cell pertussis].

Pet. Ex. 27 (Christine E. Loscher et al., *Interleukin-1β-dependent changes in the hippocampus following parenteral immunization with a whole cell pertussis vaccine*, 111 J. NEUROIMMUNOLOGY, 68-76 (2000)) at 73. The authors of that study extrapolated the findings to suggest that "the [whole-cell pertussis]-induced effect may result from the presence of the residual toxins, [pertussis toxin] and [lipopolysaccharide], in the vaccine, since both toxins also increased IL-1β." *Id*.

Petitioners also filed a follow-up study that tracked the participants of the famous NCES study, which discussed the interplay of genetics in children with seizure disorders:

> Genetic factors may contribute to children's susceptibility to convulsions. Most authors report that those affected are more likely than others to have a first-degree relative who has or has had a similar condition, though the association is found in only a minority of cases. ... Evidence on whether or not severity is associated with

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> in different countries. Whole-cell vaccines were not only not standardized between manufacturers, but also, one suspects, varied with the same manufacturer from one lot to the next. This is reflected in the marked differences in antibody response to pertussis vaccination.
>
> From the wealth of case reports and studies attempting to understand the relationship, if any, between whole-cell pertussis immunization and permanent brain damage, the Institute of Medicine has offered three conclusions: (a) DPT administration causes a serious acute neurologic illness and subsequent permanent neurologic dysfunction in children who otherwise would not have experienced either acute or chronic neurologic illness; (b) DPT vaccination triggers an acute and subsequently a chronic neurologic illness in children with an underlying brain abnormality; and (c) DPT vaccination causes an acute neurologic illness in children with underlying brain abnormalities that would eventually have led to chronic neurologic disease even in the absence of the acute, DPT-initiated neurologic illness.

Id. Of note, the vaccine was seen by the IOM as a *cause* of acute adverse reaction *even in cases where underlying abnormalities would have eventually led to the onset* of chronic illnesses of similar type.

> stronger or weaker familial links is conflicting. ... A stronger relationship has been suggested for febrile convulsions.
>
> The search for genetic patterns is hampered by a number of problems ...[in some part because] it is difficult to distinguish genetic factors from exposure to common environmental conditions [and] genetic factors are unlikely to manifest themselves in the same way in all families, and may operate only if certain environmental conditions occur. It is clear that understanding of the mechanisms in genetic transmission of convulsive disorders is very incomplete and that the magnitude of the problem is uncertain.

Pet. Ex. 28 (Nicola Madge et al., *The National Childhood Encephalopathy Study: A 10-Year Follow-Up*, 35(68) DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY (1993)) at 22-23.

One of the most contentiously-discussed articles filed by Petitioners (referred to as the "Cyr" article) focused on the "toxin catalyzed" process of ADP-Ribosylation that is central to the "pathogenic effects of pertussis":

> Pertussis toxin ... elicits a myriad of biological effects in infected patients and laboratory animals. ... The majority of the biological effects of pertussis are due to the toxin-catalyzed transfer of an adenosine diphosphate-ribose (ADP-ribose) [into G-proteins of the subject]. This [process] generally leads to an uncoupling of the modified G-protein from the corresponding receptor and the loss of effector regulation, ultimately leading to adverse reactions. ... A number of methods have been used for toxoiding including: genetic engineering to produce mutated inactive toxins, and chemical treatments of the toxin or whole cells with formaldehyde, glutaraldehyde, tetranitromethane, or hydrogen peroxide. *Chemical inactivation,* although *currently the most common approach*, is not the ideal process since the process needs to be carefully controlled to ensure that *toxoided material contains low levels of residual toxin*. It *must maintain sufficient chemical/structural integrity* to elicit an acceptable immunogenic response and have a low reversion rate to a pathogenic component with time. Consequently, pertussis vaccines are currently assessed for safety and/or pertussis toxin using several different empirical safety test methods such as: the mouse weight gain (MWG) test, Histamine sensitization (HS) test, or the Chinese hamster ovary (CHO) cell clustering test. There is a *high degree of variability* in these tests.

Pet. Ex. 39 (Terry Cyr et al., *A Quantitative Analysis for the ADP-Ribosylation Activity of Pertussis Toxin: An Enzymatic-HPLC Coupled Assay Applicable to Formulated Whole Cell and Acellular Pertussis Vaccine Products*, 29 BIOLOGICALS, 81-95 (2001)) at 81-82 (emphasis added).

That paper went on to explain that ADP-Ribosylation is the penultimate step of purported pertussis toxin action (*i.e.*, the B oligomer attaches to the targeted cells, the A (S1) unit is translocated to penetrate the targeted cells, and the A (S1) unit damages the normal functioning of the targeted cells). *Id*. at 88. The study's findings indicated "trace ribosylation activity" in certain vaccine components, including the B oligomer component, which the authors thought "could be

attributed to contamination from pertussis toxin and/or the A protomer during the co-purification process." *Id*. at 92. In their discussion section, the authors stated:

> It is conceivable that during the toxoiding process only the B pentamer is deactivated; the A subunit is unaffected and continues to possess ribosylation activity (intrinsic PT activity) and the capability of ribosylating G-proteins and initiating the cascade of adverse events, should it be translocated across the cell membrane. The fact that the pertussis toxoid, assumed to be deactivated by HS and CHO-cell testing assays, possessed 26% ribosylation activity relative to the Pertussis Toxin Standard 90/518, whereas mutated PT possessed only trace if any ribosylation activity would substantiate the hypothesis that a portion of pertussis toxoid still retains intrinsic ribosylation activity. ...
>
> *These data suggested that toxoiding processes used by different manufacturer are not equivalent with respect to their ability to deactivate pertussis toxin S1 ribosylation, and indeed within a single manufacturer large variations exist.*

Id. at 94-95 (emphasis added).

Another hotly debated article that was filed by Petitioners (referred to as the "Gomez" article) also addressed the concept of retained toxicity in the pertussis toxoid due to manufacturing limitations in the detoxification process(es):

> [T]here is evidence to indicate that [pertussis toxin] is able to induce IL-1 production in the mouse brain. IL-1 can affect neuroendocrine functions and modulate release of neurotransmitters, and has been claimed to play a role in neurological reactions observed in children immunised with pertussis vaccines of high [pertussis toxin] content. Although the biological effects of [pertussis toxin] have been under extensive research, the mechanism(s) of its toxicity is still unclear....
>
> Intact B-subunit is required for binding of the holotoxin to receptor sites on the target cell surface and entry of the A-protomer into the cells. The A-protomer catalyses the ADP-ribosylation of eukaryotic GTP-binding regulatory proteins, preventing hormonal inhibition of adenylate cyclase ... the toxic activities of [pertussis toxin] in vivo, including histamine sensitisation, are all abolished when the enzyme active site is inactivated by site-directed mutagenesis, as in a genetically detoxified [pertussis toxin]. This has formed the basis for the hypothesis that the ADP-ribosylation enzyme activity is directly responsible for the toxicity... However, the relationship between the residual ADP-ribosylation activity of [pertussis toxin] in pertussis or pertussis-containing vaccine formulations to their reactivity in the HIST has not been explored.

Pet. Ex. 40 (S.R. Gomez *et al.*, *ADP-ribosylation activity in pertussis vaccines and its relationship to the in vivo histamine-sensitisation test*, 25 VACCINE 3311-3318 (2007)) at 3311-3312.

This study used a test to track residual ADP-ribosylation in a variety of pertussis vaccine versions then in use, and found that, "Activities were detected in all vaccine formulations except [one]. However, no consensus enzyme activity could be defined amongst these different vaccine

formulations and the range of activity was wide between the products," appearing "to be product specific and batch-to-batch variability ranged." *Id*. at 3314. These results were cross-referenced with the histamine test, resulting in a finding that "A positive relationship between the enzyme activity in vaccine lots and the reactivity observed by the HIST was found for [one version] where three lots that had higher enzymatic activities [] also showed reactivity in mice," but was not true for other versions. *Id*. The authors concluded that, "Different detoxification processes can yield quite distinct products." *Id*. at 3316-17.

The last article of note filed by Petitioners accompanied Dr. Kinsbourne's supplemental expert report. It states, *inter alia*, that, "Although chemical treatment can eliminate the undesirable toxic effects of [pertussis toxin], it has been shown to affect its antigenicity[20] and immunogenicity[21] and may also alter adjuvant activities[22] for immune responses against the toxin itself and against other antigenic components of the acellular vaccine." Pet. Ex. 41, Tab A (Mark Ryan *et al.*, *Pertussis toxin potentiates Th1 and Th2 responses to co-injected antigen: adjuvant action is associated with enhanced regulatory cytokine production and expression of the co-stimulatory molecules B7-1, B7-2 and CD28*, 10(4) INTERNATIONAL IMMUNOLOGY 651-662 (1998)) at 652.

The first medical literature article of note filed by Respondent focused on the technique of genetically modifying pertussis toxin into analogs that retain immunogenicity, while doing a better, more consistent job of avoiding toxicity:

> We have identified several analogs with modified biological properties and have shown that simultaneous mutation of A and B subunits can lead to cumulative attenuation of both in vitro and in vivo biological activities. ... [Pertussis toxin] analogs were engineered to study the structure-function relationship of the B oligomer. ... [Pertussis toxin] mitogenicity[23] is an intrinsic property of the B oligomer which may or may not be of concern in a recombinant pertussis vaccine. In whole-cell or component pertussis vaccines, this activity is destroyed by treatment with aldehydes.... [R]educing the S1 enzymatic activity by site-directed mutagenesis virtually abolished both [histamine sensitization and leukocytosis promoting] properties of [pertussis toxin], indicating that they also require [ADP-ribosyltransferase] activity.... These [pertussis toxin] analogs represent an enhanced

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[20] Antigenicity is "the property of being able to induce a specific immune response or the degree to which a substance is able to stimulate an immune response." DORLAND'S, *supra* at note 3, at 105.

[21] Immunogenicity is "the property that endows a substance with the capacity to provoke an immune response, or the degree to which a substance possesses this property." DORLAND'S, *supra* at note 3, at 912.

[22] The same article "demonstrated that the adjuvanticity of [pertussis toxin] is dependent on receptor binding properties of the holotoxin [performed, presumably, by the B-oligomer], but that certain of the adjuvant effects can be dissociated from ADP-ribosyltransferase activity." *Id*. at 658.

[23] Mitogenic agents are those which "caus[e] or induc[e] mitosis [i.e. cell division] or cell transformation." DORLAND'S, *supra* at note 3, at 1162.

> genetic detoxification of [pertussis toxin] and may form the basis of the next generation of recombinant whooping cough vaccines.

Resp. Ex. F (Sheena Loosmore *et al.*, *Characterization of Pertussis Toxin Analogs Containing Mutations in B-Oligomer Subunits*, 61(6) INFECTION AND IMMUNITY 2316-2324 (1993)) at 2316, 2321-23.

Respondent also filed a history of the development of the acellular pertussis vaccines in Japan. Among some of the interesting observations made therein were the following:

> [A]cellular pertussis vaccines are efficacious and are less reactogenic than whole cell vaccines...
>
> [N]o subunit or its combinations could induce the same high protective activity as whole [pertussis toxin] antigen. We concluded that a specific conformational structure constructed by whole [pertussis toxin] subunits is important to elicit potent immunogenicity....
>
> Using [pertussis toxin] gene manipulation, several non-toxic but immunogenic mutant [pertussis toxin] proteins were engineered and proposed as new genetically detoxified [pertussis toxin] antigens in the [acellular pertussis] vaccine. Development of the genetically detoxified [pertussis toxin] as a protective antigen in the vaccine was a big step towards a next generation acellular pertussis vaccine. This antigen was also proved to have protective potency by [an *in vivo* rodent] test, in which it [performed similarly to chemically-detoxified pertussis toxoid]. This observation contradicts the view that a small amount of active [pertussis toxin] in the vaccine is indispensable to show mouse protectivity in [that test]....
>
> The most common local reactions seen at the injection site of [whole-cell pertussis] were redness, swelling, pain and induration whereas systemic reactions often seen are fever, distress, vomiting and crying. With the [acellular pertussis] vaccine, these reactions have been greatly reduced. However, the biggest concern was the rare but severe adverse reactions such as convulsions and encephalopathy after injection of pertussis vaccines. ... From 1975 to 1980, when [DTP] vaccine was given to infants 2 years and older, the rate was 1.1 per million children. From 1981 to 1989, when DTaP vaccine was introduced for children over 2 years of age and recommended from 1988 for infants 3 months of age, the rate dropped to 0.24 per million children. Clearly the incidence of severe adverse reactions decreased significantly with DTaP vaccination....

Resp. Ex. G (Yuji Sato and Hiroko Sato, *Development of Acellular Pertussis Vaccines*, 27 BIOLOGICALS, 61-69 (2001)) at 62, 65-66.

Another article filed by Respondent tested whether the A (S1) subunit could be genetically deleted, leaving only the B oligomer, and whether just the B oligomer would be enough to summon an immune response sufficient to be used as a pertussis vaccine primary component:

> Since pertussis toxin has potent biological activity, it must be inactivated in a manner which retains its immunogenicity before it can be considered for inclusion in

> vaccines. One approach that has been used for detoxification of the molecule involves chemically modifying the protein with formaldehyde or glutaraldehyde. A second approach might be to isolate a part of the molecule which itself is nontoxic yet which would induce a neutralizing antibody response to the native toxin. Such an approach has the advantage that the molecule is not toxic and therefore need not be chemically modified, thus preserving epitopes on the molecule. Moreover, conversion to a toxic form is impossible, whereas chemically inactivated toxins can revert to toxic forms. A candidate for such an immunogen is the B oligomer, which lacks the enzymatically active portion of pertussis toxin. The development of a mild procedure for [chemically] dissociating the A subunit from the B oligomer and obtaining the B oligomer in high yields has made such an approach possible. ... In this study we have examined the ability of the isolated B oligomer of pertussis toxin to induce a neutralizing antibody response in mice.

Resp. Ex. H (Juan L. Arcinega *et al.*, *Immune Response to the B oligomer of Pertussis Toxin*, 55(5) INFECTION AND IMMUNITY, 1132-36 (1987)) at 1132.

The results of that study were at odds with results of a similar study performed by others. The authors elaborate:

> The B oligomer preparation did not exhibit significant leukocytosis-promoting activity or histamine-sensitizing activity. ... Antibodies raised against B oligomer were able to neutralize the action of pertussis toxin. ... We found that the B oligomer did not exhibit the leukocytosis-promoting and histamine-sensitizing activities of pertussis toxin, findings which contrast with the conclusions of Nogimori *et al.*, who attributed these activities to the B-oligomer.

Id. at 1133-34. In their discussion, the article's authors discuss their results:

> Antibodies to the B oligomer may neutralize the activity of the holotoxin by preventing its binding to CHO cells. ... The B oligomer did not appear to be superior to inactivated pertussis toxin as an immunogen, as might be expected since inactivated pertussis toxin was chemically modified. Thus, the major advantage of using the B oligomer as a component in a vaccine would be the inability of this protein to revert to the enzymatically active form of the toxin, which has previously been reported with chemically modified toxins. Results from this study demonstrate that the B oligomer can produce a neutralizing antibody response in mice. The A subunit is also a potential vaccine candidate. Theoretically, the use of the A subunit might involve some risk, since this protein retains enzymatic activity, although the ability of the A subunit to enter a eucaryotic cell should be decreased in the absence of the B oligomer. Our preliminary attempts to use the A subunit as an immunogen have met with discouraging results. Not only have we had problems freeing A subunit preparations from contaminating B oligomer, but we have found that the A subunit appears to be a poor immunogen in mice. Other workers have found that a monoclonal antibody to the A subunit neutralized many of the activities of the holotoxin, including its leukocytosis-promoting activity, whereas a monoclonal antibody to the B oligomer had no effect on these activities.

Id. at 1135. The end of the article looks forward to the possibility (*in futuro* in 1987) of genetically deleting components of the vaccine to make them safer:

> Recently, the genes encoding the pertussis toxin subunits were cloned. It is therefore conceivable that a B. pertussis strain which lacks the gene for the "toxic" A subunit may now be engineered using recombinant DNA techniques. Such an approach has the advantage that the B oligomer could be purified from these strains without the possibility of contamination with holotoxin.

Id.

The next of Respondent's articles of medical literature was a follow-up study concerning children who suffered acute neurologic illnesses associated with pertussis vaccine:

> Over 80% of cases and controls were traced. Case children were significantly more likely than controls to have died or to have some form of educational, behavioural, neurological, or physical dysfunction a decade after their illness. The prevalence of one or more of these adverse outcomes in case children who had been immunised with diphtheria, tetanus, and pertussis vaccine within seven days before onset of their original illness was similar to that in case children who had not been immunised recently. ... Diphtheria, tetanus, and pertussis vaccine may on rare occasions be associated with the development of severe acute neurological illnesses that can have serious sequelae. Some cases may occur by chance or have other causes. The role of pertussis vaccine as a prime or concomitant factor in the aetiology of these illnesses cannot be determined in any individual case. The balance of possible risk against known benefits from pertussis immunisation supports continued use of the vaccine....
>
> This follow up ... shows that all the types of illnesses studied may be associated with important permanent sequelae....
>
> [I]llnesses such as those studied in the national childhood encephalopathy study, including a variety of encephalopathies and severe convulsions, both febrile and non-febrile, can have lasting sequelae as measured by various indices of brain function. This seems to be as true for cases associated in time with diphtheria, tetanus, and pertussis immunisation as for other cases. However, children with acute neurological illnesses, whether associated with vaccine or not, may have had a prior occult underlying condition that could have increased their susceptibility to external insults but that was not recognised at the time. A simple viral illness or immunisation with pertussis vaccine, for example, may cause fever and systemic upset, which in a susceptible child can provoke severe convulsions or encephalopathic symptoms. Furthermore, the ultimate outcome of what might have been a relatively innocent illness may be influenced by the presence of underlying pathology....
>
> [T]his does not prove that the vaccine was the sole or even the prime cause of either the illnesses or the adverse outcomes in these cases.

Resp. Ex. I (David Miller *et al.*, *Pertussis immunisation and serious acute neurological illnesses in children*, 307 BMJ 1171-1176 (1993)) at 1171,1174-1175.

Respondent also filed an article on a study that genetically modified certain sub-subunits of the B oligomer subunit, to see if that was enough of a modification to disable the potentially toxic effects of pertussis toxin without disabling its immunogenic properties:

> Whereas abolition of the ADP-ribosyltransferase activity, the last of the three molecular steps in cytotoxidty, only affects some toxin activities, reduction of all biological activities can be expected if the initial, B oligomer-mediated binding step of the toxin to the target cell receptors is abolished....
>
> Although many biological activities of [pertussis toxin] depend on its Sl-catalyzed ADP-ribosyltransferase activity, some, such as mitogenicity, are independent of this enzymatic activity. In fact, reduction in enzymatic activity may sometimes result in increased mitogenic activity. The [genetically-modified pertussis toxin] with impaired receptor-binding abilities, however, presents an undetectable level of T cell mitogenicity, as indicated by its inability to stimulate II~2 secretion by spleen cells exposed to the holotoxin, regardless of the toxin's ability to catalyze ADP-ribosylation. This demonstrates that reduction in receptor-binding not only reduces the ADP-ribosyltransferase-dependent, but also the ADP-ribosyltransferase-independent biological activities of [pertussis toxin]. It is interesting that toxin molecules used in current acellular vaccine formulations are often inactivated by treatments with formaldehyde or glutaraldehyde, chemicals that primarily affect lysine residues in proteins. Since the S1 subunit does not contain lysines, the chemical treatment is likely to affect the B oligomer-specific activities. ... [I]f the B oligomer alterations affecting IL-2-secretion induced slightly decreased total anti-[pertussis toxin] antibodies, they did not significantly affect the production of physiologically important anti-[pertussis toxin] antibodies in the mouse.
>
> The identification and subsequent alteration of the receptor-binding sites on toxins is expected to help in the design of genetically detoxified molecules devoid of any detectable activity but structurally nearly identical to the original molecule. This approach is particularly useful for the development of new generation vaccines against infectious diseases mediated by bacterial toxins. ... The genetic modifications of the [pertussis toxin] gene presented in this study clearly demonstrate that alterations of the receptor-binding sites strongly affect the biological activities of [pertussis toxin]. The reported alterations not only affected the activities that are dependent on the S1 subunit-catalyzed ADP-ribosylation, but also those that are independent of this enzymatic activity, in particular, the FIX-mediated mitogenicity. Despite the reduction of both ADP-ribosyltransferase-dependent and -independent activities, the [studied mutation] was able to elicit high titers of toxin-neutralizing antibodies, and therefore a [genetically-modified pertussis toxin] with alterations in the S1 subunit *as well as in* the B oligomer, such as the one described here, may be considered a useful candidate for the development of a new generation vaccine against whooping cough.

Resp. Ex. K (Yves Lobet *et al.*, *Site-specific Alterations in the B Oligomer that Affect Receptor-binding Activities and Mitogenicity of Pertussis Toxin*, 177 J. EXP. MED. 79-87 (1993)) at 80, 84-85 (emphasis added).

D. Post-Hearing Submissions

At the conclusion of the hearing, the Court ordered briefing by the parties, whose arguments are summarized here.

1. Petitioners argue that several of Evelyn's "treating physicians associated Evelyn's seizures with her vaccines." This argument seems an odd primary focus, inasmuch as all such associations were mere mentions in reciting her history of onset, and were not purportments of causal association. Stated otherwise, any association between Evelyn's vaccination and her seizures were statements of *temporal* association, not *causal* association.[24] Petitioners are expected to understand the difference.

2. Petitioners recapitulated the testimony of Dr. Kinsbourne and the supportive medical literature filed in this matter, and argued, without much more, that it was more persuasive than Respondent's expert and literature.[25]

3. Petitioners ended their closing brief in chief by citing to other Program decisions that found that "the DTaP vaccine can cause seizures and brain damage," by pointing out the close temporal association between vaccination and the onset of seizures (24 hours), which none of the treating doctors or expert witnesses have questioned as not being medically appropriate, and by pointing out the relative absence of other external immune challenges that were likely causes (or triggers) of Evelyn's seizures.[26]

4. The most helpful and relevant argument made by Petitioners' closing brief was in its last paragraph, on page 36:

> [A]ll vaccine injuries have a genetic base. Susceptibility always plays a role. Indeed, the Federal Circuit has held, non-vaccine environmental factors contribute to the injury. In such circumstances, when concurrent forces cause a single harm, the Federal Circuit has held, the burden is on [Respondent] to show that the alternative cause is so predominant that the vaccine is insignificant. *See Shyface v. Sec'y of HHS*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999). Therefore, the Court has stated, if evidence establishes equally plausible etiologies for an injury then the petitioner

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[24] The Court surmises that Petitioners employed this argument to take advantage of the Federal Circuit's opinions in *Capizzano v. Sec'y of HHS*, 440 F. 3d 1317 (2006), and *Andreu v. Sec'y of HHS*, 569 F. 3d 1367 (Fed. Cir. 2009). Any such reliance is misplaced where, as here, the treating doctors' opinions do not affirmatively and explicitly support vaccine causation.

[25] The Court notes its disappointment that Petitioners left almost untouched the legal issues raised by this Petition, focusing instead on summarizing and reiterating the testimonial evidence proffered at trial.

[26] Petitioners also argued that no alternative causal factor was identified by either the treating doctors or by Dr. Wiznitzer. This recitation is only accurate if one ignores genetic predisposition as a causal factor, the contention held, certainly by Dr. Wiznitzer, and arguably by one or more treating neurologists. It would have been helpful if Petitioners had provided the Court with a thoroughgoing argument why genetic predisposition is or is not a sufficient alternative or superseding cause, or the legal significance of its interplay with sensitivity to a challenge like the vaccine, an interplay stipulated by both parties' experts.

should prevail. *See Knudsen v. Sec'y of HHS*, 35 F.3d 543, 550 (Fed. Cir. 1994). In such cases, [Respondent] must eliminate the vaccine as a substantial contributing factor. *See Shyface*, 165 F.3d at 1353.

5. Respondent pointed out that none of Evelyn's treating doctors (a) diagnosed febrile seizures, (b) implicated any vaccination for the seizures, or (c) were able to determine the cause of the seizures. To this, Respondent adds that "all of her physicians agree that the cause of her seizures is unknown, although a genetic cause is suspected."

6. Respondent argues, in response to Petitioners' primary "association" argument, that "In taking their respective histories, some of [the treating] physicians noted that Evelyn received a DTaP vaccination before her seizures began, but none drew any conclusion as to causation. In fact, those who considered the vaccination as a possible cause dismissed it as a causal factor."

7. Respondent quotes at length from the Court's decision in *Simon v. Sec'y of HHS*, No 05-0941V, 2007 WL 1772062 (Fed. Cl. Spec. Mstr. Jun. 1, 2007) to argue that Dr. Kinsbourne was wrong to extrapolate from the NCES study to analogize the injury at issue in this Petition.

8. Respondent argues that Petitioner has only provided a "hypothetical model" that lacks a plausible theory or an explanation as to how that theory was at work in the instant case through "a logical sequence of cause and effect between the vaccination and the injury."

9. Respondent claimed that Dr. Wiznitzer's testimony proved the point, that "DTaP vaccines contain pertussis toxin that has been detoxified and made chemically inactive. Its functional properties as a toxin have been eliminated ... Dr. Kinsbourne simply could not demonstrate that there is sufficient residual toxin function in DTaP vaccine to provoke Evelyn's seizure disorder.

II. ULTIMATE FINDINGS OF FACT

Both parties' experts were personally and professionally credible; that premise is beyond a cavil of doubt in the Court's mind. Having heard both experts on numerous occasions over the preceding years, the Court was again impressed by the knowledge of each, and of their command over the subject matter addressed. They both comported themselves as professionals of class and academic distinction. However, the way to address whether an expert witness has proffered a credible, reliable theory, that logically conforms to the specific facts of the case, is to assess the theories of causation and the support for the experts' testimony in medical records and/or literature, not to mask personal preference with expert witness credibility determinations. *Andreu v. Sec'y of HHS*, 569 F. 3d 1367 (Fed. Cir. 2009) ("A special master [cannot] cloak the application of an erroneous legal standard in the guise of a credibility determination, and thereby shield it from appellate review. A trial court makes a credibility determination in order to assess the candor of a fact witness, not to evaluate whether an expert witness' medical theory is supported by the weight of epidemiological evidence."); *see also Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993) (An expert witness' theory is scientifically valid when it supports the conclusion that "it purports to

show."); *Garcia v. Sec'y of HHS*, No. 05-0720V, 2008 WL 5068934 (Fed. Cl. Spec. Mstr. Nov. 12, 2008) ("the question of whether an expert's theory possesses scientific bona fides goes to the persuasiveness of the evidence on the question of aetiology and causation"). "Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases.... [To say that] the special master may not 'cloak the application of an erroneous legal standard in the guise of a credibility determination, and thereby shield it from appellate review" ... is not to say, however, that a special master, as the finder of fact in a Vaccine Act case, is prohibited from making credibility determinations regarding expert testimony." *Moberly v. Sec'y of HHS*, __ F.3d __ 2010 WL 118661, *8 (Fed. Cir. 2010).

Therefore, the Court's task now is to analyze the differences between the opinions offered to determine whether Petitioner has established a logical sequence of cause and effect, having occurred in a medically appropriate time frame, which is biologically plausible to tie together the factual sequence and explain Petitioner's injury. *See Althen v. Sec'y of HHS*, 418 F. 3d 1274, 1278 (Fed. Cir. 2005); *Pafford v. Sec'y of HHS*, 451 F. 3d 1352, 1355 (Fed. Cir. 2006), *rehearing and rehearing en banc denied*, (Oct. 24, 2006), *cert. den.*, 168 L. Ed. 2d 242, 75 U.S.L.W. 3644 (2007); *Walther v. Sec'y of HHS*, 485 F. 3d 1146 (Fed. Cir. 2007); *de Bazan v. Sec'y of HHS*, 539 F. 3d 1347, 1352 (Fed. Cir. 2008).

Worthy of first mention is the fact that Evelyn's treating physicians did not settle on any acute aetiology for the onset of her seizures. Although Petitioners argued that her treaters implicated the vaccination, and Dr. Wiznitzer implicated the pre-existent gastrointestinal illness, the medical records did not indicate any immediate cause for Evelyn's condition. Likewise, despite the presumption that every doctor in this case communicated regarding a genetic predisposition, none was specifically identified. Granted, the full panoply of genetic mutation tests available at the present was only partially available in 2004. These considerations are noteworthy because of the probative weight afforded to treating doctors' diagnoses and aetiological conclusions under the law in the Vaccine Program. The absence of definitive conclusions leaves the Court to determine aetiology from the interpretation provided by medical expert testimony and supporting medical literature proffered by the parties.

From these sources, the Court draws the following conclusions: Pertussis toxin is one of a plurality of components in both the whole-cell and acellular pertussis vaccines. In the whole-cell version, it is one of a larger number of components, and vaccines vary rather widely in exact ratios and composition at the consumer level. In contrast, acellular pertussis vaccine has only a handful of components, which include pertussis toxin that has generally been partially altered and disabled in some way. From the medical literature, the Court derives the conclusion that the greater proportion of acellular pertussis vaccines are chemically toxoided, which damages certain epitopes on the toxin itself to detoxify the toxin. Some lesser proportion are crafted from genetically-altered pertussis toxin, which disable the toxin's capacity for damage while keeping the aspects needed for immunogenicity (i.e., summoning an immune response in the subject) with greater precision, consistency, permanence, and simplicity of process. Detoxifying the pertussis toxin into a non-toxic form (a toxoid) consists of either chemically crippling or genetically deleting some part of the two-branch toxin, such that the B branch cannot attach the toxin to vulnerable cell structures and/or such

that the A branch cannot be translocated across the cell membrane, and/or such that the A branch cannot damage the cell. A concern inherent to chemical detoxification remains in crippling enough of the toxin's epitopes to render it safe while allowing enough to remain for the immune system to "learn" the toxin's contours in order to form matching antibodies. There also seems to be a concern that chemically detoxified pertussis toxin has the potential to "revert" back into a toxic form.

Petitioners' theory rests on the proposition that one of the bases of those concerns came to fruition in Evelyn's case, and that her stipulated genetic predisposition made her more sensitive than an average vaccinee. That is, Petitioners' theory, as proposed by Dr. Kinsbourne, is that Evelyn received a DTaP dose with pertussis toxin that had intact capability to cause neurologic damage, either as a result of incomplete toxoiding or toxic reversion, and that the toxoid succeeded in destabilizing the inhibitory action of certain neuronal cells, causing greater neuronal excitability, which led to a seizure in Evelyn. The fact, to which Dr. Kinsbourne stipulated, that she was genetically predisposed to seizures only served to lower the threshold of neuronal excitability necessary to initiate a seizure.

Dr. Wiznitzer opined that this theory was inherently implausible as a reasonable theoretical explanation of potential vaccine injury mechanism. His disputation focused on the efficacy and reliability of industry standards in the chemical toxoiding process, and the high level of product testing and extra safety measures to prevent a vaccine dose containing functional pertussis toxin from reaching the consumer. He noted that, for the pertussis toxin to inflict the harm of which it is able in its pre-toxoided form, it must retain functionality in both the A and B portions of the toxin: If the A branch were damaged, as the primary agent of harm, it could not affect the G proteins and upset the neuronal equilibrium; if the B branch were disabled, the toxin could not bind to vulnerable cells and the A branch, even if functional, could not inflict its damage. In his estimation, it would be nearly impossible for the industrial process of chemical toxoiding to allow such an intact form of pertussis toxin to make its way into a consumer dose of acellular pertussis vaccine.

Moreover, Dr. Wiznitzer pointed out that genetically modified pertussis toxin would not suffer from either concern inherent to the chemical toxoiding process, with which Petitioners' expert seemed to agree. Nonetheless, from the record before the Court in this matter, it appears that, for the relevant period herein, chemical toxoiding remained the predominant manufacturing process for acellular pertussis. That being the case, the Court is left to presume that the dose received by Evelyn was, more likely than not, a chemically toxoided vaccine. Therefore, reference to the safety capability of those vaccines manufactured by genetic modification do not render Petitioner's theory implausible.

In actuality, the Court finds, based on a thorough review of the evidence presented in this matter, especially the medical literature filed herein, that Petitioners' theory is not incredible. Whether it is sufficiently plausible to surmount a preponderance is another matter, but it is not so farfetched to extend beyond the pale of the medically plausible. Indeed, pertussis toxin is the common denominator between whole-cell and acellular pertussis vaccines, and excluding it entirely would seem to preclude immunity to wild pertussis. Even if the threat of toxicity is all but obliterated by modern toxoiding processes, the statistically slim chance remains that a toxoid retains or regains sufficient toxicity to affect a genetically sensitive subject. And, as the medical literature

seems to reiterate, the threat of serious adverse reactions previously associated with whole-cell pertussis did not disappear with the introduction of toxoiding pertussis toxin, but continues to be a concern, one that is reflected in the medical literature filed in this matter. Even if the theory proffered by Petitioners is incorrect, there remains some association between acellular pertussis and adverse events such as complex seizures that is statistically relevant beyond the naturally-occurring seizure events of a general control population.

It may be, however, that there is some other factor at work besides the pertussis toxin directly affecting neurons that explains such an association. Dr. Wiznitzer argued as much, even proffering one such mechanism: that the acellular pertussis vaccine may cause a fever which otherwise would not have developed at that time, that the stress of a heightened temperature on the brain could aggravate a seizure, and that the seizure threshold temperature might be lower for a genetically (or otherwise) susceptible subject than it would be for someone without such predisposition. As noted *supra*, Dr. Kinsbourne stipulated that Evelyn has a genetic predisposition to seizure reactivity, which makes her more vulnerable than other children similarly situated who receive the vaccine.

In fact, it seems unnecessary for the Court to rule on the scientific reliability of Dr. Kinsbourne's latent pertussis toxicity in DTaP theory, inasmuch as both experts stipulate to a certain set of medical facts: I. That the body's reaction to the immunogenic nature of the DTaP vaccine can often include fever; II. That Evelyn did exhibit a fever, the onset of which followed within less than 24 hours of vaccination and preceded the onset of the first seizure within several minutes to a few hours; III. That fevers impose stress upon the body's metabolism, especially that of the brain, which can provoke seizures, known as febrile seizures, meaning customarily that the fever temperature must meet or exceed 102°F; IV. That most commonly, such febrile seizures are short, simple, benign, and limited in number and duration; V. That, occasionally however, a seizure provoked by a fever, when combined with a latent predisposition, such a seizure may be severe, complex, prolonged, and perhaps even initiate a chronic condition; VI. That persons with a genetic susceptibility or other predisposition may have a seizure provoked with a less severe fever than would otherwise be necessary–even as low as 100°F; and VII. That what triggers the seizures to manifest when it does in the onset seizure is the fever.[27]

The experts diverge on an epistemological point that has often plagued the analysis of *but for* causation: Had Evelyn's seizures not manifested in biologic connection and temporal association with her fever, would they have manifested regardless, either at the same moment, or very soon thereafter? The *but for* proposition is, linguistically, a past contrary to fact construction: it attempts to divine what would have been the case had events not transpired as they have; it seeks facts about an alternate reality for which we have no data. In some cases, the question might be easier to answer,

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[27] These findings are similar to those made by the Court in deciding the cases of *Simon v. Sec'y of HHS*, No. 05-0941V, 2007 WL 1772062 (Fed. Cl. Spec. Mstr. Jun. 1, 2007) (awarding compensation where both parties' "experts agree[d] vaccines, including the DTaP vaccine can cause fevers ... that fevers can trigger seizures ... [and] "that [the] initial seizure is connected to [the] subsequent seizures, [] epilepsy and death"); and *Cusati v. Sec'y of HHS*, No. 05-5049V, 2005 WL 4983872 (Fed. Cl. Spec. Mstr. Mar. 9, 2006) (where the parties' experts both agreed that vaccination "was a logical source of [] fever associated with [] initial complex febrile seizure" which was related to a "subsequent intractable seizure disorder," the injury complained of).

but otherwise, as here, it may turn problematic, because what is sought is a hypothetical outcome contrary to the facts as they actually transpired. Dr. Kinsbourne opined that the seizures may not have occurred for years, or ever, in the absence of that neurologic stress presented by that moment. Dr. Wiznitzer strongly believed that, had Evelyn's onset of seizures not manifested when they did, they surely would have within a matter of a few months. However, the Court takes notice that manifestation of genetic traits often defies specific prediction and is dependent on environmental factors.[28] One need look no further than to the doctrine within genetics of phenotypic plasticity, which explains how wide variations in gene expression are the consequence of divergent external factors in an organism's environment.[29] Indeed, adhering to a strict determinism of genetic expression, or biologic determinism generally, hearkens back as modern permutations of Leucippus' and Democritus' theory of atomic determinism, dispelled most definitively in the last century by quantum indeterminacy (subatomic chaos).[30] However, for better or for worse, the common law and the Vaccine Act itself do not adhere to such a deterministic view of reality. *See infra*. Granted, there may be some genes that will express with a greater probability–approaching certainty–at a particular moment in time, but many others do not possess that "egg-timer" quality to express at an exact moment, or they may express significantly later, contingent upon environmental factors to trigger them. Even Dr. Wiznitzer's own opinion betrays this point. Dr. Wiznitzer did not contend that Evelyn's onset seizure would have occurred of genetic necessity on the morning of 12 February 2004, regardless of the slight fever or anything else. The fact that her first seizure did occur when it did, and did not occur a few months later, is something he agreed was influenced by events transpiring at that time: *i.e.*, the fever. Indeed, he was quite clear that the fever very well may have "triggered" or "unmasked" the seizure disorder. This does not detract from the fact that she did possess a genetic predisposition to seizure vulnerability, a fact stipulated by both parties' experts on numerous occasions. In fact, Dr. Kinsbourne conceded that she would not have had the seizures without the presence of such a predisposition.

On a smaller, but related point, Dr. Wiznitzer was equivocal as to what caused the raised temperature in Evelyn on the morning of 12 February 2004: whether the DTaP vaccination of less than 24 hours preceding, or an unidentified gastrointestinal illness that the medical records state had run its course and resolved by the time of the vaccination. It rather strains logic to set in equipoise with a very recent vaccination (one which Dr. Wiznitzer agreed is known to be capable of causing fever) a condition that was not febrile in its apogee, and which Evelyn's primary care physician believed had resolved. *See* Pet. Ex. 4 at 12. It appears far more likely to the Court that Evelyn's aggravated temperature on the morning of 12 February 2004 (along with her aggravated demeanor

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[28] *See* quotations from medical literature, *supra* at 33-34 and note 19.

[29] This seems a necessary predicate for certain theories of evolutionary biology, as a corollary to speciation by natural selection due to naturally occurring genetic variations in populations.

[30] *See*, *e.g.*, Schrödinger's wave equation, or, for that matter, his cat. The Court notes that some Intelligence may comprehend every subatomic collision vector or wave pattern, and that an argument could still be made for an almost infinitely complex determinism in the universe. However, fundamental indeterminism remains the limitation of mortal knowledge.

and symptoms the night before) were the direct result of her immune response to the DTaP vaccine.

From this concatenation, the Court arrives at the following findings, in addition and continuation to those noted *supra*: VIII. That Evelyn's DTaP vaccine caused, through her immune response thereto, a heightened temperature, even if only a slight fever; IX. That Evelyn possessed a genetic predisposition to seizures, as agreed to by both parties' experts (even if such predisposition could not be localized to a single gene or otherwise identified specifically by her treating physicians); X. That therefore both the genetic predisposition and the vaccination were causal factors in bringing about Evelyn's injury.

In short, the Court finds that Evelyn's injury would not have occurred but for her genetic predisposition, but that the injury's onset would not have occurred when it did but for the vaccination-induced fever that immediately preceded it and which triggered the onset of Evelyn's seizures.

III. CONCLUSIONS OF LAW

As aforementioned, the Court is authorized to award compensation for claims where the medical records or medical opinion have demonstrated by preponderant evidence that either a cognizable Table Injury occurred within the prescribed period or that an injury was actually caused by the vaccination in question. § 13(a)(1). If Petitioners had claimed that Evelyn had suffered a "Table" injury, to them would §13(a)(1)(A) have assigned the burden of proving such by a preponderance of the evidence. In this case, however, Petitioners do not claim a presumption of causation afforded by the Vaccine Injury Table, and thus the Petition may prevail only if it can be demonstrated to a preponderant standard of evidence that the vaccination in question, more likely than not, actually caused the injury alleged. *See* § 11(c)(1)(C)(ii)(I) & (II); *Grant v. Sec'y of HHS*, 956 F. 2d 1144 (Fed. Cir. 1992); *Strother v. Sec'y of HHS*, 21 Cl. Ct. 365, 369-70 (1990), *aff'd*, 950 F. 2d 731 (Fed. Cir. 1991). The Federal Circuit has indicated that, to prevail, every petitioner must:

> show a medical theory causally connecting the vaccination and the injury. Causation in fact requires proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury. A reputable medical or scientific explanation must support this logical sequence of cause and effect.

Grant, 956 F. 2d at 1148 (citations omitted); *see also Strother*, 21 Cl. Ct. at 370.

Furthermore, the Federal Circuit has articulated an alternative three-part causation-in-fact analysis as follows:

> [Petitioner's] burden is to show by preponderant evidence that the vaccination brought about [the] 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 v. Sec'y of HHS, 418 F. 3d 1274, 1278 (Fed. Cir. 2005).

As part of that analysis, the Federal Circuit recently explained:

> [T]he proximate temporal relationship prong requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's aetiology, it is medically acceptable to infer causation-in-fact.

de Bazan v. Sec'y of HHS, 539 F. 3d 1347, 1352 (Fed. Cir. 2008).

Under this analysis, while a petitioner is not required to propose or prove definitively that a specific biological mechanism can and did cause the injury, he must still proffer a plausible medical theory that causally connects the vaccine with the injury alleged. *See Knudsen v. Sec'y of HHS*, 35 F. 3d 543, 549 (1994).

As a matter of elucidation, the Undersigned takes note of the following two-part test, which has been vindicated and viewed with approval by the Federal Circuit,[31] and which guides the Court's practical approach to analyzing the *Althen* elements:

> The Undersigned has often bifurcated the issue of actual causation into the "can it" prong and the "did it" prong: (1) whether there is a scientifically plausible theory which explains that such injury could follow directly from vaccination; and (2) whether that theory's process was at work in the instant case, based on the factual evidentiary record extant.

Weeks v. Sec'y of HHS, No. 05-0295V, 2007 WL 1263957, 2007 U.S. Claims LEXIS 127, slip op. at 25, n. 15 (Fed. Cl. Spec. Mstr. Apr. 13, 2007).

Of importance in this case, it is part of Petitioners' burden in proving actual causation to "prove by preponderant evidence both that [the] vaccinations were a substantial factor in causing the illness, disability, injury or condition and that the harm would not have occurred in the absence of the vaccination." *Pafford v. Sec'y of HHS*, 451 F. 3d 1352, 1355 (Fed. Cir. 2006), *rehearing and rehearing en banc denied*, (Oct. 24, 2006), *cert. den.*, 168 L. Ed. 2d 242, 75 U.S.L.W. 3644 (2007), citing *Shyface v. Sec'y of HHS*, 165 F. 3d 1344, 1352 (Fed. Cir.1999). This threshhold is the litmus test of the cause-in-fact (a.k.a. but-for causation) rule: that petitioner would not have sustained the damages complained of, *but for* the effect of the vaccine. *See generally Shyface, supra*. "[T]he relevant inquiry ...[is]... 'has the petitioner proven ... that her injury was in fact caused by the ...

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[31] *See Pafford v. Sec'y of HHS*, No. 01-0165V, 2004 WL 1717359, 2004 U.S. Claims LEXIS 179, *16, slip op. at 7 (Fed. Cl. Spec. Mstr. Jul. 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd* 451 F. 3d 1352, 1356 (2006) ("this court perceives no significant difference between the Special Master's test and that established by this court in *Althen* and *Shyface*"), *rehearing and rehearing en banc denied*, (Oct. 24, 2006), *cert. den.*, 168 L. Ed. 2d 242, 75 U.S.L.W. 3644 (2007).

vaccine, rather than by some other *superseding*[,] *intervening* cause?' ...[The petitioner need not] rule out every possible explanation ...[but]... must simply show ... that her injury was caused by a vaccine." *Johnson v. Sec'y of HHS*, 33 Fed. Cl. 712, 721 (1995), *aff'd* 99 F. 3d 1160 (Fed. Cir. 1996) (emphasis added).

"To prove causation, a petitioner in a Vaccine Act case must show that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Moberly v. Sec'y of HHS*, __ F.3d __, 2010 WL 118661 (Fed. Cir. 2010) quoting *Shyface v. Sec'y of HHS*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999); *see also Id*. citing *Walther v. Sec'y of HHS.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007) (for causation analysis in off-Table cases, the Restatement (Second) of Torts applies and 'the petitioner is treated as the equivalent of the tort plaintiff'). In the watershed case of *Shyface v. Sec'y of HHS*, 165 F. 3d at 1352, the Federal Circuit "adopt[ed] the Restatement [(2d) of Torts] rule for purposes of determining vaccine injury, that an action is the 'legal cause' of harm if that action is a 'substantial factor' in bringing about the harm, and that the harm would not have occurred but for the action," and that rule continues to guide the Court today in the instant matter.[32] *Cf. Hargrove v. Sec'y of HHS*, No. 05-0694V, 2009 WL 1220986 * 39-40 (Fed. Cl. Spec. Mstr. Apr. 14, 2009).

Here, *Shyface*'s incorporation of the concept of causation in tort law is essential to resolution of this matter. In this case, the central, essential facts are almost all undisputed. What is necessary is to induce what result is called for under the law when viewing these facts in relief, against the immarcescible backdrop of the common law.[33]

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[32] The mandate of the Federal Circuit in *Shyface* to follow the RESTATEMENT (2D) OF TORTS on the application of actual causation did not indicate how this Court should approach the tectonic shift of the common law into the later Restatement(s). The short answer to this question is that the Federal Circuit incorporated the RESTATEMENT (2D) OF TORTS, and until the Circuit does otherwise to change that gloss, that is the mandatory precedent binding on this Court. By way of more detailed analysis, given the Circuit's reasoning in *Shyface* for incorporating the Restatement, *i.e.* that Congress contemplated the common law (in its then contemporaneous understanding) within the Vaccine Act draftsmanship, thus presuming the common law as a background legislative intent, it would appear that only the Second Restatement is binding on this Court in matters touching on actual causation, because that is the version in use at the time of the Act's drafting and passage. Likewise, when the Federal Circuit decided *Shyface* in 1999, the RESTATEMENT (3D) OF TORTS: PRODUCTS LIABILITY had already become available in published form, and yet the Circuit did not choose to incorporate or even reference that Restatement's provisions at all, notwithstanding the potential corollary to the Program's focus on causation in the absence of a fault element. Had it done so, a contrary argument could have been made that the Circuit's reading of congressional intent was a progressing correspondence to whatever Restatement provisions were most current. However, this would seem to correspond to the more dubious "statutory purpose" canon of interpretation. The Court's reading of *Shyface* leads to a result that the Third Restatement should be viewed at most as persuasive, but not mandatory authority, and is not to be followed where it conflicts with the Second Restatement. Therefore, to the extent the Court cites to the Third Restatement herein, it shall be only to bolster or elaborate citations to other sources.

[33] For the sake of brevity, rather than discuss myriad common law case opinions, the Court will reference W. Page Keeton, PROSSER & KEETON ON TORTS (5th ed.1984) (hereinafter "Keeton at __") and leave the reader to pursue further inquiries to the cases cited therein. Mr. Prosser was a strong and respected force in the crafting of the Second Restatement, and served as Reporter thereto for some time.

Regarding the epistemological quandary raised *supra*, the Court notes the position taken by the common law, one that contemplates the radical alternatives of human choice and unpredictable events. If it is deterministic at all, it is in an absolute sense, wherein the causal factors determining eventual outcomes are overwhelming complex, so as to overwhelm, elude and confound human knowledge. "In a philosophical sense, the consequences of an act go forward to eternity, and the causes of an event go back to the dawn of human events, and beyond."[34] Keeton at 264. This is the basis for what is termed "cause in fact," which is based upon a "but for" formulation. Keeton at 265 ("[T]he classic test for determining cause in fact directs the factfinder to compare what did occur with what would have occurred if hypothetical, contrary-to-fact conditions had existed ... the term "cause in fact" embraces all things which have so far contributed to the result that without them it would not have occurred.") (some internal marks omitted). To rephrase slightly for this context the concise statement of the rule, a vaccine "is a cause of the [injury] if the [injury] would not have occurred but for that [vaccine]; conversely, the [vaccine] is not a cause of the [injury] if the [injury] would have occurred without it." Keeton at 266. Of interest in this case, "The conception of causation in fact extends not only to positive acts and active physical forces, but also to pre-existing passive conditions which have played a material part in bringing about the event." Keeton at 265.

This open-ended universe of infinite chains of cause and effect must be truncated for human comprehension in order to attach legal responsibility, however. Finitude demands an outer limit, a line to be drawn to divide what is a cause attaching liability–a legally proximate cause–from that which averts such responsibility. "As a practical matter, legal responsibility must be limited to those causes which are so closely connected with the result and of such significance that the law is justified in imposing liability." Keeton at 264. This is due to the understanding that, "The event without millions of causes is simply inconceivable; and the mere fact of causation, as distinguished from the nature and degree of the causal connection, can provide no clue of any kind to singling out those which are to be held legally responsible." Keeton at 266. Based on this conceptual understanding, therefore, it is certainly legal error to require the thing, act, or process at issue (here the vaccine) to be identified as *the* "sole cause," *the* "dominant cause," or *the* "proximate cause" of the harm complained of.[35] Keeton at 266. The correct formulation for determining proximate cause, then, is

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[34] Outside of the law, this precept is referred to as "sensitive dependence on initial conditions" or, more colloquially, "the butterfly effect." It was identified by Henri Poincaré in the nineteenth century and elucidated by Edward Lorenz, a pioneer of chaos theory mathematics. However, it is grounded in Newtonian mathematics within the concept of the "evolution rule of the dynamical system" (Φ^t).

[35] Prosser and Keeton go on to describe a circumstance where the but-for causation test fails but where liability is imposed even still, based upon the "substantial factor" test:

> If two causes concur to bring about an event, and either one of them, operating alone, would have been sufficient to cause the identical result, some other test is needed.... [E.g.,] The defendant sets a fire, which merges with a fire from some other source; the combined fires burn the plaintiff's property, but either one would have done it alone. In such cases, it is quite clear that each cause has in fact played so important a part in producing the result that responsibility should be imposed upon it...

Keeton at 266-67.

to ask if something is *a* substantial factor.[36] Of central importance in this case, if something is *a* substantial factor in causing the injury alleged, causation and liability are not avoided "merely because other causes have contributed to the result, since such causes, innumerable, are always present." Keeton at 268.

For the Court here to award compensation and hold that the vaccine "actually caused" Evelyn's injury, "it is only necessary that it be *a* legal cause of the harm. It is not necessary that it be *the* cause, using the word 'the' as meaning the sole and even the predominant cause." RESTATEMENT (2D) OF TORTS § 430, Comment d (emphases added); *cf.* RESTATEMENT (3D) OF TORTS: LIABILITY FOR PHYSICAL AND EMOTIONAL HARM § 26, comment c ("tortious conduct need only be *a* factual cause of the other's harm.") (emphasis in original). Furthermore, if the sequelae of the vaccination at issue did "actively and continuously operate to bring about" Evelyn's injury, vaccine causation is not precluded even where "the active and substantially simultaneous operation of the effects [of her genetic susceptibility] is also a substantial factor in bringing about the harm." *Id*. at § 439. The modern trend in common law cases, embedded in the rationale of the Restatement, is to ask why legal cause should be avoided where the complained-of cause coexists alongside other causes. Keeton at 301.

As explained *supra* at the Court's findings of fact, Evelyn's injury–seizures which began following an unbroken chain of events, beginning with the DTaP vaccination–would not have occurred *but for* her vaccination on 11 February 2004. The first seizure set the course for all that followed: As both experts explained, the first seizures of that morning are indivisible and inseparable from all that followed, to form Evelyn's seizure disorder. Likewise, Evelyn's genetic predisposition is a *but for* cause of Evelyn's seizures. As Dr. Kinsbourne conceded, most other children in Evelyn's position would not have suffered a seizure in response to her vaccination or the slight fever. Dr. Wiznitzer agreed that persons with a predisposition require a lesser threshold to initiate seizure activity.

Based on the foregoing, both the vaccination and Evelyn's genetic predisposition each constitute a cause in fact of her injury, because the injury would not have occurred as it did but for each of these. The remaining question–the ultimate issue presented in this case–is whether the vaccination should be adjudged a substantial cause, or whether genetic predisposition constitutes a superseding cause under the law.

Respondent proffered evidence and arguments that Evelyn's genetic predisposition was a superseding cause of her injury, rendering irrelevant the vaccine as a substantial cause. On this point, the Restatement indicates that, if the administration of the vaccine(s) to Evelyn "creates or increases the foreseeable risk of harm" that preexisted and coexisted in her genetic predisposition

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[36] "The 'substantial factor' formulation is one concerning legal significance rather than factual quantum." Keeton at 267. *See also* RESTATEMENT (2D) OF TORTS § 430, Comment a ("The word "substantial" is used to denote the fact that the defendant's conduct has such an effect in producing the harm as to lead reasonable men to regard it as a cause, using that word in the popular sense, in which there always lurks the idea of responsibility, rather than in the so-called "philosophic sense," which includes every one of the great number of events without which any happening would not have occurred.").

(as "a force of nature"), and the vaccine is found to be a substantial factor in causing her injury, then the genetic predisposition cannot constitute "a superseding cause." RESTATEMENT (2D) OF TORTS § 442A and Comment a thereunto. Likewise, "Where the [vaccine] creates or increases the risk of a particular harm and is a substantial factor in causing that harm, the fact that the harm is brought about through the intervention of another force [*e.g.*, genetic predisposition] does not relieve [Respondent] of liability, except where the harm is ... not within the scope of the risk created by the [vaccine]." RESTATEMENT (2D) OF TORTS § 442B.[37] Stated in the contrapositive, a causative factor unrelated to the vaccine may only be accounted as superseding (*i.e.*, negating the vaccine's causative impact) where its operation is "extraordinary" *and* where the resulting harm therefrom is qualitatively distinct from the risk posed by the vaccine. RESTATEMENT (2D) OF TORTS § 451.

Applying the general rule from the common law of torts, compensation is appropriate even when the vaccine "operates upon a concealed physical condition, such as ... a latent disease, or susceptibility to disease, to produce consequences" incapable of reasonable anticipation. Keeton at 291. Additionally, where the vaccine combines with a preexisting condition (such as genetic predisposition), the extent of the ultimate sequela need not have been foreseeable. Keeton at 292. As every aspiring attorney learns, "a defendant takes a plaintiff as he finds him," a rule most familiarly illustrated in the "eggshell skull" case of *Dulieu v. White & Sons*, 2 K.B. 669, 679 (1901). RESTATEMENT (2D) OF TORTS § 461 ("The negligent actor is subject to liability for harm to another although a physical condition of the other which is neither known nor should be known to the actor makes the injury greater than that which the actor as a reasonable man should have foreseen as a probable result of his conduct."). *Cf.* RESTATEMENT (3D) OF TORTS: LIABILITY FOR PHYSICAL AND EMOTIONAL HARM § 31 ("When an actor's tortious conduct causes harm to a person that, because of a preexisting physical or mental condition or other characteristics of the person, is of a greater magnitude or different type than might reasonably be expected, the actor is nevertheless subject to liability for all such harm to the person.").

On this same general theme, the concept of foreseeability may also enter a discussion of legal cause. If fever or a seizure are possible risks a specially-vulnerable vaccinee might sustain, the common law incorporated into the Restatement would militate for a finding of legal causation. *See* Restatement at § 442B. Additionally, "Foreseeable intervening forces are within the scope of the" risk created by the vaccine, and therefore also of Respondent's liability; "intervening causes which fall fairly in this category will not supersede" the substantiality of the vaccine as a cause. Keeton at 303-304; *see also Id*. at note 18.

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[37] *See also* Comment b to that section:

> If the [vaccine] has created or increased the risk that a particular harm to the [petitioner] will occur, and has been a substantial factor in causing that harm, it is immaterial to the [Respondent's] liability that the harm is brought about in a manner which no one ... could possibly have been expected to foresee or anticipate. This is true not only where the result is produced by the direct operation of the [vaccine] upon conditions or circumstances existing at the time [*e.g.*, genetic predisposition], but also where it is brought about through the intervention of other forces which the actor could not have expected, whether they be forces of nature, or the actions of animals... This is to say that any harm which is in itself foreseeable, as to which the [vaccine] has created or increased the recognizable risk, is always "proximate," no matter how it is brought about...

Respondent's argument concerning genetic predisposition as a superseding cause centers around an argument that the injury would have occurred sooner or later notwithstanding the vaccine: that it was overwhelmingly the genetic factor that caused the injury, and the vaccine only determined when such injury occurred. However, applying the same logic, one could argue in any case where the injury complained of is death, that death would have occurred eventually, even if it only occurred when it did because of the conduct or occurrence complained of. Death is certainly inevitable for mortal Man.[38] It is one of the events all can agree is biologically fated or destined: its details are only a question of timing and circumstances. However, such an argument, when raised, has been roundly rejected by the common law. Keeton at 272. *Cf.* RESTATEMENT (3D) OF TORTS: LIABILITY FOR PHYSICAL AND EMOTIONAL HARM § 26, comment b ("An act can also be a factual cause in accelerating an outcome that otherwise would have occurred at a later time. ... Acceleration may occur for harms other than death as well.")

Perhaps considering the facts of this case in a context more familiar to common law tort cases would be helpful. Respondent's argument for the genetic factor as a superseding cause could be analogized as saying, in effect, that a defendant's negligence with a fire source did not cause a forest fire; it was caused rather by an especially dry summer, persistent heavy winds, or the over-accumulation of plant debris and overgrowth. In a different environment, defendant's fire source would never have wrought the damage sustained, and there was nothing especially dangerous or otherwise extraordinary inherent or integral to the fire source. The fire was inevitable: regardless of the spark, something else would surely have triggered the dangerous conditions whereby fire blazed to such ruin, even if perhaps somewhat later (or earlier), *e.g.*, a lightning strike. The defendant's spark was merely a trigger which did not cause all the harm sustained, and at most should be limited as a cause to only its very limited immediate effects. The common law, however, has rejected this logic for the most part. *See* Keeton at 292, notes 1 and 2. Given the foregoing exemplar, the common law has invariably held a defendant liable, and has most regularly held defendant responsible for all the fire's effects which follow. *See, e.g., Burlington & M.R.R. Co. v. Westover*, 4 Neb. 268 (1876); *see also* Keeton at 294, note 15 and surrounding text; *cf* James 3:5 ("Behold, how great a matter a little fire kindleth!"). Therefore, Respondent "may be expected to take existing circumstances as they are, and be responsible for the effect of the [vaccination] upon them." Keeton at 294.

Applying the Federal Circuit's decision in *Shyface* and, by incorporation, the common law as summated in the Restatement, it seems altogether clear, that a genetic predisposition, exerting an independent influence while acting in conjunction with a vaccine reaction, cannot be accounted a superseding cause overwhelming the substantiality of the vaccine as a cause.

It may strike the casual observer that the Court is here conflating Petitioners' burden to prove the vaccine to be a substantial cause with Respondent's burden (*see Walther*, *supra*; *cf. Pafford*,

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[38] *See* Hebrews 9:27 ("And as it is appointed unto men once to die, but after this the judgment"); Ecclesiastes 3:20 ("All go unto one place; all are of the dust, and all turn to dust again"); Isaiah 40:6-8 ("All flesh is grass, and all the goodliness thereof is as the flower of the field: The grass withereth, the flower fadeth: because the spirit of the LORD bloweth upon it: surely the people is grass. The grass withereth, the flower fadeth: but the word of our God shall stand for ever.").

supra) to prove that a factor unrelated was the superseding cause (*see Hargrove*, *supra*). As the Federal Circuit explained in *de Bazan*, *supra*, this is not improper in actual causation cases within the Program. In fact, in the experience of the Undersigned, it is typically unavoidable. Dividing Respondent's task (*i.e.*, proving that a factor unrelated was *the* actual cause) from Petitioner's case in chief is only logical or coherent in Table cases, where vaccine causation is presumed, and therefore the question of actual causation has not been already raised. Bifurcating into two modes or phases in an actual causation case defies logic and practicality. At common law, affirmative defenses used by the party against whom the claim is brought invariably proffer some new set of facts, with distinct elements, after the claimant party has offered the facts to prove the elements of his cause of action. A construct in which an affirmative defense contains all the same elements as the cause of action's main component, addresses the same question–indeed, the very same transaction or occurrence, and where the Court's findings of fact and conclusions of law on the case in chief often work issue preclusion on the affirmative defense–in short, a situation like this one–amounts to a *vox nihili* in the context of the common law. The Federal Circuit in *Walther* remarked that a party can hardly be held to prove a negative, and yet bifurcating factor unrelated analysis from the petitioner's case in chief, where the Court has found that the vaccine did actually cause the injury complained of, would require Respondent to disprove what the Court has just found to be true! Inevitably, the factor unrelated issue will be decided during the case in chief. It would be an odd case indeed were the Court to find that the vaccine did actually cause the injury complained of, but then ruled that a factor unrelated was the actual cause of the injury complained of. Perhaps this point may be deemed too esoteric by some, but they need only look at the last five years of Federal Circuit opinions discussing actual causation to see that it is not an idle query.

In sum, the Court concludes as a matter of law that, weighing Evelyn's DTaP vaccination of 11 February as a causal factor, it was a substantial factor in bringing about her injury, and was not superseded by her genetic predisposition, which was also a substantial factor. Hence, the Court **RULES** that Petitioners are entitled to compensation, to be determined by further proceedings.

IV. CONCLUSION

Therefore, in light of the foregoing, the Court **RULES** in favor of entitlement in this matter. The parties are instructed to contact the Court for further proceedings, regarding the issue of damages. The Court may be reached *via* my law clerk, Isaiah Kalinowski, Esq., at 202-357-6351.

IT IS SO ORDERED.

Richard B. Abell
Special Master