In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 01-417V
September 24, 2008
To be Published

ROSEANNE BORRERO,	*	
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Petitioner,	*	
	*	
v.	*	Entitlement; hepatitis B vaccine followed by transverse myelitis and multiple sclerosis
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SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Ronald C. Homer and Sylvia Chin-Caplan, Boston, MA, for petitioner.
Richard F. Topping, Jr., Washington, DC, for respondent.

MILLMAN, Special Master

RULING ON ENTITLEMENT[1]

Petitioner filed a petition dated July 18, 2001, under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that her first hepatitis B vaccine administered

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision or designated substantive order is filed, petitioner has 14 days to identify and move to delete such information prior to the document's disclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall delete such material from public access.

on March 26, 1999 significantly aggravated her pre-existing demyelinating[2] disease, beginning with numbness in her hand four days later. Subsequently, petitioner took the position that she did not have a demyelinating disease prior to her hepatitis B vaccination without amending her petition.

A hearing was held on April 21, 2008. Testifying for petitioner was Dr. Carlo Tornatore. Testifying for respondent was Dr. Benjamin Greenberg.

Petitioner filed a post-hearing brief on June 18, 2008. She states that hepatitis B vaccine caused her transverse myelitis (TM)[3] and subsequently multiple sclerosis (MS)[4] and, in the alternative, that hepatitis B vaccine significantly aggravated an underlying demyelinating disorder resulting in TM and MS. P. Br. at 1.

Respondent filed a post-hearing brief on July 15, 2008.

Background to the Proceedings

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[2] Demyelination is "destruction, removal, or loss of the myelin sheath of a nerve or nerves." Dorland's Illustrated Medical Dictionary, 30th ed. (2003), at 488. The myelin sheath is "the cylindrical 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." *Id.* at 1689.

[3] Myelitis is "inflammation of the spinal cord, often part of a more specifically defined disease process." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1209. Transverse myelitis is "myelitis in which the functional effect of the lesions spans the width of the entire cord at a given level." *Id.*

[4] 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." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1669.

On July 18, 2001, this case was assigned to chief special master Gary Golkiewicz. On May 7, 2003, the case was reassigned to former special master Margaret M. Sweeney. On January 11, 2006, this case was reassigned to the undersigned as part of 65 hepatitis B vaccine-demyelinating diseases cases reassigned to the undersigned in January 2006 after former special master Sweeney became a judge on the United States Court of Federal Claims.

As part of her role in determining the outcomes of these 65 cases, the undersigned issued decisions after the Omnibus hearing that former special master Sweeney held on October 13, 14, and 15, 2004 to determine whether hepatitis B vaccine can cause demyelinating diseases and, specifically, whether it caused the illnesses in four paradigm cases concerning TM, Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and MS. The undersigned ruled in favor of petitioners in all four paradigm cases, i.e., that hepatitis B vaccine could and did cause TM, GBS, CIDP, and MS in those four paradigm cases.[5]

The undersigned now turns to the instant action.

FACTS

Before the Hepatitis B Vaccination

Petitioner was born on October 16, 1954.

[5] Stevens v. Secretary of HHS, No. 99-594, 2006 WL 659525 (Fed. Cl. Spec. Mstr. Feb. 24, 2006) (hepatitis B vaccine caused TM); Gilbert v. Secretary of HHS, No. 04-455V, 2006 WL 1006612 (Fed. Cl. Spec. Mstr. Mar. 30, 2006) (hepatitis B vaccine caused GBS and CIDP); Werderitsh v. Secretary of HHS, No. 99-310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006) (hepatitis B vaccine caused MS); Peugh v. Secretary of HHS, No. 99-638V, 2007 WL 1531666 (Fed. Cl. Spec. Mstr. May 8, 2007) (hepatitis B vaccine caused GBS and death).

On July 18, 1995, petitioner went to Royal Oaks Medical Center. Med. recs. at Ex. 2, p. 14. She had an auto accident on Sunday, July 16, 1995. *Id.* She had pain across the chest where the shoulder strap crossed. *Id.*

On July 24, 1995, petitioner filled out a patient history form for the Orthopedic Clinic of Titusville. Med. recs. at Ex. 3, p. 31. The onset of her pain was an auto accident. In answer to what activities made the pain worse, petitioner listed: exercise/movement, rest, sitting, standing, walking, bending, and twisting. *Id.* For areas where she felt numbness and burning, she indicated both shoulders, her right hip, her right wrist, and her right leg. *Id.* For areas where she felt pins and needles and stabbing, she indicated: her upper back, her right hip, and both hands. *Id.* She stated that she generally was tired, discomforted, fatigued, sore, stiff, dizzy, and sharply pained in her hip. Med. recs. at Ex. 3, p. 32. She checked off that she had frequent or severe headaches, dizziness or fainting spells, chest pain, shortness of breath, swollen or painful joints, and depression or excessive worry. *Id.*

On September 11, 1995, petitioner saw Dr. Joseph E. Rojas. Med. recs. at Ex. 3, p. 3. She had been injured in an auto accident on July 16, 1995 and was seen at Royal Oaks Medical Center. She had pain over her shoulders, anteriorly and posteriorly, and over her right hip area and lateral area with some clicking in it. She had some tingling in her right hand. Exercise, rest, sitting, standing, walking, bending, or twisting aggravated the pain. *Id.* Petitioner stated she had frequent headaches, dizziness, chest pain, shortness of breath, swollen joints, and depression. *Id.* Petitioner had been having some weakness in the left hand and some pain developed. Med. recs. at Ex. 3, p. 4. On physical examination, petitioner was losing the use of her left hand and had difficulty with

weakness in it. There was weakness of the interossei of the long finger flexors and of the thenar. The biceps and triceps were strong. Her condition seemed progressive. *Id.*

On October 12, 1995, petitioner saw Dr. Rojas. Med. recs. at Ex. 3, p. 1. Petitioner still had some problems with her right hip, but her neck felt better. *Id.*

On November 10, 1995, petitioner saw Dr. Rojas with continuing back pain. *Id.*

On February 3, 1997, petitioner saw Dr. Rojas with continuing neck, back, right hip, and shoulder pain. She had continuing nausea with headaches. *Id.*

On February 6, 1997, petitioner saw Dr. Roberto Mixco, a neurologist, complaining of headaches since she had been in an automobile accident on July 16, 1995. Med. recs. at Ex. 4, p. 5. Initially, she had pain in her neck with headaches and pain radiating to her shoulder. Over the prior several weeks, the headaches worsened in frequency and intensity. *Id.*

On February 8, 1997, petitioner had a brain MRI done. It was unremarkable. Med. recs. at Ex. 5, p. 7.

Also on February 8, 1997, petitioner had an MRI of her cervical spine. Med. recs. at Ex. 3, p. 22. Dr. J. Swalchick's impression was congenital central canal stenosis of a minimal degree, and mild cervical spondylitic changes at C5-C6 and C6-C7. *Id.*

On March 6, 1997, petitioner saw Dr. Mixco again. He reviewed an MRI of her brain, which was normal. A cervical MRI was slightly abnormal, suggesting congenital stenosis that was minimal. There were also spondylitic changes mainly at C5-C6 and C6-C7. At C5-C6, petitioner had a small central disc protrusion with some osteophytes. Med. recs. at Ex. 4, p. 4.

On March 7, 1997, petitioner saw Dr. Rojas. She still had pain in her neck and some stiffness and tenderness. Med. recs. at Ex. 3, p. 2.

On April 23, 1997, petitioner saw Dr. Rojas. She still had shoulder spasms. Med. recs. at Ex. 3, p. 6.

On May 21, 1997, petitioner saw Dr. Rojas. She had severe pain in her neck the day before. *Id.*

On August 10, 1997, petitioner went to Royal Oaks Medical Center, having fallen in the shower, traumatizing her left arm. Med. recs. at Ex. 2, p. 13. She had multiple contusions. *Id.*

On November 10, 1997, petitioner saw Dr. Rojas. Med. recs. at Ex. 3, p. 5. She was still having some spasms and problems with pain. Med. recs. at Ex. 3, p. 5.

On November 11, 1997, petitioner went to Royal Oaks Medical Center, complaining of tingling in her fingers and pain in her forearm. She had a positive Tinel's sign.[6] She also noted weight gain and fluid retention. Med. recs. at Ex. 2, p. 12. She was diagnosed with carpal tunnel syndrome, obesity, fluid retention, and left shoulder pain. *Id.*

On December 8, 1997, petitioner saw Dr. Rojas. Her left shoulder was much better. She had some limitation in abduction of the left shoulder. Med. recs. at Ex. 3, p. 5.

On December 12, 1998, petitioner went to Royal Oaks Medical Center, complaining of tingling in her leg since November, and a twisted neck. Med. recs. at Ex. 2, p. 11.

On December 27, 1998, petitioner saw Dr. Robert Bartemus. She complained of tingling and slight weakness in the right leg ongoing for some time, radiating down to approximately knee level posteriorly and some anterior irritation as well. Med. recs. at Ex. 2, p. 10. The discomfort appeared to originate from her low back area, right side. This had been a recurring problem since twisting her

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[6] Tinel's sign is "a tingling sensation in the distal end of a limb when percussion is made over the site of a divided nerve. It indicates a partial lesion or the beginning regeneration of a nerve." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1703.

neck in November. She stated her neck felt fine, but she had some low back muscle spasm, trouble moving around with sitting for a period creating the discomfort in her right leg. She now felt it also crept over the medial part of the upper portion of the left lower extremity as well. The leg was not specifically weak, however. *Id.* Dr. Bartemus' impression was acute low back pain, right-sided, with sciatica and no specific neurological dysfunction in the right lower extremity. *Id.*

On December 31, 1998, petitioner went to Royal Oaks Medical Center, complaining of having difficulty moving her right leg. Med. recs. at Ex. 2, p. 9. Dr. Bartemus saw petitioner. Her lower back had improved somewhat with manipulation since he last saw her. She continued to notice unsteadiness in the right leg. She weighed 218 pounds, which possibly contributed to the current complaint. She felt a loss of sensory function in the anterior thighs even down to the posterior calf area, right greater than left, for the past four weeks. She had no particular weakness in the left leg. *Id.* On physical examination, petitioner had difficulty standing from a sitting position and used her hands for assistance. She was slightly unsteady on her feet, but showed no cerebellar signs. No weakness was noted on flexion or extension of the lower extremities. She had good quadriceps tone and no atrophy. Her deep tendon reflexes (DTRs) were hypoactive in the patella area and in the Achilles tendon area. *Id.*

On January 19, 1999, petitioner saw Dr. Len Van Eaton for back pain which was dull and aching. She had severe intensity of symptoms. Pain was in the right lumbar area with radiation to the right ankle. Associated neurological symptoms included positive right leg weakness, and whole leg numbness. Med. recs. at Ex. 2, p. 7. Any kind of movement aggravated the pain which was getting worse. On examination, petitioner had decreased range of motion. Her strength and tone were normal. Dr. Van Eaton diagnosed lumbosacral strain/sprain and low back pain and sciatica. *Id.*

After the Hepatitis B Vaccination

On March 26, 1999, petitioner received her first hepatitis B vaccination. Med. recs. at Ex. 1, p. 10.

On April 12, 1999, petitioner saw Dr. Miguel Rivera Rivera, a neurologist, complaining of tingling involving both legs, numbness and weakness of her left arm, and unusual abdominal muscle contractions. Med. recs. at Ex. 4, p. 2. She stated she first had problems with her legs around November 19, 1998. These problems were weakness and persistent burning sensations in both feet and both legs distally. The problems with her left arm began on March 30, 1999 (four days after vaccination). She initially experienced numbness in the tips of the fingers of her left hand which later radiated upward. She also had skin hypersensitivity and tingling involving the entire left upper extremity. More recently, she experienced weakness and lack of coordination of the left arm. She could not control her left arm when she combed her hair. *Id.*

On physical examination, she did not have atrophy, abnormal movement, fibrillation, or fasciculation. She had weakness of the left arm and a significantly weak grip. Her left hand exhibited hypertension and involuntary, irregular movements of her fingers both in flexion and extension. Astereognosis[7] was present in the left hand. Med. recs. at Ex. 4, p. 3. DTRs (deep tendon reflexes) were brisk and present in the right upper extremity, hyperactive in the left biceps and triceps, and absent in the left lower extremity and right ankle. Hoffman's sign[8] was present on

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[7] Astereognosis is "loss or lack of the ability to understand the form and nature of objects that are touched . . . ." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 167.

[8] In Hoffman's sign, "a sudden nipping of the nail of the index, middle, or ring finger will produce flexion of the terminal phalanx of the thumb and of the second and third phalanges of some other finger . . . ." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1699.

the left and there was a transient upgoing toe on each foot. *Id.* Sensation was decreased bilaterally in both lower extremities distally with some degree of dissociation of deep and superficial sensation. Petitioner had ataxia on finger to nose and heel to shin on the left, particularly finger to nose. Dysmetria[9] was also present on the left. Petitioner could not perform alternating movements with her left hand. *Id.* Dr. Rivera Rivera's impression was a possible low intracranial lesion or a high spinal cord lesion. *Id.*

On April 14, 1999, petitioner underwent a brain MRI, which showed mild supratentorial atrophy but was otherwise unremarkable. Med. recs. at Ex. 5, p. 5.

Also on April 14, 1999, petitioner underwent a cervical spine MRI, which showed a 22 x 10 x 8 mm enhancing central to left lateral cervical cord mass which had developed since a prior cervical spine MRI done on February 8, 1997. This could be a cord astrocytoma or glioma. Med. recs. at Ex. 5, p. 6.

On April 15, 1999, petitioner saw Dr. Rivera Rivera. They discussed her MRIs. The MRI of the brain was unremarkable. Med. recs. at Ex. 4, p. 1. The MRI of the cervical spine showed the presence of a 22 x 10 x 8 mm enhancing central to left lateral cervical cord mass which had developed since the prior MRI scan of February 8, 1997. Possible diagnoses were cord astrocytoma and/or glioma. Cystic changes were present. The region of enhancement was associated with focal cord enlargement. Objectively, her neurological examination was unchanged. *Id.*

On April 21, 1999, petitioner saw Dr. Barth A. Green, a neurosurgeon. Med. recs. at Ex. 5, p. 11. She had neck and left upper extremity paresthesias in March 1999. Her first symptoms occurred

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[9] Dysmetria is "a condition in which there is improper estimation of distance in muscular acts, with disturbance of the power to control the range of muscular movements, often resulting in overreaching." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 575.

in November 1998 when she twisted her neck and had pain. She also had it the next day and felt tightening of her legs around her knee caps. In March 1999, she had tingling of her fingertips and left hand which gradually progressed to mild clumsiness which progressed over the prior two weeks. An MRI showed a mass in the left side of the cervical cord from C2-C4. She now complained of numbness in her left hand extending up her arm into the left axilla and down her whole left hemibody. She had bilateral numbness in her legs to her feet. Her fingertips became weak that week. She reported increased impairment of her hand dexterity, inability to write and hold a pen, and difficulty dressing herself. She had progressive left upper extremity weakness and numbness. She noticed increased tightness in the legs, thighs, and knee caps. She had no leg pain. She had an electrical shock-type pain in her anterior axillary area, radiating to the scapula. She had a banding tightness over her left breast and below the breast bilaterally, left more than right. She had loss of balance and a tendency to run into things. Occasionally, she was dizzy when standing up. *Id.*

Petitioner had headache due to post-concussion secondary to her auto accident in 1997. [Petitioner's auto accident occurred in 1995.] The headaches were occipital to the forehead and better with therapy and magnets. Med. recs. at Ex. 5, p. 12.

On examination, petitioner's cerebral, cerebellar, and cranial nerve examinations were normal, except for some flattening of her left nasal labial fold with some decreased rapid fine movements and rapid alternative movements in the left hand. She had a lag on the left on arm roll and pronator drift. She had atrophy of her left forearm about 3/4 inch smaller than the right. She had numbness down the whole left side of her body from the chin down, numbness in both thighs and on the left side anteriorly and posteriorly. She had numbness in both feet and ankles and in a stocking-glove distribution in both hands. She had mainly numbness in all sensory modalities and less so in

the dorsal column than on the right; bad proprioceptive problems, and vibratory compromise of the left upper extremity. Her reflexes were hyperactive in the left upper extremity compared to the right. She had a slight increase in her ankle jerk on the left compared to the right. She had a positive Romberg.[10] She had tenderness in the left medial scapular area with fairly good range of motion of her head and neck. *Id.*

Petitioner's x-rays were unremarkable. Med. recs. at Ex. 5, p. 13. Her MRI of the brain and cervical spine from 1997 were unremarkable. The brain MRI from 1999 had some slight increased signal, but that might be artifact. The cervical spine MRI showed a lesion in the left side of the cord at C2, C3, and C4, centered at C3. The differential diagnosis would be inflammatory (such as MS) versus tumor (such as astrocytoma). *Id.*

On April 26, 1999, petitioner received her second hepatitis B vaccination. Med. recs. at Ex. 1, p. 10.

On April 28, 1999, petitioner saw Dr. Van Eaton for a presurgical evaluation. She had a history of weakness. Dr. Van Eaton diagnosed a cervical spinal cord tumor. Med. recs. at Ex. 2, p. 2.

On May 3, 1999, Dr. Green had an MRI conference. Med. recs. at Ex. 5, p. 10. Petitioner's MRI showed a large herniated disc at C2-C3 compressing the cord on the right. At C3 was a large intramedullary mass which was enhanced with gadolinium and was bright on T2. The differential diagnosis was tumor such as astrocytoma versus inflammatory lesions. So far, the workup for MS was negative, including electrophysiology, brain MRI, and CSF (cerebrospinal fluid) analysis. The

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[10] Romberg's sign is a "swaying of the body or falling when standing with the feet close together and the eyes closed; the result of loss of joint position sense . . . ." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1702.

somatosensory evoked potentials (SSEP) were abnormal. The brainstem and visual evoked potentials (VEP) were normal. *Id.*

On May 6, 1999, Dr. Green performed a partial laminectomy of the C2 and C4 and a total laminectomy of C3 on petitioner. Med. recs. at Ex. 6, p. 45.

On May 19, 1999, Dr. Carol K. Petito wrote a pathology report stating there was no tumor. The biopsy suggested a demyelinating lesion. Med. recs. at Ex. 16, p. 4. (The pages in Exs. 14-22 are unnumbered; the undersigned numbered the pages of her copy.) In an addendum, Dr. Petito noted that myelin and axon stains showed demyelination with loss of myelin and preservation of axons. Med. recs. at Ex. 16, p. 5.

On May 21, 1999, Dr. Green noted that the final pathology result was demyelinating disease, multiple sclerosis. Med. recs. at Ex. 5, p. 9.

On June 28, 1999, petitioner saw Dr. Thomas G. Hoffman for follow-up of a cervical myelopathy. Med. recs. at Ex. 7, p. 7. Petitioner developed some symptoms of leg numbness in November 1998 followed by some left-handed weakness in April 1999. She related the onset of her left-handed weakness to hepatitis B vaccine. Since April, she had not only left-handed weakness and numbness, but also some numbness over the entire left side of her body and a tight feeling around her chest and underneath her breasts. *Id.*

She underwent partial laminectomy and exploration of myelotomy on May 6, 1999. Pathology revealed no evidence of tumor. Brain MRI, spinal fluid, visual brainstem, and somatosensory evoked potential tests were all negative. Since the surgery, petitioner had been stable, bothered mostly by symptoms of tightness in her legs and chest, numbness on the left side, and profound numbness and incoordination with some swelling in the left hand. *Id.*

On physical examination, petitioner had good strength in her extremities. Rapid alternating movements were impaired in the left hand. The legs had minimal increased tone. Left arm reflexes were slightly hyperactive. There was some subjective sensory loss over the left side of her body. There was profound position sense loss in the left hand up to the shoulder. She had no visual symptoms and no problem with bladder or bowel. *Id.* Dr. Hoffman's impression was cervical myelopathy, etiology uncertain. *Id.*

On August 10, 1999, petitioner saw Dr. Hoffman for follow-up. Petitioner had completed physical therapy paid for by insurance and wanted to continue therapy by paying for herself. Her left hand function was improving slowly. She was able to walk three miles to school and back with her daughter on August 9, 1999. Med. recs. at Ex. 7, p. 5. She continued to have weakness in the left shoulder and some paresthesias and itching in the left upper chest and shoulder region. Dr. Hoffman told petitioner he could not differentiate whether she had an exacerbation of MS or a single mild temporal illness such as cervical myelitis. On examination, she had minimal spasticity in her legs, mild hyperreflexia in the left arm, and some mild left-sided subjective sensory loss. *Id.*

On September 26, 1999, petitioner received her third hepatitis B vaccination. Med. recs. at Ex. 1, p. 10.

On September 27, 1999, petitioner returned to Dr. Hoffman. Med. recs. at Ex. 7, p. 1. She complained of tightness as if she were wearing a girdle. The left side still felt numb and swollen and she still had difficulty using the left hand with fine coordination. She had difficulty using a computer keyboard because of this. Sometimes, when she moved her neck, she felt it crunching. She had a mild left pronator drift and moderate slowing and impairment of fine coordination in the left hand. She walked fairly well independently but had significantly increased tone in both legs. *Id.*

On November 15, 1999, petitioner saw Dr. F. Espinoza at Titusville Family Practice for a referral to neurology. She had severe spasticity and severe hyperreflexia in her left upper extremity. Med. recs. at Ex. 8, p. 1.

On November 22, 1999, Dr. Wasim Niazi, a neurologist, wrote that petitioner had normal distal motor latencies, normal CMAP (compound muscle action potential) amplitudes, and motor conduction velocities in the left median nerves and both ulnar nerves. Med. recs. at Ex. 8, p. 2. Petitioner had normal F wave latencies in the left median and both ulnar nerves. She had normal SNAPs (sensory nerve action potentials) and NAPs (nerve action potentials) amplitudes and sensory conduction velocities in the left median nerves and in both ulnar nerves. *Id.* Petitioner had normal needle EMG (electromyography) of the muscles of the left upper extremity including median innervated muscles and right first dorsal interosseous. Dr. Niazi's impression was that petitioner's study was normal. "There is no evidence of left cervical radiculopathy, brachial plexopathy, or ulnar or median neuropathy in the left extremity." *Id.*

Dr. Niazi wrote a longer report on November 22, 1999. Med. recs. at Ex. 9, p. 3. Petitioner was seen for evaluation of loss of motor skills associated with atrophy of the muscles, paresthesias, burning pains and swelling of the left upper extremity of eight months' duration. There was numbness and tingling involving the inner three fingers on the right side and pain and stiffness on both sides of the neck. *Id.* Petitioner reported that, in March 1999, she was at work and attempted to pick up a bottle of water which dropped from her hand. A few days later, she was unable to put her hand in a latex glove because her fingers would not stop moving. She saw Dr. Rojas who referred her to Dr. Rivera Rivera. She underwent laminectomy of C2-C4 on May 6, 1999. Unless she concentrated, she could not control the motor skills in her left hand. She could not wash her hair,

wash dishes, cook without help, iron, dress herself, or tie her shoelaces. She had a constant burning sensation in the posterior aspect of the forearm and hand. She had pressure in the tips of all fingers. She had constant swelling in the entire hand. She experienced numbness and tingling, particularly at night, that often interfered with sleep. She was unable to hang her arm or hand over the bed.. She also felt that the hand, fingers, and muscles of the forearm were shrinking, and her left hand fingernails had curved markedly during the last two months. She gained significant weight on Prednisone for four months. *Id.*

Petitioner stated that two months before the onset of these symptoms (presumably January 1999), she experienced tightness throughout both legs associated with a feeling of sand on the soles of her feet. These symptoms of numbness, tingling, and stiffness remained unchanged. She also reported numbness and tingling in the inner three fingers of her right hand. She reported no new events during the last seven months. Dr. Hoffman saw her in June 1999. She reported marked stiffness involving both sides of the cervical region. She did not report problems with vision, speech, or swallowing. *Id.*

On physical examination, petitioner had appropriate strength in all four extremities except marked spasticity and loss of dexterity involving the left hand with almost complete inability to open the hand after closure except manually with the other hand. There was no pronator drift. Muscle bulk was normal with suggestion of spasticity in the lower extremities, more on the left than on the right side. There were no abnormal movements. Med. recs. at Ex. 8, p. 5.

Her DTRs were 1-2+ in the brachioradialis, 1-2+ in the biceps, 2+ in the triceps bilaterally, 2+ in the knee jerks, and 1-2+ in the ankle jerks bilaterally. She did not have Hoffman's or Babinski's sign and there was no ankle clonus. *Id.* Touch, pinprick, proprioception, and vibratory

sense were intact throughout. Double simultaneous stimulation was intact. There was no sensory level in the trunk. She was able to perform tip-toe and heel walking, and her gait was normal. The range of motion of her neck was somewhat limited. There were some spasms of the paraspinal muscles. Her range of motion was normal in all joints. Her lumbar spine had normal range of motion. *Id.* A biopsy report of the cervical lesion dated May 19, 1999 was reviewed: it was a demyelinating lesion. *Id.*

Dr. Niazi's impression was transverse myelitis (TM), manifesting as left-sided sensory motor manifestation, monophasic disease versus polyphasic demyelinating disease, with no clinical evidence of progression during the last six months. Med. recs. at Ex. 8, p. 6. Other diagnoses were symptomatology suggestive of right ulnar neuropathy, and bilateral cervical stiffness and pain most likely related to cervical spondylosis. *Id.*

On December 28, 1999, petitioner returned to Dr. Niazi, complaining that the tightness around her chest had gotten worse and she had associated pain in the bend, pain in the left forearm and hand, and a worsened gait (although she walked unaided). Med. recs. at Ex. 9, p. 5. A report of petitioner's MRI done December 1, 1999 showed nonspecific foci of deep white matter T2 hyperintensity. One of the right frontal deep white matter areas of T2 hyperintensity was new compared to a prior examination. This was worrisome, given the prominent spinal cord lesion previously, because of white matter disease such as MS with lesions evolving in space and time. Med. recs. at Ex. 9, p. 6.

On January 26, 2000, petitioner saw Dr. Niazi. Med. recs. at Ex. 9, p. 7. Since petitioner had been on Neurontin, she had about 50% improvement in her painful symptoms and could do things she could not do before. She still had problems with intermittent tightness around the chest and

trunk associated with pain in the bend. There was pain in the left forearm and hand as well as pressure feeling in the fingers and arms. She still felt spasticity in the legs. *Id.*

On May 23, 2001, petitioner saw Dr. Niazi. Med. recs. at Ex. 14, p. 7. Petitioner still had pains and spasms in the upper and lower extremities, mostly in the right leg from the knee down. She felt heat, cold, and lack of feeling in the left arm. Her marked spasms in the muscles of the extremities were worse at night. She had no problem with bladder or bowel control. She reported some blurring of vision. *Id.*

On June 26, 2001, petitioner underwent a brain MRI, which was normal except for subtle white matter lesions in the frontal lobes that appeared non-specific. Med. recs. at Ex. 19, p. 1.

On July 5, 2001, petitioner took a visual evoked response test, which Dr. Niazi interpreted as normal. Med. recs. at Ex. 14, p. 13. Also on July 5, 2001, petitioner took a somatosensory evoked response test, which Dr. Niazi interpreted as abnormal, suggesting dysfunction involving the dorsal column associated with central sensory pathways. Med. recs. at Ex. 14, p. 14.

On July 25, 2001, petitioner saw Dr. Niazi. Med. recs. at Ex. 14, p. 5. She remained bothered by tightness from the neck down with bend at the waist. She had problems swallowing without any epigastric burning sensation. Her fingers had spasms, causing anxiety when they were severe. She had stress, anxiety, and impaired sleep. *Id.*

On October 25, 2001, petitioner saw Dr. Niazi. Med. recs. at Ex. 14, p. 3. She reported she had gained 12 pounds. Her muscles felt tighter than ever though she did not have as many spasm attacks as previously. She had difficulty maintaining balance for long periods of time. *Id.*

On December 6, 2001, petitioner saw Dr. Niazi. Med. recs. at Ex. 14, p. 1. Petitioner complained of aching pains in the extremities that worsened since last seen October 25, 2001. She

had leg pains primarily in the areas above the knees. *Id.* There was no hyperreflexia in the lower extremities and the spasticity in the left leg was better. Med. recs. at Ex. 14, p. 2.

On June 26, 2002, petitioner underwent an MRI of her cervical spine, which Dr. Niazi interpreted as showing signal changes in the mid-portion of the cervical spinal cord consistent with old TM and spinal cord biopsy without suggestion of recurrent or acute myelitis; cervical spondylosis with multi-level disc disease and protrusions at C4-C5 and C5-C6; and evidence of previous laminectomy in the upper cervical region. Med. recs. at Ex. 23, p. 3. She had recent worsening of her symptoms in consideration of a reoccurrence of cervical myelopathy. *Id.*

On November 12, 2002, petitioner saw Dr. Niazi, complaining that her gait had worsened as well as the spasticity of her lower extremities. Med. recs. at Ex. 23, p. 1. It took her ten minutes to exit a car. She could not wear closed shoes. *Id.*

On June 24, 2004, petitioner saw Dr. Niazi. Med. recs. at Ex. 26, p. 7. She complained her gait had worsened as well as her lower extremities' spasticity. She could not walk any distance because of leg tightening. She had gained 20 pounds. Her headaches, fatigue, neck pain, and head heaviness had worsened. *Id.*

On July 1, 2004, petitioner underwent a brain MRI, which Dr. Niazi interpreted as showing signal changes involving the corpus callosum and periventricular white matter suggestive of MS. Med. recs. at Ex. 26, p. 13. The study showed interval development of white matter disease compared to the brain MRI done on June 26, 2001. *Id.*

On July 21, 2004, petitioner saw Dr. Niazi, with worsened pain, vision, and spasticity. Med. recs. at Ex. 26, p. 4. She had moderate asymmetrical spasticity in the lower extremities. Her gait was stable. Med. recs. at Ex. 26, p. 5.

On August 4, 2004, petitioner had a median somatosensory evoked response test, which Dr. Niazi interpreted as being abnormal because of depressed amplitudes of N20 bilaterally, more on the left than on the right, suggesting dysfunction of the median nerve associated with central sensory pathways. Med. recs. at Ex. 26, p. 12. An auditory evoked potential test on the same date was normal. Med. recs. at Ex. 26, p. 11.

Also on August 4, 2004, petitioner underwent a tibial somatosensory evoked response test which Dr. Niazi interpreted as showing prolongation of P37 bilaterally. This suggested either primary demyelinating disease or L5-S1 radiculopathy. Med. recs. at Ex. 26, p. 10. Also on the same date, petitioner had a visual evoked response test which showed mild prolongation of the P100 bilaterally, suggesting a dysfunction of the optic nerve-associated pathways as may be seen in association with a primary demyelinating disorder. Med. recs. at Ex. 26, p. 9.

On September 29, 2004, petitioner saw Dr. Niazi with continued pain and spasticity with episodes of shortness of breath. Med. recs. at Ex. 26, p. 1.

Other Submitted Material

On May 9, 2007, petitioner filed three medical articles as Ex. 29, Tabs A-C. Tab A is "Molecular mimicry between HLA B27 and *Yersinia, Salmonella, Shigella* and *Klebsiella* within the same region of HLA α-helix" by R. Lahesmaa, et al., 86 *Clin Exp Immunol* 399-404 (1991). The article is a discussion of molecular mimicry between microbial antigens and HLA B27-associated spondyloarthropathies.

Petitioner's Ex. 29, Tab B, is "A study of molecular mimicry and immunological cross-reactivity between hepatitis B surface antigen and myelin mimics" by D-P Bogdanos, et al., 12 *Clinical & Developmental Immunology* 3:217-24 (2005). The authors looked for amino acid

similarities between the small hepatitis B virus surface antigen (SHBsAg) and the multiple sclerosis autoantigens myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) that could serve as targets of immunological cross-reactivity. The authors posit that infection probably occurs years before clinically overt autoimmune disease. *Id.* at 217. They also posit that vaccination against infectious agents might activate pathways of molecular mimicry in genetically susceptible hosts. *Id.* at 218.

The authors state that the current hepatitis B vaccine is a non-infectious viral subunit consisting of the small hepatitis B virus surface antigen. *Id.* In multiple sclerosis and its animal analogue, experimental allergic encephalomyelitis (EAE), the major target is myelin basic protein. *Id.* In addition, humoral immunity against myelin oligodendrocyte glycoprotein (MOG) is associated with myelin damage in MS. *Id.* The authors found extensive homologies between known epitopic regions on hepatitis B surface antigen and myelin basic protein and myelin oligodendrocyte glycoprotein (MOG). *Id.*

They tested a total of 234 serum samples which were collected before and after hepatitis B vaccinations. *Id.* The authors found reactivity to at least one of the surface antigen peptides in 41 out of 45 (or 92%) of the vaccinated subjects three months post-vaccination. Fifty-three percent of the subjects had reactivity to at least one of the MOG mimics. *Id.* at 220. The same percentage held after six months for the surface antigen peptides, but some of the MOG mimics had lost their reactivity. *Id.* None of the vaccinees reported symptoms of demyelinating diseases at the six-month post-vaccination follow-up. *Id.* at 222. The authors conclude:

> Not only does SHBsAG share strong homologies with major myelin antigens such as MBP and MOG but also specific viral/self pairs were found to be targets of antibody responses induced by the administration of the viral vaccine. ... All of the vaccinees were free of

> autoimmune phenomena before vaccination and remain free of any adverse reactions during the follow up. Clues as to the pathogenic link between the vaccine and specific autoimmune disorders, therefore, could not be established. Cross-reactive immunity was found only after vaccination, though decreasing in magnitude over time with a significant proportion of vaccinated subjects maintaining the anti-viral response but losing that against self. These findings suggest that upon vaccination, induction of an anti-viral response is initially capable of promoting cross-reactive anti-self immune responses, which decrease over time, possibly as a result of peripheral tolerance mechanisms. This scenario may explain why very rarely adverse post-vaccination autoimmune reactions occur . . . .

Id. at 222-23.

Interestingly, the minority of vaccinees who had an anti-myelin reactivity before they received hepatitis B vaccination "almost universally lost this reactivity post-vaccination." *Id.* at 223. The authors speculate that the viral components of the vaccine and particularly the self-mimicking surface antigen sequences "may play a role as altered peptide ligand, i.e., may represent sequences unable to induce cross-reactive responses but able to promote tolerance to a given autoepitope . . . ." *Id.* The authors thought that this mechanism could benefit patients with multiple sclerosis, i.e., hepatitis B vaccine would help them by restoring their tolerance toward myelin antigens. *Id.* The authors suggest further investigation. *Id.*

Petitioner's Ex. 29, Tab C, is "Multiple sclerosis and hepatitis B vaccination: Adding the credibility of molecular biology to an unusual level of clinical and epidemiological evidence" by Y. Comenge and M. Girard, 66 *Medical Hypotheses* 84-86 (2006). The article is basically a protest against the administration of hepatitis B vaccine.

On July 31, 2007, respondent filed four articles following the expert report of Dr. Greenberg. The first article is "Commentary: Sorting the wheat from the chaff: identifying the demyelinating components of the myelin oligodendrocyte glycoprotein (MOG)-specific autoantibody repertoire" by

E. Mathey, et al., 34 *Eur J Immunol* 2065-71 (2004). In the animal model of multiple sclerosis called experimental allergic encephalomyelitis (EAE), myelin oligodendrocyte glycoprotein (MOG) is the only myelin protein known to initiate a demyelinating autoantibody response in test animals. But, in humans, the pathophysiological significance of MOG-specific autoantibodies in MS is controversial because high titer antibody responses to MOG are also detected in many people with non-demyelinating neurological diseases. Another scientist has found that demyelination in a primate model of MOG-induced EAE is mediated by MOG-specific antibodies directed against discontinuous, instead of linear, MOG epitopes. The authors think it may be crucial to segregate pathogenic from non-pathogenic autoantibodies in terms of epitope specificity in order to understand the relevance of MOG-specific responses in human disease.

The authors state:

> Loss of immunological self-tolerance to myelin antigens in genetically susceptible individuals plays a major role in the pathogenesis of multiple sclerosis (MS), a complex inflammatory demyelinating disease of the central nervous system (CNS).

Id. at 2065.

Although doctors refer to MS as a purely T-cell-mediated disease, increasing direct evidence points to antibody-dependent mechanisms (humoral factors) as being involved in disease pathogenesis. *Id.* However, the authors note that there is no evidence at all that antibody is involved in lesion formation in 20-40% of MS patients while in some subtypes of MS (Devic's disease, for example), antibody-mediated effects may play the dominant role in disease pathogenesis. *Id.* In guinea pigs, however, MOG is the target for antibody-mediated demyelination. *Id.* at 2066. Injection of MOG-specific antibodies enhanced demyelination and inflammation, causing a dramatic increase in disease severity in the animals. *Id.* In mice, however, tumor necrosis factor-mediation

plays a role. *Id.* Enhanced B-cell/autoantibody responses to MOG in MS patients and the identification of MOG-reactive antibodies in MS lesions suggest to the authors that MOG is also a major target of demyelinating antibodies in MS. But autoantibody responses to MOG occur not only in MS, but also in many non-demyelinating diseases of the nervous system, which surprised the authors. *Id.* Epitope specificity is the crucial factor determining the pathogenicity of the MOG-specific autoantibody response in a marmoset model of MOG-induced EAE. *Id.*

MOG is a quantitatively minor type 1 membrane glycoprotein incorporated into the outermost surface of the myelin sheath. Demyelinating MOG-specific antibodies recognize this domain. *Id.* MOG is not detectable outside the nervous system. *Id.* The authors state it is therefore not surprising that active immunization with MOG induces a complex autoimmune response and severe EAE in susceptible animals. *Id.* at 2067. Demyelinating antibody responses were directed against discontinuous, rather than linear, epitopes in marmosets. *Id.* In people, the MOG-specific antibody response in MS recognizes a far more complex repertoire of linear epitopes than in marmosets or rodents. Further inquiry is necessary to understand what determines the balance between responses to linear (benign) and discontinuous (demyelinating) MOG B-cell epitopes. *Id.*

The second article filed with respondent's expert Dr. Greenberg's report is "Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein" by K.D. O'Connor, et al., 13 *Nature Medicine* 2:211-17 (2007). The authors found that MOG-specific autoantibodies were in a subset of acute disseminated encephalomyelitis (ADEM) cases, but rarely in adult-onset MS cases, indicating that MOG is a more prominent target antigen in ADEM than in MS. Although myelin basic protein (MBP) is inaccessible in intact myelin, MOG, a minor component of myelin localized on the outer surface of the multilamellar myelin structure, is accessible to

antibodies. *Id.* at 211. Although autoantibodies cause an MS analogue, i.e., EAE, in marmosets, in other animals, EAE occurs without autoantibodies. *Id.* Thus, the pathogenesis of human inflammatory demyelinating diseases such as MS and ADEM is far less certain. *Id.* However, one recipient out of 400 recipients of a CNS-derived rabies vaccine contaminated with MBP developed encephalomyelitis which was strongly correlated with the presence of serum autoantibodies to MBP. *Id.* at 212. Extensive studies in EAE models show that only antibodies that recognize folded MOG protein are pathogenic while antibodies that bind solely to denatured protein or short synthetic peptides fail to induce demyelination. *Id.* The authors developed a new method for identifying autoantibodies and used it to investigate their role in human demyelinating diseases of the CNS. *Id.* They discovered that ADEM represents more than one pathogenic entity by identifying a subset of individuals who had antibody-associated autoimmunity. On the other hand, MOG autoantibodies were identified in serum or cerebrospinal fluid of only rare MS cases and not in individuals with clinically isolated syndrome. *Id.* at 215. MOG is a more prominent target autoantigen in a subgroup of ADEM than in individuals with adult-onset MS. *Id.* at 216.

The third article filed with respondent's expert Dr. Greenberg's report is "Hepatitis B Vaccination and the Risk of Multiple Sclerosis" by A. Ascherio, et al., 344 *NEJM* 5:327-32 (2001). Using a nested case-control study, the authors found no epidemiological result indicating that hepatitis B vaccine was associated with the development of MS. They engaged in this study after studies in France and in the United Kingdom reported a nonsignificant increase in the risk of MS among vaccinees. *Id.* at 327. The results of Ascherio's study are consistent with others in the US and Canada. *Id.* at 331. Although the authors found plausible the causation hypothesis of acute autoimmune reaction to vaccination in susceptible persons soon after vaccination, they doubted it

applicable to MS because demyelinating lesions in the central nervous system likely precede by weeks or months the onset of neurologic symptoms. *Id.* at 332.

The fourth article filed with respondent's expert Dr. Greenberg's report is "Postmarketing Surveillance for Neurologic Adverse Events Reported After Hepatitis B Vaccination. Experience of the First Three Years" by F.E. Shaw, et al., 127 *Amer J Epidemiology* 2:337-52 (1988). The epidemiologic surveillance deals with plasma-derived hepatitis B vaccine, not the recombinant hepatitis B vaccine which petitioner in the instant action received. The authors did not find any epidemiologic association between neurological adverse events and the plasma-derived hepatitis B vaccine.

Respondent submitted three articles (Ex. C) after the hearing to which Dr. Greenberg referred during his testimony. The first article is "Vaccinations and the Risk of Relapse in Multiple Sclerosis" by C. Confavreux, et al., 344 *NEJM* 5:319-26 (2001). The authors' epidemiological analysis of MS patients led them to conclude that hepatitis B vaccine did not appear to cause relapses. *Id.* at 324. The authors used a case-crossover approach instead of a case-control approach, which means there were no control subjects since the patients served as their own controls. *Id.* This allowed the authors to account for the confounding factor that there is a large variability in the course of MS. *Id.* The case-crossover design required, however, that the authors assume that the risk of MS relapse was the same after each vaccination. *Id.* at 324-25. The second assumption was that vaccine exposure was constant over time during the control periods. *Id.* at 325. The authors recognized there was the problem of recall bias since they were comparing exposures at different times. *Id.* The authors opined that one month "was probably the most relevant risk period in this population of patients with multiple sclerosis who had received inactivated vaccines . . . ." *Id.* Relative risk

decreased over time. The patients who were the subjects of this study had been relapse-free for at least 12 months before the relapse of interest. *Id.*

The second article in respondent's exhibit C is "Hepatitis B vaccine and the risk of relapse after a first childhood episode of CNS inflammatory demyelination" by Y. Mikaeloff, et al., 130 *Brain* 1105-10 (2007). The authors conclude that vaccination against hepatitis B or tetanus does not increase the risk of children who already had central nervous system demyelination for developing subsequent MS. *Id.* at 1109. However, they note that there was a lack of power in their study because only six patients relapsed within three years and ten within the entire follow-up period. *Id.* Thus, although the authors could exclude a large increase in risk of relapse and conversion to MS, they could not exclude a smaller increase in risk. *Id.* They comment that most previous studies also did not exclude small increases in the risk of MS. *Id.* at 1105. They criticize the 2004 Hernán study finding an increase in the incidence of MS within three years of hepatitis B vaccination as due to "imprecise case definition or timing, limited statistical power and a lack of validation of vaccination status," citing a 2006 Hernán paper entitled "Recombinant hepatitis B vaccine and multiple sclerosis: the jury is still out." *Id.* and at 1110. They comment that the Confavreux study did not take into account hepatitis B vaccination in the early phase of MS, but evaluated patients solely with long-term MS. *Id.* at 1108. The authors recommend studying an initial episode of demyelination after hepatitis B vaccine in children. *Id.* at 1109.

The third article in respondent's exhibit C is "Vaccinations and Risk of Central Nervous System Demyelinating Disease in Adults" by F. DeStefano, et al., 60 *Arch Neurol* 504-09 (2003). The authors conclude that vaccinations against hepatitis B, influenza, tetanus, measles, or rubella do not increase the risk of MS or optic neuritis. *Id.* at 507. There was a statistically significant

decreased risk of MS or optic neuritis associated with tetanus vaccine. *Id.* The authors describe MS as an autoimmune disease in which unknown environmental factors, including vaccines, may be involved as either a cause or a trigger. *Id.* at 504. The authors state that vaccinations that occur shortly before initial clinical symptoms would be most likely acting as triggers of clinical disease expression in individuals who already had an underlying disease process. *Id.* at 507. But the authors did not find any increased relative risk regardless of the timing of vaccination, indicating that vaccines do not cause or trigger MS or optic neuritis. *Id.*

TESTIMONY

Dr. Carlo Tornatore testified for petitioner. Tr. at 3. He directs the multiple sclerosis center at Georgetown. Tr. at 4. On March 26, 1999, petitioner received her first hepatitis B vaccination. Tr. at 6. Three days later, she had left hand weakness that subsequently progressed over the next two weeks. *Id.* She saw Dr. Miguel Rivera 16 or 17 days after the vaccination, on April 12, 1999, with a complaint of tingling of both lower extremities and numbness and weakness of her left arm with unusual abdominal contractions. *Id.* She also reported a problem with her left leg beginning on March 30, 1999 and initially experienced numbness in the tips of the fingers of her left hand radiating upwards with lack of coordination of her left arm. Tr. at 7.

On examination, Dr. Rivera found irregular movements of her fingers, astereognosis, basic difficulty with space in the left hand, hyperactive reflexes, and a Babinski reflex on the left, as well as some tremors and dystaxia in the arm. *Id.* This was basically a presentation of someone with a problem in the spinal cord, involving three extremities. *Id.* Dr. Rivera said petitioner probably had a low intracranial lesion or a high spinal cord lesion. *Id.* Dr. Tornatore agreed with Dr. Rivera's assessment. *Id.*

On April 14, 1999, she had a cervical spinal MRI showing that there was a fairly large enhancement of the cervical cord at the C2-3 to C4 levels. *Id.* It went across almost a full vertebral body and there was edema or swelling around it. *Id.* This enhancement indicates that the lesion happened quickly. *Id.* The blood-brain barrier was broken down. Tr. at 8. The lesion was fairly new and was the cause of her symptoms on March 29th. *Id.* The lesion could not have been there previously. *Id.* This lesion was unrelated to petitioner's September 11, 1995 complaint of weakness of her left hand because petitioner had a prior cervical spine MRI on February 10, 1997 which showed no cord abnormality. Tr. at 8-9. It did show she had some arthritic changes in her neck. Tr. at 9. Those changes could cause numbness and weakness in her arm. *Id.*

On February 8, 1997, petitioner had a normal MRI of her brain. Tr. at 10. There is no evidence that she had any demyelination at that time. *Id.* On December 31, 1998, petitioner complained of right leg weakness and tingling which indicated spasm, but no neurologic dysfunction. Tr. at 10-11. She had a lumbosacral spasm. Tr. at 11. Dr. Tornatore agrees with the diagnosis of sciatica by Dr. Bartemus in December 1998 and Dr. Van Eaton in January 1999. *Id.*

In response to respondent's expert Dr. Greenberg's statement in his report that petitioner would not have whole leg numbness due to sciatica and he thought she had a thoracic core demyelinating lesion instead, Dr. Tornatore disagreed. Tr. at 12. He said that sciatica can cause numbness extending down the back of the leg. Tr. at 12-13. If petitioner had something wrong in the cervical cord, she would not have had lumbar spasms. Tr. at 13. Petitioner never had an MRI of her thoracic spine. *Id.* None of petitioner's treating physicians thought she had a lesion in the thoracic spine. Tr. at 14, 16-17.

Also on December 31, 1998, petitioner's reflexes were hypoactive. Tr. at 17. If she had had central nervous system disease at the time, her reflexes should have been hyperactive. *Id.* When she did have problems in the cervical spine, her reflexes changed and they were hyperactive on the left. *Id.*

Dr. Tornatore stated that the contemporaneous medical records demonstrate problems referable to the lumbar spine before the vaccination. Tr. at 22. But if we assume that petitioner had some previous demyelination in her spinal cord, it got significantly worse after the vaccination and the vaccine significantly aggravated it. *Id.* After the vaccination, petitioner had significant demyelination in the cervical spine which was new at that time. *Id.*

With reference to the appropriate temporal interval between vaccination and onset, Dr. Tornatore referred to the Bogdanaos article (Appendix B, Ex. 29). Tr. at 24. Dr. Greenberg had told respondent's counsel that he thought three days (Dr. Tornatore's testimony) or four days (the medical records) was too soon for onset and he would not accept less than a week for an appropriate onset interval. *Id.* Dr. Tornatore stated that even in the normal population, there are T-cells that recognize self-antigens even though these people do not have MS. Tr. at 25. These people's immune systems are primed. When you give them a vaccination, you get almost an anamnestic response, which is what petitioner had. *Id.* Even in people who do not have demyelination, they have antibody responses to MOG (myelin oligodendrocyte glycoprotein). Tr. at 26, 28. Dr. Tornatore said it is biologically plausible in someone who has these types of antibodies circulating without clinical disease to have a quick immune response when antigenically challenged. Tr. at 26-27.

Since petitioner herein had not received hepatitis B vaccine before her first vaccination, what primed her was a peculiarity of her immune system to fail to ward off the autoimmune response

which would have kept her T-cells and B-cells from recognizing her self-antigen, but they did not cause disease because her immune system still had enough capacity to prevent the disease. Tr. at 27. Dr. Tornatore said we know there is a group of patients primed for autoimmune disease and all they need is something such as a vaccine to cause overt disease. Tr. at 27-28.

Dr. Greenberg in his report questioned the concept of homology as applied to the hepatitis B surface antigen in the vaccine and the amino acid sequences exposed on the myelin of the spinal cord where petitioner had her first lesion. Tr. at 28-29. But the literature in the record shows that people receiving rabies vaccine contaminated with myelin basic protein still developed encephalomyelitis even though their own myelin basic protein was not exposed. Tr. at 31. Experimentation with animals results in demyelination even though epitopes in MOG which are similar to those in hepatitis B vaccine are not on the animals's cell surface. Tr. at 32.

Dr. Tornatore said that vaccine reactions are extremely rare. Tr. at 34. Epidemiologic studies are never going to be able to say something does not happen. Tr. at 35.

He stated that petitioner's transverse myelitis was the first symptom of her MS. Tr. at 37. Dr. Tornatore's opinion was that, had she not received hepatitis B vaccine, she would not have had TM. Tr. at 42. His answer is based on his review of the literature, his background as a neurologist, and the reasonable mechanisms he discussed. Tr. at 43. In addition, petitioner's MRI subsequent to her hepatitis B vaccination showed an acute formation of a lesion rather than a chronic process whereas prior MRIs had not demonstrated any problem in the cervical spine or in the brain. *Id.*

On cross-examination, Dr. Tornatore stated that petitioner's pre-vaccination problems were explainable by lumbar issues and neck problems which were structural problems. Tr. at 44. Two of

petitioner's treating doctors documented lumbar spine spasms before vaccination. *Id.* Arthritis could account for the pain in her arm pre-vaccination. Tr. at 45.

Dr. Benjamin Greenberg testified for respondent. Tr. at 47. He is an assistant professor at Johns Hopkins School of Medicine, a member of the division of neuroimmunology and neurological infectious disease, and co-director of the transverse myelitis center there, which is the only center in the world dedicated to treating patients with TM. Tr. at 47-48. He is also on the full-time faculty with the MS Center at Johns Hopkins. Tr. at 48.

His opinion is that petitioner had a pre-existing demyelinating disorder that started long before she received hepatitis B vaccine, and that hepatitis B vaccine did not cause her MS. Tr. at 48-49. Petitioner's original diagnosis before hepatitis B vaccination was lumbosacral spine disease, but her physician Dr. Bartemus doubted this and requested she have a connective tissue disorder work-up. Tr. at 49-50. This would be highly unusual for lumbosacral back disease which is a mechanical event, not an immune-mediated process. It is a disc pressing on a nerve. Tr. at 50. Dr. Greenberg thinks petitioner had TM or a thoracic TM before she was vaccinated. *Id.* More than half of Dr. Greenberg's patients who have early TM were told by their physicians that they had a pinched nerve. Tr. at 51.

Dr. Greenberg testified that Dr. Bartemus did not document an objective sensory examination when petitioner came to him with unsteadiness in the lower extremities and loss of sensory function for four weeks. Tr. at 52. Deep tendon reflexes that are hypoactive, as petitioner's were, are consistent when someone is in the beginning stage of transverse myelitis. Tr. at 52-53. Sciatica does not include the whole leg, as in petitioner's case. Tr. at 53. She was misdiagnosed with sciatica which causes sensory loss radiating pain to the ankle, which petitioner did not have. Tr. at 54. What

petitioner had was localized back pain which is very common in TM. *Id.* This is one of the most common misdiagnoses he sees in TM, especially a thoracic lesion, because it can look like common sciatica when it is an intramedullar and intraspinal cord lesion. Tr. at 54-55. Dr. Greenberg thinks that petitioner's presentation was classic for a small, thoracic, demyelinating lesion in the spinal cord. Tr. at 55. However, Dr. Greenberg said he had to hedge the diagnosis because petitioner never had a thoracic MRI. *Id.* We may never know. *Id.* His opinion is that Dr. Van Eaton's and Dr. Bartemus's records support a diagnosis of a spinal cord event occurring before petitioner received hepatitis B vaccine. Tr. at 59. He thinks the onset was in late 1998. Tr. at 60.

Dr. Greenberg agreed with Dr. Tornatore that the enhancing gadolinium on MRI of petitioner's cervical spine after her vaccination showed an onset of the cervical lesion from weeks to maybe one month. Tr. at 61. This was a separate lesion from the thoracic lesion that Dr. Greenberg opined she had before the vaccination. *Id.* The thoracic lesion was never imaged. *Id.* He thinks they are two separate events and, therefore, when she was diagnosed with TM, she really had MS because she already had two lesions separated over space and time. *Id.*

Dr. Greenberg did not believe that hepatitis B vaccine caused petitioner's cervical lesion. Tr. at 65. Epidemiologic studies do not show a link. *Id.* In discussing the Bogdanos article, Dr. Greenberg said that when a positive response was created to MOG in a dish, the response was to seven or 10 amino acids that happen to be in MOG. Tr. at 69. Rather than a response to MOG, it is a response to peptide. Tr. at 70. Seven amino acids are not a complete protein. *Id.* The authors of the Bogdanos study even mention that hepatitis B vaccine might benefit patients with MS. Tr. at 71. In animals, when you flood the system with protein, you induce a tolerant state and the animals no longer attack that target. Tr. at 72. This has to do with feedback loops in the immune system, i.e.,

the difference between recognizing self and not self. *Id.* This is a theory and there are 10 different theories to explain why flooding a person who has autoimmune disease with the target of that disease lowers the risk of that disease. Tr. at 73.

Dr. Greenberg admitted that there were many variables at play at any given time, including the substance to which someone is exposed, the dose of exposure, the timing, and other issues. Tr. at 77. If there is a one in a billion event and we study 999 million patients, we may miss the event. Tr. at 78. Dr. Greenberg testified that molecular mimicry is an excellent theory. *Id.* However, he does not believe it is relevant in hepatitis B and MS. *Id.* One would assume, if the theory were applicable, that the rates of MS would go up with the wild hepatitis B infection. *Id.* If the vaccine could increase the incidence of MS, the infection would surely do so. Tr. at 78-79. However, the epidemiologic studies show the opposite. Tr. at 79. The highest rates of hepatitis B in the world occur in Southeast Asia. But that area also has the lowest rate of MS in the industrialized world. *Id.* Dr. Greenberg asked why, in the Bogdanos paper, the number of people with pre-existing reactive antibodies did not come down with autoimmune disease. *Id.* It takes more than an antibody reacting against 12 amino acids to cause MS. *Id.*

Dr. Greenberg admitted that most cases of MS occur in people who live further from the equator. Tr. at 80. There are huge rates of MS in Australia. *Id.* There is more and more evidence that Vitamin D and a couple of other factors make the difference in the rate of MS. *Id.* There is a theory that canine distemper virus is associated with MS and keeping dogs inside longer in winter time in northern latitudes causes more exposure to the virus. Tr. at 81. There is also a preponderance of data that Epstein Barr virus is associated with MS. *Id.* Not only the exposure but the timing of the exposure is important in prompting the disease. *Id.* This is a complicated issue and

we are picking at the surface, trying to apply theories to it. *Id.* He admitted that his statement that he would expect to see more MS in Southeast Asia because of their high rate of hepatitis B infection if the two had any association was a little too facile, but he also said that equatorial distribution is only one factor in association because there are huge rates of MS in Texas and Mississippi which are closer to the equator. Tr. at 82. There are other demyelinating diseases in Japan. *Id.* He insisted that there should be more people in Southeast Asia coming down with MS if 50 percent of people have antibodies that recognize MOG as defined in Bogdanos' paper. Tr. at 82-83. When hepatitis B vaccine was administered to people who already had MS or a demyelinating attack, they did not have an increased rate of relapses. Tr. at 85. When hepatitis B vaccine was administered to children with demyelinating attacks, they did not have an increased incidence of developing MS. *Id.* We should see a blip on the radar in these two enriched populations and we do not. Tr. at 86. Although Dr. Greenberg thinks that the theory is sound, the data does not support the theory that hepatitis B vaccine and MS are related. *Id.*

The undersigned asked Dr. Tornatore if he had any response to Dr. Greenberg's discussion of the two epidemiologic articles showing that adults with MS did not have a higher rate of relapse after receipt of hepatitis B vaccine and children with demyelinating disease did not have MS after receipt of hepatitis B vaccine. Tr. at 89. Dr. Tornatore said there are multiple antigens involved in MS. It is a very heterogeneous disease and no one knows what causes MS. *Id.* We are talking about a very rare event. Tr. at 90. We do not have the technology to prove that something causes MS or the scientific basis for testing any individual antigen. Tr. at 91.

Dr. Greenberg disagreed with Dr. Tornatore because the epidemiologic studies do not show that people with a risk for demyelinating disease have a higher rate of that disease after receiving

hepatitis B vaccine. Tr. at 94. He described the Hernán study linking hepatitis B vaccine to MS as merely a hypothetical because it was published in a journal called "Medical Hypotheses". Tr. at 94. He thought there might have been a contaminant protein, one of the polymerases, and not the hepatitis B surface antigen, that caused the MS in France and that it was an epiphenomenon unique to France because of a poor manufacturing technique. Tr. at 95.

When the undersigned asked Dr. Greenberg to comment on the plausibility of Dr. Tornatore's biological theory of antigen specificity underlying his opinion of hepatitis B vaccine causing MS, Dr. Greenberg replied: "I think it's biologically plausible that there are individuals who have specific triggers." Tr. at 96. He continued that "somebody got a vaccine and had some symptoms. They got reexposed, and the symptoms got more magnified. We see that, even with somebody exposed to the vaccine, and then they have a urinary tract infection, or they don't sleep well the night before, or a variety of things other than just the molecular events after the vaccination." Tr. at 98.

Dr. Tornatore stated that the ideal situation would be to take anyone who had demyelination after hepatitis B and then rechallenge him because then you have the specificity. Tr. at 100. Dr. Greenberg stated that Dr. Tornatore's theory was plausible: you need a select group. *Id.* The studies already done argue against the phenomenon, but the theory is plausible. Tr. at 100-01. There could be antigen specificity and there may be a subset of patients who are uniquely at risk based on certain exposures. Tr. at 101. Dr. Greenberg agreed with the theory but did not think the evidence supported it. *Id.* Dr. Greenberg has not seen antigen specificity in any study. Tr. at 101-02. However, even if there are people who are more susceptible to the effects of hepatitis B vaccine, we do not know if petitioner is one of them. Tr. at 103.

Dr. Greenberg also said the timing of petitioner's onset of three days after the hepatitis B vaccination is too short for causation. Tr. at 103-04. In the animal analogue to MS called EAE (experimental autoimmune [or allergic] encephalomyelitis), the onset of EAE is six to 10 days after immunization with MOG or with animal spinal cord and adjuvant. Tr. at 104. Not only do you need time to develop antibodies, but also for them to cross the blood-brain barrier into the tissue. *Id.* You do not see an antibody response in people within three days of hepatitis B vaccination. Tr. at 105. Seven days to a mouse would be a couple of months to humans. *Id.* Dr. Greenberg thought it would take at least two months for the onset of clinical symptoms of MS after hepatitis B vaccination if the latter caused MS. *Id.* Dr. Greenberg admitted that a prior stimulus would shorten the onset to the four- to five-day range. Tr. at 128.

Dr. Greenberg stated petitioner's first clinically identified symptom was two months prior. Tr. at 105. There was probably something in play for some amount of time before that first symptom because the first symptom is a manifestation of the biology. Tr. at 105-06. He stated petitioner's demyelination occurred weeks to months earlier than her April 14, 1999 MRI. Tr. at 106.

Dr. Tornatore responded to Dr. Greenberg's testimony on timing by stating that the animals in whom it took six to 10 days for a symptom of EAE had not been previously immunologically primed. Tr. at 107. Once someone has been primed, the response is very quick. Tr. at 108. He called this an anamnestic response to an antigen. *Id.* Dr. Tornatore said that three days is not too short for a causative relationship if someone has autoimmune T-cells circulating that are primed to respond to that antigen. *Id.* The B-cells act in response to the T-cells. *Id.* Dr. Tornatore said that petitioner had already been primed before receiving her first hepatitis B vaccination. Tr. at 108-09.

Dr. Greenberg said, "I think the theory is absolutely plausible. I don't think any study that's been done proves it." Tr. at 109.

In answer to a question on cross-examination, Dr. Greenberg stated that data bears out that, in MS, as a person develops and his or her immune system matures, there are time points when his or her immune system differs from others' immune systems. Tr. at 111. He believes that petitioner had thoracic demyelination before she received hepatitis B vaccination even though no MRI was done of her thoracic spine. Tr. at 115-16. He disagrees with petitioner's treating doctors that, before her vaccination, petitioner's low back pain was due to lumbosacral strain. Tr. at 120. He agreed that on MRI, for a lesion to enhance under gadolinium, the lesion would only be as old on average as weeks to a month. Tr. at 121. The average age of the lesion would be three to four weeks. *Id.* Petitioner had a cervical spine MRI on April 14, 1999 which had an enhancing lesion. *Id.* Within that three- to four-week period, she had a hepatitis B vaccination. *Id.*

Dr. Greenberg stated that the cause of MS is a combination of genes and environment. Tr. at 124. Timing also plays a role. Tr. at 125. MS symptoms are predominantly an inflammatory-mediated event. *Id.* MS patients are treated with immunomodulators. Tr. at 126. Dr. Greenberg's argument about timing derives from the laboratory and the published literature. Tr. at 130. Animals need about one week to have inflammation after immunization with MOG. *Id.* To attempt to explain why Dr. Roland Martin, a well-known neuroimmunologist whom Dr. Greenberg has met at a conference, testified at the Omnibus proceeding that he would expect a reaction in humans from three to 30 days after vaccination (if Dr. Martin accept causation), Dr. Greenberg opined that Dr. Martin may have been talking about a pathological example where you would see a couple of immune cells that showed up (if you sacrificed an animal) on day 4 while the animal is still perfectly

healthy without demyelination. Tr. at 129-30. He agrees with Dr. Martin that you could see cells four days after immunization, but you would not see any symptoms or profound demyelination until you have seven more days pass. Tr. at 131.

DISCUSSION

This is a causation in fact case. To satisfy her burden of proving causation in fact, petitioner must prove by preponderant evidence "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Secretary of HHS, 418 F. 3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Secretary of HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992):

> A persuasive medical theory is demonstrated by "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" the logical sequence being supported by "reputable medical or scientific explanation[,]" *i.e.*, "evidence in the form of scientific studies or expert medical testimony[.]"

In Capizzano v. Secretary of HHS, 440 F.3d 1274, 1325 (Fed. Cir. 2006), the Federal Circuit said "we conclude that requiring either epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect is contrary to what we said in Althen . . . ."

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, 956 F.2d at 1149. Mere temporal association is not sufficient to prove causation in fact. *Id.* at 1148.

Petitioner must show not only that but for the vaccine, she would not have had TM and MS, but also that the vaccine was a substantial factor in bringing about her TM and MS. Shyface v. Secretary of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

Close calls are to be resolved in favor of petitioners. Capizzano, 1440 F.3d at 1327; Althen, 418 F.3d at 1280. *See generally*, Knudsen v. Secretary of HHS, 35 F.3d 543, 551 (Fed. Cir. 1994).

In essence, the special master is looking for a medical explanation of a logical sequence of cause and effect (Althen, 418 F.3d at 1278; Grant, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen, 35 F.3d at 548-49). To the undersigned, medical probability means biologic credibility or plausibility rather than exact biologic mechanism. As the Federal Circuit stated in Knudsen:

> Furthermore, to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program. The Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal "compensation program" under which awards are to be "made to vaccine-injured persons quickly, easily, and with certainty and generosity." House Report 99-908, *supra*, at 3, 1986 U.S.C.C.A.N. at 6344.
>
> The Court of Federal Claims is therefore not to be seen as a vehicle for ascertaining precisely how and why DTP and other vaccines sometimes destroy the health and lives of certain children while safely immunizing most others.

35 F.3d at 549.

The Federal Circuit stated in Althen, 418 F.3d at 1280, that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body."

The Federal Circuit in Capizzano emphasized that the special masters are to evaluate seriously the opinions of petitioner's treating doctors. 440 F.3d at 1326.

As for epidemiological support for causation, the Federal Circuit in Knudsen ruled for petitioners even when epidemiological evidence directly opposed causation from a vaccine. In Knudsen, even though epidemiological evidence supported the opposite conclusion, i.e., that viruses were more likely to cause encephalopathy than vaccinations, the Federal Circuit held that that fact alone was not an impediment to recovery of damages. In Knudsen, the Federal Circuit stated:

> The bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies is not evidence that in a particular case an encephalopathy following a DTP vaccination was in fact caused by a viral infection present in the child and not caused by the DTP vaccine.

35 F.3d at 550.

In Stevens v. Secretary of HHS, No. 99-594V, 2006 WL 659525 (Fed. Cl. Spec. Mstr. Feb. 24, 2006), the undersigned ruled that hepatitis B vaccine can cause TM and did so in that case. The onset intervals after Ms. Stevens' two hepatitis B vaccinations were eight and nine days, appropriate temporal periods for an immune reaction. Respondent's expert, Dr. Roland Martin, testified that the appropriate onset interval, if a vaccination were to cause an acute reaction, would be a few days to three to four weeks. *Id.* at *18.

In Werderitsh v. Secretary of HHS, No. 99-310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006), the undersigned ruled that hepatitis B vaccine can cause MS and did so in that case. Onset of visual difficulties was a few days to one week post-vaccination.

In the instant action, petitioner had the onset of left-handed numbness, a neurologic symptom, four days after vaccination. She was eventually diagnosed with TM and, as her demyelinating condition progressed, she developed lesions in the brain and visual difficulties,

resulting in her being diagnosed with MS. The definition of MS is lesions occurring over space and time.

Petitioner's expert Dr. Tornatore testified that it was biologically plausible, using the theory of molecular mimicry, that hepatitis B vaccine caused petitioner's TM based on the newness of her cervical spinal cord lesion after vaccination. The gadolinium enhancement of her cervical spinal lesion in an MRI done within a month of her vaccination was proof that this lesion was new. Before vaccination, petitioner had undergone both brain and cervical spinal MRIs, both of which did not show lesions or demyelination. The reason petitioner had undergone brain and cervical spinal MRIs before vaccination was that she had a history since 1995, four years before vaccination, of neurologic symptoms which two treating doctors diagnosed as due to sciatica or lumbosacral sprain. A number of her physical issues occurred after an automobile accident in 1995.

Interpreting petitioner's pre-vaccination neurologic symptoms was a matter of dispute between Dr. Tornatore and respondent's expert Dr. Greenberg. Whereas Dr. Tornatore agreed with petitioner's treating doctors that the cause of these pre-vaccination neurologic symptoms was structural, Dr. Greenberg opined that petitioner actually had MS before her vaccination. He criticized the lack of thoroughness of her medical examinations before vaccination and was particularly concerned that her doctors did not have petitioner undergo a thoracic spinal MRI because he believed that if she had had a thoracic spinal MRI, it would have shown a lesion there.

The Federal Circuit in Capizzano has stressed the importance of the special masters' heeding the diagnoses of petitioner's treating doctors. Here, petitioner's treating doctors opined that her neurologic symptoms before vaccination were due to structural spinal problems. Dr. Tornatore agrees with them. The Federal Circuit in Althen and Capizzano also said that close calls are to be

resolved in favor of petitioner. The undersigned holds that petitioner's pre-vaccination symptoms were not due to MS but due to structural problems in her spine.

As for whether the medical theory about which Dr. Tornatore testified is biologically plausible, Dr. Greenberg testified, after being questioned twice on this point, that Dr. Tornatore's theory was biologically plausible and absolutely plausible. This agreement on the biologic plausibility causally connecting hepatitis B vaccine to petitioner's TM and MS satisfies petitioner's burden of proving the first criterion of Althen.

Dr. Tornatore also testified that there was a logical sequence of cause and effect between the vaccination and petitioner's TM and MS.

As for timing, Dr. Greenberg thought at first that two months would be an appropriate time if he accepted that hepatitis B vaccine causes demyelinating disease. He later agreed that someone could have the first cells of immune damage in four days although this would not be clinically noticeable. This change in his consideration of temporal appropriateness occurred when Dr. Greenberg tried to interpret why Dr. Roland Martin, respondent's expert during the Omnibus proceedings, testified that the appropriate time interval between hepatitis B vaccination and onset of demyelinating disease would be between three and 30 days (if Dr. Martin accepted that such a causal connection exists). Dr. Greenberg stated that sacrificing a research animal (after using MOG immunization to create the animal analog of MS called EAE) at four days would show lesions even though the animal was clinically normal. Petitioner's onset of left-hand numbness four days after hepatitis B vaccination in the instant case puts her squarely within the time period that Dr. Martin testified was appropriate for a causal relationship.

The undersigned has great respect for respondent's expert Dr. Greenberg and understands his reluctance to draw a causal thread between hepatitis B vaccination and demyelinating diseases based on his understanding of animal research and epidemiologic studies that have not generally shown a causal relationship. But the special masters are in the legal profession, not in the medical profession, and the Federal Circuit's decisions determine the special masters' interpretation of the evidence in Vaccine Program cases. The Federal Circuit, first in Knudsen in 1994, stated expressly that the lack of epidemiologic support for a petitioner's allegations is not an impediment to prevailing in a Vaccine Act case. The Federal Circuit reiterated this point strongly in Althen in 2005, repeated in Capizzano in 2006.

Dr. Greenberg's opinion of no causality was not only based on lack of epidemiologic support, but also on the lack of transferability of animal research to humans. Proving the applicability of animal research to a theory that hepatitis B vaccine causes TM and MS in humans is not essential for petitioner to satisfy her burden of proof as long as petitioner satisfies the three criteria of Althen.

The medical literature that petitioner filed provides some support for Dr. Tornatore's medical theory, particularly the Bogdanos article which shows that hepatitis B vaccine caused anti-myelin reactivity in vaccinees but without producing demyelinating disease in them. However, in the minority of vaccinees who had prior anti-myelin reactivity before vaccination, administration of the vaccine caused them to lose their anti-myelin reactivity, a distinct benefit that led the authors to suggest that hepatitis B vaccine might help people who already had MS by restoring their tolerance to myelin antigens. They suggested further investigation. The relevance of the Bodganos article is in the authors' showing that hepatitis B vaccine affects anti-myelin reactivity. Beyond that, application of that effect to individual cases of demyelinating disease is limited.

As long as petitioner proves a biologically plausible medical theory, a logical sequence of cause and effect, and appropriate timing, petitioner has satisfied her burden of proof. When Dr. Greenberg stated that Dr. Tornatore's medical theory causally connecting hepatitis B vaccine to petitioner's TM and MS was biologically plausible and absolutely plausible, his statements exceeded the requirement that petitioner prove biologic plausibility by a preponderance of the evidence (which means more likely than not). This is the rare case in which the experts from both sides agreed that petitioner's medical theory is biologically plausible. Petitioner has proved a logical sequence of cause and effect, and appropriate temporal interval between vaccination and onset.

Dr. Tornatore testified that, without the vaccine, petitioner would not have had TM and MS.

Petitioner has proved the three criteria for causation in fact: (1) a biologically plausible medical theory causally connecting the vaccine with her injury; (2) a logical sequence of cause and effect; and (3) a medically appropriate time frame between vaccination and injury. Petitioner has proved causation in fact. Since the undersigned has held that petitioner did not have demyelinating disease before her hepatitis B vaccination, deciding her alternate allegation of significant aggravation of a preexisting demyelinating disease is unnecessary.

CONCLUSION

Petitioner is entitled to reasonable compensation. The undersigned hopes that the parties may reach an amicable settlement, and will convene a telephonic status conference soon to discuss how to proceed in resolving the issue of damages.

IT IS SO ORDERED.

September 24, 2008
DATE

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