

Subramaniam Sriram. Petitioners filed a post-hearing brief in this matter on January 27, 1997. Respondent filed her responsive brief on February 11, 1997. Petitioners filed a reply brief on March 3, 1997.

II.

FACTUAL BACKGROUND

The following evidence is contained in the record in this matter:⁽³⁾

Katie was born with an identical twin sister, Christen, on September 10, 1979. No complications were noted and Katie developed into a healthy child. According to Mrs. Williams, Katie developed a hard knot at the injection site that lasted about two months following her third DPT vaccination on June 17, 1980. P. Ex. 10 at 19-20. Katie reached developmental milestones at appropriate ages. She sat up at six months, walked at 10 months and was toilet-trained at two years of age. P. Ex. 12 at 6. Prior to Katie's July 31, 1984, DPT vaccination, her pediatrician's records note only minor childhood ailments. On July 31, 1984, Katie and Christen both received DPT and OPV immunizations during a physical examination for kindergarten at the offices of Dr. Whitlatch in Columbus, Ohio. P. Ex. 9 at 1-2; P. Ex. 10 at 22-23. Two days later, Katie was seen by Dr. Ruppel, one of Dr. Whitlatch's associates, who noted a local reaction to the DPT immunization of redness, swelling and itching. P. Ex. 9 at 2. According to Mrs. Williams, the swelling and tenderness lasted about 24 hours. P. Ex. 10 at 41-42.

Katie returned to Dr. Whitlatch's office on August 21, 1984. The nurse's notes indicate Katie had experienced a headache on the right side for the preceding three days with a low grade fever. On that date, Katie could not see from her right eye. P. Ex. 9 at 3. Dr. Whitlatch noted papilledema in Katie's right eye.⁽⁴⁾ After examination, Dr. Whitlatch referred Katie to Dr. Steiman, a neurologist, at Children's Hospital in Columbus, Ohio, who admitted Katie that day. P. Ex. 9 at 3; P. Ex. 12 at 2.

Admission notes indicate that Katie was in her usual state of good health until four days prior to admission when she developed a headache intermittently on the right side. The headache was temporarily relieved by Tylenol, but returned with increased severity. The morning of admission, Katie complained that she could not see with her right eye. The headaches and lack of vision were not associated with any other symptoms. It was also noted that there was no previous history of similar problems. P. Ex. 12 at 3. An examination by an ophthalmologist revealed papilledema in both eyes. P. Ex. 12 at 2.

Dr. Steiman's letter to Dr. Whitlatch of August 27, 1984, summarizes her condition:

Kathy [sic] is being discharged from Children's Hospital on August 27. As you recall, she suddenly developed right monocular visual loss approximately one week ago. Historically, she had been feeling a bit under the weather complaining of headache and tiredness for the week prior to this. She also noticed a little bit of right sided headache. . . . A CT scan was normal. . . .

P. Ex. 14 at 1. Dr. Steiman also noted that there was "a small but definite incidence of multiple sclerosis" following optic neuritis. He expressed his belief that it would take several weeks, if not months, for her to fully recover. *Id.* at 2.

A consult from an infectious disease expert was ordered. The notes from that examination state that Katie had been well and that two weeks prior to admission she had received DPT and OPV immunizations with a moderate local reaction. P. Ex. 12 at 19. The notes indicate Katie had had a sore

throat the day before her immunizations. The impression of the consulting physician was that Katie had optic neuritis. The physician noted that the etiology of optic neuritis was "usually due to inflammation, demyelination, degeneration or toxin." *Id.* It was also noted that optic neuritis sometimes occurred during or following acute illness with mumps, measles, EBV, influenza, poliomyelitis, smallpox, cytomegalovirus, pertussis, and varicella. *Id.* The report continued, "At the present time there is little info to suggest [history] of acute infectious illness. She did complain of sore throat 2 weeks ago. . . . Post immunization (esp. DPT) has been reported." *Id.*

Progress notes from Katie's hospital admission note that her parents had expressed concern that her July immunizations may have caused her problems because of the local reaction she experienced. P. Ex. 12 at 11. Katie was started on steroid medication during her hospital stay and discharged in an improved condition on August 27, 1984, after an uneventful hospital course. Her primary diagnosis on discharge was optic neuritis. P. Ex. 12 at 2. At home, she continued on a tapering dose of Prednisone. P. Ex. 12 at 2. Notes from a September 10, 1984, visit with Dr. Bremer, an ophthalmologist, indicate that Katie's optic neuritis had resolved and she had a normal ocular examination at that time. P. Ex. 15.

On December 6, 1984, Katie was seen by Dr. Ruppel. P. Ex. 10 at 54. The notes from that visit state that Katie's left eye had been hurting for three days and she had experienced a cough, congestion, runny nose, low grade fever and tiredness since the day before. P. Ex. 9 at 3. Dr. Whitlatch noted Katie "can see but outline of image is fuzzy." *Id.* The doctor observed papilledema in her left eye. His assessment was optic neuritis with a question of multiple sclerosis. *Id.*

Katie was seen by Dr. Steiman the following day. At the time, Dr. Steiman confirmed that Katie had developed optic neuritis in her left eye and noted, "I suspect we are dealing with a second bout of optic neuritis. I am concerned for this young girl that a diagnosis of multiple sclerosis may lay ahead." P. Ex. 14 at 3. Dr. Steiman started Katie on another tapering dose of Prednisone. *Id.* On December 24, 1984, Dr. Whitlatch noted decreased papilledema. P. Ex. 9 at 3.

Katie was reevaluated by Dr. Steiman on January 4, 1985. His records from that visit state, in part:

This is Kathy's [sic] second episode of optic neuritis, clearly affecting both eyes. Two detailed evaluations for multiple sclerosis have proved negative and I really do not believe that this can be considered as her diagnosis. Rather, I suspect she had a reaction to her DPT shot. Although the DPT shot occurred ten days prior to the first episode, it is not unheard of for the reaction to be this delayed. In addition, although it is unusual to have a biphasic reaction, this too is not unheard of. Rather, I believe that Kathy suffered a post-DPT optic neuritis.

P. Ex. 14 at 4.

In May 1985, Mrs. Williams became concerned about changes she perceived in Katie. P. Ex. 10 at 64. She took Katie to a pediatric neurologist, Dr. Kosnik, who apparently did not find any problems. *Id.* at 65-66. In August 1985, the family went on a camping trip. During the trip, Katie began to vomit and could not keep any liquids down. She also began to sleep excessively. *Id.* at 67-70. The family drove home and took Katie to the Emergency Room at Mt. Carmel East Hospital on August 23, 1985. Katie was transferred to Children's Hospital that day, where she was admitted. *Id.* at 71.

Katie was hospitalized for a presumed encephalitis of unknown origin from August 23, to September 5, 1985. P. Ex. 22 at 19-20. Her discharge summary from that hospitalization states the following:

This is the second CCH admission for this five year old white female admitted with a four day history of

right sided headache, backache, nausea and vomiting, and changing neurological status. The symptoms began while the family was on a camping trip in Wisconsin. Four days prior to admission, the child awoke with backache and right sided headache. The backache resolved, the headache became worse and the patient had intermittent periods of wellness alternating with terrible headaches and sleepiness. Two days prior to admission, the child began to have nausea and vomiting. . . . Past medical history was significant for two episodes of unilateral headaches and vision loss which occurred approximately 15 months prior to this admission. Initially, they involved both the right side of the head and right vision with edema of the right optic nerve. The first episode was treated with Prednisone for six weeks with good return of sight. Two weeks after the Prednisone was stopped, however, the vision loss occurred on the left side. This required treatment with four more weeks of Prednisone. Headache and visual problems resolved after this until the present admission. In the spring of 1985, the patient experienced "abnormal behavioral changes" during an episode of tonsillitis. A work-up was done with the diagnosis of multiple sclerosis in mind; this work-up was negative. No diagnosis was made.

P. Ex. 22 at 20. The summary described that Katie's mental status during her hospitalization would "wax and wane." P. Ex. 22 at 19. At the time of discharge, she was felt to have "Presumed encephalitis" and was sent home despite the continued presence of some complaints of headache and lethargy. *Id.* at 19.

Katie was rehospitalized from September 7 to September 23, 1985, for continued symptoms of increased fatigue as well as headaches and incontinence. She also was reported to have left-sided weakness and an unsteady gait. She apparently responded well to treatment with steroids and was discharged with a primary diagnosis of meningismus⁽⁵⁾ with secondary diagnoses of headache, urinary tract infection, E coli and spastic bladder. P. Ex. 22 at 2-3. A letter from Dr. Steiman to Dr. Whitlatch dated October 8, 1985, states, in part:

This is a brief note to inform you that Katie was admitted to Children's Hospital for a rather extensive six weeks stay towards the end of August. Her complaints began with headache, nausea and vomiting following a camping trip in Wisconsin. She was admitted to the hospital [where] a spinal tap showed increased [protein] and elevated white blood cell count. Her course was exceedingly complicated in that she had [multiple] spinal taps, CT scans, EEG's, bone scans, and even a nuclear magnetic [image] of her brain. All of the studies were normal. After several weeks of observation, consultation and discussion with various sub-specialist[s] it was decided that she must have a post-immune encephalomyelitis. She was put back on Decadron and within a few days she was back to her usual self.

P. Ex. 9 at 16.

In 1991, Katie was seen for intermittent vertical diplopia in her eyes.⁽⁶⁾ P. Ex. 32 at 2-3. Dr. Kosmorsky, a neuro-ophthalmologist who saw Katie on July 3, 1991, noted the following:

Historically, Katherine has had recurrent optic neuropathies associated with steroid sensitive encephalopathy and myelopathy. This was related to a DPT shot according to her mother which brings about the possibility of a post-vaccinial type of disorder. However, recurrent bouts of steroid-sensitive central nervous system demyelination [sic] from a single DPT shot, if they exist, are indeed rare.

P. Ex. 23 at 3. Mrs. Williams testified she was informed by Dr. Kosmorsky that Katie's double vision was due to the damage that was done to her optic nerve. Tr. at 9-10. In 1993, Katie had surgery to correct her double vision. Tr. at 11. More recently, Katie again began experiencing double vision and headaches.⁽⁷⁾

III. EXPERT TESTIMONY

Petitioners presented the testimony of Dr. Kottil Rammohan, currently Vice Chairman of the Department of Neurology at Ohio State University Medical Center and Director of the Multiple Sclerosis Center there.⁽⁸⁾ P. Ex. 41. Dr. Rammohan opined, to a reasonable degree of medical probability, that Katie's optic neuritis and her subsequent course were related to her July 31, 1984, DPT vaccination.⁽⁹⁾ Tr. at 15. Dr. Rammohan explained that optic neuritis involves loss of myelin that covers the fibers in the optic nerve. Tr. at 17. According to Dr. Rammohan, this disease process ("demyelination") is caused by an attack on the immune system and results in bare nerve fibers. Tr. at 18.

Dr. Rammohan examined Katie on December 21, 1984, and was struck by the fact that she is an identical twin. P. Ex. 34. Her sister, Christen, also received a DPT vaccine the same day Katie did although she did not become symptomatic. Tr. at 18-19. For that reason, Dr. Rammohan decided to order magnetic resonance imaging ("MRI") testing on both twins. Both twins demonstrated the presence of white matter lesions in the brain.⁽¹⁰⁾ Tr. at 19. Then, Dr. Rammohan ordered histocompatibility tests on both twins and found they both had two antigens, A-3 and B-7, which are commonly seen in patients with multiple sclerosis. On the basis of this testing, Dr. Rammohan concluded both twins have a genetic predisposition for a disorder like multiple sclerosis, although neither has been diagnosed with the disease.⁽¹¹⁾ *Id.*

Dr. Rammohan believes that the pertussis vaccine, coupled with Katie's genetic predisposition, caused loss of myelin and resulted in her optic neuritis. Tr. at 22. In this regard, Dr. Rammohan believes that a genetic predisposition alone, without an environmental factor that acts as a "trigger," would not be enough to cause illness. In fact, according to Dr. Rammohan, most persons with such predispositions lead normal, healthy lives. Tr. at 27.

Dr. Rammohan believes that the second bout of optic neuritis Katie suffered in December 1984, was related to the first bout, although he conceded that most attacks of optic neuritis associated with infectious problems are monophasic.⁽¹²⁾ Tr. at 49, 100. Dr. Rammohan also testified that the use of oral steroids to treat optic neuritis is thought to be associated with an increased incidence of optic neuritis in the opposite unaffected eye. Tr. at 51. He believes Katie's second occurrence of optic neuritis "could . . . have been aggravated by the use of oral steroids. . . ." Tr. at 52.

Dr. Rammohan believes that Katie's August 1985 bout of steroid-responsive meningo-encephalitis was also related to her initial bout of optic neuritis because no infectious agent was ever found and she responded well to steroids, signifying a probable immune-mediated process. Tr. at 54-55. He testified:

I would have to say if indeed it was immune-mediated, that it would probably be related to the first event, and there was no infectious agent [found] and she responded well to steroids[.] I would say that all these events are probably related to the original event.

Tr. at 55. Dr. Rammohan believes that Katie suffered from a rare recurring form of meningo-encephalitis that was a consequence of her original immunization. *Id.* No organism, viral or bacterial, was cultured from Katie's blood, and she responded well to steroids, an indication of an immune-mediated process, according to Dr. Rammohan. Tr. at 56-57, 106. However, Dr. Rammohan conceded that viral encephalitis is difficult to culture and most infectious encephalomyelitis is set off by a viral infection. Tr. at 108.

As to Katie's bout of double vision that occurred in 1994, and, again recently, Dr. Rammohan testified it was probably related to her "early events" and not a new attack. Tr. at 57-58, 106, 112-13.

Dr. Rammohan bases his opinion on several factors. First, vaccines have been shown to cause a loss of myelin in the brain. Tr. at 15. Second, pertussis vaccine has been shown to act as an adjuvant in autoimmune diseases involving demyelination. Further, the temporal association between the vaccination and the onset of Katie's optic neuritis is compelling and within a time frame that would be expected for an immune-mediated response. Moreover, the literature supports a relationship between vaccines and optic neuritis. Finally, experimental animal models point to a relationship between pertussis and demyelinating disease. *Id.*

Dr. Rammohan pointed to scientific literature which suggests vaccinations may cause optic neuritis and transverse myelitis, both of which, he testified, Katie experienced.⁽¹³⁾ Tr. at 16. Dr. Rammohan explained that vaccines, including DPT, have been shown to produce a loss of myelin in the brain. Tr. at 15. According to Dr. Rammohan, "there are case reports of that phenomenon occurring following immunizations." *Id.* Dr. Rammohan believes that the medical literature is supportive of his testimony. Petitioners have submitted nine medical articles which purportedly buttress their claim.⁽¹⁴⁾

In particular, Dr. Rammohan focused on one article, R. Riikonen, *The Role of Infection and Vaccination in the Genesis of Optic Neuritis and Multiple Sclerosis in Children*, 80 *Acta Neurol. Scand.* 425 (1989); P. Ex. 37D (hereafter "the Finnish Article"). In the Finnish Article, an association was described between previous infection and/or vaccination and the development of optic neuritis in 18 children.⁽¹⁵⁾ *Id.* Ten of those children subsequently developed multiple sclerosis ("MS"). In six patients, vaccination preceded the onset of the first optic neuritis attack. (All but one went on to develop MS.) Ten of the patients had a bacterial or viral infection within the two weeks prior to the onset of symptoms of optic neuritis. Dr. Rammohan believes the article is significant because it involved a large number of children with multiple sclerosis, a majority of whom had optic neuritis and other manifestations that occurred following infections or immunizations.⁽¹⁶⁾ Tr. at 39. Dr. Rammohan also pointed to another case report of a child who developed optic neuritis in temporal association with DPT and OPV vaccines.⁽¹⁷⁾ Tr. at 77-78; P. Ex. 37B.

In addition, Dr. Rammohan referred to a report known as *Adverse Events Associated with Childhood Vaccines -- Evidence Bearing on Causality*, a Report of the Institute of Medicine (National Academy Press, 1994) (hereafter, "IOM Report").⁽¹⁸⁾ In this report, an observation was made that there was a "biological plausibility for a causal relation between vaccines and demyelinating disorders," including transverse myelitis and optic neuritis. IOM Report at 85.

As to the mechanism by which Katie's optic neuritis occurred, Dr. Rammohan posited two theories. First, he testified, the endotoxins in the pertussis vaccine may have been the mechanism by which Katie was injured. Tr. at 44. He explained that endotoxins can act as "super antigens" which trigger the immune system into reacting in the brain. *Id.* He described the mechanism by which this can happen.

Any vaccine can cause . . . auto-immune problems of the brain . . . by what is called an antigenetic mimicry, meaning that there are sequences in proteins in the bacteria that mimic sequences that are seen in normal brains and . . . when the immune system attacks the organism, it ends up attacking [healthy] cells. That is what is called molecular mimicry.

Tr. at 103-04. Another mechanism by which the DPT vaccine may cause optic neuritis, according to Dr. Rammohan, is the process by which the vaccine acts as an "adjuvant" or agent to "rev up" the immune system. Tr. at 16, 45, 104. Under this model, it is thought, cells that were previously dormant are activated to act against the brain. Tr. at 104-05.

On cross-examination, Dr. Rammohan conceded that viral illnesses are also seen in association with optic neuritis. Tr. at 80. Katie had an upper respiratory infection two days prior to her first hospital admission with optic neuritis. Tr. at 79; P. Ex. 12 at 2. Another hospital record noted she had a sore throat one day prior to immunization and, at the time of the consultation, her sibling had a sore throat and nasal congestion. Tr. at 85; P. Ex. 12 at 19. Dr. Rammohan opined:

[L]et's say she had a viral infection prior to getting the DPT, maybe that was the trigger that led to the problems. In other words, the vaccine by itself may have not caused the injury without the presence of the antecedent. The viral infection probably set the stage for more problems. I'm speculating.

Tr. at 86.

Dr. Rammohan believes the experimental animal model in which experimental auto-immune encephalomyelitis ("EAE") can be induced by injection of pertussis is also supportive of his theory that Katie's attacks of optic neuritis were related to her DPT immunization. Tr. at 45. According to Dr. Rammohan, pertussis has been used as an adjuvant in producing demyelination in animals. Tr. at 16. According to Dr. Rammohan, pertussis is administered to mice to produce a recurring pattern of auto-immune encephalomyelitis. Tr. at 71. While conceding that "it is a big jump from mouse to man," Dr. Rammohan believes that the mouse model is relevant to this case because it is a model for humans with multiple sclerosis. Moreover, treatments for MS are first tested using animal models. Tr. at 142-43.

Finally, Dr. Rammohan believes the temporal association between her DPT vaccination and the onset of the symptoms of her optic neuritis, approximately two weeks, fits within the time frame one would expect with an autoimmune reaction causing a loss of myelin . Tr. at 16-17.

Dr. Rammohan conceded there is no "hard core evidence" that DPT causes the problems that Katie has suffered because "the kind of evidence that one needs to do to prove the point can never be done in humans." Tr. at 138. Accordingly, everything supportive of his theory must necessarily be anecdotal. *Id.* In addition, he conceded that the relapsing and remitting course Katie experienced, is a "distinctly unusual" pattern for a post-immunization encephalomyelitis. Tr. at 70-71.

As to the issue of significant aggravation, Dr. Rammohan's testimony was rather vague. He stated the DPT acted as a "facilitator" for someone genetically prone to develop either multiple sclerosis or post-immunization encephalomyelitis. Tr. at 73.

Dr. Subramaniam Sriram

Testifying for respondent was Dr. Subramaniam Sriram, Director of the Multiple Sclerosis Clinic and professor of experimental neurology at Vanderbilt University Medical Center.⁽¹⁹⁾ R. Ex. C. In his practice, Dr. Sriram treats at least five to ten cases of optic neuritis a year because it is a common manifestation of multiple sclerosis. Dr. Sriram believes, to a reasonable degree of medical certainty, that there is no causal relationship between Katie's DPT vaccination and the development of her optic neuritis. Tr. at 115. Dr. Sriram bases his opinion on his review of the medical literature and epidemiological studies. *Id.*

Dr. Sriram testified that although there has been anecdotal information linking DPT and optic neuritis, the only case reports that petitioners filed reflecting such a temporal association involved a DPT plus polio vaccination and a DPT plus smallpox vaccination. Tr. at 116-17. According to Dr. Sriram, there

have been many more case reports of an association between optic neuritis and viral infections than with vaccinations.⁽²⁰⁾ He believes that even the Finnish Article does not establish a link between optic neuritis and live viruses because it does not involve a case controlled study. Tr. at 119. Further, he testified, of the patients studied who developed optic neuritis following vaccination and did not go on to develop multiple sclerosis, the vaccination preceded the onset of symptoms mostly by years, "way beyond what we would consider temporally related."⁽²¹⁾ Tr. at 42.

Dr. Sriram also rejects the molecular mimicry theory propounded by Dr. Rammohan as just speculation, not proven by scientific methods. Tr. at 120. According to Dr. Rammohan, that theory, in which there is cross-reactivity between an environmental agent and the nervous system, has been attributed to viruses and not to bacterial toxins such as pertussis. Tr. at 135-36. Additionally, with respect to the animal models by which pertussis is used as an adjuvant to exaggerate a preexisting disease, Dr. Rammohan is not aware of its use to produce a recurring disease such as Katie experienced. Tr. at 120-21; 131. The fact that Katie had such a relapsing and remitting course tends, in Dr. Sriram's view, to make the association between her DPT vaccination and her optic neuritis more tenuous. Tr. at 121.

Dr. Sriram conceded that pertussis given to mice can aggravate a pre-existing condition called auto-immune encephalitis. Tr. at 129. However, the pre-existing condition that is aggravated in mice is not optic neuritis. Tr. at 134. Further, according to Dr. Sriram, in the mouse model, the pertussis is injected under the animal's skin in an oil emulsion and therefore it sits "like a depot" underneath the skin, unlike the situation in humans where the vaccination clears the body very quickly. Tr. at 122.

Dr. Sriram questions the accuracy of the MRI scans performed on Katie and her twin, Christen. Only one sequence of testing was done at that time, which is "unusual." Tr. at 123. Further, later imaging performed on Katie was entirely normal, according to Dr. Sriram. *Id.* As to the question of A-3 and B-7 histocompatibility findings in Katie, Dr. Sriram testified they are present in 15 to 18 percent of normal individuals.

In sum, although Dr. Sriram believes that it may be theoretically possible for DPT to play a role in optic neuritis, there is not sufficient evidence to conclude that it can. Tr. at 135. While Katie may have had a predisposition to develop optic neuritis, he does not believe the DPT vaccination played a role in her optic neuritis or subsequent encephalomyelitis. Tr. at 124-25. According to Dr. Sriram, the most common cause of optic neuritis is multiple sclerosis, with the next most common cause being a viral infection. Tr. at 126. Dr. Sriram does not believe Katie has MS. Tr. at 122. He believes a viral infection most likely caused her optic neuritis. Tr. at 126.

IV. **DISCUSSION**

Causation in Vaccine Act cases can be established in one of two ways: either through the statutorily prescribed presumption of causation, or by proving causation-in-fact. Petitioners must prove one or the other in order to recover under the Act.⁽²²⁾ The Vaccine Injury Table lists certain injuries and conditions which, if found to occur within a prescribed time period, create a rebuttable presumption that the vaccine caused the injury or condition.⁽²³⁾ A rebuttable presumption also obtains when a petitioner proves that a Table injury has been significantly aggravated, within the Table time period, by a listed vaccine.⁽²⁴⁾ Petitioners may also prove that an injury not listed on the Vaccine Injury Table actually caused an injury.⁽²⁵⁾ Further, petitioners may prove that an underlying injury not listed on the Vaccine Injury Table was significantly aggravated by a listed vaccine.⁽²⁶⁾ In the latter two instances, there is no presumption of causation and the burden does not shift to respondent to prove a factor unrelated to the administration of the vaccine caused the injury.

Petitioners have two theories of recovery here. One is that the DPT and/or OPV vaccine Katie received actually caused her optic neuritis. Alternatively, petitioners argue that the DPT/OPV immunization significantly aggravated a pre-existing condition, namely, a genetic predisposition to contract optic neuritis. Optic neuritis is not a condition found on the Vaccine Injury Table. Accordingly, both of petitioners' claims must be analyzed under the framework of an off-Table injury. That is, no presumption of causation exists and petitioners must prove it is more likely than not that the inoculation in question in fact caused the injuries alleged.

Causation-in-fact

In order to demonstrate entitlement to compensation in an off-Table case, petitioners must affirmatively demonstrate by a preponderance of the evidence that the vaccination in question more likely than not caused the injury alleged. §§ 11(c)(1)(C)(ii)(I) and (II); *Grant v. Secretary of HHS*, 956 F.2d 1144 (Fed. Cir. 1992); *Strother v. Secretary of HHS*, 21 Cl. Ct. 365, 369-70 (1990), *aff'd*, 950 F.2d 731 (Fed. Cir. 1991). The Federal Circuit in *Grant* summarized the legal criteria required to prove actual causation under the Vaccine Act. The court held that a 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.

Petitioners do not meet this affirmative obligation by merely showing a proximate temporal association between the vaccination and the injury. Rather, petitioners must explain *how* and *why* the injury occurred. *Strother*, 21 Cl. Ct. at 370; *see also Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1993), *cert. denied*, 469 U.S. 817 (1984) (inoculation is not the cause of every event that occurs within a ten day period following it). If petitioners view the temporal relationship as "key," the claim must fail. *Thibaudeau v. Secretary of HHS*, 24 Cl. Ct. 400, 403 (1991). Nor may petitioners meet their burden by eliminating other potential causes of the injury. *Grant*, 956 F.2d at 1149. Petitioners' theory "must be supported by a sound and reliable medical or scientific explanation." *Knudson v. Secretary of HHS*, 35 F.3d 543 (Fed. Cir. 1994)

"[E]vidence in the form of scientific studies or expert medical testimony is necessary to demonstrate causation" for petitioners seeking to prove actual causation. H.R. Rep. No. 990908, 99th Cong. 2d Sess., pt. 1 at 15 (Sept. 26, 1986), *reprinted in* 1986 U.S. Code Cong. and Admin. News 8344, 8356. The general acceptance of a theory within the scientific community of a scientific theory can have a bearing on the question of assessing reliability while a theory that has attracted only minimal support may be viewed with skepticism. *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 113 S. Ct. 2786, 2797 (1993).

Under the Table injury route, after petitioners have demonstrated the requirements of Section 13(a)(1) (A), the burden shifts to the respondent to prove the injury was caused by factors unrelated to the vaccination in question pursuant to section 13(a)(1)(B). *Matthews v. Secretary of HHS*, 18 Cl. Ct. 514, 518 (1989); *O'Connor v. Secretary of HHS*, 24 Cl. Ct. 428, 429-30 n. 2 (1991), *aff'd*, 975 F.2d 868. In an actual causation case such as this, however, the inquiry is "collapsed into a single determination: On the record as a whole, have petitioners proven, by a preponderance of the evidence, that her injury was in fact caused by the administration of a listed vaccine, rather than by some other superseding intervening cause?" *Johnson v. Secretary of HHS*, 33 Fed. Cl. 712, 722 (1995); *aff'd* 99 F.3d 1160 (Fed. Cir. 1996). *See also, Bradley v. Secretary of HHS*, 991 F.2d 1570,

1575 (Fed. Cir. 1993); *Munn v. Secretary of HHS*, 970 F.2d 863, 865 (Fed. Cir. 1992); *Wagner v. Secretary of HHS*, No. 90-2208V, 1997 WL 617035 (Fed. Cl. Spec. Mstr. Sept. 22, 1997) (dec. on remand).

In both Table and non-Table cases, it is the special master's responsibility to ascertain, based on the record as a whole, whether a preponderance of the evidence shows that the claimed injury is due to a factor unrelated to the administration of the vaccination. In a Table case, once an injury is proven, the burden shifts to respondent to prove a factor unrelated caused the injury. In a non-Table case, however, the special master must weigh all the evidence and decide whether the vaccination more likely caused the injury than anything else. As Special Master Hastings has set forth in his decision in *Wagner*, it is petitioners' burden in a non-Table case, as it is in non-Program tort proceedings, to show that "the likelihood that the vaccination caused an injury is greater than the likelihood that any other factors caused the injury. In other words, the evidence that the vaccination caused the injury must be weighed *directly against* any evidence indicating that any other factor caused the injury." *Wagner* at *11 (emphasis in original).

Inasmuch as neither optic neuritis nor an underlying genetic predisposition to develop optic neuritis are injuries listed in the Vaccine Injury Table, petitioners' claim that the DPT vaccination in question either caused Katie's optic neuritis or significantly aggravated her genetic predisposition to develop optic neuritis is one of actual causation. The analysis in cause-in-fact cases is two-fold: (1) *can* DPT cause optic neuritis or significantly aggravate an underlying genetic predisposition for optic neuritis? And (2) *did* the DPT inoculation in question in-fact cause Katie's optic neuritis or the significant aggravation of Katie's underlying genetic predisposition for optic neuritis *in this case*? See *Guy v. Secretary of HHS*, No. 92-779V, 1995 WL 103348 (Fed. Cl. Spec. Mstr. Feb. 21, 1995) (two-step causation-in-fact analysis used); *Alberding v. Secretary of HHS*, No. 90-3177V, 1994 WL 110736 (Fed. Cl. Spec. Mstr. March 18, 1994)(two-step causation-in-fact analysis used); *Housand v. Secretary of HHS*, No. 94-441V, 1996 WL 282882 at *5 (Fed. Cl. Spec. Mstr. May 13, 1996) (two-step cause-in-fact analysis used).

1) Can a DPT vaccination in-fact cause optic neuritis or significantly aggravate an underlying genetic predisposition for optic neuritis?

Causation-in-fact

The evidence supporting the notion that a DPT vaccination can in-fact cause optic neuritis is thin.⁽²⁷⁾ Dr. Rammohan relies on several journal articles as well as the IOM report to buttress his theory. Further inquiry reveals, however, that there is no literature *directly supporting* petitioners' claimed relationship between DPT/OPV vaccine and optic neuritis. Petitioners have pointed to articles purporting to establish a causal relationship between *other* vaccines and optic neuritis as support for the proposition that the DPT/OPV vaccine can cause optic neuritis. Tr. at 16, 61. In other words, petitioners believe that because some vaccines can cause optic neuritis, it is reasonable to believe that the DPT/OPV vaccines administered to Katie could do so. As Dr. Rammohan himself observed, however, "there is no hard science" to establish such a causal relationship. Indeed, Dr. Rammohan conceded there is no epidemiological evidence establishing a causal relationship between the DPT or OPV vaccines and optic neuritis. Tr. at 138.

Petitioners rely on the IOM Report to buttress their claim. The IOM Report addresses the causal relationship between tetanus toxoid, DT, or Td vaccines and "ADEM, transverse myelitis, or optic neuritis," not the DPT and OPV vaccines at issue here. While the IOM concurred that it is "biologically plausible that an injection of inactivated virus, bacterium, or live attenuated virus might induce an autoimmune response," it ultimately concluded that the evidence is "inadequate to accept or reject a

causal relation between tetanus toxoid, DT, or Td and demyelinating diseases of the [central nervous system] (ADEM, transverse myelitis, and optic neuritis)." IOM Report at 86. However, biological plausibility alone is insufficient to establish causation.

The Finnish Article is only supportive of petitioners' claim in a theoretical sense. As noted, the article did not reflect a case-controlled study. Tr. at 75. The article discussed the occurrence of optic neuritis in 18 children after exposure to various vaccines and/or infection.⁽²⁸⁾ Of the eighteen children studied in the article, ten had experienced common bacterial or viral infections prior to the onset of optic neuritis; only one of the eighteen subjects studied had received the DPT/OPV vaccine in temporal relationship to the onset of optic neuritis. Finnish Article at 426. This patient went on to develop MS, which both experts testified Katie does not have. Whatever conclusion one may be tempted to draw from this case report is further undermined by the fact that that child may have been one of the ten subjects also exposed to a viral or bacterial agent. Only one other case report was cited by petitioners in which a child received DPT and OPV immunizations and developed optic neuritis in temporal proximity thereto. In that case, however, the child also experienced a viral prodrome (sore throat, fever and nausea) two weeks prior to the onset of optic neuritis and, at about the same time, was exposed to another child with viral encephalitis. (P. Ex. 37B).

The two case reports, while worthy of note, do not prove causality.⁽²⁹⁾ According to Dr. Sriram, there have been more case reports of optic neuritis occurring in temporal association with viral infection than with vaccines. Tr. at 117. Thus, petitioners' theory is not only devoid of epidemiological support, it is not buttressed by strong anecdotal support.⁽³⁰⁾ In short, the fact that there exists a "biological plausibility" of a link between certain vaccines and optic neuritis does not establish a causal relationship between those vaccines and optic neuritis.

Dr. Rammohan attempted to use certain experimental animal models purportedly used by Dr. Sriram as support for his theory that DPT can cause optic neuritis. Specifically, he pointed to experiments in which Dr. Sriram injected pertussis into mice in order to induce immediate paralysis. Dr. Sriram explained, however, that the pertussis was injected into mice to activate a pre-existing autoimmune encephalitis, not optic neuritis. That pertussis may activate a pre-existing autoimmune encephalitis in mice does not establish that it can activate a different injury, optic neuritis, in people.⁽³¹⁾

Finally, Dr. Rammohan believes that the temporal relationship between the DPT/OPV inoculations Katie received and the onset of her optic neuritis supports petitioners' claim. While it may be the case that the onset of Katie's optic neuritis falls within the window one might expect for an autoimmune reaction, this alone is insufficient to establish causation. *Grant*, 956 F.2d at 1150 (A "proximate temporal association alone does not suffice to show a causal link between vaccination and the injury."). Moreover, the initial temporal link between Katie's vaccinations and her initial bout of optic neuritis does not explain the vaccination's causal relationship to her subsequent bout of optic neuritis, meningoencephalitis and other eye problems. Even Dr. Rammohan conceded that a DPT/OPV would typically cause a monophasic reaction and testified that such a course as Katie experienced would be "distinctly unusual." Tr. at 71. In short, petitioners have simply not met their burden of proving that DPT/OPV can cause optic neuritis.

Significant Aggravation

The question whether a DPT vaccination can significantly aggravate an underlying genetic predisposition for optic neuritis requires an analysis of exactly what significant aggravation means in the context of the Vaccine Act. The term "significant aggravation" is defined in the Act as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness

accompanied by a substantial deterioration of health."⁽³²⁾ In *Whitecotton v. Secretary of HHS*, 81 F.3d 1099 (Fed. Cir. 1996), the U. S. Court of Appeals for the Federal Circuit announced a new test for determining whether a petitioner has satisfied the requirements for demonstrating the significant aggravation of a pre-existing injury, condition or illness. Contrary to petitioners' assertions, however, the test enunciated in *Whitecotton* is *specifically* limited to Table injuries. 81 F.3d at 1107, citing *Reusser v. Secretary of HHS*, 28 Fed. Cl. 516, 527 (1993). Other than merely asserting that there is no reason the test enunciated in *Whitecotton* should not apply to causation-in-fact claims, petitioners provide no cogent argument for such application.

The test enunciated in *Whitecotton* is not stringent, requiring only that the special master (1) assess the person's condition prior to the administration of the vaccine, (2) assess the person's current condition, (3) determine if the person's current condition is substantially worse than his or her pre-vaccination condition and (4) determine whether the onset of the significant worsening began within the Table time period. *Whitecotton v. Secretary of HHS*, Nos. 92-5083, 93-5101, 81 F.3d 1099, 1107, 1996 WL 179978 (Fed. Cir. Apr. 16, 1996), *aff'd in part, rev'd in part, remanded in part*, No. 90-692V (Fed. Cl. Jan. 7, 1993) (unpub. order). Such a relaxed standard clearly was not envisioned to apply in a situation in which the petitioners have the burden of proving actual causation.

Even if the *Whitecotton* framework were applicable, however, petitioners still have not proven their case. While Dr. Rammohan apparently believes the DPT vaccinations caused the lesions present on MRI scanning in both Katie and her twin sister, there is no proof of that fact. Dr. Rammohan was not at all convincing that they were caused by the vaccinations and conceded the lesions may have predated the vaccinations.⁽³³⁾ Moreover, the record contains an incomplete description of Katie's current condition. Finally, Dr. Rammohan did not address whether her current condition is a "significant aggravation" of her prevaccination condition. Indeed, he seemed uncomfortable with the terminology. While he believes that Katie was predisposed genetically to develop optic neuritis, presumably because of the histocompatibility markers she possesses, these markers are present in a significant percentage of the general population. When asked about the theory of significant aggravation, Dr. Rammohan replied, "I would not say [the DPT/OPV] aggravated a pre-existing condition. I would . . . consider the DPT to be a facilitator for somebody who is genetically prone for it." Tr. at 73.

Petitioners have submitted no literature or other scientific support for the notion that DPT vaccinations significantly aggravate or "facilitate" an underlying genetic predisposition for optic neuritis. Dr. Rammohan was vague and somewhat ambivalent about the notion. There is certainly not a preponderance of the evidence in the record that DPT/OPV vaccinations can significantly aggravate an underlying genetic propensity to develop optic neuritis.

2) Did the DPT vaccination administered to Katie cause her optic neuritis or significantly aggravate an underlying genetic predisposition for optic neuritis?

As to the second prong of the inquiry, petitioners have an even more onerous challenge. Even though Katie's optic neuritis became manifest within a time period in which an autoimmune type reaction might occur, again, a temporal relation alone is insufficient to prove causation. Moreover, Katie's course was distinctly unusual, a point conceded by Dr. Rammohan. Petitioners did not offer even anecdotal evidence of a vaccinee who suffered a relapsing and remitting course as did Katie, nor did they offer a single case report of a vaccinee who suffered meningoencephalitis following optic neuritis in temporal relation with DPT/OPV immunizations.

In their brief, petitioners only contend that the DPT/OPV immunizations Katie received caused her optic neuritis. I note that Katie's treating physicians initially entertained the notion that her immunizations

might have been a possible cause of her optic neuritis. However, none of her treating physicians indicated her DPT/OPV played any role in her subsequent meningoencephalitis. Indeed, Dr. Kosmorsky specifically indicated that recurrent bouts of central nervous system demyelination from a DPT vaccination would be exceedingly rare, if they exist at all. While perhaps petitioners do not believe the evidence is strong that her subsequent meningoencephalitis was also related to her optic neuritis, Dr. Rammohan believed it was, although he could not satisfactorily explain the causal relationship. Katie's subsequent illness is certainly pertinent in that it suggests a course never reported in the scientific literature. As a result, petitioners cannot establish that Katie's current condition is the sequela of her alleged vaccine-related injury. Dr. Rammohan was unable to provide the "logical, direct causal link" between the alleged vaccine injury and the alleged sequela. *Hossack v. Secretary of HHS*, 32 Fed. Cl. 769 (1995).

Most importantly, Katie was noted to have a sore throat the day preceding her immunizations, evidence she may have had a viral illness at that time. It is undisputed that viral illnesses are certainly more likely to cause optic neuritis than immunizations. In short, even if petitioners were to prevail in showing that DPT/OPV could plausibly cause optic neuritis, they have failed to prove, *in this particular case*, that the immunizations were more likely to have caused Katie's optic neuritis than any other factor. After carefully reviewing and considering all of the contemporaneous medical records and the testimony presented, I find that petitioners have not met their burden of demonstrating, by a preponderance of the evidence, that Katie's optic neuritis was caused by her immunizations or that she had a genetic predisposition for optic neuritis that was significantly aggravated by her DPT/OPV vaccines.

V.

FINDINGS OF FACT

1. As the parents of their minor daughter, petitioners have the requisite capacity to bring this action. Section 11(b)(1)(A).
2. Petitioners have not previously collected an award or settlement of a civil action in connection with any alleged injury sustained by Katie due to the administration of the DPT vaccine in question. Section 11(c)(1)(E); Petition at 3.
3. Katie was administered a vaccine listed in the Vaccine Injury Table. Section 11(c)(1)(B)(I)(I); P. Ex. 9 at 1-2; P. Ex. 10 at 22-23.
4. Said vaccine was administered in the United States, in Columbus, Ohio. Section 11(c)(1)(B)(I)(I); P. Ex. 9 at 1-2; P. Ex. 10 at 22-23.
5. There is not a preponderance of the evidence that Katie's optic neuritis was caused by the DPT and/or OPV vaccination she received on July 31, 1984.
6. There is not a preponderance of the evidence that the DPT and/or OPV vaccination administered to Katie on July 31, 1984, significantly aggravated an underlying genetic predisposition for optic neuritis.
7. There is not a preponderance of the evidence that petitioners expended in excess of \$1000 in unreimbursed medical expenses as a result of a vaccine-related injury.⁽³⁴⁾

VI.

CONCLUSION

Based on the foregoing, the undersigned finds, after considering the entire record in this case, that petitioners are not entitled to compensation under the Vaccine Act. In the absence of a motion for review filed pursuant to RCFC Appendix J, the clerk of the court is directed to enter judgement in accordance herewith.

IT IS SO ORDERED.

Elizabeth E. Wright

Special Master

1. The National Vaccine Injury Compensation Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended at 42 U.S.C.A. §§ 300aa-1 through -34 (West 1991 & Supp. 1997)). References shall be to the relevant subsection of 42 U.S.C.A. § 300aa.
2. As noted *infra*, while petitioners' pre- and post-hearing briefs argued that the DPT vaccination caused Katie's injuries, petitioners' expert witness testified that he could not state which vaccination actually caused her injuries.
3. The evidence in the record consists primarily of exhibits submitted as part of the petition filed in this case ("P. Ex. ____"), respondent's exhibits filed in this matter ("R. Ex. ____"), plus evidence taken at the evidentiary hearing in this matter ("Tr. at ____").
4. Papilledema is "edema of the optic disk. . . ." *Dorland's Illustrated Medical Dictionary* 1220 (27th ed. 1988) (hereafter, "*Dorland's* at ____").
5. Meningismus is "the signs and symptoms of meningeal irritation associated with acute febrile illness or dehydration without actual infection of the meninges." *Dorland's* at 1004.
6. Diplopia is "the perception of two images of a single object." *Dorland's* at 479. The lay term for diplopia is double vision.
7. At the time of Katie's first surgery, Dr. Kosmorsky informed Mrs. Williams that corrective surgery would probably be necessary again. Tr. at 9.
8. Dr. Rammohan is board certified in internal medicine and neurology and is also trained in neuroimmunology. He has published numerous articles in the fields of neurology and neuroimmunology. Tr. at 14; P. Ex. 41.
9. Dr. Rammohan did not know which vaccine, the DPT or the OPV, triggered Katie's optic neuritis, but he surmises it was probably the pertussis. Tr. at 89.

10. Dr. Rammohan conceded that it was impossible to tell whether the lesions preceded their DPT/OPV immunizations. Tr. at 22, 95. Dr. Rammohan hypothesized that both twins developed lesions as a consequence of the immunizations but Christen did not go on to suffer the same problems Katie did. Tr. at 91-94.

11. Dr. Sriram, respondent's expert, testified that about 17 percent of the general population has the B-7 marker as compared to 33 percent of the population of multiple sclerosis patients. Tr. at 25.

12. Dr. Rammohan testified that most auto-immune illnesses that occur after immunization are monophasic -- that is, they occur once and seldom recur. Tr. at 20.

13. Although Katie was noted to have left-sided weakness during her hospitalization, the undersigned is unaware of any diagnosis during her hospitalization of transverse myelitis. Dr. Rammohan pointed to a letter written by Dr. Kosmorsky in July 1991 indicating Katie had steroid sensitive myelopathy as indicative of the fact she had transverse myelitis. Tr. at 64; P. Ex. 32 at 2. In addition, during her hospitalizations in August and September 1985, Katie lost bladder function, another indication of transverse myelitis, according to Dr. Rammohan. Tr. at 66. Mrs. Williams testified Katie was never diagnosed with transverse myelitis as such but that she lost control of her bowel and lower extremities during her August 1985 hospitalization. Tr. at 67. Hospital records indicate she suffered a loss of bladder control, was unable to stand and was "wobbly." P. Ex. 22 at 6.

14. At the hearing, Dr. Rammohan testified he found 22 articles reporting optic neuritis occurring in association with a variety of vaccines. Tr. at 61.

15. The article concluded that, of the patients studied, "common infections and notably vaccination with live or inactivated viruses (polio, vaccinia, rubella, influenza) were often preceding events in [optic neuritis] and in relapses of MS. Their close temporal correlation strongly suggests a causal association. . . ." P. Ex. 37D at 429.

16. Dr. Rammohan testified that "optic neuritis occurs in well over 80 percent of patients with multiple sclerosis." Tr. at 60.

17. The child described in this case report had recurrences of optic neuritis upon tapering of the steroid treatment but her condition had resolved six months later. P. Ex. 37B at 19.

18. This report was prepared by a committee called together by the Institute of Medicine, as legislated by Congress, to conduct a scientific review of the possible adverse consequences of various childhood vaccines.

19. Dr. Sriram is board certified in neurology and internal medicine. He has held several academic appointments and is credited with over sixty publications. R. Ex. C

20. Even in those cases, Dr. Rammohan testified, "the link is not very tight," because it is based on anecdotal case reports involving temporal proximity alone. Tr. at 117.

21. Only one person in the group of eight patients who developed optic neuritis without developing multiple sclerosis is listed as having had a DPT vaccination. In that case, the vaccination preceded onset of symptoms by 4.5 years. In the group of ten patients who went on to develop multiple sclerosis after the optic neuritis, only one patient was immunized with DPT and polio vaccinations. In that case, vaccination preceded onset of symptoms by four weeks. P. Ex. 37D at 426.

22. Petitioners must prove their case by a preponderance of the evidence, which requires that the trier of fact "believe that the existence of a fact is more probable than its nonexistence before [the special master] 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 U.S. 358, 372-73 (1970) (Harlan, J., concurring) quoting F. James, *Civil Procedure* 250-51 (1965). Mere conjecture or speculation will not establish a probability. *Snowbank Enter. v. United States*, 6 Cl.Ct.. 476, 486 (Cl. Ct. 1984).

23. Section 14(a).

24. Section 11(c)(1)(C)(i).

25. Section 11(c)(1)(C)(ii).

26. *Id.*

27. It should be noted that petitioners rely on essentially the same evidence to support both theories of causation-in-fact and significant aggravation.

28. The Finnish Article focused on the relationship between viruses and optic neuritis -- as opposed to bacterially based vaccines such as DPT. Finnish Article at 429.

29. Petitioners point to a case decided by the undersigned, *Leary v. Secretary of HHS*, No. 90-1456V, 1994 WL 43395 (Fed. Cl. Spec. Mstr. Jan. 31, 1994) in which I found the vaccinee's underlying subclinical myocarditis was in fact significantly aggravated by a DPT vaccination, resulting in his death. In that case, the vaccinee was healthy and without symptoms at the time of immunization and died of myocarditis within two days of receiving the immunization. In *Leary*, I noted a case report of a similar situation in which a child developed myocarditis following a DPT immunization. However, I did not rely on that case report alone. Petitioners' theory was supported by a prominent medical textbook indicating that any stress, such as infection or fever, could unmask an underlying subclinical myocarditis. I found plausible the notion that the added stress of fever produced by a DPT vaccination could exacerbate a subclinical myocarditis where the heart was previously compensating. It should be noted that in a subsequent case, *Crockett v. Secretary of HHS*, No. 94-0015V, 1997 WL 702559 (Fed. Cl. Spec. Mstr. Sept. 30, 1997), while I noted the plausibility of the theory that DPT immunization could significantly aggravate an underlying myocarditis, I distinguished the circumstances from *Leary*. In *Crockett*, the child had also experienced a concurrent illness, otitis media, a factor I found could also have aggravated an underlying myocarditis. Petitioners in *Crockett* thus failed to meet the second prong of the proof necessary in an actual causation case -- that is, that the immunization produced in the injury in that particular case.

30. As Dr. Sriram observed, the dearth of epidemiological and case report evidence of optic neuritis in association with DPT and/or OPV vaccines is telling given the hundreds of millions of DPT vaccinations administered over time which would be expected to pick up even a rare causal relationship. Tr. at 116.

31. A further distinguishing factor is that in the animal models, the pertussis is injected in a special oil emulsion which remains under the skin, unlike DPT vaccine, which clears the body quickly.

32. Section 33(4).

33. Indeed, assuming such lesions were caused by the immunization in question, one wonders why

Christen did not also become symptomatic.

34. This is because I cannot conclude that any expenses incurred on Katie's behalf were vaccine-related.