OFFICE OF SPECIAL MASTERS

Filed: April 29, 2005

SHARON BUBB,	*	
	*	
Petitioner,	*	
	*	No. 01-721V
v.	*	
	*	TO BE PUBLISHED
SECRETARY OF HEALTH	*	
AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Sylvia Chin-Caplan, Boston, Massachusetts, for Petitioner.

Catharine E. Reeves, United States Department of Justice, Washington, D.C., for Respondent.

ERRATA[*]
DECISION[1]

SWEENEY, Special Master

I. ISSUES PRESENTED

This case implicates the tetanus toxoid vaccine. The questions presented are whether the change in petitioner's underlying condition, multiple sclerosis, rose to the level of significant aggravation as defined by the Vaccine Act, whether the tetanus toxoid vaccine can cause the significant aggravation of multiple sclerosis, and whether the tetanus toxoid vaccine caused the significant aggravation of petitioner's multiple sclerosis. Although the opposing experts agreed that petitioner's condition significantly worsened after the vaccine was administered, the experts disagreed concerning what caused the significant aggravation. Petitioner argued that the cause was the vaccine, while respondent contended that a subclinical urinary tract infection caused the significant worsening of petitioner's condition. After reviewing the medical records, petitioner's affidavits, and medical literature, and weighing the testimony of two expert witnesses, the special

[*] This errata corrects the numbering of the headings; no other changes were made.

[1] The court encourages the parties to review Vaccine Rule 18, which affords each party 14 days to object to disclosure of (1) trade secret or commercial or financial information that is privileged or confidential or (2) medical information that would constitute "a clearly unwarranted invasion of privacy."

master finds that petitioner failed to carry her burden of proving by a preponderance of the evidence that the vaccine caused the significant aggravation of her underlying condition. Although the special master was not persuaded that the worsening of petitioner's underlying disease resulted from a urinary tract infection as respondent alleges, neither respondent nor the special master has the burden of showing what caused the worsening of petitioner's multiple sclerosis.

II. PROCEDURAL BACKGROUND

On December 28, 2001, Sharon Bubb filed a petition for compensation under the National Childhood Vaccine Injury Act of 1986 ("Vaccine Act"), 42 U.S.C. §§ 300aa-1 to -34 (2000 & Supp. II 2003), alleging neurologic injuries, including multiple sclerosis ("MS"),[2] as the result of the tetanus toxoid ("TT")[3] vaccination she received on January 6, 1999. On October 28, 2002, petitioner filed an amended petition further alleging that she suffered a significant aggravation of her MS due to the TT vaccine. Hearings in Washington, D.C. were conducted on August 14, 2003, and October 10, 2003. Because of seemingly contradictory testimony concerning onset, additional written testimony was submitted by respondent's expert on January 24, 2005.[4] The case is now ripe for decision.

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[2] Multiple sclerosis is

> a disease in which there are foci of demyelination of various sizes throughout the white matter of the central nervous system, sometimes extending into the gray matter. Typically, the symptoms of lesions of the white matter are weakness, incoordination, paresthesias, speech disturbances, and visual complaints. The course of the disease is usually prolonged, so that the term multiple also refers to remissions and relapses that occur over a period of many years. Four types are recognized, based on the course of the disease: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing. The etiology is unknown.

Dorland's Illustrated Medical Dictionary 1669 (30th ed. 2003).

[3] The tetanus toxoid vaccine, used for immunization against tetanus, consists of a formaldehyde-treated Clostridium tetani toxin and is available in two forms: adsorbed toxoid and fluid toxoid. Ctrs. for Disease Control & Prevention, U.S. Dep't of Health & Human Servs., Epidemiology and Prevention of Vaccine-Preventable Diseases 69-70 (8th ed. 2005), http://www.cdc.gov/nip/publications/pink/tetanus.pdf.

[4] It was the special master's initial view, based upon the testimony of the parties' respective experts, that this case turned on the question of onset. Specifically, it appeared that petitioner was alleging that her initial, immediate onset of symptoms was the result of demyelination–a fact that is not biologically plausible. If this were the case, the questions of

whether TT can cause and did cause the significant aggravation of petitioner's MS would not need to be reached. The issue arose from petitioner's seemingly offering of different onset dates for two sets of symptoms. According to petitioner's initial affidavit, the first onset event occurred within minutes of receiving the TT vaccination and was manifested by the recurrence of old symptoms (i.e., the MS hug). The second date, marked by leg and feet numbness– hallmarks of demyelination–occurred within 7 to 14 days after vaccination. Clearly, even though symptoms can develop over time, there can be only one date of onset for the aggravation of petitioner's disease. Petitioner's assertion that she suffered the onset of some of her old MS symptoms within an hour or less of her vaccination seemingly defeated her claim because demyelination takes days to manifest. Thus, the special master was concerned that the underlying facts concerning onset did not support petitioner's theory of causation.

On the one hand, Dr. Vera S. Byers, petitioner's expert, remained firm throughout her testimony that petitioner's initial aches and pains shortly after vaccination were a typical vaccine reaction unlike the demyelinating symptoms, which manifested themselves about 10 days later.

The testimony of respondent's expert, Dr. Kottil Rammohan, however, was not as clear on this point. Dr. Rammohan discussed petitioner's experiencing the Uhthoff phenomenon–the reoccurrence of MS symptoms when a patient's core body temperature is raised–as a result of a urinary tract infection, "within hours, or days, after immunization." See Transcript of August 14, 2003 Proceedings at 126-27. Dr. Rammohan also cited portions of petitioner's affidavit to support his conclusion that "onset" occurred very quickly. He testified, "This is within minutes. I suspect it's not an hour we're talking about. . . . This is not two weeks later we are talking about." Id. at 129. According to Dr. Rammohan, "The onset occurred within a very short time. . . . And all of these symptoms were part and parcel of her initial package. In other words, she's describing everything having occurred in the beginning." Id. at 130. Later in his testimony, Dr. Rammonhan acknowledged that onset of demyelination takes weeks to manifest. Because Dr. Rammohan testified that onset occurred within minutes and that the symptoms were all part of one package, the special master was uncertain which date Dr. Rammonhan was offering as the date of onset.

This conflicting testimony necessitated the special master's consideration of the issue of onset. If petitioner's onset of MS symptoms occurred within minutes, petitioner could not prevail because demyelination cannot occur within minutes; the process requires days to develop and for symptoms to become manifest. As Dr. Rammohan explained, "the reactivity that occurs to the vaccine occurs about 7 to 10 days in a primary response. We're not talking about days [in this case], we're talking about hours." Id. at 81-82. An immediate reaction to a vaccine is hypersensitivity, not a T-cell-mediated response. Id. at 82-83.

On January 24, 2005, respondent filed Dr. Rammohan's response to certain questions posed by the special master. In his written testimony, Dr. Rammohan confirmed his prior testimony that the petitioner "experienced fever and malaise minutes or hours after vaccination,

In a nutshell, petitioner's theory of causation is that the January 6, 1999 TT vaccination caused her immune system to direct an attack against her body. Petitioner alleges that rather than experiencing the body's typical response to vaccination, which results in the body producing protective antibodies, petitioner's immune defense mechanisms misread the TT vaccine as a harmful invader that had to be eradicated. Petitioner claims that the introduction of the vaccine into her body activated certain cells that either directly or indirectly attacked the myelin sheath.[5] In essence, the body mistakes its own myelin for the antigen. Petitioner further argues that the manifestation of new and more extreme MS symptoms confirmed the attack on her body's myelin sheath. Conversely, respondent argues that petitioner's clinical course of MS has progressed as would be expected–fifty percent or more of all patients with relapsing remitting MS ("RRMS") experience deterioration at the ten-year mark, the precise time frame when petitioner's MS became exacerbated. Thus, this case presented the classic "battle of the experts." At hearing, one expert witness for each party testified.

III. FACTUAL HISTORY

The factual history is undisputed. Petitioner was born on February 9, 1955.[6] Am. Pet. at 1. In 1977, petitioner began working as a wallpaper installer. Am. Pet. at 2. Beginning in about

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which resulted in the return of MS related symptoms . . . . This phenomenon . . . is well known . . . as the Uhthoff's phenomenon." Respondent's Exhibit L at 1. Dr. Rammohan further explained that what petitioner initially experienced was "a reversible deterioration of symptoms due to fever." Id. Dr. Rammohan concluded, "[Petitioner's] subsequent problems are related to the urinary tract infection which she was experiencing." Id. at 2. The special master interprets Dr. Rammohan's reference to "subsequent problems" as the demyelinating symptoms–leg and feet numbness–first experienced by petitioner while playing at the bluegrass festival in mid-January 1999. Consequently, the written testimony supplied by Dr. Rammohan on January 24, 2005, resolved the question concerning the biologic plausibility of onset in petitioner's favor: the demyelinating symptoms did not occur until 7 to 14 days after the TT vaccination.

[5] The myelin sheath is

> the cyndrical covering on the axons of some neurons; it consists of concentric layers of myelin, formed in the peripheral nervous system by the plasma membrane of Schwann cells, and in the central nervous system by oligodendrocytes. . . . Myelin is an electrical insulator that serves to speed the conduction of nerve impulses.

Dorland's Illustrated Medical Dictionary, supra note 2, at 1689.

[6] All references to the Amended Petition shall be designated herein as "Am. Pet. at __." All references to the pertinent Petitioner's Exhibits shall be designated herein as "Am. Pet. Ex. __ at __."

1985, petitioner began to have back pain and incidents of both arms going to sleep. Am. Pet. Ex. 1 at 1.

Petitioner was not diagnosed with MS until 1996. Am. Pet. at 2. Specifically, on March 7, 1996, Robert M. Lindsey, M.D. evaluated petitioner for multiple complaints of pain and numbness. Am. Pet. Ex. 4 at 11-13. Dr. Lindsey's records indicate that petitioner's difficulties began approximately six weeks prior to his March 7 examination. Id. at 11. Petitioner reported experiencing a heavy or tingling sensation throughout her upper extremities and trunk, which occasionally also ran into her lower extremities. Id. Petitioner also complained of reduced strength throughout all of her extremities, stiffness, fatigue, and susceptibility to cold in both of her hands. Id. She denied experiencing any bowel or bladder problems. Id. Petitioner stated that she did not take any medications for these problems and that chiropractic adjustments tended to improve her condition. Id.

Based upon her clinical profile and family history, Dr. Lindsey suspected that petitioner might suffer from rheumatoid arthritis and ordered blood and urine tests. Id. at 12-13; Am. Pet. Ex. 15 at 3. He also ordered seven plain radiographs of petitioner's spine that were taken that same day. Am. Pet. Ex. 4 at 13; Am. Pet. Ex. 7 at 127. The flexion extension radiographs of the cervical spine did not indicate problems with rheumatoid arthritis, but did show mild degenerative changes throughout the cervical spine and some evidence of spurring at C1-C2. Am. Pet. Ex. 4 at 13. Thus, Dr. Lindsey ordered a magnetic resonance image ("MRI")[7] of petitioner's cervical spine "to rule out cord impingement." Id. The March 13, 1996 MRI of petitioner's cervical spine, performed with and without contrast, revealed a "C2 to C4 intramedullary lesion measuring about 4 cm . . . and occupying most of the cross section of the cord . . . ." Am. Pet. 7 at 130. Further, there was only "[m]ild enlargement of the cord with no significant enhancement of the lesion." Id. The March 18, 1996 follow-up MRI of petitioner's head revealed:

> Right cerebral peduncle and right centrum semiovale lesions . . . in addition to the cervical cord lesion are most suspicious for multiple sclerosis. The right cerebral peduncle lesion has signal characteristics consistent with demyelination, whereas the lesion in the right centrum semiovale is highly suspicious for a proteinaceous cyst. This latter lesion is oriented perpendicular to the ventricle which can be seen with a multiple sclerosis plaque.

Id. at 132. Subsequent to the review of the radiographs and MRIs, petitioner was referred to Jeffrey E. Dunn, M.D., a neurologist.

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[7] An MRI is "a method of visualizing soft tissues of the body by applying an external magnetic field that makes it possible to distinguish between hydrogen atoms in different environments." Dorland's Illustrated Medical Dictionary, supra note 2, at 908.

Petitioner had her initial visit with Dr. Dunn on March 20, 1997. Am. Pet. Ex. 2 at 4-6. Dr. Dunn reported that on January 22, 1996, petitioner noticed an acute onset of neck stiffness "marked by increasing numbness, initially in the occipital area, and subsequently numbness and paresthesias[8] all about the upper extremities, body and lower extremities." Am. Pet. Ex. 2 at 4 (footnote added). Petitioner explained to Dr. Dunn that she felt as if she had been "coated with Ben-Gay" and that her symptoms increased when she flexed her neck. Id. Petitioner also reported that she had intermittent numbness in her right hand nine years prior and paresthesias in both hands in March 1994. Id. At the time, those symptoms were attributed to carpal tunnel syndrome.[9] Id. Dr. Dunn further noted that petitioner suffered from significant fatigue, hot and cold sensitivity, and "had a clear history to suggest urinary frequency." Id. Dr. Dunn then described the results of petitioner's MRIs of her head and cervical spine:

> MRI of the cervical spine reveals a large high T2 signal lesion occupying most of the distribution of the cervical cord extending from C2 through C4 levels. MRI of the head . . . reveals a large ovoid periventricular lesion in the right centrum semiovale at the callosal septal interface oriented perpendicular to the long axis of the right lateral ventrical. There is, in addition, evidence of a high T2 signal lesion in the right cerebral peduncle.

Id.

Dr. Dunn's clinical impression concluded: "Probable multiple sclerosis. Clinical presentation is of concern for some evidence of long tract signs and initial cerebellar signs." Id. at 6. Dr. Dunn referred petitioner for diagnostic testing, including a lumbar puncture, evoked potential studies, and a serologic workup, to confirm an MS diagnosis. Id.

The diagnostic testing ordered by Dr. Dunn, coupled with the prior MRI results, confirmed his tentative MS diagnosis. Id. at 7. Specifically, Dr. Dunn diagnosed "definite relapsing remitting MS." Id. Dr. Dunn further noted that because MS is a "spectrum illness with early signs," and that "in Sharon's case, being somewhat favorable for no clear evidence of neurophysiologic disruption," the lack of such indicators might "portend a favorable prognosis." Id. Dr. Dunn recommended biannual neurologic follow-up evaluations. Id. However, petitioner did not heed Dr. Dunn's advice.

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[8] A paresthesia is "an abnormal touch sensation, such as burning, prickling, or formication, often in the absence of an external stimulus." Dorland's Illustrated Medical Dictionary, supra note 2, at 1371.

[9] Carpal tunnel syndrome is "a complex of symptoms resulting from compression of the median nerve in the carpal tunnel, with pain and burning or tingling paresthesias in the fingers and hand, sometimes extending to the elbow." Dorland's Illustrated Medical Dictionary, supra note 2, at 1812.

Instead of pursuing regular medical evaluations, petitioner relied upon advice from Judy Graham's Multiple Sclerosis: A Self-Help Guide to Its Management, including the suggestion that a low-fat diet and vitamin supplements helped manage MS. Am. Pet. Ex. 8 at 1. Petitioner did not see Dr. Dunn or her primary care physician, Kay Taylor, M.D., for almost three years. Id. at 2. In petitioner's view, there was no need for periodic check-ups because she had "reached a very stable remission through [her] own research and strict dietary habits." Id. Petitioner continued operating her wallpaper installation business, working steadily from June 1996 to early January 1999, and performing in a bluegrass band. Am. Pet. at 2.

Petitioner was not examined by a physician until January 6, 1999, three years after her MS diagnosis. Id. Up until this date, with the exception of her MS, petitioner had been otherwise healthy. Id. at 1-2. On January 6, petitioner visited Dr. Taylor for a routine check-up. Id. During the pelvic exam, Dr. Taylor advised petitioner that "she thought she felt a lump on one of [her] ovaries and prescribed birth control pills to shrink any cyst." Am. Pet. Ex. 8 at 2. Dr. Taylor also discussed with petitioner her MS as well as her need for a TT vaccination. Id. Petitioner reports that in discussing the need for a TT vaccination, she asked Dr. Taylor whether the vaccination could make the MS flare again. Id. Petitioner asked this question because she believed that her MS was related to the influenza ("flu") vaccination she received in late 1995 or early 1996.[10] Am. Pet. Ex. 3 at 2. Dr. Taylor replied that she "didn't know anything about that." Am. Pet. Ex. 8 at 2. Dr. Taylor continued to pressure petitioner into having the vaccination, and "[a]fter much resistance," petitioner acceded. Id.

Petitioner describes the events immediately following her departure from Dr. Taylor's office:

> By the time I had arrived home from Dr. Taylor's office, the muscles in my jaw, neck, shoulders, chest and abdominal area were in painful spasm. I remember telling my husband something was wrong, and maybe I was having a reaction to the tetanus shot and I needed to rest. I felt even worse the next day, and for many afterwards. Just like in 1996, when I was diagnosed with MS, tightness had totally engulfed my torso. I refer to this as the "MS hug," as if a very strong person with big arms is giving a bear hug around your ribs, sides, back and arms. It is painful even breathing. The terrible crushing fatigue returned and I found it more and more difficult to get out of bed each day, let alone install or remove wallpaper. My legs felt as if 50 pound sacks were tied to them. The foul smelling urine returned. I hurt all over, like I'd been run over by a bus. My arms and hands were numb, and I couldn't make fine motor motions. I became painfully weak over just a couple of weeks. Our bluegrass band had a show to do in mid January 1999. During the performance, my feet and parts of my legs had become numb. I remember removing my shoes so I could feel more steady and secure. As I shifted my weight from one foot to the other while playing my electric bass

[10] Petitioner also attributes her MS to the medication Zoloft. Am. Pet. Ex. 3 at 2.

> guitar and singing, I felt so crushed by the fatigue that with the numbness I thought I was going to collapse on stage in front of the audience. My mom and a couple of close friends were there and were very concerned for me. I had never had numb legs or feet before that day. It was obvious my old symptoms were returning along with some new symptoms.

Id. at 2-3. Petitioner further explained that she drove directly home from Dr. Taylor's office, a distance of approximately 27 miles, and that the travel time between Dr. Taylor's office and her residence was approximately 45 to 60 minutes. Am. Pet. Exs. 18 & 19.

Petitioner's condition worsened. Am. Pet. at 3-4. On February 24, 1999, petitioner returned to see Dr. Taylor to recheck the possible cystic lesion. Id.; Am. Pet. Ex. 3 at 4. Dr. Taylor reported that petitioner expressed significant frustration with her MS, her bad marriage, and her childhood, and said that if the pelvic mass were serious, she was not sure that she would do anything about it. Am. Pet. Ex. 3 at 4.

On March 15, 1999, petitioner returned to see Dr. Dunn for the first time since April 1996. Am. Pet. Ex. 2 at 2-3. Dr. Dunn noted that petitioner reported experiencing periods of significant fatigue since her last visit. Id. at 2. Petitioner also reported that the symptoms of paresthesia in her upper torso had improved. Id. Dr. Dunn further noted:

> Most recently Sharon underwent a tetanus vaccination on [January 6, 1999,] and after this reported new symptoms of significant tightness about the mid torso region. She has had since this time intermittent periods of spasm such as involuntary extension about the torso such as when she sleeps at night and increased difficulty walking. She reports increased symptoms of paresthesia primarily in the right lower extremity. For three years since last evaluation she has also been bothered by symptoms of intermittent urinary urgency.
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> When I last saw Sharon [in April 1996] I recommended neurologic follow up that same year for re-evaluation. This is the first I have seen Sharon since that time.
>
> She is taking many multivitamins, but no prescription medications.

Id. Dr. Dunn concluded that petitioner's "clinical course is . . . of concern for likely several or multiple demyelinating[11] plaques affecting the spinal cord. This combined with clinical findings of clear neurologic progression with respect to gait disturbance and urinary urgency . . . represents a clear indication for immunomodulatory therapy." Id. (footnote added). Dr. Dunn

[11] Demyelination is the "destruction, removal, or loss of the myelin sheath of a nerve or nerves." Dorland's Illustrated Medical Dictionary, supra note 2, at 488.

prescribed several medications typically used for controlling MS and asked petitioner to return in one month for a follow-up neurologic examination. Id. at 3.

On March 29, 1999, petitioner called Dr. Taylor and stated that she was absolutely convinced that the TT vaccination caused the exacerbation of her MS. Am. Pet. at 4; Am. Pet. Ex. 3 at 4. Petitioner explained that she started having spasms immediately after leaving Dr. Taylor's office. Am. Pet. 3 at 4. Petitioner reiterated to Dr. Taylor that she believed her MS flared several years prior as a result of a flu vaccination and the medication Zoloft. Id. Petitioner stated that the TT vaccination and resulting MS flare had ruined her life and that she had "lost faith in the medical profession and [was] very leery about participating in any care recommended by [Drs. Taylor and Dunn]." Id. Dr. Taylor acknowledged petitioner's anger and told petitioner she would complete and file a report with the Vaccine Adverse Event Reporting System ("VAERS")[12] on petitioner's behalf. Id. Dr. Taylor filed the VAERS report on April 5, 1999, reciting petitioner's belief that the TT vaccination exacerbated her MS. Id. If Dr. Taylor shared petitioner's belief that the TT vaccine caused petitioner's MS to worsen, she did not so indicate on the VAERS report. Id.

On April 14, 1999, petitioner had a follow-up examination with Dr. Dunn. Am. Pet. at 4; Am. Pet. Ex. 2 at 1. Dr. Dunn noted that petitioner had not followed his recommendation that she take Avonex with outpatient neurologic follow-up, but instead chose to follow a holistic approach, relying upon dietary therapy and other nonallopathic strategies. Pet. Ex. 2 at 1. During their discussions, Dr. Dunn renewed his recommendation that petitioner follow a more traditional course of treatment. Id. Dr. Dunn explained to petitioner that while the medications he advocated would not cure MS, they would reduce her disability. Id. Dr. Dunn added that he could be of no neurologic assistance to petitioner if she refused to comply with his treatment recommendation. Id. Dr. Dunn also discussed with petitioner her belief that the TT vaccination caused her MS flare: "I also reviewed with her that her previous tetanus shot was clearly indicated and did not contribute to progression of her multiple sclerosis. I believe it is important that Sharon accepts this diagnosis and its condition to face this soberly." Id. (emphasis added). Dr. Dunn, like Dr. Taylor, did not believe that the January 6, 1999 TT vaccination caused the significant aggravation of petitioner's MS.

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[12] VAERS is

> a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS collects and analyzes information from reports of adverse events following immunization. . . . By monitoring such events, VAERS helps to identify any important new safety concerns and thereby assists in ensuring that the benefits of vaccines continue to be far greater than the risks.

VAERS–Frequently Asked Questions, at http://www.vaers.org/vaers.htm (last visited April 8, 2005). Any person can file a report with VAERS. Id.

On September 24, 1999, petitioner was evaluated by a second neurologist, Linda M. Wray, M.D. Am. Pet. at 5; Am. Pet. Ex. 5 at 1-3. Dr. Wray noted that petitioner had been under the care of Dr. Dunn, but was "transferring her care due to a 'break down and difference of opinion, and [that she] will not be swayed in [her] thinking.'" Am. Pet. Ex. 5 at 1. Dr. Wray then recounted petitioner's medical history. Id. at 1-2. Dr. Wray noted that after petitioner's March 1996 MS diagnosis, her symptoms improved and she "initiate[d] the Swank diet and other dietary changes and did relatively well with some residual paraesthesias of the lower abdomen and both arms and hands." Id. at 1. Dr. Wray further noted that there was no neurologic follow-up until January 1999, when petitioner had a general physical, including an updated tetanus vaccination. Id. Petitioner told Dr. Wray that she experienced "lock up" of her neck on her way home from the January 1999 appointment and that she became "progressively weaker with pins and needles over her torso." Id. Petitioner told Dr. Wray that since January 1999, her symptoms had improved gradually. Id. But, petitioner was keenly aware of her changed, more fragile condition, as evidenced by her statements that, "the stakes are really jacked up and I am more high maintenance now," and that she wakes up in the morning "like a pretzel" and has to do yoga. Id. Petitioner reported that she "still has a tight uncomfortable girdle around her lower abdomen" and that "[h]er gait was intermittently unsteady but is better now . . . ." Id. Dr. Wray noted:

> [Petitioner] is already well informed and well read on M.S. I have recommended that she initiate immunomodulating treatment and gave her a couple more up to date references comparing the three available agents. The presence of a spinal cord plaque and history of significant gait difficulty and two exacerbations within the past three years supports this recommendation. . . .
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> I told her that while various stresses including immunizations could trigger individual exacerbations of M.S., there is no data indicating that such vaccinations alter or accelerate the long term progression of the disease. In fact, flu shots are recommended for M.S. patients and when her Tetanus needs to be updated I will be recommending that she have it. We would probably be well advised to consult with one of the larger study centers about managing the possibility of an exacerbation and perhaps pretreat her with a short course of steroid at that time.

Id. at 2-3 (emphasis added). Thus, while Dr. Wray recognized that "immunizations could trigger individual exacerbations of MS," it was clearly her belief that there was no data indicating that vaccinations could "alter or accelerate the long term progression" of petitioner's MS. Indeed, Dr. Wray recommended that petitioner receive future TT boosters.

Petitioner returned to see Dr. Wray on October 21, 1999, with complaints of vision problems.[13] Id. Dr. Wray noted that the subtle findings were suggestive of petitioner suffering from a mild optic neuritis[14] in her left eye. Id. Dr. Wray encouraged petitioner to reconsider immunomodulating therapy to slow the progressive disability of her MS and to reduce the frequency and severity of its exacerbations. Id. On November 12, 1999, petitioner telephoned Dr. Wray and left a message stating that her optic neuritis had "cleared up." Id. at 10.

On March 29, 2000, petitioner was seen at the Virginia Mason Medical Center by a third neurologist, Michael A. Elliott, M.D., for an evaluation of her MS. Am. Pet. Ex. 1 at 1-4. Dr. Elliott recorded a detailed medical history. Id. at 1-2. Dr. Elliott then confirmed the diagnosis of RRMS. Id. at 3. Dr. Elliott commented:

> The patient indicates she desires no medical treatment. Does not believe the Avonex, betaseron or Copaxone are therapies that would be right for her. She is reluctant to try standard medical therapy and is quite concerned about the problems she has had with side effects in the past. I was very frank with [petitioner] and told her that as a medical physician, I may have very little to offer her as I believe that many of the medications she is reluctant to use can be quite helpful in patients with multiple sclerosis. Moreover, if she is to have problems, I will have little means by which to help her if she does not ascribe to any medical therapies. She understands this and desires a medical relationship with me simply to document her condition.
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> With this understanding, I will agree to follow her and plan for a return visit in six months' time. I can continue to document her level of disability, if needed, for other purposes and will respect her unwillingness to take any

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[13] Prior to her October 21, 1999 follow-up examination, petitioner telephoned Dr. Wray's office on multiple occasions. For example, on September 27, 1999, Dr. Wray received a telephone message stating, "It's a miracle! Completely unlocked!! No pain!" Am. Pet. Ex. 5 at 3. However, two days later on September 29, 1999, petitioner again telephoned and reported that she had a skin rash that was "moving around," knuckle swelling with ache, and an aching neck. Id. at 4. Petitioner's October 4, 1999 telephone message to Dr. Wray advised that she had discontinued the nortriptyline due to an adverse reaction of swollen limbs and joints. Id. at 5. The following day, October 5, 1999, petitioner telephoned Dr. Wray and left a message reporting that she was very upset and that she "feels uncared for–feels she was made ill by flu shot!" Id. at 6.

[14] Optic neuritis is the "inflammation of the optic nerve." Dorland's Illustrated Medical Dictionary, supra note 2, at 1252.

> medicines at this time but have been honest with her with regard to my belief that there are many therapies that can be quite helpful in multiple sclerosis and I would be happy to revisit these with her if she so desires.

Id. at 3-4.

On January 12, 2001, petitioner saw George Gillson, M.D. at the Tahmoa Clinic for "a number of really bothersome complaints." Am. Pet. Ex. 6. Dr. Gillson noted that her problems predated her involvement with Procarin,[15] and that in addition to being very busy with her wallpapering business, she had the added stress of a chronically-ill spouse. Id. Dr. Gillson recommended a topical cream and some additional vitamins and planned to monitor these treatments via e-mail. Id.

On April 11, 2001, petitioner returned to see Dr. Elliott. Am. Pet. Ex. 1 at 5. Once again, petitioner made it clear that she was not interested in immunosuppresive or immunomodulatory therapy. Id. On April 23, 2001, Dr. Elliott again saw petitioner. Id. at 9-10. Dr. Elliott diagnosed petitioner with a herpes zoster infection in her left eye. Id. at 9. On May 9, 2001, and June 7, 2001, petitioner was again examined by Dr. Elliott. Id. at 17-18. Petitioner's herpes zoster infection had greatly improved. Id. However, Dr. Elliott noted that petitioner's MS was clinically worse. Id. Dr. Elliott informed petitioner that he would work with her to get full disability. Id. at 18.

On June 26, 2001, petitioner filed an application for disability insurance benefits. Am. Pet. Ex. 7 at 3-5. Petitioner wrote in her application for disability that she was forced to stop working because hanging wallpaper aggravated her MS. Id. at 39. Petitioner explained: "I believe the work [aggravated] my condition. The constant 'electric shock spasms' throw me to & fro. . . . I cannot control my body. I have no balance . . . ." Id. Petitioner dedicated several pages of her application to setting forth her frustrations with the medical profession and her belief that her 1995 flu vaccination and her 1999 TT vaccination exacerbated her MS. Id. at 46-49.

On August 1, 2001, Bret J. MacDermott, D.C., petitioner's chiropractor, submitted a narrative on behalf of petitioner's application for disability. Am. Pet. Ex. 7 at 109-11. Dr. MacDermott considered petitioner "totally permanently disabled from the unfortunate progression of her [MS] syndrome." Id. at 110. On October 10, 2001, petitioner was found to be disabled as of February 14, 2001. Id. at 1.

On February 26, 2002, petitioner returned to see Dr. Elliott. Am. Pet. Ex. 1 at 20. Dr. Elliott noted that petitioner's MS had worsened from RRMS to secondary progressive MS

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[15] Procarin is a nonformulary, experimental treatment for MS that is also known as "Prokarin." See Multiple Sclerosis Society of Canada, Results of Clinical Trial of Prokarin (Procarin) To Treat Multiple Sclerosis Fatigue, at http://www.mssociety.ca/en/research/CAT020207.htm (Feb. 7, 2002).

("SPMS"). Id. Petitioner's main symptoms were fatigue, neuropathic pain, and spasticity.[16] Id. Dr. Elliott recommended that petitioner continue Neurontoin and Baclofen as prescribed. Id. Dr. Elliott also discussed with petitioner immunomodulatory therapies, but just as before, petitioner was not interested in pursuing this treatment. Id.

The above-described medical records clearly document the progression of petitioner's MS and her belief that a flu vaccination and Zoloft caused her MS. The records also document her view that her January 6, 1999 TT vaccination was the precipitating event causing the significant aggravation of her MS. It is noteworthy that not one of petitioner's treating physicians opined in their medical records that the TT vaccine played any role in the worsening of petitioner's MS. To the contrary, the records of Drs. Dunn and Wray clearly state their opinion that the TT vaccination in no way caused the worsening of petitioner's underlying disease. Indeed, Dr. Wray indicated that it was appropriate for petitioner to receive the TT vaccine and that boosters should be given in the future. In sum, not one of petitioner's treating physicians supports her view of causation.

IV. TESTIMONY AT HEARING

Testimony of Petitioner's Expert: Vera S. Byers, M.D., Ph.D.

Vera S. Byers, M.D., Ph.D. testified on behalf of petitioner at the August 14 and October 10, 2003 hearings.[17] Dr. Byers received her Ph.D. in immunology in 1969 from the University of California, Los Angeles. Tr. I at 9. After being awarded her medical degree in 1981 from the University of California, San Francisco ("UCSF"), Dr. Byers did postdoctorate fellowships in clinical immunology and cancer immunology. Id. Dr. Byers is board-certified in internal medicine and has practiced both internal medicine and allergy and immunology. Id. at 10. Dr. Byers sees allergy patients, including patients with multiple chemical sensitivity and chronic fatigue syndrome, and patients with autoimmune diseases, such as rheumatoid arthritis and MS. Id. Dr. Byers has also performed research in the field of MS. Id. For example, in 1986, Dr. Byers carried out the necessary preclinical research of an immunosuppressive molecule she was developing. Id. at 10-11. Subsequent to that project, Dr. Byers designed clinical trials for MS and approximately 20 other autoimmune diseases for the immunosuppressive molecule. Id. at 11. Dr. Byers has also published between 200 and 250 articles in basic and clinical immunology. Id. at 11-12. None of these articles involves MS, but Dr. Byers has presented abstracts concerning MS. Id. at 12. In addition, Dr. Byers is on the faculty at UCSF. Id.

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[16] Spasticity is the state of being "hypertonic, so that the muscles are stiff and the movements awkward." Dorland's Illustrated Medical Dictionary, supra note 2, at 1729.

[17] All references to the Transcript of the August 14, 2003 proceedings shall be designated herein as "Tr. I at __." All references to the Transcript of the October 10, 2003 proceedings shall be designated herein as "Tr. II at __."

Dr. Byers testified that her review of medical records and medical literature, combined with her training as a physician, led her to conclude that the TT vaccination petitioner received on January 6, 1999, was the cause in fact of the significant aggravation of petitioner's MS. Id. at 43. According to Dr. Byers, "The basis for my opinion is . . . the temporal relationship of the vaccine, coupled with the fact that tetanus has been shown to trigger or worsen central [nervous system] demyelinating diseases." Id. Dr. Byers contended that the close temporal association of the vaccination to petitioner's onset of symptoms, two molecular mechanism theories of injury, and the medical literature supported her view.

The Temporal Relationship Between the Vaccination and Onset

Dr. Byers explained that MS is a disease in which lesions occur "separated in time and space," meaning that lesions and MS symptoms can manifest themselves over a period of years and that multiple areas of the central nervous system can be affected.[18] Id. at 19. Dr. Byers discussed two subtypes of MS: RRMS and SPMS. Id. at 19-20. Dr. Byers explained that the most common form of the disease is RRMS. Id. at 19. When flares of RRMS occur, the patient will develop symptoms such as muscle weakness, slurred speech, vision problems, or urinary incontinence. Id. The flare will last for awhile, the symptom(s) will remit, and the patient will return to baseline. Id. If fortunate, the patient can continue with this pattern for a long time. Id. The second most common form of MS is chronic SPMS. Id. at 19-20. According to Dr. Byers, about fifty percent of all people with RRMS will eventually develop SPMS. Id. The key difference between these two forms of MS is that although flares occur with SPMS, rather than returning to the original baseline as one does with RRMS, the patient instead plateaus to a generally worsened condition with each new episode. Id. at 20. According to Dr. Byers, petitioner was just about at the right time, 10 years after presenting with RRMS, to convert from RRMS to SPMS. Id. at 40.

Dr. Byers also testified that there is a genetic and an environmental component to MS. Id. at 30-31, 40. Dr. Byers explained that a genetic predisposition for developing MS, coupled with some sort of environmental component, which can trigger the demyelination process in a genetically-susceptible person, are key factors in causing MS. Id.

Dr. Byers's review of petitioner's medical records led her to conclude that this is a "very simple case." Id. at 12. According to Dr. Byers, petitioner's MS had "declared itself" by 1996, but petitioner remained very stable until 1999. Id. at 13. Dr. Byers testified:

> I think the most important thing about this is that she had been completely silent, as far her illness, from 1996 until 1999, when she received her tetanus shot. The only reason that she had gone to her primary care doc[tor] is for health care maintenance. And now all of a sudden we have this absolute flurry of phone calls,

[18] Respondent's expert, Dr. Kottil Rammohan, did not dispute Dr. Byers's description of MS, but rather elaborated on her testimony. See Tr. I at 72-74.

of entries in doctors' notes, et cetera, et cetera, confirming the fact that something had really changed.

Id. at 14-15. Specifically, with regard to onset, Dr. Byers explained that petitioner's neurologic symptoms began very rapidly. Relying on petitioner's affidavit, Dr. Byers recalled that petitioner claimed to have had widespread muscle spasms by the time she reached home, which Dr. Byers assumed was about four hours, given the driving time normally associated with "Montana."[19] Id. at 13-14. Dr. Byers also testified that postvaccination, petitioner made numerous telephone calls to her physician and began to describe her symptoms as the "MS hug," which according to Dr. Byers, is a myalgia[20] associated with MS. Id. at 15. Dr. Byers testified that petitioner's condition continued to deteriorate and that, by mid-January 1999, petitioner had developed numbness in her feet and that, by March 1999, petitioner had developed bladder problems.[21] Id. at 16.

Dr. Byers further testified that petitioner's immediate strong reaction after leaving Dr. Taylor's office necessarily was caused by the vaccine's activation of her immune system and was the typical desired reaction to vaccination. Tr. II at 7-8. Dr. Byers explained that the Physician's Desk Reference ("PDR")[22] enumerates the following possible side effects associated with the TT vaccine: malaise, fever, pain, hypotension, nausea, and arthralgia.[23] Id. at 7. Dr. Byers's review of petitioner's affidavit confirmed for her that petitioner experienced the symptoms described in the PDR. Specifically, Dr. Byers noted that petitioner had "widespread muscle spasms . . . about

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[19] At hearing, both Dr. Byers and Dr. Rammohan mistakenly testified that petitioner resided in Montana. See Tr. I at 13-14, 129. After the initial hearing, petitioner confirmed that at the time of the TT vaccination, she resided in Federal Way, Washington and Dr. Taylor's office was in Issaquah, Washington. See Am. Pet. Ex. 18. This approximately 27 mile drive takes 45 to 60 minutes. See id. As confirmed in their respective testimony on October 10, 2003, Dr. Byers's and Dr. Rammohan's mistaken assumption about the driving time between petitioner's residence and Dr. Taylor's office did not alter their opinions about onset and causation. See Tr. II at 7, 16.

[20] Myalgia is defined as pain in the muscles. Dorland's Illustrated Medical Dictionary, supra note 2, at 1205.

[21] Dr. Byers described petitioner's postvaccination numbness and bladder problems as new. However, Dr. Dunn's March 20, 1996 medical record describes "numbness and paresthesias all about the upper extremities, body and lower extremities" and "a clear history to suggest urinary frequency." Am. Pet. Ex. 2 at 4. Although similar, urinary frequency and urinary incontinence are not identical.

[22] Dr. Byers explained that the PDR contains a description of the adverse reactions associated with each listed drug. Tr. II at 5-6.

[23] Arthralgia is joint pain. Dorland's Illustrated Medical Dictionary, supra note 2, at 149.

an hour after she received the injection, which is just about the right time for the muscle aches and pains." Id. Dr. Byers testified that the normal aches and pains typically associated with vaccination are due to the release of cytokines.[24] Id. at 8. Dr. Byers explained that "specific cells like macrophages"[25] pick up the vaccination and begin to produce a "cascade of cytokines that will ultimately result in the immune response that you want to see" between 7 and 21 days later. Id. Dr. Byers further explained that this cascade of cytokines is the desired reaction because it shows that the immune system is functioning properly. Id. Indeed, as Dr. Byers made clear, the cytokine cascade that caused petitioner's aches and pains is not unique to MS patients. Id.

Of greater significance to Dr. Byers was the fact that petitioner's new demyelinating symptoms manifested themselves within the expected 7-to-21 day timeframe. See Tr. I at 14, 16, 42; Tr. II at 9-10, 12. Dr. Byers referred to petitioner's affidavit, noting that it was not until mid-January 1999 that petitioner experienced for the first time feet and leg numbness. Tr. I at 14, 16. According to Dr. Byers, the March 1999 medical records document that petitioner also suffered from urinary incontinence. Id. at 14, 19.

Dr. Byers testified that it is difficult, both medically and emotionally, to "upgrade" a patient's diagnosis from RRMS to SPMS because the new diagnosis recognizes a significant and permanent change for the worse in the patient's condition. Id. at 15-16. Here, petitioner moved from RRMS, a condition which can be relatively benign, to SPMS, a form of the disease that is far more disabling. Id. In considering a diagnosis, a physician must determine whether a recent MS episode was just a flare from which the patient will return to baseline, or whether the patient's condition will continue to worsen. Id. at 15. Dr. Byers's opinion, based upon her review of petitioner's medical records, was that petitioner's condition worsened to SPMS well before the formal diagnosis of SPMS because there was no real indication that petitioner ever returned to baseline after her 1999 TT vaccination. Id. at 15-16. And as explained above, on October 10, 2001, petitioner was declared disabled as of February 2001. Am. Pet. Ex. 7 at 1.

Petitioner's Two Molecular Mechanism Theories

Dr. Byers testified that demyelination can most easily be explained by using an analogy to electricity. Tr. I at 17. She explained that electrical impulses in the body travel through axons, which are like electrical wires. Id. She then explained that the myelin sheath is like the plastic

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[24] A cytokine is "a generic term for nonantibody proteins released by one cell population (e.g., primed T lymphocytes) on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response." Dorland's Illustrated Medical Dictionary, supra note 2, at 469.

[25] Macrophages are "any of the many forms of mononuclear phagocytes found in tissues. . . . Their functions include . . . killing of ingested microorganisms [and] digestion and presentation of antigens to [T-cells]." Dorland's Illustrated Medical Dictionary, supra note 2, at 1085.

coating on the electrical wire that allows the electrical impulse to travel straight through the axon. Id. The myelin sheath acts as an insulator. Id. at 18. In MS, the axon's myelin sheath is destroyed by three components of the immune system–antibodies,[26] T-cells, and macrophages. Id. at 18. Normally, these three components of the immune system serve a protective role. But, as explained below, none of them is infallible. And when any one of the three goes awry, the results can be devastating.

Dr. Byers identified two molecular mechanisms involving T-cells that she believed could cause the significant aggravation of petitioner's MS. Her first theory involves the concepts of degeneracy, cross-reactivity, and molecular mimicry to explain how T-cells, stimulated by a vaccine, will chew directly upon and thus destroy the myelin sheath. See id. at 31-32. Her second theory relies on autoreactivity. See id. at 27.

1. *T-cell degeneracy, cross-reactivity, and molecular mimicry*

Dr. Byers defined a T-cell in the following manner:

> A T-cell is a subpopulation of while blood cells. It circulates in your body . . . . They live in the spleen. And what they do in life is go out of the spleen and into the bloodstream, and then into organs. And basically, they just cruise through the body looking for trouble.

Tr. I at 20. When working properly, T-cells seek out foreign antigens, and either directly chew on those antigens or "throw out proteins that will call in the macrophages." Id. at 22. But, when a T-cell works improperly:

> [I]t's cruising through the body, and it thinks it's looking for trouble, but in fact it is missing the boat. Because in fact, in this case, for example, it is going after some of the neuronal antigens. And . . . , it thinks that these are bad guys. That's the problem. . . .
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> That's why [the T-cells are] eating up the myelin sheath, because it thinks it's eating up a bug.

Id. Under the scenario described by Dr. Byers, the body's T-cells turn against the myelin sheath. Rather than acting as a defender against foreign invaders, the wayward T-cells are transmogrified into wayward destroyers.

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[26] An antibody is "an immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen that induced its synthesis . . . or with antigen closely related to it." Dorland's Illustrated Medical Dictionary, supra note 2, at 100.

Dr. Byers then testified that the abnormal behavior of T-cells can be explained by the degeneracy of T-cell receptors.[27] Id. at 22, 26. T-cell degeneracy means that a T-cell receptor can recognize several different types of peptides,[28] none of which resembles each other. Id. at 23. The degeneracy of T-cells was not initially recognized; according to Dr. Byers, "When we first started looking at the T-cell receptor, we thought it was exquisitely sensitive. . . . And slowly but surely, we realized, in fact, they're very promiscuous." Id. at 24. Dr. Byers illustrated the change in thought:

> [I]n one set of studies they took T-cells that were specific, that had receptors specific for myelin basic protein,[29] and they came up with this peptide library, and just measured which of these peptides would activate this T-cell. And they found that, I think they found about seven of [the peptides] would activate [the T-cell], six of which had no relationship to myelin basic protein.

Id. (footnote added). Dr. Byers analogized T-cell degeneracy to a lock and key system. Id. at 24-25. The old belief was that only one peptide (the key) would fit into one T-cell receptor (the lock). Id. at 24. However, experiments with T-cells revealed that more than one peptide could fit into a T-cell receptor. Id. at 25. Dr. Byers explained that it was "as though all of a sudden you thought that you have only your key, and all of a sudden all of your neighbors have the keys, too, that will fit." Id. at 24-25.

When a T-cell binds with a peptide, it is activated. Id. at 23. The subpopulation of T-cells that are primarily involved in MS are CD4 T-cells. Id. In MS, the errant CD4 T-cell locates something with which to bind, such as the myelin sheath. Id. After binding to the myelin sheath, the CD4 T-cell emits numerous proteins, called pro-inflammatory cytokines, which Dr. Byers analogized to "kind of like a loudspeaker." Id. at 23-24. These cytokines "call" for help from the macrophages. Id. at 24. "The macrophages are only specific for the site . . . . [T]hey go right to where the T-cell is, and then they start chewing." Id. The "chewing" results in the destruction of the myelin sheath. Once sufficient myelin destruction occurs (i.e., demyelination), MS symptoms will manifest themselves. In Dr. Byers's view, T-cell degeneracy explains how certain infections or certain vaccinations can cause MS to flare. Id. at 25. Dr. Byers then described the theory of molecular mimicry, which, in the case of MS, is the process whereby an antineuronal T-cell is activated by a peptide from the infection or vaccination that resembles a neuron protein,

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[27] The receptor is the location on the T-cell where the T-cell binds with an antigen. Dorland's Illustrated Medical Dictionary, supra note 2, at 1593, 1595.

[28] A peptide is "any number of a class of compounds of low molecular weight that yield two or more amino acids on hydrolosis. They are the constituent parts of proteins . . . ." Dorland's Illustrated Medical Dictionary, supra note 2, at 1396.

[29] Myelin basic protein ("MBP") constitutes about 30 percent of the proteins forming the myelin sheath. Dorland's Illustrated Medical Dictionary, supra note 2, at 1525.

such as MBP. Id. at 25, 31. Further, Dr. Byers explained, the peptide that is activating the T-cell might only partially resemble the MBP, but since a little piece of it is foreign, it is still able to activate the T-cell. Id. at 25, 31-32. This is called cross-reactivity.[30] Id.

In sum, Dr. Byers opined that T-cell receptors are, in general, degenerate. The theories of degeneracy, cross-reactivity, and molecular mimicry are similar because all of these processes explain how the myelin sheath can be destroyed by the body's T-cells. Id. at 26-27. This destruction occurs regardless of whether the triggering molecules look exactly like, look similar to, or bear no resemblance at all to the antigen that the T-cell is targeting. Id. at 26. Indeed, Dr. Byers noted that given the degeneracy of T-cell receptors, coupled with the many ways an individual could acquire an autoimmune disease, it was remarkable that such diseases were not more prevalent. Id.

2. *Autoreactive T-cell Behavior*

Dr. Byers's second theory, which she asserts can also explain the significant aggravation of petitioner's MS, involves autoreactive T-cells. Under this alternative theory, the normal "flurry of cytokines" produced in the typical response to a vaccination or an infection,[31] activates existing "autoreactive T-cells." Id. at 27-28. These activated autoreactive T-cells, in turn, attack and destroy the myelin sheath. Id. at 27, 32. Dr. Byers explained that the typical reaction of the body's immune system to vaccination or infectious illness is to rid the body of the foreign material by producing a flurry of cytokines. Id. at 27. However, if bystander autoreactive T-cells get in the way of the cytokine storm, the autoreactive T-cells can be activated. Id. at 27, 32. This kind of inflammatory reaction occurs in every episode of infection unless an individual is immunosuppressed. Id. at 28.

Dr. Byers then testified how the above-described theories can explain how petitioner's TT vaccination significantly aggravated her MS:

> [T]he main two molecular mechanisms that I described would certainly be operative with Mrs. Bubb. The first is that the tetanus vaccination produced a release of all of these cytokines, and one or more of the autoreactive T-cells that she has floating around–and we all have them; you can actually clone them out of

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[30] Specifically, cross-reactivity is "the interaction of an antigen with an antibody formed against a different antigen with which the first antigen shares identical or closely related antigenic determinants." Dorland's Illustrated Medical Dictionary, supra note 2, at 1589.

[31] The same inflammatory reactions that occur with an infection also occur with a vaccination because the same process is at work. The purpose of vaccination is to enable the body to make an immune response against that vaccine, i.e., to cause the body to produce the necessary antibodies to fight a particular infection. Tr. I at 28-29.

> everybody–one of those escaped from the suppressor cell[32] that was probably sitting on its head, and became activated by all of these cytokines. And that causes two things.
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> It causes, first of all, the cell to go into cell division. And secondly, the cell to be able to produce its own cytokines, so that it will attract macrophages to the area of the myelin basic protein, which is where it's tracking.
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> The other thing is these things are sensitive to the genetics of a person. And if she had a T-cell receptor, or the propensity to a T-cell receptor which reacts and sees the peptides that were broken down, because the tetanus will be broken down into small peptides. The tetanus is a big protein, it gets broken down. And if that tetanus peptide fits into one of those T-cells, then it could also directly activate it.

Id. at 29-30 (footnote added).

With respect to the generally-accepted appropriate temporal relationship between the administration of an antigen and the onset of neurological symptoms, Dr. Byers explained that the answer was dependent on whether or not it was the first time that the antigen was introduced into the body. Id. at 41. When an antigen is seen for a second time, Dr. Byers believes that "you could have initial symptoms within hours . . . because you have a population of cells that have already been built up that are directed against the myelin basic protein. And they can get triggered, and they will produce their cytokines." Id. Then, after the pre-existing cells are triggered, Dr. Byers explained that it takes the body about 6 to 20 days to generate a new population of cells to attack the myelin and cause demyelination. Id. at 41-42.

According to Dr. Byers, petitioner was "set up" for a significant aggravation of her MS because petitioner's January 6, 1999 TT vaccination was the second time petitioner was exposed to the same antigen. Id. Petitioner experienced pain in her jaw, neck, shoulders, chest, and abdomen (i.e., the MS hug) within 45 to 60 minutes after leaving Dr. Taylor's office. Am. Pet. at 2-3; Am. Pet. Ex. 18. Dr. Byers points to this MS hug as the result of the triggering of the pre-existing cells directed against the MBP. Tr. I at 41. Dr. Byers then points to petitioner's subsequent numbness and weakness as a demonstration of the triggering of a new population of cells. Id. at 42.

Dr. Byers concluded "that the tetanus vaccination contributed to the significant worsening of [petitioner's] disease" and but for the administration of the TT vaccination at this particular

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[32] Dr. Byers explained that suppressor cells prevent reactive T-cells from acting. Tr. I at 26.

time in petitioner's life, "she would not have developed a significant aggravation of her MS at that time." Id. at 43. Dr. Byers summarized:

> The basis for my opinion is that the temporal relationship of the vaccination, coupled with the fact that tetanus has been shown to trigger or worsen central demyelinating diseases, leads me to feel that if it were not for her tetanus, she would not have worsened at the time that she did.

Id.

Petitioner's Medical Literature

Petitioner submitted 23 articles in support of her theory that the TT vaccination can cause the significant aggravation of MS and did cause it in her case. In discussing the medical literature, Dr. Byers began her testimony by explaining that the strongest association between tetanus and a demyelinating disease occurs in cases of Guillian-Barré syndrome, which unlike MS, is a disease of the peripheral nervous system.[33] Id. at 35. Dr. Byers also explained that she would not expect to find a wealth of articles concerning adverse reactions to the TT vaccine because "instances of tetanus worsening demyelinating diseases will usually be seen by the practicing [doctors]. It's not going to be seen by the academics, and the academics are the ones that write the papers." Id. That said, Dr. Byers testified there were approximately 10 or 12 case reports of TT causing or worsening central nervous system demyelinating diseases. Id. To support her position, Dr. Byers cited two instances of transverse myelitis[34]–one developing after a TT booster and the other after a tetanus infection.[35] Id. at 36. In addition, she described a case of relapsing acute encephalitis,[36] followed by optic neuritis, in a child after he received a combination diphtheria, tetanus, and poliomyelitis vaccination.[37] Id. Another example Dr. Byers referred to concerned a 43-year-old man who in 1993, developed acute disseminated

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[33] See Am. Pet. Exs. 11-B, 11-K, 11-M, & 11-P.

[34] Transverse myelitis is "the inflammation of the spinal cord . . . in which the functional effect of the lesions spans the width of the entire cord at a given level." Dorland's Illustrated Medical Dictionary, supra note 2, at 1209.

[35] See Am. Pet. Ex. 11-N.

[36] Encephalitis is the "inflammation of the brain." Dorland's Illustrated Medical Dictionary, supra note 2, at 608.

[37] See Am. Pet. Ex. 11-J.

encephalomyelitis ("ADEM")[38] after his last dose of the TT vaccine.[39] Id. Petitioner also submitted medical literature that showed that patients with ADEM may develop MS. See Am. Pet. Ex. 17.

Dr. Byers also relied upon two articles by Utz et al. to support her theory that there is cross-reactivity between the T-cell receptor triggered by MBP and the T-cell receptor that is triggered by tetanus. Id. at 36-38, 52-54; see also Am. Pet. Exs. 11-R & 11-S. Although not required by the Vaccine Act, the special master notes that unlike respondent, petitioner offered no epidemiological studies to support her theory of causation.

Testimony of Respondent's Expert: Kottil Rammohan, M.D.

Respondent presented the testimony of Kottil Rammohan, M.D., a neurologist. In 1967, Dr. Rammohan graduated with his medical degree from the University of Madras in India. Tr. I at 70. He subsequently served a one-year internship at Cook County Hospital in Chicago, after which he completed residencies in internal medicine and neurology at Ohio State University ("OSU"). Id. at 70-71. Dr. Rammohan is board-certified in internal medicine, neurology, and neurorehabilitation, and is licensed to practice medicine in Ohio. Id. In 1976, he was awarded a fellowship in neuroimmunology at the National Institutes of Health ("NIH"), where he remained for six years. Id. at 71. After leaving the NIH, Dr. Rammohan returned to OSU to become the Director of the Division of Clinical and Experimental Neuroimmunology and the Director of the MS Center, one of the largest MS centers in the country with over 4,000 patients. Id. On average, for the past 15 years, Dr. Rammohan has seen about 60 MS patients per week. Id. at 99. Dr. Rammohan is now a full professor at OSU. Id. at 71.

Dr. Rammohan began his testimony by providing the following description of the clinical patterns of MS, expanding on Dr. Byers's testimony:

> [M]ultiple sclerosis is a disease that occurs in time and space. And what we mean by that is there [are] multiple areas of the central nervous system affected, which is a dissemination in space; and the other is a dissemination in time, which means over a period of many years. The individual will experience what is called [] relapses and remissions. So the most common type of multiple sclerosis is what is called relapsing remitting multiple sclerosis.
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> Now, a number of different scenarios are possible. An individual can have relapses and remissions, and have, after a while, nothing happen through the rest

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[38] Encephalomyelitis is "inflammation involving both the brain and the spinal cord." Dorland's Illustrated Medical Dictionary, supra note 2, at 610. ADEM is "characterized by perivascular lymphocyte and mononuclear cell infiltration and demyelination . . . ." Id.

[39] See Am. Pet. Ex. 11-D.

of their life until almost the end, and then all of a sudden an attack occurs after maybe 50 years of quiescence.

Or the individual can go on to . . . secondary progressive multiple sclerosis, which basically means that between attacks, the person is not quiet with regards to the disease. The disease is active even between the exacerbations. And after awhile you can no longer say that this attack occurred on such-and-such day; all you can say is that this individual is worse today compared to six months ago, or as compared to a year ago, and so on. And that state, which is the progressive state, is probably the most difficult phase of the disease to treat.

Over half the patients who start with relapsing disease, over a 10-year period, will go on to develop progressive disease. And that is a rule of thumb. And this is a study that was done by Dr. Brian Weinschenker from the Mayo Clinic, where the natural history of this disease was followed. And what he found was the majority of people who have relapsing disease will go on to develop secondary progressive multiple sclerosis.

Id. at 72-74. Dr. Rammohan then described the treatment of MS:

A number of treatments have been tried in secondary progressive MS, and virtually all of them have failed. And the reason why they fail in the secondary progressive phase of the disease is because it is too late. There is an inflammatory component, which means the inflammation, which you can treat. Then there is a degenerative component, which you cannot treat.

The dogma today is at the earliest possible moment, intervene and treat. Today it would be unusual for a patient who comes with the first attack that can lead to the future occurrence of multiple sclerosis–and we can identify that by magnetic resonance imaging–it can just be an attack of optic neuritis, we do not wait until the second attack to start immunomodul[ary] treatment. Based on Avonex, Copaxone, Rebif, which are three interferons, and a fourth unrelated compound, are the first drugs to come to change the natural history of this disease.

. . .

To have not put this young lady on treatment is one of the worst things that anybody can do. And I think it was by her choosing, and not by that of her physicians. These are drugs that are invaluable. They are not great, they are invaluable nevertheless in the people who respond in getting them out of trouble.

Id. at 74-75.

Dr. Rammohan agreed with Dr. Byers that petitioner originally suffered from RRMS. Id. at 75. However, he disagreed with Dr. Byers's contention that during the period 1996-1999, petitioner's MS remained "quiet." Id. Dr. Rammohan could not point to any hard evidence in the record in this case, such as an MRI, to support his theory. Rather, Dr. Rammohan relied upon a study conducted in Vancouver, British Columbia, and at the NIH that tracked the course of illness in MS patients. Id. at 75-76. Every six weeks, for six years, MS patients in the study had an MRI, blood tests, and a neurological examination. Id. at 75. The results of the study showed that during those periods when the disease appeared to be clinically silent, the patients were, in fact, experiencing active brain inflammation that was evidenced by MRIs showing new lesions coming and going. Id. at 75-76. Thus, according to Dr. Rammohan, it is a mistake to consider a patient clinically quiescent merely because there are no outward signs of clinical activity. Id. at 76. Dr. Rammohan stated that even though MS is one of the worst diseases a person can get, most of the time, the MS is not active. Id. Dr. Rammohan further explained that "[a]ctivity with regards to the disease occurs at a time when the clinical activity is minimal or none. What you see clinically is the tip of the iceberg. The bulk of the activity is going on that you can see by [MRIs]." Id. Thus, Dr. Rammohan argued, based upon the results of this study, one could not conclude that petitioner's MS was dormant between 1996 and 1999 merely because she did not suffer outward clinical manifestations of the disease.

Next, Dr. Rammohan commented upon petitioner's medical records and noted that her 1996 MRI revealed that three segments of her spinal cord were affected. Id. at 77. These results were very significant to Dr. Rammohan because the presence of spinal cord lesions is

> clearly one of the worst prognostic indicators, in terms of multiple sclerosis. Because the spinal cord is no bigger than the size of your thumb. And if you have lesions in there, they are always in eloquent parts. In other words, there is no part of the spinal cord that one can spare.
>
> In the brain, for example, if you had a large lesion, the size of a golf ball, in the frontal area of the brain, it can go completely unnoticed. You cannot have that happen in the spinal cord. Spinal cord lesions become very prominent. And when you have lesions in the spinal cord where you are getting destruction of myelin, you are just a time bomb waiting for things to happen.

Id.

Dr. Rammohan then testified about the current understanding of MS:

> The other point that I wanted to make from the testimony that you heard this morning, MS is not a disease of just the insulation of the nerve fiber. It is not a disease of myelin. It is a disease of the neuron, meaning the gray matter; it is a disease of the myelin; and it's a disease of the axon. In other words, myelin, the axon, which is the nerve fiber itself, and the gray matter are all affected in

> multiple sclerosis. Myelin is the part that stands out, it's the part that becomes apparent. So it is not just a disease of myelin. And we've been looking at just myelin all these years. In the last five years there's been a huge change in our thinking regarding this disease.

Id. at 77-78. Dr. Rammohan further explained that researchers no longer believe that MBP is the antigen implicated in the immune attack in MS. Id. at 78. Instead, researchers now believe that MBP-reactive cells are necessary regulatory cells. Id. There is no consensus as to whether MBP is the antigen that causes MS. Id. at 79. Dr. Rammohan did acknowledge that in the case of ADEM, a disorder that can occur during the course of an infection, there is good evidence that myelin proteins are the cells responsible for the disorder. Id. But, Dr. Rammohan noted that even though ADEM is a "close cousin" to multiple sclerosis, it is not MS. Id.

Based on his extensive practice and research in the area of MS, coupled with his review of the medical records, medical literature, and the report and testimony of petitioner's expert, Dr. Rammohan opined, "There is absolutely no basis on what I have seen here to implicate tetanus toxoid as the basis of [petitioner's] worsening." Id. To support his conclusion, Dr. Rammohan explained that petitioner:

> had all the factors that would have caused difficulty in later years. The spinal cord involvement is a good example of that. She refused disease-modifying therapies, which was the only chance that she would have had to prolong the occurrence of secondary progressive disease, or prevent the occurrence of secondary progressive disease. She chose to do that.
>
> Both of these are situations that actually would have led to the future occurrence of secondary progressive disease, with or without an inciting factor. In other words, if she got no vaccination, this would have been the course.

Id. at 80. Dr. Rammohan also cited to other evidence in the medical records and petitioner's affidavit to support his contention that the TT vaccination did not significantly aggravate petitioner's MS. With respect to petitioner's affidavit, Dr. Rammohan notes that by the time she reached home, petitioner was symptomatic. Id. at 81. Petitioner's muscles were aching and she had foul-smelling urine.

Dr. Rammohan concluded, based upon petitioner's description of "foul-smelling urine," that petitioner suffered from a urinary tract infection ("UTI") as a result of the pelvic examination:

> [I]t's well-known that any manipulations can result in bacteria spilling over into the blood. And I suspect she was probably in the middle of a urinary tract infection, probably because of her multiple sclerosis because she had urinary urgency at the time, which basically means that she was in the setting for urinary

> tract infection, which is one of the biggest problems in patients with multiple sclerosis. And when she had the Pap smear and had the vaginal examination, she probably resulted in the entry of bugs into the blood. And that type of a situation will lead to all of the symptoms that she's talking about: the muscles aching, feeling bad, feeling fatigued almost within hours. And that is not what happens in a vaccine-related injury.

Id. Dr. Rammohan further explained that it is well established that the seeding of petitioner's bladder with bacteria could have occurred within minutes of the manipulation involved with the pelvic examination. Id. at 139. If petitioner had an infection, that manipulation (the pelvic examination) could have easily seeded bacteria into her blood, causing a UTI. Id. In evaluating Dr. Rammohan's testimony with respect to his belief that petitioner had a UTI, the special master notes that, at the time of the January 6, 1999 examination, petitioner did not complain about or describe any UTI symptoms. Additionally, petitioner did not call Dr. Taylor after the January 6 examination to complain of UTI symptoms or request medication to cure that condition. There are no medical records evidencing a UTI at the time of the January 6 examination. Nor was there testimony at trial that a UTI is the exclusive cause of foul-smelling urine. And, of course, Dr. Rammohan was not present during the January 6, 1999 examination; he therefore cannot speak from direct knowledge. Although Dr. Rammohan's theory is possible, especially given his many years of experience treating MS patients, his theory lacks objective medical evidence. Without actual support in the medical records, Dr. Rammohan's premise is only conjecture that must be rejected by the special master.

Dr. Rammohan further testified that the timing of petitioner's onset ruled out the possibility of an adverse reaction to TT: "It's absolutely impossible that a vaccine-related injury of the type that we are talking about occurs within minutes to hours. . . . Because it is a T-cell-mediated response, it doesn't happen in seconds to minutes to hours." Id. at 82-83. As the special master discussed above, however, she finds that the onset of demyelination did not manifest until mid-January 1999 when petitioner was performing at the bluegrass concert and experienced feet and leg numbness.

Dr. Rammohan also disagreed with Dr. Byers's application of the molecular mechanism theories, opining that he was unaware of any scientific evidence that demonstrated that molecular mimicry occurs between the TT vaccine and MBP. Id. at 83. Dr. Rammohan stated that he has researched the issue of whether there was any homology between either of the two chains of tetanus toxoid and MBP and determined that the research shows that "[t]here is no part of the tetanus toxoid that cross-reacts with any protein in the central nervous system, leave alone myelin." Id. at 83-84. Although Dr. Rammohan conceded that molecular mimicry is "a very real thing," he further explained that it has not been shown to occur between tetanus toxoid and MBP. Id. at 85-86. To that end, Dr. Rammohan explained that T-cell degeneracy has only been shown in a test tube, but has never been shown in animals or humans. Id. at 89. Therefore, Dr. Rammohan disagreed with Dr. Byers's interpretation of the Utz studies. Contrary to Dr. Byers's view, Dr. Rammohan explained that in the Utz experiments, TT was used as a control since it is

an antigen that always causes a reaction, because everyone has been immunized against tetanus. Id. at 90. The study's purpose was to show the extent of the T-cell repertoire regarding reactivity to MBP and had no relation to whether TT could cause or significantly aggravate MS. Id. at 90-93, 106-07.

Indeed, Dr. Rammohan argued that if tetanus toxoid could function as a superantigen, with the ability to bind with all T-cell receptors, given the widespread use of the TT vaccination in this part of the world, many more people would become ill; it would be very unsafe.[40] Id. at 94.

Based upon his many years treating MS patients and years of research and study in the field of MS, Dr. Rammohan rejected the notion that TT can cause the significant aggravation of a patient's MS:

> I have never, ever seen a vaccine-related aggravation in my practice. And I can say that with a great deal of confidence, that it is not something that we see. Most centers do not see it; most centers recommend the use of vaccines. Patients ask us all the time, do you think I should have my flu shot, and the answer is yes.
>
> . . .
>
> There is no biological explanation for tetanus vaccine inducing exacerbation, or causing multiple sclerosis, either of those scenarios. Extremely unlikely, if not impossible.

Id. at 100, 102. However, Dr. Rammohan did agree that the timing in which a person is exposed to an environmental stimulus can be a major factor in the course of the disease. Id. at 122. Dr. Rammohan cited the work of Dr. Geoffrey Dean, who used MS patients as his control group for a study of the disease porphyria, primarily found in Africa. Id. One of the significant findings from Dr. Dean's study was the realization that patients in South Africa did not acquire MS; only patients who moved from England to South Africa developed the disease. Id. Because the native African population seemed to be resistant to developing MS, Dr. Dean showed both a geographic and an ethnic basis for the occurrence of the disease.[41] Id. at 123; see also Resp. Ex. E at 2.

Building on that finding, Dr. Dean proceeded to examine the age of migration and determined that MS susceptibility is decided in the first 15 years of a person's life. Tr. I at 123.

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[40] Dr. Byers agrees with Dr. Rammohan that there is no evidence that tetanus toxoid acts as a superantigen. Tr. I at 140. The special master notes that the transcript incorrectly attributes Dr. Byers's testimony on this point to the court.

[41] All references to the pertinent Respondent's Exhibits shall be designated herein as "Resp. Ex. __ at __."

Dr. Dean, and the researchers who later replicated his work, determined that if an individual moved from a high-risk zone to a low-risk zone (e.g., moving from England to Africa) at age five or younger, the emigrating individual was relatively protected from the disease. Id. Conversely, if the same individual emigrated at age 30, the person carried the same risk of acquiring MS as his family members who remained in the high-risk zone. Id. As a result of this research, it is now accepted that in addition to genetic susceptibility, environmental stimuli play a role in the development of MS. Id. at 124-25; see also id. at 104-05 (Dr. Rammohan's testimony regarding his strong belief that here is an environmental cause of MS).

Respondent's Medical Literature

Dr. Rammohan cited two recent epidemiological studies, which he described as "extremely well-designed" and therefore of greater value than case studies, to rebut petitioner's theory of causation. Id. at 94-95. The first, by Confavreux et al.,[42] was a case-crossover study that found that "vaccination does not appear to increase the short-term risk in [MS]." Resp. Ex. F at 319. Of importance to the instant case, the Confavreux study found that "most vaccinations, especially those against tetanus plus poliomyelitis or diphtheria, were actually associated with a lower risk of relapse, although the difference was not significant." Id. at 324.

The second study cited by Dr. Rammohan, by DeStefano et al.,[43] was a case-control study from three large health maintenance organizations that found that vaccination against, inter alia, tetanus, was not associated with an increased risk of MS or optic neuritis. Resp. Ex. G at 504, 507. Indeed, the DeStefano study showed a statistically significant decreased risk in MS and other central nervous system demyelinating diseases in patients who received tetanus vaccine. Id. at 506-07. Pertinent to the case sub judice, the authors determined: "We did not find any increased relative risks regardless of the timing of vaccination, indicating that vaccinations do not cause CNS demyelination, nor do they trigger its clinical manifestation in those with subclinical disease." Id. at 507. Another significant feature of the DeStefano study is that it considered two of the case studies offered by petitioner in support of her claim[44] and concluded: "Ours is the first epidemiologic study, to our knowledge, to evaluate several of the adult vaccines, and our results indicate that the observations in the published case reports probably represent coincidental temporal associations rather than causal association." Id. at 507-08.

The Institute of Medicine ("IOM") reinforces Dr. Rammohan's view that epidemiological studies are more persuasive than case studies. According to the IOM:

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[42] Christian Confavreux et al., Vaccinations and the Risk of Relapse in Multiple Sclerosis, 44 New Eng. J. Med. 319 (2001).

[43] Frank DeStefano et al., Vaccinations and the Risk of Central Nervous System Demyelinating Diseases in Adults, 60 Archives of Neurology 504 (2003).

[44] See Am. Pet. Exs. 11-J & 11-Q.

> Epidemiological studies carry the most weight in a causality assessment; these studies measure health-related exposures or outcomes in a defined sample of subjects and make inferences about the nature and strength of associations between exposures and outcomes in the overall population from which the study sample was drawn. . . .
>
> Case reports and case series are generally inadequate by themselves to establish causality.

Resp. Ex. C at 28. Further, in its 1994 report entitled Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality, the IOM indicated: "The evidence is inadequate to accept or reject a causal relation between tetanus toxoid, DT, or Td and demyelinating diseases of the CNS . . . ."[45] Resp. Ex. D at 86.

Respondent also provided other compelling medical literature. For example, in a recent nested case-controlled study conducted in the United Kingdom involving the recombinant hepatitis B vaccine and the risk of MS, the authors found, inter alia, that there was no increased risk of MS associated with TT and flu vaccines.[46] Resp. Ex. M at 839 tbl.2. In another recent article,[47] the pertinent commentary stated:

> Schoenfeld . . . and Pless . . . reviewed different aspects of a suggested link between infection or immunization and autoimmune disease . . . . Both stressed the lack of sufficient data to be able to draw strong conclusions. However, they agree that, as of today, the link between currently used immunizations and autoimmune disease is weak at best and that the benefits of immunization outweigh the risks by far. Rigorous analysis of the available data has failed to confirm most allegations.

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[45] However, the court does acknowledge that in the same report, the IOM did find a causal relationship between tetanus toxoid and brachial neuritis, a disease of the peripheral nervous system: "The evidence favors acceptance of a causal relation between tetanus toxoid and brachial neuritis. If the evidence favors acceptance of a causal relation between tetanus toxoid and brachial neuritis, then in the committee's judgment the evidence favors acceptance of a causal relation between DT and Td and brachial neuritis." Resp. Ex. D at 94. Brachial neuritis is a Table injury for tetanus toxoid-containing vaccines. 42 C.F.R § 100.3(a).

[46] Miguel A. Hernán et al., Recombinant Hepatitis B Vaccine and the Risk of Multiple Sclerosis, 63 Neurology 838 (2004).

[47] Matthias Regner & Paul-Henri Lambert, Autoimmunity Through Infection or Immunization?, 2 Nature Immunology 185 (2001).

Resp. Ex. H at 186-87. In sum, respondent's medical literature was qualitatively superior because it offered evidence that was both stronger and more current. That twin combination severely undercuts petitioner's theory of causation.

V. DISCUSSION

The Vaccine Act and Federal Circuit Precedent

Pursuant to 42 U.S.C. § 300aa-13(a)(1), the court shall award compensation if petitioner proves, by a preponderance of the evidence, all of the elements set forth in § 300aa-11(c)[48] of the Vaccine Act and that the illness is not due to factors unrelated to the administration of the vaccine.[49] While the TT vaccine is included on the Vaccine Injury Table ("Table"), 42 C.F.R. § 100.3(a), MS is not a Table injury. Thus, petitioner is proceeding on an actual causation theory.

Petitioner claims that her MS was significantly aggravated by her January 6, 1999 TT vaccination. The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." 42 U.S.C. § 300aa-33(4).[50] Here, the parties agree that

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[48] Petitioner, an adult allegedly injured by a Table vaccine, is the appropriate person to maintain this action. In addition, subsection (c)(1) requires, inter alia, that the following elements be satisfied: (1) that the vaccine in question is set forth in the Vaccine Injury Table; (2) that the vaccine was received in the United States or in its trust territories; (3) that the petitioner either sustained an injury as a result of the administration of a Table-designated vaccine for a period of more than six months after the administration of the vaccine, suffered illness, disability, injury, or condition from the vaccine which resulted in inpatient hospitalization and surgical intervention, or died from the administration of the vaccine; and (4) that the petitioner or petitioner's legal representative has not previously collected an award or settlement of a civil action for damages arising from the alleged vaccine-related injury. The records submitted by petitioner clearly reflect that she has satisfied all of these requirements.

[49] Of course, the petition must also be filed within the statutory period. 42 U.S.C. § 300aa-16(a). The petition in this case was timely filed.

[50] The legislative history has discussed the magnitude of deterioration required for a petitioner to successfully prove significant aggravation:

> The committee has included significant aggravation in the Table in order not to exclude serious cases of illness because of possible minor events in the person's past medical history. This provision does not include compensation for conditions which might legitimately be described as pre-existing (e.g., a child with monthly seizures who, after vaccination, has seizures every three and a half weeks), but is

petitioner's MS was significantly aggravated. At no time during the proceedings did respondent argue that the worsening of petitioner's MS did not rise to the level of "significant aggravation" as defined by the Vaccine Act. Indeed, no testimony was offered at hearing or legal arguments advanced in memoranda disputing petitioner's allegation of significant aggravation. Consequently, the special master finds that the change in petitioner's condition postvaccination constitutes a significant aggravation as contemplated by the Vaccine Act. Therefore, the need a lengthy and detailed discussion describing and explaining why petitioner's MS progressing from RRMS to SPMS constitutes a significant aggravation is obviated. However, the mere fact that petitioner's MS became much worse after her TT vaccination does not end the matter. To the contrary, as described above, there was vigorous disagreement as to whether the TT vaccine can and did cause the significant aggravation of petitioner's MS.

In order to prevail under a theory of causation in fact, petitioner must show by a preponderance of evidence that the vaccine in question caused her injury. Bunting v. Sec'y of HHS, 931 F.2d 867, 872 (Fed. Cir. 1991). The Federal Circuit has explained what is required to meet that burden. Specifically, petitioner must establish that the vaccine can cause the injury in question, as well as show that the vaccine is in fact the cause of the injury alleged. Hines ex rel. Sevier v. Sec'y of HHS, 940 F.2d 1518, 1525 (Fed. Cir. 1991). To make the requisite showing, petitioner must offer "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Shyface v. Sec'y of HHS, 165 F.3d 1344, 1353 (Fed.

> meant to encompass serious deterioration (e.g., a child with monthly seizures who, after vaccination, has seizures on a daily basis).

H.R. Rep. No. 99-908, at 15 (1986). The test for determining whether a significant aggravation occurred has changed substantially throughout the Vaccine Program's history. Whitecotton ex rel. Whitecotton v. Secretary of HHS, 81 F.3d 1099 (Fed. Cir. 1996), is the seminal Federal Circuit decision that enunciated a test for evaluating whether a petitioner has successfully demonstrated a prima facie Table claim of significant aggravation under the Vaccine Act**.** This test consists of four prongs that petitioners must meet to carry their burden: (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 prevaccination condition, and (4) determine whether the onset of the significant worsening began within the Table time period. Id. at 1107. If a petitioner successfully shows all four prongs, the burden of showing that the pre-existing illness is the cause in fact of petitioner's worsened condition passes to respondent. Id. The instant case presents a claim for off-Table significant aggravation. Given that petitioner experienced a flare of her MS from which she has not recovered, there can be no question as to whether petitioner suffered a significant aggravation of her MS. Indeed, respondent does not dispute that the worsening would qualify as a significant aggravation under the Vaccine Act. However, respondent is adamant that the TT vaccine is not responsible for the change in petitioner's condition.

Cir. 1999) (quoting Grant v. Sec'y of HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992)). Although petitioner need not demonstrate her theory of causation to medical or scientific certainty, Knudsen ex rel. Knudsen v. Secretary of HHS, 35 F.3d 543, 548-49 (Fed. Cir. 1994), causation in fact requires a reputable medical or scientific explanation supporting this logical sequence of cause and effect. Jay v. Sec'y of HHS, 998 F.2d 979, 984 (Fed. Cir. 1993) (quoting Grant, 956 F.2d at 1148). As Congress directed, "[E]vidence in the form of scientific studies or expert medical testimony is necessary to demonstrate causation" for a petitioner seeking to prove causation in fact. H.R. Rep. No. 99-908, at 15 (1986).

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, 956 F.2d at 1149. Petitioner must not only show that but for the vaccine he would not have had the injury, but also that the vaccine was a substantial factor in bringing about his injury. Shyface, 165 F.3d at 1352. In essence, the special master is looking for a reputable medical explanation of a logical sequence of cause and effect (Grant, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen ex rel. Knudsen, 35 F.3d at 548-49). As the Federal Circuit explained in Knudsen, medical probability means biologic credibility or plausibility: "Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast per se scientific or medical rules." 35 F.3d at 547.

Precedent in the Vaccine Program: Rogers

In Rogers v. Secretary of HHS, No. 94-89V, 2000 WL 1337185 (Fed. Cl. Spec. Mstr. Sept. 6, 2000), the special master found that TT was capable of causing an MS-like central nervous system demyelinating disease in a healthy person. In that case, Ms. Rogers's previous medical history was "unremarkable," with the exception of an incidence of vertigo that occurred three years prior to her TT vaccination and a bronchial infection about three months prior to vaccination. 2000 WL 1337185, at *1. Rogers is distinguishable from the case at bar in several respects. First, unlike the instant petitioner, whose odds of developing SPMS were at least 50 percent, Ms. Rogers was healthy prior to her TT vaccination, id., although the special master found it probable that her condition predated her TT vaccination. Id. at *9. Second, the special master in Rogers made it clear that her decision was heavily influenced by the fact that Ms. Rogers's "treating physicians, with their practical wisdom" linked her injury to the vaccine. Id. at *4. Conversely, in this case, not one of petitioner's treaters linked the significant aggravation of her MS to the TT vaccination. Moreover, two of petitioner's neurologists believed that the TT booster was warranted and one, Dr. Wray, said that she would recommend TT booster for petitioner in the future. Third, the special master in Rogers did not have the benefit of Dr. Rammohan's interpretation of the Utz studies. Fourth, when the special master in Rogers issued her ruling in 2000, she did not have the benefit of the two later-published epidemiological studies, namely, the Confavreux and DeStefano studies, published in 2001 and 2003, respectively.

The passage of time affords the undersigned the benefit of two well-designed epidemiological studies. This is not to say that the now-available medical literature would have altered the outcome in Rogers. Regardless, the undersigned special master is not bound by the holding in Rogers and choose not to follow it. "Special masters are neither bound by their own decisions nor by cases from the Court of Federal Claims, except, of course, in the same case on remand." Hanlon v. Sec'y of HHS, 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999).

Petitioner Has Not Met Her Burden

Petitioner argues that she has produced sufficient proof to prevail because she offered expert testimony by a credentialed physician and medical literature that lends support to her theory of causation. The special master agrees that petitioner's expert, Dr. Byers, is a very capable and well-credentialed immunologist. But, that fact cannot be viewed in a vacuum. Respondent had the duel tasks of cross-examining Dr. Byers to test her theories and offering his own competing theories. In this case, Dr. Byers's theories of causation were effectively rebutted by another excellent and highly-credentialed physician, Dr. Rammohan.[51] The special master gives greater weight to Dr. Rammohan's testimony because he spoke more knowledgeably about the disease of MS and its underlying process. Dr. Rammohan has devoted his medical career to MS research and to the treatment of MS patients. Indeed, Dr. Rammohan is the quintessential "practicing doc" referred to by Dr. Byers in her testimony. According to Dr. Byers, treating physicians are the ones most likely to see adverse reactions to vaccines; not the physicians who author papers or studies. Dr. Rammohan remained firm throughout his testimony that he has never seen a vaccine-related aggravation in any of his MS patients, let alone an adverse reaction to the TT vaccine. Further, he opined that the TT vaccine is incapable of causing an adverse reaction.

Petitioner was not required to show that the TT vaccine was the sole cause or even the predominate cause of the significant aggravation of her MS. However, petitioner did have the affirmative burden of establishing that the TT vaccine was a but-for cause of her injury and also a substantial factor in bringing about her injury. She failed to do so.

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[51] Expert testimony must be "supported by appropriate validation." Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 590 (1993). Dr. Byers's expert testimony lacks appropriate validation and thus falls into the realm of speculation and conjecture. Thus, petitioner's theory of causation rests on "personal opinion, not science." See Daubert v. Merrell Dow Pharmaceuticals, Inc., 43 F.3d 1311, 1319 (9th Cir. 1995) (on remand from the U.S. Supreme Court). Regardless of how genuinely a theory is believed by an expert, the passion with which it is believed is no substitute for scientific support. In the absence of reliable medical evidence to advance a theory, petitioner cannot establish a claim by a preponderance of the evidence.

To be clear, the special master is cognizant that the law does not require the rejection of a novel theory of causation. As the Supreme Court recognized in Daubert, the theory need rest only upon a reliable foundation of medical knowledge. 509 U.S. at 597; see also id. at 593 ("In some instances well-grounded but innovative theories will not have been published. . . . Some propositions, moreover, are too particular, too new, or of too limited interest to be published."). The special master further recognizes that the theory of molecular mimicry falls into the "theoretical-only category of biological mechanism." Tr. I at 65-66. However, the molecular mimicry theory espoused by Dr. Byers has not been rejected by the IOM. And, petitioner did furnish medical literature in support of her theory of causation. The special master is also keenly aware that petitioner's MS was significantly worsened postvaccination.

The forgoing favorable points to petitioner notwithstanding, weighing the totality of the evidence, I find that there was no causal connection between the worsening of petitioner's MS and her January 6, 1999 TT vaccination. My decision is based upon the specific facts presented in this case, the medical literature, and the experts' testimony. For example, not one of petitioner's treating physicians opined that the TT vaccine caused petitioner's MS to worsen. Additionally, both experts agree that at least 50 percent of all RRMS patients will worsen to SPMS and that petitioner was at the critical stage in her disease–the 10-year mark–when her condition would deteriorate. The experts further agree that the presence of spinal cord lesions is a poor prognostic indicator for MS. There is no dispute that petitioner's MRIs reveal spinal cord lesions and MS plaque. And despite petitioner's claim that her MS has been quiet between her 1996 MS diagnosis and her TT vaccination, as Dr. Rammohan explained, the lack of outward symptoms does not prove that the disease was inactive. To the contrary, Dr. Rammohan provided a very cogent explanation that MS can be active despite no manifestation of symptoms (although MS can be insidious and pronounced).

Next, petitioner's theory of causation, as explained by Dr. Byers, was not well grounded in the medical literature. Molecular mimicry cross-reactivity has not been shown in humans. The IOM's 1994 report, which examined the suspected association between, inter alia, the TT vaccine and MS, concluded that the evidence is inadequate to accept or reject a causal association between the TT vaccine and demyelinating diseases of the central nervous system. Although not dispositive of the issue, the IOM's conclusion lends support for respondent's view. Of far greater importance were the well-designed epidemiological studies presented by respondent. Because epidemiological studies are afforded greater weight than case studies, this evidence significantly undercut the case studies offered by petitioner. Indeed, two of the case studies discussed in detail by Dr. Byers and upon which she placed great emphasis were criticized as unreliable by respondent's epidemiological studies. And, despite Dr. Byers's testimony that there is a strong temporal relationship between the TT vaccination and the onset of petitioner's numbness in her legs and feet, the Federal Circuit has cautioned that such facts, standing alone, are insufficient to establish causation–additional supporting evidence linking the vaccine to the injury is required.

Although the undersigned rejects respondent's suggestion that a UTI caused petitioner's flare of MS, respondent is not required to demonstrate an alternative theory of causation. The burden of proof falls on petitioner and she was unable to prove that the TT vaccine caused the significant aggravation of her MS. Neither respondent nor the special master is required to pinpoint the cause for the change in petitioner's condition.

VI. CONCLUSION

Based upon a review of the medical records, medical literature, and expert reports, coupled with the testimony presented at hearing, the special master finds that the totality of evidence demonstrates that more likely than not, petitioner's January 6, 1999 TT vaccination was not a substantial factor in causing the significant aggravation of her MS; the TT vaccine was not the "but-for" cause of the worsening of her condition. In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of Court is directed to enter judgment accordingly.

IT IS SO ORDERED.

Margaret M. Sweeney
Special Master