OFFICE OF SPECIAL MASTERS
No. 99-319V
May 26, 2006
For Publication

DOROTHY WERDERITSH,	*	
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Petitioner,	*	
	*	
v.	*	Entitlement; hepatitis B vaccine and multiple sclerosis
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SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Clifford J. Shoemaker, Vienna, VA, for petitioner.
James A. Reistrup, R. Lynn Harris, Alexis B. Babcock, Washington, DC, for respondent.

MILLMAN, Special Master

DECISION[1]

This case was one of four paradigm cases tried as part of the Hepatitis B-Neurological Demyelinating Omnibus Proceeding described in Stevens v. Secretary of HHS, No. 99-594V, 2006 WL 659525, at *1-*3 (Fed. Cl. Spec. Mstr. Feb. 24 2006). For an overview of the proceedings, please see the first three pages of Stevens. This case was to represent those

[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.

petitioners with multiple sclerosis (MS) who allege that hepatitis B vaccine caused or exacerbated their illness. The undersigned has already held that hepatitis B vaccine can cause transverse myelitis (TM) (Stevens), and Guillain-Barre Syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) (Gilbert v. Secretary of HHS, No. 04-455V, 2006 WL 1006612 (Fed. Cl. Spec. Mstr. Mar. 30, 2006)).

The fourth case, also dealing with GBS (Peugh v. Secretary of HHS, No. 99-319V) is still pending because Mr. Peugh died from hypertension after the hearing. Petitioner has the burden of proving Mr. Peugh's death was causally related to his GBS. Hodges v. Secretary of HHS, 9 F.3d 958 (Fed. Cir. 1993); Hellebrand v. Secretary of HHS, 999 F.2d 1565 (Fed. Cir. 1993). In an unpublished Order dated April 21, 2006, which is posted electronically on the website of the Office of Special Masters, the undersigned held that hepatitis B vaccine did cause Mr. Peugh's GBS with spinal cord involvement and ordered petitioner to provide an expert opinion that Mr. Peugh's vaccine injury caused his demise.

Petitioner in the instant action filed a petition on May 18, 1999, under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that her first and second hepatitis B vaccinations caused her an unspecified injury, later specified as MS. No medical records accompanied the petition.

The case was initially assigned to the undersigned on May 18, 1999. On August 3, 1999, the chief special master Gary Golkiewicz transferred this case to him. Petitioner failed to file medical records and, on April 3, 2000, switched counsel to the current counsel.

On April 5, 2001, the chief special master reassigned the case back to the undersigned. Petitioner's counsel still had not filed medical records and, on July 31, 2001, moved for authority

to issue a subpoena for the records, which the undersigned granted on August 8, 2001. On August 27, 2001, the undersigned issued an Order stating that if petitioner did not file records by February 8, 2002, the undersigned would dismiss the case.

On January 7, 2002, petitioner filed the first of her medical records. On March 29, 2002, petitioner filed three witness statements. On April 5, 2002 and May 10, 2002, petitioner filed more medical records. On December 5, 2002, the chief special master reassigned the case back to himself as part of the hepatitis B-demyelinating Omnibus proceeding.

On May 7, 2003, the chief special master transferred this case together with the other hepatitis B-demyelinating Omnibus proceeding cases to former special master Margaret M. Sweeney. Further records were filed as well as expert reports. Former special master Margaret M. Sweeney held a hearing on October 13-15, 2004. Further motions and briefings are described in the Stevens decision. See especially Stevens, at *2. On December 14, 2005, former special master Sweeney was sworn in as a judge of the United States Court of Federal Claims.

On January 11, 2006, the chief special master reassigned the case to the undersigned.

FACTS

Petitioner, a nurse, was born on May 12, 1959.

On November 11, 1992, she received her first hepatitis B vaccination. On December 16, 1992, she received her second hepatitis B vaccination. Med. recs. at Ex. 3, p. 1.

On January 22, 1993, petitioner saw Dr. Scott W. Hoyer, a neurologist, because of left body and leg numbness. Beginning the prior Saturday (January 16, 1993), petitioner noted some left-sided body numbness which had been slowly progressive. Since Monday or Tuesday, it had involved her left leg. Since Wednesday, she had noted difficulty knowing when her bladder was

full and noticed some decreased sphincter control on urination. There were no bowel difficulties. She felt her left leg was heavier than the right and somewhat uncoordinated. Her left arm and face were not involved.

Over the prior ten years or so, she had intermittent visual disturbances with partial loss of vision to one side, probably the left but also possibly the right. (She did not remember.) The last episode occurred one month previously when, for one-half hour, she had a left hemianopsia[2] with blurring of vision and decreased vision to the left side involving both eyes. This was associated with some bright spots over to that side which spontaneously cleared. She did not have any significant headache. She has had dull headaches associated with these episodes in the past. She had two hepatitis B vaccinations. Med. recs. at Ex. 2, p. 49 (also Ex. 3, p. 3).

On physical examination, petitioner had mild discoordination of the left lower extremity. She had mild proximal and distal weakness involving the left lower extremity and a mild left limp. Her plantar responses were downgoing. Petitioner felt that light touch and pin prick were decreased between 50% and 75% for the left leg involving the L3, L4, L5, and S1 dermatomes. Dr. Hoyer's assessment was left ipsilateral spinal cord symptoms at the T4, T6 level. He had to rule out the possibility of extrinsic spinal cord or intrinsic spinal cord compression as well as inflammatory TM or MS given her recent left hemianopsia with previous problems with transient visual disturbances (which could represent migraines). Med. recs. at Ex. 2, p. 9.

On January 22, 1993, petitioner had an MRI of her thoracic spine and brain. Med. recs. at Ex. 2, p. 2 (also Ex. 3, p. 13). Dr. Mark C. Arvin wrote that her thoracic spine was essentially

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[2] Hemianopsia is a synonym of hemianopia which means loss of vision for one half of the visual field of one or both eyes. Stedman's Medical Dictionary, 27th ed. (2000) at 798.

normal. As for her head, there was at least one and possibly a small second white matter lesion with the more prominent of the two being just lateral to the trigone of the right lateral ventricle. This was suspicious for MS due to her age and the location of the lesion on the right. *Id.*

On January 28, 1993, petitioner went to St. Elizabeth Hospital Medical Center. Dr. Hoyer recorded that she began noticing two weeks previously numbness in her left torso which spread to her left lower extremity and caused difficulty walking. She also had a history of some intermittent visual field deficits that sounded migrainous, occurring off and on over the years with the last approximately two months earlier.

Protein electrophoresis demonstrated some oligoclonal banding in the gamma globulin region and immunophoresis demonstrated kappa and lambda chains. Med. recs. at Ex. 2, p. 43 (also Ex. 3, p. 8). Over the weekend, petitioner felt she had worsened and had intermittent problems with incontinence. The presumptive diagnosis was MS with a partial Brown-Séquard syndrome.[3] *Id.*

Petitioner was dismissed from St. Elizabeth on February 2, 1993 with a discharge diagnosis of MS and monoparesis of the left lower extremity secondary to MS. Med. recs. at Ex. 2, p. 45. She was given high doses of Solu-Medrol. She was discharged on AFO. *Id.*

On February 7, 1993, petitioner returned to St. Elizabeth with urinary retention causing pain. Med. recs. at Ex. 2, p. 50. Dr. Dana S. Pfaff wrote that petitioner had no voiding

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[3] "The *Brown-Sequard syndrome* is an eponym given to a hemicord syndrome consisting of ipsilateral mono- or hemiplegia, accompanied by ipsilateral loss of joint position and vibration sense, with contralateral loss of pain and temperature (spinothalamic) sensation. The segmental level for pain and temperature loss is sometimes one or two levels below the anatomic lesion. Segmental signs, such as radicular pain, muscle atrophy, or decreased tendon reflexes when they occur, are often unilateral." Harrison's Principles of Internal Medicine, 12th ed., Vol. 2 (1991), at 2082.

symptoms until about three weeks previously when her MS became severe. *Id.* She was discharged on February 10, 1993 with a diagnosis of MS, myelopathy, neurogenic bladder, and phlebitis. Med. recs. at Ex. 2, p. 47 (also Ex. 3, p. 19).

On February 9, 1993, petitioner had an MRI done of her lumbar spine. Dr. Arvin found mild facet degenerative changes at L4-L5, but no evidence of disc herniation or nerve root compression. Med. recs. at Ex. 2, p. 3 (also Ex. 3, p. 18).

On February 10, 1993, petitioner had an MRI done intracranially and of her cervical and thoracic spines. Dr. Jeffrey S. Cahoon wrote there were two areas of focally increased T-2 signal located just laterally to the optic radiations on the right. The largest of the two was located more inferiorly and measured 7 x 6 mm. in size. They could be consistent with vasculitis or MS. The cervical and thoracic spine appeared normal. Med. recs. at Ex. 2, p. 4 (also Ex. 3, p. 17).

On February 12, 1993, Dr. Hoyer wrote a note that petitioner had been discharged from the hospital on February 10, 1993 with a diagnosis of MS with a monoparesis of the left lower extremity and a hypotonic neurogenic bladder. On examination, petitioner had a monoparesis of the left lower extremity. Med. recs. at Ex. 2, p. 13.

On April 2, 1993, petitioner returned to Dr. Hoyer. Her numbness was gone and she was just weak. Med. recs. at Ex. 2, p. 14.

On November 1, 1993, petitioner went to Lafayette Home Hospital with a complaint of severe low back pain. Med. recs. at Ex. 2, p. 53. The history given was that she had an episode of apparent partial transverse myelitis during the summer of 1992. She was subsequently diagnosed with probable MS. She had a mild to moderate monoparesis of the left lower extremity. Subsequently, she was hospitalized with neurogenic bladder with over 1,000 cc. of

urine in her bladder which compressed the lumbosacral plexus, causing leg pain. Catheterization successfully treated this and Thorazine resolved the neurogenic pain. Those symptoms were back in December 1992. *Id.*

Petitioner did well over the winter. Over the last two months, she had chronic low back pain. It was worse when sitting in bed, lying supine, or standing. Coughing or straining would accentuate it. She denied pain radiating into the lower extremities. Her gait had not changed and she had no change in her bowel or bladder difficulties. Her back pain was significantly worse over the weekend. She stated she had a hepatitis B vaccination prior to developing her neurologic MS symptoms. *Id.*

On November 2, 1993, petitioner had an MRI done of her lumbar spine. Dr. J. Michael Phelps interpreted the MRI as normal. Med. recs. at Ex. 2, p. 5.

Petitioner was discharged from Lafayette Home Hospital on November 4, 1993. Med. recs. at Ex. 2, p. 55. Her discharge diagnosis was exacerbation of her MS with consequent severe low back pain and neurogenic bladder. *Id.* Dr. Hoyer reiterated that petitioner had an episode of partial TM one and one-half years previously and had been well over the past year. Med. recs. at Ex. 3, p. 48.

On December 3, 1993, petitioner had an MRI done of her head. Dr. Arvin found no definite change in the lesion lateral to the trigone of the right lateral ventricle compared to her January 22, 1993 MRI. MS was a possibility although it would help the diagnosis if additional lesions were present. It is atypical for MS to remain unchanged over any significant period of time. Med. recs. at Ex. 2, p. 6.

On December 8, 1993, petitioner saw Dr. Catherine I. Hatvani. Petitioner had a relapse of MS in September when she had severe radicular pain involving the low back and both lower extremities with weakness and numbness. She was there to get a rehab evaluation. Med. recs. at Ex. 2, p. 21.

Dr. Hoyer wrote a letter to petitioner, dated December 14, 1993, stating that her hepatitis B antibody test did not demonstrate any antibody activity. Med. recs. at Ex. 2, p. 41.

On March 18, 1996, petitioner had a bilateral knee MRI because of pain. Dr. Joseph C. George interpreted the study as showing abnormal serpentine signal involving the distal femur and proximal tibia bilaterally consistent with bone infarction. There is an association of this condition with chronic steroid use. Med. recs. at Ex. 3, p. 72.

On March 22, 1996, petitioner saw Dr. Jeffrey B. McIntosh who notes that petitioner's being on steroids for her MS might be the cause of this vascular necrosis involving her bone marrow. Med. recs. at Ex. 3, p. 73.

On June 7, 1996, petitioner's knees were radiographically examined again. Dr. Brian E. Stakem stated that there were cystic changes on both femurs and both tibias which appeared progressive from the prior radiograph in March. They appeared to be erosive changes of the bony structures. Med. recs. at Ex. 3, p. 75.

On October 3, 1996, petitioner visited Dr. Hoyer at the Arnett Clinic. She had a viral illness, but no major problems in the past three to four years. Med. recs. at Ex. 3, p. 88. She had transient sensory disturbances below the mid thoracic region worse on the left than on the right with increased bladder retention and mild problems with bowel incontinence. *Id.* She had

presented to St. Elizabeth Hospital Emergency Room and was diagnosed as having an ileus.[4] *Id.* Dr. Hoyer's assessment was that petitioner had a viral infection with elevated temperature that triggered recurrent symptoms of MS with partial TM at the T6 or T8 region. This was resolving and may have been responsible for the abdominal ileus. Med. recs. at Ex. 3, p. 89.

On what appears to be July 29, 1997, petitioner's knees were again examined radiographically. Dr. Alexander G. Boutselis compared the study to the one of June 7, 1996 and found fairly extensive sclerosis in the distal femur and proximal tibia which had a serpentine pattern. This suggested osteonecrosis. There were subchondral lucencies in the distal aspects of the femurs bilaterally, the most pronounced being in the medial joint space on the left. His impression was extensive osteonecrosis of the knees. Med. recs. at Ex. 3, p. 86.

On November 12, 1997, Dr. Hoyer wrote a note stating that he saw petitioner initially on January 22, 1993 with symptoms of TM. She had previously received two hepatitis B vaccinations. One vaccination was several days to a week before her initial presentation and the second was the previous month in December. After the first vaccination, petitioner had transient monocular visual symptoms in the right eye suggestive of optic neuritis. After the second vaccination, she had symptoms of TM with a Brown-Séquard syndrome. Since then, she had had a more typical course of MS. The onset of her symptoms are temporally related to the hepatitis B vaccination. Med. recs. at Ex. 2, p. 57.

On November 20, 1997, Dr. Shamik Bafna, an ophthalmologist, wrote that petitioner had a history of MS and, in the past, had episodes of blurriness in her right eye which improved

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[4] An ileus is an obstruction of the bowel. Stedman's Medical Dictionary, 27th ed. (2000) at 874.

spontaneously. About two weeks previously, she noted an episode of movement in her left eye which resulted in decreased vision. Dr. Hoyer started her on oral steroids one week previously and felt her left vision improved over the prior two days. Dr. Bafna's impression was probably retrobulbar optic neuritis on the left. Med. recs. at Ex. 3, p. 84.

On November 19 and 20, 1998, an MRI was done intracranially and of the thoracic spine. Dr. Cahoon interpreted both. He compared the results to the previous MRI done on February 10, 1993. The ventricular system was unremarkable in appearance. There were four small areas of increased T2 signal present. The largest was 8 x 5 mm. located in the left parietal white matter immediately adjacent to the upper left occipital horn. There was an additional lesion higher in the central left parietal white matter and one on the right in a similar place. These measured only 3 to 4 mm. There was also a tiny lesion in the right cerebellum. The lesions were not in the same location as the two lesions seen on the previous MRI in 1993. These findings were consistent with active MS plaques. The two 1993 lesions were vaguely identifiable but did not demonstrate any enhancement. On the thoracic spine, there was a small vascular malformation along the posterior thoracic cord from the T9 to L1 levels. Otherwise, the study was unremarkable. Med. recs. at Ex. 6, pp. 2, 3.

On November 19, 1998, petitioner went to St. Elizabeth Medical Center Emergency Room with a one-month history of pain across the lower abdomen. It went away after a week, but returned three to four days later. Med. recs. at Ex. 6, p. 6. The assessment of Dr. Martin J. Maassen was neurogenic right rib and flank pain. Med. recs. at Ex. 6, p. 7. Dr. Hoyer agreed with the assessment. Med. recs. at Ex. 6, p. 10.

A total body bone scan done on November 23, 1998 showed moderately increased activity in the right 8th rib and mildly increased uptake in the right 5th rib which might be related to trauma although x-rays showed no definite fracture. Moderately increased activity in the lateral aspect of the left foot at the metatarsal level was likely post-traumatic. Dr. Timothy J. Lach called the findings to Dr. Hoyer. Med. recs. at Ex. 6, p. 11.

On July 9, 1999, Dr. Hoyer gave petitioner an impairment rating of 10-19% for station and gait impairment, 1-10% for upper extremity impairment for a whole body impairment rating of 34%. Combining that with a 1-9% impairment rating for her neurogenic bladder gave her a whole body impairment rating of 40%. Med. recs. at Ex. 16, p. 155. Petitioner had station and gait problems secondary to monoparesis of the left lower extremity, bilateral dexterity problems in the upper extremities, and a neurogenic bladder. *Id.* Petitioner could rise to a standing position and walk some distance with difficulty, but was limited to level surfaces. She had difficulty with finger dexterity. *Id.* She had urgency and intermittent incontinence. *Id.*

On July 21, 1999, Dr. Mark D. Griffith wrote a permanent impairment rating. Med. recs. at Ex. 5, p. 53. She smoked a pack of cigarettes daily and had done so since she was 20. Her left leg had increased tone, pulled in, and was weak. She had bladder difficulties requiring intermittent catheterization. She had loss of fine motor skill bilaterally. She could not perform fine tasks such as IVs and manipulating small objects. She had difficulty with cognition and stated she was forgetful. She had sequencing problems and difficulty with executive functioning. She used a cane in the home for safety. Physical examination confirmed increased spasticity in the left lower extremity with a very wide based gait. She had decreased fine motor skills and decreased sensation in the forearm. She had intermittent visual problems. Dr. Griffith awarded

petitioner 10% for cognitive impairment, 9% for bearing gait with need for AFO, 10% for decreased fine motor skills, 15% for bladder dysfunction, 5% for visual impairment for a total of 41% impairment. *Id.*

On October 14, 2000, petitioner saw Dr. M. Kassab for disability review. Med. recs. at Ex. 16, pp. 142, 143. Dr. Kassab states that petitioner's MS began in 1982 with numbness starting in her waist and spreading to both legs, especially the left leg accompanied by weakness. He states she has had dribbling, urgency, and frequency for the last 15 years. She had severe weakness, especially in her right arm. She lost vision in both eyes intermittently. *Id.* Her visual examination was normal. Med. recs. at Ex. 16, p. 144. Deep tendon reflexes were normal and symmetric. There was some atrophy and rigidity in the legs. Med. recs. at Ex. 16, p. 145. Petitioner could not remember things easily. She repeatedly fell. Med. recs. at Ex. 16, p. 147.

On January 5, 2001, petitioner saw Dr. Hatvani who states that petitioner has the continuously progressive type of MS. Med. recs. at Ex. 5, p. 17. She has a sister with epilepsy. *Id.* Petitioner's right upper extremity was extremely weak and she had difficulty with wrist extension. She had numbness in her fingers with tingling there and in her toes. She had occasional problems with swallowing and with constipation. She wore bilateral plastic AFOs. Her left upper extremity had normal strength. *Id.*

On March 6, 2003, petitioner and her employer entered into a settlement agreement of petitioner's workmen's compensation claim for $80,000.00 although they disputed the cause of her illness. Med. recs. at Ex. 22, pp. 3, 4.

On June 25, 2003, petitioner had an x-ray done of her left wrist after injuring it. She had a transverse metaphyseal nondisplaced fracture of the distal left radius, according to Dr. Michael Jennewein. Med. recs. at Ex. 21, p. 19.

Other Submitted Material

As P. Ex. 7, petitioner filed an affidavit from her co-worker Kristina L. Mathis, dated March 5, 2002. Before petitioner received hepatitis B vaccine, she was always early at work, energetic, and wore high-heeled shoes. After petitioner received her second hepatitis B vaccination, she did not seem to be her old self. She was often sick and missed work. She was listless and sad and began using a brace on one leg and then a cane. She could no longer wear high-heeled shoes and could not administer injections because her fingers were numb.

As P. Ex. 8, petitioner submitted the affidavit of a co-worker and friend Laura M. LaVal, dated March 4, 2002. She has known petitioner since 1987 and roomed with her since 1990. Before her MS diagnosis, petitioner was employed full time as a nurse and was very active, being an avid golfer and socializing with many friends. Now she has extreme fatigue and physical limitations. She uses a rolling walker, bilateral lower leg braces or a motorized cart to walk. She cannot write her name legibly and needs adaptive silverware to feed herself. She will not eat in public or in front of her family and friends. She cannot use her dominant hand.

As P. Ex. 9, petitioner submitted the affidavit of a co-worker named Raelene Wing, dated March 4, 2002. Ms. Wing has known petitioner since 1978 and states she was always very active and energetic, enjoying both golf and tennis. Petitioner changed after her second hepatitis B vaccination. Ms. Wing was the Director of Nursing Services and petitioner was Staff Development Coordinator/Infection Control Nurse. Petitioner told Ms. Wing that she was

concerned about her vision. It was blurred and she had been losing peripheral vision for a significant period of time. After one to two weeks, petitioner's trunk was numb. A few days later, the numbness extended to her left leg and she was diagnosed with MS. Her stamina has declined and her job took much more out of her.

In the Stevens case (one of the four paradigm cases in this Omnibus proceeding),[5] petitioner filed Ex. 20, with numerous articles. Tab B is an article entitled "Hepatitis B Vaccination and the Risk of Multiple Sclerosis," by A. Ascherio, et al., 344 *N Eng J Med* 5:327-32 (2001) (this is also Tab 9 of R. Ex. A in the instant action). The authors conclude after conducting a nested case-control study of two large cohorts of nurses that there was no association between hepatitis B vaccine and the development of MS. *Id.* at 331. They used two years for their definition of recent exposure. *Id.* Their result was consistent with the results of studies in Canada and the United States, but inconsistent with three other studies, two of which were in France, which reported nonsignificant increases in risk of MS after hepatitis B vaccination. *Id.*

Tab M of P. Ex. 20 in Stevens is an article entitled "Vaccinations and the Risk of Relapse in Multiple Sclerosis," by C. Confavreux, et al., 344 *N Eng J Med* 5:319-26 (2001) (this is also Tab 12 of R. Ex. A in the instant action). The authors conducted a case crossover study of patients (in which patients serve as their own controls) included in the European Database for MS who had a relapse between 1993 and 1997, and concluded that hepatitis B vaccine, inter alia,

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[5] Since Stevens, Gilbert, Peugh, and Werderitsh were tried together as the paradigm cases for the hepatitis B vaccine-demyelinating diseases Omnibus proceeding, the undersigned regards any exhibit filed in any of the four cases to be filed in all of the paradigm cases. The exhibits relevant to Werderitsh concern MS.

did not increase the short-term risk of relapse in MS. *Id.* at 319, 320. The risk period they evaluated was two months post-vaccination. *Id.*

Tab U of P. Ex. 20 in Stevens is an article entitled "Vaccinations and multiple sclerosis" by O. Gout, 22 *Neurol Sci* 151-54 (2001). Dr. Gout states that, although causation from hepatitis B vaccine is not established, several hundred cases of an acute central demyelinating event following hepatitis B vaccination were reported in France after 25 million inhabitants were vaccinated between 1991 and 1999, leading to a modification of vaccination policy in the schools. *Id.* at 151. ADEM (acute disseminated encephalomyelitis) has been observed following vaccinations and is similar to EAE (experimental allergic encephalitis), suggesting an immune process. Optic neuritis or myelitis has been reported following vaccinations, and occasionally been counted as the first attack of MS. *Id.* Possible biologic mechanisms are molecular mimicry between hepatitis B vaccine proteins and myelin components; indirect immunological stimulation by the large quantity of exogenous hepatitis B surface antigen; and direct or indirect immunological toxicity of vaccine contaminants, not neglecting the role of genetic susceptibility. *Id.* at 153. Although epidemiological studies do not demonstrate a causal relationship between hepatitis B vaccine and MS, a trend is definitely present. *Id.* Dr. Gout states, "Although HB vaccines do not cause MS, they could be a triggering factor in susceptible individuals in the same manner as infections." *Id.*

Tab W of P. Ex. 20 in Stevens is a poster description entitled "Development of Multiple Sclerosis after Hepatitis B Vaccination: An Immunologic Case Report," by B. Gran, et al., 54 *Neurology* Supp. 3:A164 (2000). The authors studied a patient who developed MS three months after hepatitis B vaccination. They found cross-recognition of hepatitis B surface antigen and a

proteolipid protein-derived peptide by a T-cell line isolated from the patient's peripheral blood. These preliminary findings suggested to the authors that molecular mimicry might trigger autoimmune demyelination after hepatitis B vaccination. *Id.*

Tab BBB of P. Ex. 20 in Stevens is an article entitled "Molecular Mimicry and Antigen-Specific T Cell Responses in Multiple Sclerosis and Chronic CNS Lyme Disease," by R. Martin, et al., 16 *J Autoimmunity* 187-92 (2001). (Dr. Martin was respondent's expert herein.) Dr. Martin and his co-authors define MS as follows:

> Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) with various degrees of axonal damage. ... It is believed that a T cell-mediated autoimmune process against CNS myelin underlies its pathogenesis. This concept is based on the inflammatory nature of MS plaques, on parallels to an animal model, experimental allergic encephalomyelitis (EAE), on the response to immunomodulatory and suppressive therapies, and also on genetic factors, particularly HLA genes. ...
> Epidemiological studies demonstrate that viral infections often precede MS exacerbations, and it is thought that such infections with foreign agents either activate myelin-specific T cells by molecular mimicry, i.e., cross-recognition of a viral and a myelin peptide, or by bystander activation, e.g. via inflammatory cytokines. [footnotes omitted.]

Id. at 187.

Dr. Martin and his co-authors then describe the change over two decades in the understanding of how molecular mimicry works. They describe MS as not "an induced disease, but rather a process that is already ongoing for a long time before it is diagnosed and directed against multiple, usually unknown epitopes." *Id.* at 190.

Tab DDD of P. Ex. 20 in Stevens is an article entitled "Myelin Basic Protein-specific T Lymphocyte Repertoire in Multiple Sclerosis. Complexity of the Response and Dominance of

Nested Epitopes Due to Recruitment of Multiple T Cell Clones," by E. Meinl, et al., 92 *Amer Soc for Clin Investigation, Inc.* 2633-43 (1993). The authors state, "There are several reasons to consider myelin basic protein (MBP) as a candidate autoantigen involved in the immuno-pathogenesis of multiple sclerosis (MS). MBP is a strong encephalitogen in many animal species, and MBP-specific T cells have been found in experimental and human postviral encephalitis. The frequency of MBP-reactive T cells is increased in the cerebrospinal fluid of MS patients, and MBP-specific T cells in the blood of MS patients display increased rates of somatic mutation, presumably reflecting sustained cell proliferation [footnotes omitted]." *Id.* at 2633.

Tab EEE of P. Ex. 20 in Stevens is an article entitled "Prognostic factors in multiple sclerosis: role of intercurrent infections and vaccinations against influenza and hepatitis B," by E. Merelli and F. Casoni, 21 *Neurol Sci* S853-856 (2000). The authors state that despite case reports of hepatitis B vaccinations in France followed by onset of MS, epidemiological studies in large populations argue against a causal relation between hepatitis B vaccination and MS or other demyelinating diseases. *Id.* at S854-55. Recombinant hepatitis B vaccine contains only a portion of the outer protein of hepatitis B virus and does not contain any live component. *Id.* at S854. In case reports of MS following hepatitis B vaccination, more than half of the patients had a personal or familial history or symptoms suggesting a demyelinating disease before vaccination. As a precaution, these patients were advised to avoid hepatitis B vaccination in future. *Id.* at S855.

Tab XXX of P. Ex. 20 in Stevens is an article entitled "Immunization and MS. A summary of published evidence and recommendations," by O.T. Rutschmann, et al., 59

Neurology 1837-43 (2002). The authors conclude, inter alia, that hepatitis B vaccine does not increase the risk of relapse in patients with MS. *Id.* at 1840.

Tab PPPP of P. Ex. 20 in Stevens is an article entitled "Encephalitis after hepatitis B vaccination. Recurrent disseminated encephalitis or MS?" by A. Tourbah, et al., 53 *Neurology* 396-401 (1999). The authors define acute disseminated encephalomyelitis as follows:

> Acute disseminated encephalomyelitis (ADEM) is an acute or subacute condition characterized by the occurrence, one to several weeks after a triggering infection or vaccination, of widespread multifocal neurologic deficits of variable severity, ranging from asymptomatic to fulminant. Pathologically, it is characterized by perivenous inflammation and demyelination in the CNS. ADEM is classically differentiated from MS by the intensity of inflammation and the monophasic course of the disease.

Id. at 396. The authors analyzed eight cases, in which the mean onset between the last hepatitis B vaccination and presenting symptoms was 4.4 weeks. One of the patients had complained a few years before of a unilateral loss of vision with spontaneous recovery. *Id.* at 398. This was compatible with optic neuritis. *Id.* at 399-400. The authors could not determine if hepatitis B vaccine causes ADEM or MS. *Id.* at 400. They suggest that patients with a personal or familial history of symptoms suggestive of an inflammatory or demyelinating disease of the central nervous system avoid hepatitis B vaccination. *Id.*

Tab QQQQ of P. Ex. 20 in Stevens is an article entitled "Hepatitis B Vaccination and First Central Nervous System Demyelinating Event: A Case-Controlled Study," by E. Touzé, et al., 21 *Neuroepidemiology* 180-86 (2002). The authors concluded that hepatitis B vaccine might raise the risk of a first demyelinating event within two months of vaccination without increasing the long-term risk of MS. In other words, the vaccine might trigger the onset of MS but not

cause it. *Id.* at 184. They stated that because vaccination, just like natural infection, is a strong antigenic challenge, an association between hepatitis B vaccine and MS was not implausible. *Id.* at 185.

Attached to petitioner's expert Dr. Tornatore's report in Stevens as P. Ex. 23, p. 1, is an article entitled "Epidemiology of Autoimmune Reactions Induced by Vaccination," by R.T. Chen, et al., 16 *J Autoimmunity* 309-18 (2001). The authors state that current evidence does not support a causal association between hepatitis B vaccine and onset or exacerbation of MS. *Id.* at page 5 of the exhibit. However, they continue:

> Environmental factors, such as vaccines, could be involved in actually causing the disease, resulting in an overall excess of MS in the population, or as possible triggers for the clinical expression of MS in genetically susceptible individuals, without causing an excess in disease incidence.

Id.

Attached to Dr. Tornatore's report in Stevens as P. Ex. 23, p. 66 (also P. Ex. 20, Tab EE, in Stevens), is a case report entitled "Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine," by L. Herroelen, et al., 338 *Lancet* 1174-75 (1991). The authors describe two patients with neurological symptoms six weeks after administration of recombinant hepatitis B vaccine. One had definite MS before immunization. The other had probable MS after immunization. The authors assumed the vaccine triggered the relapse or onset of MS, although causation was not proved, and suggest that MS patients avoid hepatitis B vaccine. *Id.* at page 67 of the exhibit.

Attached to Dr. Tornatore's report in Stevens as P. Ex. 23, p. 81 (also P. Ex. 20, Tab UU, in Stevens), is a brief report entitled "Two Episodes of Leukoencephalitis Associated with

Recombinant Hepatitis B Vaccination in a Single Patient," by D. Konstantinou, et al., 33 *Clin Infect Dis* 1772-73 (2001). The authors express concern about reports of hepatitis B vaccine causing central nervous system demyelinating diseases. They report two separate instances of leukoencephalitis in a 39-year-old woman, the first occurring four weeks after her second hepatitis B vaccination, and the second occurring 11 days after her third hepatitis B vaccination. Brain biopsy and MRIs were performed. Histologic examination was consistent with demyelinating disease. Follow-up visits showed no abnormal neurologic findings other than residua. *Id.* at page 81 of the exhibit.

The authors concluded that their case showed a strong suggestion of causation from hepatitis B vaccine because of the following factors: (1) absence of previous disseminated neurologic disease; (2) resolution of the lesions; (3) the absence of new neurologic deficits; (4) the occurrence of two similar but separate clinical and radiological neurologic events soon after administration of the second and third doses of hepatitis B vaccine. *Id.* at page 82 of the exhibit.

Petitioner filed Ex. 30 in Stevens, an article entitled "Recombinant hepatitis B vaccine and the risk of multiple sclerosis. A prospective study," by M.A. Hernán, et al., 63 *Neurology* 838-42 (2004). The authors conducted a nested case-control study in the United Kingdom of 163 patients with a first MS diagnosis occurring between 1993 and 2000 with 1,604 controls, and found an increased risk of MS following immunization with recombinant hepatitis B vaccination. *Id.* at 838. There was no increased risk of MS following tetanus and influenza vaccinations. *Id.*

A greater number of immunizations was not clearly related to greater risk. *Id.* at 840. The authors estimated that hepatitis B vaccine was associated with a threefold increase in the incidence of MS within the three years post-vaccination. *Id.* They could not distinguish whether

hepatitis B vaccine hastened the onset of MS in persons destined to develop MS years later or whether it caused new cases of MS in susceptible individuals. *Id.* However, the age of first symptoms of MS was similar between vaccinated and unvaccinated cases, which would not support the thesis that hepatitis B vaccine caused MS in individuals who were destined to develop MS later. *Id.* The authors stressed that 93 percent of the MS cases in their study were not vaccinated. *Id.* The authors used the date of first symptoms of MS, rather than the date of diagnosis, to define the period of risk. *Id.* at 841. When they used the date of diagnosis of MS to define the period of risk, they had a null finding (no relationship), consistent with other epidemiological studies that did not find a relationship between hepatitis B vaccine and MS. *Id.* The authors conclude:

> The recombinant hepatitis B vaccine is a non-infectious viral vaccine derived from hepatitis B surface antigen (HBsAg) produced in genetically engineered yeast (*Saccharomyces cerevisiae*) cells. Although several viruses (e.g., Epstein-Barr virus) have been postulated to cause MS, the hepatitis B virus has not been prominent in the discussions of viral triggers of MS. It is therefore unclear how a recombinant vaccine that contains purified HbsAg [sic], a portion of the hepatitis B virus, could trigger the immunologic processes that lead to MS. The vaccine also contains an adjuvant (aluminum hydroxyphosphate sulfate), a mercury-based preservative (thimerosal, eliminated from recent formulations), and yeast proteins (up to 5%), but these components have not been separately studied in relation to the risk of MS.

Id. at 842 (footnotes omitted).

Petitioner filed Ex. 37 in Stevens, an article entitled "The initiation of the autoimmune response in multiple sclerosis," by S. Markovic-Plese, et al. (the last author is respondent's expert Dr. Martin), 106 *Clin Neurology & Neurosurgery* 218-22 (2004). The authors define MS as "a chronic demyelinating disease of the central nervous system (CNS)...." *Id.* at 218. The

etiology of MS is suspected to be an autoimmune pathogenesis. *Id.* An initial development in the MS autoimmune disease process is the activation of autoreactive T-cells. *Id.* Current studies support the critical role of CD4+ myelin-specific cells in the initiation of MS autoimmune responses. *Id.* It is the frequency of activated myelin-reactive cells that is increased in MS patients in comparison to healthy individuals rather than the presence of myelin-reactive cells since normal people have them, too. *Id.* Peripherally activated autoreactive CD4+ lymphocytes cross the blood brain barrier and initiate chronic inflammatory central nervous system response, as the animal model (EAE) of MS shows. *Id.* One T-cell receptor (TCR) can recognize many peptides in the autologous major histocompatibility complex (MHC). *Id.* at 219. Molecular mimicry results in the autoimmune disease only when it occurs with local inflammation, released self antigens, and enough autoreactive T-cells. *Id.*

In addition to TCR specificity, functional characteristics of autoreactive T-cells determine their propensity for activation. *Id.* at 220. The authors identified in MS patients a functionally distinct subset of CD4+ cells with no CD28 surface expression. *Id.* at 221. After CD28-independent activation, CD4+ CD28-cells become fully activated, producing proinflammatory cytokines, and exhibiting prolonged proliferation and increased survival. *Id.* Myelin-specific cells are represented in a high frequency in this CD4+ subset. *Id.* The authors state that local antigen presentation is critical to initiate and perpetuate inflammatory responses within the CNS. *Id.*

Respondent filed Ex. A (Dr. Leist's report) to which are attached 12 articles. Tab 1 is from the World Health Organization (WHO) entitled "Vaccines, Immunization and Biologicals" (2001). Page 2 summarizes the literature pertaining to demyelinating diseases following hepatitis

B vaccination. In spite of French concerns about MS following or flaring up after hepatitis B vaccination, WHO's position is that there is a lack of evidence showing that hepatitis B vaccine causes MS. *Id.* at 2.

Tab 8 of R. Ex. A is WHO's "Weekly Epidemiological Record," dated May 23, 1997, an article entitled "Expanded Programme on Immunization (EPI). Lack of evidence that hepatitis B vaccine causes multiple sclerosis." WHO states that there is no epidemiological proof that hepatitis B vaccine causes MS and no understanding of the underlying pathological process of MS. *Id.* at pp. 149, 150.

Tab 10 of R. Ex. A is a letter to the editor entitled "No increase in demyelinating diseases after hepatitis B vaccination," by F. Zipp, et al., 5 *Nature Medicine* 9:964-65 (1999). The authors did a retrospective cohort study on 134,698 people in a US healthcare database from 1988 to 1995. *Id.* at 964. They found no significant difference between vaccinated and non-vaccinated people for demyelinating illness. *Id.*

Tab 11 of R. Ex. A is a letter entitled "School-based hepatitis B vaccination programme and adolescent multiple sclerosis," by A.D. Sadovnick and D.W. Scheifele, 355 *Lancet* 549-550 (2000). Admitting that MS is scarce in adolescents, the authors found nine cases of adolescent MS before vaccination compared to five cases of adolescent MS among after vaccination. *Id.*

Respondent's Ex. C is the Institute of Medicine's "Immunization Safety Review. Hepatitis B Vaccine and Demyelinating Neurological Disorders," by K. Stratton, et al. (2002). Pages 29-33, 40-45 discuss MS. On page 45, based on the epidemiologic studies, the authors (the committee) rejected a causal relationship in adults between hepatitis B vaccine and MS and between the vaccine and MS relapse. *Id.* at 45. The committee discusses possible biological

mechanisms at pages 62-69. After discussing the various mechanism theories, the committee states: "There is no reason in theory why hepatitis B surface antigen in the vaccine could not function in this way. Thus there is a theoretical basis for a hepatitis B vaccine-induced immune response that could possibly lead to demyelination." *Id.* at 66. But the committee found the evidence in support of this theory scant and indirect. *Id.*

Respondent filed Ex. D, an article entitled "Vaccinations and Risk of Central Nervous System Demyelinating Diseases in Adults," by F. DeStefano, et al., 60 *Arch Neurol* 504-09 (2003). The authors studied the onset of MS or optic neuritis among 440 case subjects and 950 controls to determine whether hepatitis B, influenza, tetanus, measles, or rubella vaccinations increased the risk of these diseases. They concluded the vaccinations did not increase the risk. They concede: "Environmental factors, such as vaccines, could be involved in actually causing the disease, resulting in an overall excess of MS in the population, or as possible triggers for the clinical expression of MS in individuals with subclinical disease." *Id.* at 504. Hence, they conducted their case-control study and found no increased risk of optic neuritis or MS, regardless of the timing of the vaccination. *Id.* at 507. They regarded reports of MS following vaccination to be merely coincidences. *Id.* at 508.

Respondent filed Ex. F, an abstract entitled "Determining Risk of Multiple Sclerosis after Hepatitis B Vaccine: Time Since Vaccination and Source of Data," by F. DeStefano, et al., 13 *Pharmacoepidemiology and Drug Safety* S1-S334 (S143) (2004). The authors state that, although a recent analysis of a large United Kingdom medical records data base (the Hernán paper; P. Ex. 30 in Stevens) found increased risks of MS within three years of vaccination, DeStefano and his co-authors did not find any higher risk of MS up to five years after hepatitis B

vaccination using data from three United States health maintenance organizations participating in the Vaccine Safety Datalink project of the Centers for Disease Control and Prevention.

Respondent filed Ex. M in Stevens, an article entitled "Relationship Between Vaccinations and Multiple Sclerosis," by E.J. Sievers and C.A. Heyneman, 36 *Ann Pharmacother* 160-62 (2002). The authors did a literature review on studies relating immunizations with autoimmune disorders such as MS and conclude there are "no data linking vaccinations to MS." *Id.* at 162.

Respondent filed Ex. A, Tab 1, in Gilbert, a January 2004 report from WHO entitled "Hepatitis B vaccination and multiple sclerosis: update." A meeting of Dec. 3-4, 2003 was convened to discuss what would subsequently be published as the Hernán article (P. Ex. 30 in Stevens) which found an increased incidence of MS among patients in the United Kingdom who had received hepatitis B vaccine. *Id.* at 1. (The committee had received an abstract and an oral presentation. *Id.*) The committee concluded that the methods and patient data revealed were insufficient to address their concerns of selection bias that could have distorted the authors' conclusions. *Id.* Those conclusions were based on small numbers, bringing in the element of chance. *Id.*

On December 2, 2005, after the hearing, respondent filed Ex. G, a letter from respondent's expert neurologist, Dr. Leist, discussing the article by Piaggio, et al., in the *Journal of Autoimmunity* 24:33-37 (2004) (see discussion below), to wit, the authors' conducting in vitro stimulation of peripheral blood lymphocytes with recombinant hepatitis B surface antigen yielded the same results in individuals who had contracted demyelinating diseases after vaccination as it did in individuals who remained healthy post-vaccination. R. Ex. F, p. 1. Dr. Leist concluded

that the lack of producing an elevated T-cell response against hepatitis B surface antigen in those with neurological symptoms was evidence against a causal relationship between hepatitis B vaccine and demyelinating diseases. *Id.* Dorothy Werderitsh had serum samples drawn on December 6, 1993 and December 20, 1997, both of which failed to detect antibodies in her serum to hepatitis B surface antigen. To Dr. Leist, this failure indicates a lack of significant hepatitis B surface antigen specific T-cell response in Ms. Werderitsh, consistent with the observations of Piaggio and his co-authors. Dr. Leist concluded that it is highly improbable that hepatitis B vaccine induces autoreactive T cells that cause demyelination of the vaccinee's nerves. R. Ex. F, p. 2.

Respondent filed as Ex. 1, the article Dr. Leist discussed in Ex. G, entitled "Hepatitis B vaccination and central nervous system demyelination: an immunological approach," by E. Piaggio, et al., 24 *J Autoimmunity* 33-37 (2005). The authors compare the T-cell response to hepatitis B surface antigen in patients with central nervous system demyelination or multiple sclerosis or other inflammatory or autoimmune diseases following hepatitis B vaccination with the T-cell response in healthy hepatitis B vaccinees. Their data showed no difference in T-cell proliferation or cytokine production between the two groups, thus not favoring a causal link between demyelinating illness and hepatitis B vaccine, although the authors say that their result was not sufficient to exclude the causal link because the sample size, being quite small, limited the power of the study. *Id.* at 36.

TESTIMONY

Former special master Sweeney held a hearing on October 13, 14, and 15, 2004 in this and the other paradigm hepatitis B-demyelinating cases aforementioned. Dr. Vera S. Byers, an

immunologist, testified for petitioners. Tr. at 10. She testified that she had created clinical trials for a vaccine technology in order to protect against MS that had been effective in the animal model of MS called EAE (experimental allergic neuritis). Tr. at 12. She followed the vaccine technology for MS and further developed the vaccine. Tr. at 13. She has been a consultant to multiple biotech companies running clinical trials in a wide variety of autoimmune diseases including atopic dermatitis, MS, and rheumatoid arthritis. *Id.* She is board-certified in internal medicine, but not in immunology. Tr. at 15, 19. She has treated patients with MS, but not currently. Tr. at 15, 20-21.

The main requirement for MS is lesions separated in time and space. Tr. at 23. By space, she means after an initial manifestation, you have a second manifestation which is different. It involves a different place in the body and is separated in time. *Id.* At the time of the first symptoms, the brain lesions are often very advanced. People feel there is a period of silent demyelination when there are no symptoms. *Id.* With MS, it is not unusual to have subclinical disease. Tr. at 24. There are five mechanisms that can cause demyelination: molecular mimicry, degenerate specificity, bystander effect, the liberation of sequestered antigens, and super antigens. Tr. at 27-28.

Molecular mimicry means that a pathogen has something in it that looks the same as someone's myelin basic protein. If you are exposed to the foreign protein which looks like a self-antigen, you break tolerance and produce T-cells which react against the self body proteins. Tr. at 28. Historically, this process was described for antibodies, but it could be used for T-cell receptors. Tr. at 29. A study showed that an MS patient who developed symptoms reasonably

close to a hepatitis B vaccination had T-cells that would cross-react with both hepatitis B and myelin basic protein. Tr. at 31.

Degeneracy means that a T-cell is not as specific as was thought, that is, a wide variety of triggers can set T-cells off. Tr. at 30. In a study, the authors isolated anti-myelin basic protein cell clones from MS patients and produced about 128 random peptides. They found that eight of these random peptides could trigger a myelin basic protein reactive T-cell, yet only one of them could have been predicted to be a molecular mimic. Tr. at 31, 41.

Bystander effect involves autoreactive T-cells that serve a regulatory function in downregulating an immune response that is trying to get out of control. Tr. at 32. A cytokine storm can activate those autoreactive T-cells. This occurs when someone is exposed to a protein producing an inflammatory response. If the autoreactive T-cells are in the wrong place at the wrong time, they could be activated and produce autoimmune disease. *Id.* Inflammation in the nervous system attracts cytokines which pull in inflammatory cells such as macrophages which result in demyelination. Tr. at 33. This results in holes in the myelin and neurologic symptoms such as weakness, sensory problems, etc. Tr. at 34.

The liberation of sequestered antigens occurs when the myelin has holes punched in it because now proteins are exposed to the body that were hidden or else these proteins have been denatured so that they look different than in their normal shape. The body does not recognize these newly-exposed proteins as its own and it reacts against them, producing inflammation. Tr. at 36. This liberation of sequestered antigens explains how some diseases become chronic. Tr. at 37. In one study, the authors looked at a subpopulation of MS patients who had initially very focused T-cell reactivity and followed them over a six-year period, during which the specificity

became very broad, explaining how the inflammation and demyelination became chronic. Tr. at 38-39.

The super antigen has the ability to bind to an unusual site and stimulate it, which may be more important in non-demyelinating diseases. Tr. at 38. In vitro, staph super antigens can activate human myelin basic protein reactive T-cells, but Dr. Byers has not seen literature discussing this as being responsible for clinical disease. *Id.*

MS is a chronic disease of the central nervous system manifested by inflammation and demyelination. Tr. at 39-40. It has a very strong genetic component. Tr. at 40. Dr. Byers feels that molecular mimicry is not that common in autoimmune diseases. *Id.* It would be very difficult to predict with any accuracy whether or not a particular antigen will cross-react with a T-cell. Tr. at 41.

In one study, the authors took an MS patient who had received hepatitis B and whose symptoms developed soon afterwards. They examined the patient's T-cells and demonstrated that the T-cell clone lines reacted to myelin proteolipid protein and hepatitis B. Tr. at 42. Myelin proteolipid protein is one of the antigens on the myelin sheath. Tr. at 43. Thus, in vitro data would support the conclusion that hepatitis B vaccine can either trigger or exacerbate MS. Tr. at 44.

An example of cytokine release is the attempt to ameliorate MS with interferon gamma, which was in a clinical trial that was halted when the interferon gamma caused 18 patients' MS to worsen. *Id.* Dr. Byers assumes the interferon gamma was enhancing antigen presentation. Tr. at 45. In a subpopulation of patients (not all of whom had MS), in their initial phase of disease, the reactivity was very focused, but later on in the disease process, it spread. Tr. at 46.

The 2002 Institute of Medicine (IOM) report said that it was biologically plausible that hepatitis B vaccine could cause demyelinating diseases. Tr. at 48. Hepatitis B vaccine is considered to be a foreign protein because it is recombinant. Tr. at 55-56.

The average time between the first symptom of MS and the diagnosis is three years. Tr. at 71. MS is primarily T-cell-mediated. *Id.* It is an assault on the proteins in the myelin sheath. *Id.* The initial lesion may be optic neuritis or TM. *Id.* Usually, on MRI, the central nervous system lesions are much more florid than the symptoms, which is why people think that this silent demyelination occurs for some period of time prior to the actual symptoms. *Id.* There is also a very strong genetic component. *Id.* There is also an environmental component. *Id.* A vaccination could be that environmental component. Tr. at 72. The environmental factor can either dysregulate the T-cell so it assaults myelin or activate myelin specific T-cells. Tr. at 72-73. Not only demyelination occurs in MS, but also inflammatory mediators causing neuronal injury. Tr. at 74.

When the nervous system does not repair itself, it is due to scarring or gliosis. Tr. at 75. MS can be relapsing remitting (the most common MS) where you return to baseline or secondary progressive where you do not return to baseline. Tr. at 76. MS is closely associate with febrile illnesses, especially upper respiratory infections. *Id.* Medical literature has associated MS with vaccinations. Tr. at 77.

Dr. Byers stated that rechallenge cases with MS are more difficult to interpret than those with monophasic disease because MS as a disease can be relapsing and remitting. *Id.* Viral

infections can initiate and also exacerbate MS. Tr. at 106. The IOM rejected a causal relationship between hepatitis B vaccine and MS as well as MS relapse. Tr. at 115.[6]

Dr. Roland Martin, a board-certified neurologist, testified for respondent. Tr. at 189. He heads the cellular immunology section of the National Institutes of Health (NIH), whose main interest is MS and the molecular mechanisms leading to MS. Tr. at 190. Dr. Martin stated that cross-reactivity is entirely normal and necessary to protect us from environmental agents. Tr. at 193. We have a very limited number of T-cells in our bodies, and we would never be able to protect ourselves with that small number unless there were a tremendous amount of cross-reactivity. Tr. at 194. Therefore, cross-reactivity is not per se the reason for the autoimmune response. *Id.*

Molecular mimicry really refers to a similarity between a foreign protein and a self-protein which initially was thought to be a complete homology. Tr. at 195-96. We realize now that the amino acids do not have to be completely shared. Tr. at 196. To have demyelinating disease, you need either damage in the brain already or an infectious organism that strongly activates the innate immune system. Tr. at 198.

In MS, the latest genetic studies show there are probably 200 to 400 weakly-associated genes in various mixes in the patients that are responsible for the disease. Tr. at 200. Genetic influences may be a small modifier of disease expression. Tr. at 201. Dr. Martin did a study on a patient with MS after hepatitis B vaccination and generated T-cells for the vaccine protein and also against myelin. Tr. at 202. Initially, he and his co-authors had a few cell lines that looked

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[6] Professor Bonnie Dunbar's brief testimony on MS is summarized in Stevens v. Secretary of HHS, No. 99-594V, 2006 WL 659525, at *14. Dr. Lawrence H. Moulton's general testimony about epidemiologic studies is summarized in Stevens at *16-17.

promising because they showed cross-reactivity. This finding is reflected in their published abstract. *Id.* But, when they continued the research, the cell lines did not keep their specificity, meaning their reactivity was most likely spurious. *Id.* He never published the complete data set because it was inconclusive. He believes this work needs to be done on several people from their spinal fluid and blood in order to be really conclusive. *Id.*

Dr. Martin stated that MS involves a very complex genetic trait of many weakly associated genes that contribute to susceptibility to MS together with potentially an environmental trigger that may be needed around puberty or even earlier or sometimes later. Tr. at 208. It is unclear what that trigger is. Most likely it is a common environmental agent. *Id.* The clustering of MS exacerbation with upper respiratory infections suggests that they may be one of the environmental factors and there are probably many different agents involved. *Id.* The genetic predisposition to MS is absolutely critical and also complex. *Id.*

In some patients, MS inflammation is antibody-mediated. Tr. at 209. In others, MS occurs because the brain is vulnerable to damage. Other cases of MS are likely T-cell-mediated. *Id.* Live virus vaccines, such as polio, measles, or mumps, probably differ in their likelihood of causing damage and propagating infection, whereas recombinent protein such as in hepatitis B vaccine would never do that. Tr. at 210. At the moment, we are more confused than ever. *Id.*

Dr. Martin testified that the evidence is so slim that hepatitis B vaccine causes MS that he cannot accept it. Tr. at 212. This is one of the main topics that he works on. *Id.* Dr. Martin's branch sees 15 to 20 MS patients a week. Tr. at 213. Two of these patients came in after vaccinations. Tr. at 214. Dr. Martin could not come to any conclusion about them. Tr. at 215. It is remotely possible and plausible that hepatitis B vaccine is a cause. Tr. at 217. In a case

where someone has had reactions twice and the temporal relationship suggests there might be causation, Dr. Martin would advise against a third hepatitis B vaccination. *Id.* One can expect that an immune response to an antigen will take a few days to a maximum of three to four weeks for an acute reaction. Tr. at 219. If something occurred earlier than a day, it must be related to super antigen stimulation. Tr. at 219-20. Dr. Martin expects that the time frame for an adverse reaction would be five to six days to four weeks in an acute event. Tr. at 220.

In the case of vaccines, super antigens are not involved because they are not part of the vaccine. *Id.* Dr. Martin would want to see T-cells really increase in number in a relevant organ compartment. Tr. at 221. In MS, he would want to see expansion or stimulation of T-cells by either the vaccine or the infectious agent and the cross-reacting protein from the cerebral spinal fluid. Tr. at 221-22. Cross-reactivity alone is not useful any more. Tr. at 222. One in a thousand individuals in our population has MS. Tr. at 230. Dr. Martin cannot answer how likely it is that somebody's MS is exacerbated or develops de novo in the context of an infection or a vaccination. *Id.* In MS patients, when cells are stimulated long enough, there may be populations of cells that do not need that second stimulus any more. Tr. at 239. Dr. Martin strongly believes that immune activation that is strong enough to lead to an autoimmune condition needs a certain context, i.e., innate immune activation and other things to occur during a natural infection that do not occur during vaccinations in almost any instance unless the vaccination includes a live virus. *Id.*

Dr. Martin stated that our T-cells develop and T-cell receptor selection occurs in the thymus. Tr. at 240. T-cells in the thymus recognize self peptides, which are important for selecting cells negatively and positively. *Id.* Those cells that respond very strongly to self

peptides are eliminated. *Id.* Although Dr. Martin agrees that you need host susceptibility, some kind of environmental antigen at the proper time, local inflammation, release of self antigens, and a sufficient number of autoreactive T-cells to have an autoimmune reaction, he would not say a vaccine causes this without epidemiologic support. Tr. at 243-44.

There are genetic factors that are important in determining the ease of activating a cell, and how easily it grows and makes cytokines that are dysregulated in patients with autoimmune diseases. Tr. at 245-46. Co-stimulation is needed to activate T-cells under usual circumstances and this system may be disturbed in MS patients. Tr. at 246. The most recent categorization of MS patients has defined four subgroups of MS and antibodies are important in one of the four subgroups. Tr. at 260.

Dr. Carlo Tornatore, a neurologist, testified for petitioner. Tr. at 496. Mrs. Werderitsh's first hepatitis B vaccination was on November 11, 1992. She experienced transient left hemianopsia, meaning she lost vision in one segment of her eye, lasting about 30 minutes. Tr. at 522. She also had some bright spots in her visual field which resolved spontaneously. These visual symptoms had occurred intermittently over the prior 10 years and were associated with dull headaches, but this one episode was not. *Id.* Dr. Scott Hoyer, her neurologist, opined that these transient monocular visual symptoms in Mrs. Werderitsh's right eye were suggestive of optic neuritis. Tr. at 523. They occurred several days to a week after the first vaccination. *Id.*

After the second hepatitis B vaccination on December 16, 1992, she had symptoms of transverse myelitis with the Brown-Séquard syndrome, which is inflammation of the spinal cord. *Id.* Dr. Tornatore testified that Mrs. Werderitsh seemed immediately to fit into the phenomena of challenge/rechallenge we had seen in the Stevens case. *Id.* But these were not the same

symptoms occurring twice. These were symptoms in different areas of the central nervous system (the eye and the spine). Tr. at 524. In that sense, Mrs. Werderitsh's case is unlike Mrs. Stevens' case where the same symptoms occurred after each of her two hepatitis B vaccinations. *Id.* Mrs. Werderitsh had an inflammatory component in two symptoms separated in space. The brain MRI showed two lesions of the centrum semiovale area posteriorly. However, clinically, the problem was more in the spinal cord. *Id.*

Subsequently, Mrs. Werderitsh had tremendous difficulties with bladder and bowel related to her spinal cord problem. Tr. at 525. She developed optic neuritis in November 1997. Her MRI in November 1998 got worse, revealing four enhancing lesions. *Id.* Following the first vaccination, she had symptoms, and following the second vaccination, she had more symptoms. Whether she was normal before hepatitis B vaccination is very hard to say. Tr. at 526. Either the vaccinations caused her MS or significantly aggravated an undiagnosed. MS. *Id.* Dr. Tornatore thinks Mrs. Werderitsh's MS is pretty typical except for the two vaccinations. Tr. at 530.

Dr. Thomas P. Leist, a neurologist, testified for respondent. Tr. at 619. Mrs. Werderitsh developed left leg numbness of several days duration six to eight weeks after her first hepatitis B vaccination. Tr. at 620. She told Dr. Hoyer that she had a longstanding history of transient visual symptoms dating back 10 years, and that she also had one of these symptoms in the prior months. It is unclear from the records whether this happened after the vaccination. Dr. Hoyer documented a sensory level at the T4-T6 level of the spine, indicating a possible transverse myelitis. Tr. at 620-21. A spinal cord MRI was normal. Tr. at 621. Since spinal cord MRIs done in the early nineties had technical difficulties, Dr. Leist places more value on the findings of the physician. *Id.* A brain MRI found two lesions. *Id.* A lumbar puncture showed oligoclonal

banding. *Id.* Mrs. Werderitsh had clinical and MRI findings of dissemination in space, i.e., brain lesions and, on clinical examination, spinal cord lesion. *Id.*

Oligoclonal banding indicates dissemination in time. Tr. at 622. Mrs. Werderitsh also had a longstanding history of transient visual symptoms. *Id.* Visual evoked potentials (an objective test to determine injury to the nerves) were not done. *Id.* As of January 1993, Ms. Werderitsh had signs of a disseminating process over time, as well as oligoclonal bands and a history of visual disturbance. Tr. at 623. In 1998, she had new lesions on MRI and four gadolinium-enhancing lesions, indicating acutely active areas of inflammation. *Id.* In addition, she had progression of motor findings. Dr. Leist testified that Mrs. Werderitsh unquestionably has MS. *Id.*

Dr. Leist's opinion is that Mrs. Werderitsh's MS began before her first hepatitis B vaccination. Tr. at 624. His basis is the presence of oligoclonal banding and her long history of visual symptoms. *Id.* Mrs. Werderitsh's serum titers were negative for hepatitis B surface antigen on two occasions, indicating to Dr. Leist that she did not have a fulminant immune response to hepatitis B vaccination, at least as measured by serum titers. Tr. at 625. Therefore, Dr. Leist doubts there was an association between the vaccine and Mrs. Werderitsh's MS. Tr. at 625-26.

On cross-examination, Dr. Leist admitted that Mrs. Werderitsh may have had MS with minimal clinical symptoms for an extended period of time before she received hepatitis B vaccination. Tr. at 627. It is often difficult to pinpoint when MS starts. Tr. at 628. Oligoclonal bands indicate a subacute process of longer standing (months, not weeks). Tr. at 631. Dr. Leist finds fault with the Konstantinou report about two episodes of leukoencephalitis after two

hepatitis B vaccinations because the authors did not examine the patient's spinal fluid. Tr. at 641-42. The case report is an interesting observation but does not amount to a rechallenge. Tr. at 642. The authors could have found oligoclonal banding if they had looked. *Id.* They did not do cytology, i.e., taking cells from the patient's spinal fluid and seeing whether there were inclusions (viruses that can cause demyelinating diseases). Tr. at 643. However, Konstantinou is not discussing a patient with MS. Tr. at 644. Dr. Leist did not deny the patient had leukoencephalitis. He just did not know if she had other diseases because there are multiple viruses that can cause it. *Id.*

There are various phenotypes of MS, including primary progressive, which is insidious in onset and continues a long time; the general course, which is relapsing and remitting; and when someone has MS for a period of time, the secondary progressive MS, where relapses occur less frequently, and the neurologic disability progresses in the absence of relapses. Tr. at 646-47. Afterwards, there is the intermediate, which is the relapsing progressive MS, in which the patient has an initial event and afterwards develops a more progressive course. Tr. at 647. The cause of MS has a genetic element as well as an environmental component. Tr. at 648. In Mrs. Werderitsh's case, there is very little evidence of a T-cell or B-cell response to the vaccination. Tr. at 650.

According to the medical literature, there is no evidence that hepatitis B vaccine exacerbates MS. Tr. at 693-94. The statistical and experimental evidence indicates to Dr. Leist that it is unlikely that recombinant hepatitis B vaccine causes MS. Tr. at 702. Mrs. Werderitsh's MS, which predates her vaccination, and the vaccine are completely independent events. Tr. at 702-03.

On rebuttal, Dr. Tornatore testified that the oligoclonal band and spinal fluid analysis were done two and one-half months after Mrs. Werderitsh's first hepatitis B vaccination. Tr. at 812-13. That is an adequate time frame for the first vaccination to have caused the oligoclonal bands to develop. This is shown in animal models where oligoclonal bands occur six weeks after inoculation. Tr. at 813. The oligoclonal bands do not by themselves indicate a chronic condition and could have been a result of the first vaccination. *Id.*

The ten-year history of Mrs. Werderitsh's visual problems is difficult to interpret. *Id.* Mrs. Werderitsh's treating neurologist felt she had an episode of optic neuritis after the first vaccination and, if her visual symptoms prior to vaccination were due to migraine headaches, she still remains a challenge/rechallenge case. Tr. at 813-14.

DISCUSSION

This is a causation in fact case. To satisfy her burden of proving causation in fact, petitioner must offer "(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, supra, at 1149. Mere temporal association is not sufficient to prove causation in fact. Hasler v. US, 718 F.2d 202, 205 (6th Cir. 1983), cert. denied, 469 U.S. 817 (1984).

Petitioner must show not only that but for the vaccine, she would not have had MS or an exacerbation of MS, but also that the vaccine was a substantial factor in bringing about her MS or exacerbation of 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, supra, at 1327; Althen, supra, 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, supra, at 1278; Grant, supra, at 1148), and medical probability rather than certainty (Knudsen, supra, 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, supra, at 549:

> 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.

The Federal Circuit stated in Althen, supra, 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."

As the Federal Circuit stated in Knudsen, supra, at 548, "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." The undersigned's task is to determine medical probability based on the evidence before the undersigned in this particular case. Althen, supra, at1281 ("judging the merits of individual claims on a case-by-case basis").

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, supra, at 550, 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.

The Federal Circuit in Knudsen, supra, at 549, also stated: "The special masters are not 'diagnosing' vaccine-related injuries." In the instant action, both sides agree that petitioner has

MS. No one seems to know the onset. She could conceivably have had a subacute or mild case of MS for ten years prior to her first hepatitis B vaccination because her visual difficulties a few days to one week after her first hepatitis B vaccination were similar to what she had experienced in the context of migraines for ten years.

However, there is no question that when petitioner finally saw Dr. Hoyer, a neurologist, the month after her second hepatitis B vaccination, she had symptoms of TM. Her neurologic course was diagnosed as MS because she had lesions disseminated over time and space. MRIs of her brain showed two and later four lesions. MRIs of her spine were inconclusive, but the clinical evidence of inability to use her left leg and loss of bladder control ineluctably led to the conclusion that Mrs. Werderitsh has a particular central nervous system, demyelinating disease identified as MS.

The Federal Circuit in Capizzano emphasized the opinions of petitioner's four treating doctors in that case in concluding causation of rheumatoid arthritis from hepatitis B vaccination. 440 F.3d at 1326. In the instant action, none of Mrs. Werderitsh's the treating doctors opines that hepatitis B vaccine caused her MS. The closest any of them comes is Dr. Hoyer's statement that her MS is temporally related to her vaccinations. However, the fact that the treating doctors in this case do not support petitioner's allegation of causation from hepatitis B vaccine does not mean that petitioner's case fails.

In a topic as heavily studied, both biologically and epidemiologically, as MS's relationship to hepatitis B vaccine, it is a particularly serious question that the undersigned has to answer. Certainly, to paraphrase petitioner's expert Dr. Vera Byers, if someone with the phenotype of MS that is relapsing/remitting were to allege that hepatitis B vaccine worsened his

or her MS, the undersigned might find it impossible to determine whether the vaccine played any role in the course of an illness that, by itself, is episodic.

This case, however, does not concern relapsing/remitting MS. It concerns a progressive MS whose onset may or may not have preceded vaccination. If Mrs. Werderitsh did have MS before her first hepatitis B vaccination, it was certainly mild, manifesting only as visual disturbances, the same symptom she had a few days to a week after her first hepatitis B vaccination. But the symptoms she had within weeks of her second hepatitis B vaccination, i.e., inability to use her left leg and bladder incontinence, were far more serious symptoms of her MS, showing the progression.

Although there are many articles supporting or denying whether there is epidemiologic proof that hepatitis B vaccine causes MS, the Federal Circuit in Knudsen, supra, does not require epidemiologic support in order for petitioner to prevail. In addition, the Federal Circuit in Knudsen states that petitioner does not have the burden of proving the specific biologic mechanism to support her allegation of causation in order to prevail. Here, as is clear from the testimony of respondent's Dr. Martin, the scientific concepts that specialists in the MS area, such as Dr. Martin, are discussing today are different than the concepts they enunciated when they published their articles (many of which both parties filed in evidence herein). Whereas formerly, cross-reactivity of T-cells and the idea of molecular mimicry were the focus of investigative doctors, now Dr. Martin asserts these concepts are out of favor. The least we know in demyelinating diseases is that the body, for both genetic and environmental reasons, attacks itself, resulting in stripping away of the myelin sheath (GBS, CIDP) or in lesions (TM, MS).

The article respondent filed as Ex. 1, the Piaggio article, to show that there was no difference in T-cell proliferation or cytokine production among hepatitis B vaccinees who had demyelinating diseases and hepatitis B vaccinees who remained healthy is not dispositive because the authors admit their study was small and its power thereby reduced. In any event, the authors may have been looking for the wrong specific biological mechanism. That medical science still does not have the complete explanation for the causation of demyelinating diseases post-vaccination is legally irrelevant. *See* Knudsen, supra.

All the experts herein agree that Mrs. Werderitsh has a genetic propensity for MS. All the experts involved in the study of MS agree that in order for a patient to have MS, that person also needs an environmental component. But what that component is (virus? vaccination?) and when it should occur (puberty? post-puberty?) is unclear. Petitioner's expert Dr. Tornatore believes that hepatitis B vaccine is the environmental component. If Mrs. Werderitsh had a mild form of MS before her first hepatitis B vaccination, the vaccination (and its second dose) significantly aggravated her MS, bringing on the progressive form. If Mrs. Werderitsh had merely migraine-headache-induced visual disturbances before her first hepatitis B vaccination, then the vaccination (and its second dose) caused and worsened her MS. His basis is that the temporal relationship of days to a week after the first vaccination of optic neuritis and a month after the second vaccination of mononeuritis in the left leg and neurogenic bladder make medical sense for a cause and effect relationship, and that vaccines can cause demyelinating diseases (Dr. Tornatore was petitioners' neurological expert for the Omnibus proceeding concerning hepatitis B vaccine and GBS, CIDP, TM, and MS). Petitioner's immunologic expert Dr. Byers testified about the numerous biologic theories (cross-reactivity, molecular mimicry, autoimmunity). The

very least we know is that due to both genetic propensity and environmental influence, the body of someone with MS attacks itself, causing lesions in the brain and spinal cord over space and time.

Respondent's expert Dr. Leist thinks that the hepatitis B vaccinations and Mrs. Werderitsh's MS have no relationship to each other. His opinion is based on the failure of valid epidemiologic studies to show a relationship, the absence of the knowledge of the appropriate biologic mechanisms responsible, and Mrs. Werderitsh's not producing antibody to hepatitis B surface antigen according to two test results. Legally, the absence of epidemiologic support for linking hepatitis B vaccine and MS, and the lack of identification of the specific biologic mechanism at work if hepatitis B vaccine causes MS do not prevent petitioner from satisfying her burden of proof. *See* Knudsen.

As for Dr. Leist's conclusion that Mrs. Werderitsh's not producing antibodies to hepatitis B surface antigen means that hepatitis B vaccine could not have caused her MS, his statement was based on the Piaggio article. But the authors of that article stated that their conclusions were tempered by the fact that their study was small and its power thereby reduced. Moreover, Dr. Leist's statement presumes that whatever biologic mechanism is involved in petitioner's body's attacking itself is linked to antibody production. But since we do not know the specific biologic mechanism involved, the undersigned cannot conclude that petitioner's failure to produce antibodies to hepatitis B vaccine's surface antigen means she did not have another type of mechanism unrelated to antibody production in response to hepatitis B vaccine that caused or exacerbated her MS. Dr. Martin, respondent's expert, testified that some patients' MS is antibody-mediated, but other patients' MS is T-cell-mediated. In addition, Dr. Martin said there

are four subgroups of MS, and antibodies are relevant for only one of those four subgroups. Dr. Leist's conclusion that hepatitis B vaccine, since it failed to produce antibodies in Mrs. Werderitsh, could not have caused or exacerbated her MS ignores the other three types of MS that Dr. Martin described for which antibodies are irrelevant.

Dr. Martin's explanation of how MS occurs is that, together with host susceptibility (the genetic factor), a MS patient had to have been exposed to some kind of environmental antigen at the proper time, leading to local inflammation, release of self antigens, and a sufficient number of autoreactive T-cells to have an autoimmune reaction. (The undersigned notes that Dr. Martin does not believe that vaccines, particularly non-live virus vaccines, cause MS because of the lack of epidemiologic evidence and of an understanding of the specific biologic mechanism involved. These two deficiencies are not legally relevant. *See* Knudsen.)

The undersigned accepts Dr. Martin's testimony of the current explanation of how MS occurs and regards it as the best description among those Dr. Byers and Professor Dunbar offered in arriving at a medical theory causally connecting the vaccinations and petitioner's injury, which is the first criterion that petitioner must satisfy. Althen, supra, 418 F.3d at 1278, 1282. (That this best explanation comes from respondent's expert, rather than petitioner's experts, is irrelevant to the undersigned's task to determine the issues in this case. *See* Sword v. Secretary of HHS, 44 Fed. Cl. 183, 188 (1999) (the undersigned's reliance on both sides' experts' testimony in ruling for petitioners was "the most intellectually satisfactory explanation of the entire factual record.")

The undersigned concludes that the medical theory causally connecting the vaccinations and petitioner's injury is that Mrs. Werderitsh, who is genetically predisposed to developing MS, was exposed to the environmental antigen of two hepatitis B vaccinations, producing

inflammation, self antigens, and a sufficient number of T-cells to have an autoimmune reaction later diagnosed as MS.

Dr. Tornatore's testimony satisfies the second criterion of Althen that petitioner has the burden of providing a logical sequence of cause and effect from the first hepatitis B vaccination to optic neuritis and the second hepatitis B vaccination to mononeuritis and neurogenic bladder. He testified that, although petitioner's symptomatology after each vaccination was different, the fact that she had central nervous system symptoms within a medically appropriate time after each vaccination is reminiscent of the challenge/rechallenge Dr. Tornatore described in the Stevens case in which Mrs. Stevens had two episodes of TM within a medically appropriate time after each of her two hepatitis B vaccinations, thus indicating both in this case and Mrs. Stevens' case that petitioners were immunologically reacting to hepatitis B vaccine..

As for the third criterion in Althen that petitioner prove a proximate temporal relationship between vaccination and injury, Dr. Martin testified he would expect that an immune response to an antigen will take a few days to a maximum of three to four weeks for an acute reaction. Mrs. Werderitsh's visual disturbance occurred a few days to a week after her first vaccination, and her mononeuritis and neurogenic bladder occurred four weeks after her second vaccination. He also testified that when someone has had reactions twice and the temporal relationship suggests there might be causation, Dr. Martin would advise against a third hepatitis B vaccination. Dr. Tornatore's testimony about the appropriate temporal relationship for causation was consistent with Dr. Martin's. Thus, Dr. Martin's and Dr. Tornatore's testimony satisfies the third criterion to prove causation in fact. Althen, supra.

The undersigned holds that hepatitis B vaccine caused or significantly aggravated petitioner's MS. It appears that she had a decade's worth of visual disturbance that was similar to her visual problem a few days to a week after the first hepatitis B vaccination, which Dr. Hoyer opined could be optic neuritis. The undersigned notes that the Federal Circuit in Althen affirmed the Honorable Susan G. Braden's decision that tetanus toxoid caused petitioner's optic neuritis and acute disseminated encephalomyelitis (ADEM), which is TM plus brain lesions. 418 F.3d at 1281. Ms. Althen's optic neuritis, which preceded her ADEM, occurred a little over two weeks after vaccination, which was "a medically-accepted time period for causal connection." 418 F.3d at 1277. (The difference between ADEM and MS, since both concern lesions in the brain and spinal cord, is that MS lesions occur over time as well as space. ADEM is monophasic, whereas MS is polyphasic.)

A month after Mrs. Werderitsh's second hepatitis B vaccination, she lost the ability to use her left leg and to vacate her bladder. MRIs identified brain lesions, at first two and then later four. Although the spinal MRIs never revealed abnormalities, Mrs. Werderitsh's clinical symptoms underscore the correctness of the diagnosis of MS (which no expert in this case doubted in any event).

Petitioner has shown a medical theory causally connecting the vaccination and the injury, a logical sequence of cause and effect showing the vaccine caused her injury, and a proximate temporal relationship between her vaccinations and injury through the testimony of both sides' witnesses, the facts elicited from the medical records, and the medical literature. Petitioner has prevailed in proving that hepatitis B vaccination caused or significantly aggravated her MS.

This is the last of the four paradigm cases in the Omnibus proceeding concerning whether hepatitis B vaccine can cause demyelinating diseases. The undersigned has held that hepatitis B vaccine can cause TM, GBS, CIDP, and MS. Sixty-two other cases alleging hepatitis B vaccine caused demyelinating diseases have been pending the resolution of this Omnibus proceeding, and the undersigned will now address these pending cases, expecting that issues will arise as to proper diagnosis, onset intervals, and, in the case of MS, what type of MS is involved (relapsing/remitting or progressive). It would speed the resolution of these cases if petitioners' counsel ascertained that they have filed all the medical records (particularly pre-vaccination and immediate post-vaccination records) in these cases.

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 to resolve the issue of damages.

IT IS SO ORDERED.

_____ _____

DATE Laura D. Millman
Special Master