In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 08-865V
March 14, 2011
To be Published

LISA CALISE,	*	
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Petitioner,	*	
	*	
v.	*	Neuromyelitis Optica (NMO);
	*	Devic's disease; flu vaccine;
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	antigenic trigger
	*	
Respondent.	*	

Ronald C. Homer, Sylvia Chin-Caplan, Boston, MA, for petitioner.
Michael P. Milmoe, Katherine C. Esposito, Washington, DC, for respondent.

MILLMAN, Special Master

RULING ON ENTITLEMENT[1]

Petitioner filed a petition on December 4, 2008 under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that flu vaccine which she received on December 19, 2005 caused her neurologic injuries, specifically Devic's disease.[2]

On July 16, 2009, petitioner filed an amended petition.

[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 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.

[2] Devic's disease is also known as neuromyelitis optic or NMO. Dorland's Illustrated Medical Dictionary, 31st ed. (2007) at 539. (Hereinafter, Dorland's.)

A hearing was held on June 29, 2010. Testifying for petitioner were Dr. John G. Steel and petitioner. Testifying for respondent was Dr. Martin Bielawski.

FACTS

Petitioner was born on August 14, 1959.

On December 7, 2002, she saw Dr. Anthony Adamo, a neurologist. She had clinical evidence of diabetic neuropathy, but her symptoms were also consistent with L5-S1 lumbosacral radiculopathy. Med. recs. at Ex. 2, p. 5.

On March 10, 2004, petitioner saw Dr. Stephen Greenberg with anisocoria[3] for one month. Her right eye had a larger pupil by 1 mm. Med. recs. at Ex. 8, p. 20.

On August 18, 2004, petitioner saw Dr. Alan Jacobson complaining of arthralgias that began about May 2004 in her joints as well as fatigue. She had a history of hypothyroidism. Her antinuclear antibody (ANA) measured 1:320 in a homogeneous pattern. Dr. Jacobson diagnosed petitioner with arthralgias with a history of increased parathyroid hormone. Med. recs. at Ex. 29, pp. 1, 2.

On December 19, 2005, petitioner received influenza vaccine.

On January 11, 2006, she went to Peninsular Regional Medical Center where she saw Dr. Jacek Malik. She gave a history that she was in the process of moving from New York to North Carolina and was particularly active in packing. She noticed pain and aching in her arms. While driving, she felt her right foot go numb. The numbness progressed to her entire right lower extremities. She was admitted to the hospital with weakness in her lower extremities, incontinence of urine, and the loss of most of the motor function in her lower extremities. Med. recs. at Ex. 5, p. 14. Petitioner was diagnosed with transverse myelitis after an MRI showed

[3] Anisocoria is "inequality in diameter of the pupils." Dorland's, at 93.

abnormal signal from C2-3 extending to T2 to T7-8. She had a swollen spinal cord. Med. recs. at Ex. 5, p. 15.

On January 12, 2006, Dr. Richard E. Bird, a neurologist, wrote, "The only possible antigenic focus would be a flu shot taken 3-4 weeks ago. She has had no insect bites. She has had no other viral illnesses." Med. recs. at Ex. 5, p. 17.

On January 13, 2006, petitioner was transferred to the ICU. Med. recs. at Ex. 5, p. 84.

On January 16, 2006, Dr. Camille Khawand noted petitioner had no fevers and no prior history of trauma and/or infectious processes. In mid-December, she received a flu shot. She denied any recent travel to the tropics, mosquito bites or tick bites, rashes, joint symptoms, chest pain, or shortness of breath. Med. recs. at Ex. 5, p. 19.

On February 1, 2006, Dr. Hilary S. Koyanagi noted that petitioner's oligoclonal bands were positive, her IgG index was elevated, and her ANA was 1:160. Med. recs. at Ex. 7, p. 3.

From June 26 to 29, 2006, petitioner was at Craven Regional Medical Center. Med. recs. at Ex. 14, p. 22. In his discharge summary, Dr. Wright D. Shields notes that her neuromyelitis optica[4] was "possibly vaccine related due to temporal association of flu vaccination." Med. recs. at Ex. 14, p. 23.

On May 12, 2006, Dr. Cameron noted that, about three days previously, she noticed pain in and behind her left eye especially on movement of her eye. Her vision started to fade. Now, she was getting a brown spot out of the vision on the temporal side, but could still see nasally. Dr. Cameron diagnosed her with optic neuritis. Med. recs. at Ex. 9, p. 10.

[4] Neuromyelitis optica is a "combined, but not usually clinically simultaneous, demyelination of the optic nerve and the spinal cord; it is marked by diminution of vision and possibly blindness, flaccid paralysis of the extremities, and sensory and genitourinary disturbances." Dorland's, at 1286.

On November 13, 2006, Dr. J. Griffith Steel, a neurologist, diagnosed petitioner with Devic's syndrome and stated in a letter to petitioner's prior attorney that petitioner had Devic's syndrome "(neuromyelitis optica) and continued:

> I believe that it is highly likely that the NMO is causally related to her receiving a flu shot a few weeks before onset of the illness. Vaccinations are known to cause a variety of inflammatory demyelinating syndromes in the central nervous system. I am not sure that NMO has specifically been reported as a consequence of flu vaccination, but there are many other similar disorders which have been causally related to the flu vaccination. There are no other potential causal factors present in this case. I believe that, within a reasonable degree of medical certainty, the flu vaccination was causally related to the NMO. I have personal experience with at least one other case when an individual experienced a severe form of transverse myelitis which was causally related to a vaccination. In retrospect, it is very likely that this individual also had NMO, although at the time (about 25 years ago), we did not recognize it as such.

Med. recs. at Ex. 15, pp. 59-60.

On February 12, 2008, Dr. Cameron did a recheck of petitioner's Devic's. She had no further episodes of optic neuritis and her color vision was back to normal in both eyes. Med. recs. at Ex. 19, p. 28.

On April 18, 2008, petitioner had an MRI done of her cervical spine. It showed worsening disc disease at the C5-6 and C6-7 levels. Her previous MRI showed atrophy of the thoracic spinal cord. Med. recs. at Ex. 20, p. 10.

On April 24, 2008, petitioner returned to Dr. J. Griffith Steel, who diagnosed her with right ulnar neuropathy. She had bilateral median neuropathies, worse on the left, and marked atrophy of the upper thoracic spinal cord. Med. recs. at Ex. 20, p. 17.

Other Submitted Material

As Exhibit 40, petitioner filed her affidavit stating that, within three weeks following flu vaccination, she had extreme pain in both arms. Ex. 40, p. 2. Subsequently, she had a tingling sensation in her right foot. Id. Then her right leg hurt and her arm pain worsened. Ex. 40, p. 3. On January 11, 2006, she limped to the emergency room and that was the last time she was able to walk. Id. Within one day, she had numbness in both legs and her trunk. Id. The doctors diagnosed transverse myelitis. In May 2006, she had a blinding brown spot in her left eye which was diagnosed as optic neuritis. Ex. 40, p. 4. In August 2006, she had optic neuritis in her right eye. Ex. 40, p. 5. The doctors diagnosed Devic's disease or neuromyelitis optica. Id. Petitioner has had relapses of Devic's four times and remains a paraplegic. Ex. 40, p. 6. She and her husband experienced their first wedding anniversary in the hospital. Ex. 40, p. 7.

As Exhibit 42, petitioner filed the expert report of Dr. J. Griffith Steel, petitioner's treating neurologist. Filed as Exhibit 43 is Dr. Steel's CV. He states that petitioner developed neuromyelitis optica, formerly known as Devic's syndrome, as a result of receiving an influenza virus vaccination on December 19, 2005. Three weeks after vaccination, on January10, 2006, she noticed paresthesias in the right foot and pain in the right leg. Ex. 42 at 1. By January12, 2009, both legs were weak. Id. A neurosurgical examination found a sensory level in the upper thoracic region. Id. An MRI of petitioner's cervical and thoracic spine showed a large enhancing process from C6-T5 with further extension of the abnormal signal from C3-T7 with swelling of the cord thought to be transverse myelitis. Id. Petitioner had no antecedent immune stress apart from the flu vaccination. Id. at 2. She had no fever, chills, rash, insect bite, or viral or bacterial illness for the prior two months. Id. The cerebrospinal fluid (CSF) IgG (immunoglobulin G) Index (a ratio of CSF IgG/CSF albumin to serum IgG/serum albumin) was 0.6, with the upper limit of normal 0.71. This was normal, thus indicating that an increased

amount of immunoglobulin in petitioner's cerebrospinal fluid was due to seepage from the blood through a disrupted blood-brain barrier rather than from intrathecal synthesis. Id. The spinal fluid data was consistent with an acute necrotizing myelitis. Id. On May 6, 2006, petitioner developed pain in and behind her left eye with diminished visual acuity. She was diagnosed with optic neuritis. Id. at 3. On June 26, 2006, Dr. Steel saw petitioner and diagnosed Devic's syndrome based on petitioner's history, neurological findings, and MRI findings. Id. On August 8, 2006, petitioner had optic neuritis in the right eye. Id. Petitioner has had recurrent attacks of optic neuritis and spinal cord exacerbations. Id. Dr. Steel defined neuromyelitis optica (NMO) and described its immunopathology as follows:

> Neuromyelitis optica, also known by its eponym Devic's Syndrome, is an inflammatory demyelinating disease of the central nervous system with a predilection for the spinal cord and optic nerves. … In a major single-center review from the Mayo Clinic, Wingerchuk et al. [citing to Dr. Steel's third attachment] identified 71 cases from 1950 to 1997. Antecedent viral illness preceded onset in 25% and immunizations in 3% (two patients, both with swine flu vaccine). Recently a case was reported of bilateral optic neuritis and ADEM occurring within 3 weeks of inactivated flu vaccination [citing to Dr. Steel's fifth attachment]. Thirty percent of NMO patients had some form of concomitant autoimmune disease [citing Wingerchuk]. … The pathology of NMO consists of extensive demyelination across multiple spinal cord levels, necrosis with cavitations, acute axon damage, and loss of astrocytes, immune complex deposition, and inflammatory infiltration with macrophages, granulocytes and eosinophils. … Lucchinetti et al. [citing to Dr. Steel's 12th attachment] …reported … findings [that] support humoral immune mechanisms in the pathogenesis of NMO. In particular, they found prominent eosinophil activation and infiltration in a perivascular pattern which is distinct from MS. Eosinophils are involved in acute allergic reactions. Misu et al. [citing to Dr. Steel's 13th attachment] reported marked loss of aquaporin-4 protein from NMO lesions and destruction of astrocytes, as distinct from Multiple Sclerosis. Analysis of the NMO lesions suggested that tissue injury is the result of classical humoral-mediated antibody-antigen activation of the complement cascade.

Id. at 4.

Dr. Steel then discusses inflammatory demyelinating diseases that occur typically two to three weeks after an infection or a vaccination. Id. at 5. The clinical course is rapid, involving weakness, paraplegia, incontinence, confusion, visual disturbances, and sometimes seizures. Id. The general category under which these illnesses fall is acute disseminated encephalomyelitis (ADEM). Id. Post-vaccination ADEM has been associated with numerous vaccines including influenza vaccine. Id. These disorders are presumed to be autoimmune, caused by a mistaken attack of the immune system against self-antigens. Id. at 6.

Although influenza vaccination has not been reported in the medical literature to cause NMO, Dr. Steel is personally aware of two cases from unpublished data. Id. In addition, his fifth referenced article (Huynh, et al.) reports a case of bilateral optic neuritis occurring within three weeks of flu vaccination followed three months later by ADEM. Id. This case fits within the NMO-spectrum disorder. Id.

Dr. Steel's arguments in favor of petitioner's Devic's disease or NMO being caused by influenza vaccination are: (1) influenza vaccine is a killed virus vaccine whose purpose is to engender a humoral antibody immune response which rises over the first two to three weeks and then gradually subsides (citing his 24th referenced article); (2) petitioner's illness onset occurred when she had peak antibody levels from the flu vaccine, which is typical for ADEM-spectrum disorders for which the medical community recognizes a causal connection; (3) NMO is a humoral-mediated immunological disease; the NMO-IgG antibody is the likely causative agent, but flu vaccine likely engenders a non-specific immune response that opens the blood-brain barrier, thus exposing the aquaporin-4 (AQP4) channel protein to circulating B-lymphocytes that manufacture antibodies leading to a classic antibody-antigen reaction, causing complement and

natural killer cell-mediated death of astrocytes and release of more AQP4 into the blood, precipitating more antibody in a self-reinforcing cycle, causing devastation; the frequent co-existence of other preexistent immunological disorders in patients with NMO (citing his ninth referenced article) suggests that the disease trigger may require two hits; (4) NMO is an acquired inflammatory central nervous system demyelinating disorder whose pathology is similar to the ADEM-spectrum disorders; NMO is more similar clinically to ADEM-related disorders than to MS; ADEM-spectrum disorders have been attributed to viral exanthems and vaccinations; (5) two previous cases of vaccine-related NMO were reported in the Wingerchuk article (citing his third referenced article); and (6) one case of bilateral optic neuritis three weeks after receipt of flu vaccine, followed later by ADEM, has been reported in the Huynh article (citing his fifth referenced article). Id. at 6-7. Dr. Steel concludes that NMO is a diagnosis that is often missed by most doctors who mistake it for MS. Id. at 7.

Attached to Dr. Steel's report (Ex. 42) are articles marked Tabs A through Y that consist of the references at the end of his report.

Tab C attached to Ex. 42 is an article entitled "The clinical course of neuromyelitis optica (Devic's syndrome)" by D.M. Wingerchuk, et al., 53 Neurology 5:1107-14 (1999). (The exhibit petitioner filed does not have page numbers.) On the fifth unnumbered page, Table 2, the authors note nine antecedent events before onset of monophasic NMO. Seven were viral illnesses, constituting 30% of the total. Two events were swine flu vaccination just before onset of monophasic NMO, constituting nine percent of the total.

Tab E attached to Ex. 42 is a review entitled "Post-vaccination encephalomyelitis: Literature review and illustrative case" by W. Huynh, et al., 15 J Clin Neuroscience 1315-22 (2008). The authors state that ADEM is one of several categories of primary inflammatory

demyelinating disorders of the CNS (central nervous system). Others include NMO, MS, transverse myelitis, and optic neuritis. Id. at 1315. Optic neuropathy and ADEM are rare complications associated with vaccinations. Id. Optic neuropathy recurred in one patient after repeat administrations of influenza vaccine. Id. "The presumptive mechanism is immune-mediated demyelination …." Id. The authors state, "Post-vaccination ADEM is associated with several vaccines including those for rabies, diphtheria-tetanus-polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B, and the Hog vaccine." Id. at 1316. As for ADEM after influenza vaccination, the authors state:

> The association between the influenza vaccination and ADEM has only come to light in the recent years, and hence there have been no large population studies and no estimated incidence rates. A 14-year-old female developed ADEM 2 weeks after an influenza vaccination, while 2 adult males, aged 62 and 70, were diagnosed with ADEM and transverse myelitis with acute motor axonal neuropathy respectively within 1 week of vaccination. [references omitted]

Id. at 1317.

The authors state that "patients who have a certain underlying genetic predisposition may be more prone to developing ADEM post-vaccination." Id. They make this comment after reflecting on the recognition by Berkovic et al.[5] that 11 of 14 children with SMEI (severe myoclonic epilepsy in infancy) in their study had mutations in the SCN1A gene and experienced vaccine-induced encephalopathy. Huynh and his co-authors queried "whether the SCN1A mutation was a predisposing factor waiting to be triggered by fever or other stresses. More than 50% of SMEI patients experienced their first seizure after DPT vaccination." Id. Similarly,

[5] S.F. Berkovic, et al., "De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study," 5 Lancet Neurol 488-92 (2006).

Huynh and his co-authors posit that ADEM post-vaccination may be related to an underlying genetic predisposition. Id.

In an illustrative case report, the authors discuss a 61-year-old man who received inactivated flu vaccine that was followed three weeks later in July with bilateral visual blurring, worse in the right eye, and bilateral pain on eye movement. Id. at 1321. "A clinical diagnosis of bilateral optic neuropathies complicating influenza vaccination was made." Id. In late September, he presented with a one-week history of increasing daytime somnolence, fluctuating alertness, and delirium. Id. The patient was diagnosed with ADEM. Id. at 1322. The authors state, "The patient's clinical presentation was most likely due to post-influenza vaccination optic neuritis and encephalomyelitis." Id.

Tab K attached to Ex. 42 is an article entitled "Neuromyelitis optica" by M. Matiello, 20 Current Opinion in Neurol 255-60 (2007). The authors (who include Wingerchuk) state that NMO is an idiopathic inflammatory disease of the CNS that primarily affects the optic nerves and spinal cord. Id. at 255. The specific biomarker of NMO is NMO-IgG whose target is the dominant water channel aquaporin-4 located in the astrocytes abutting cerebral microvessels at the blood-brain barrier. Id. at 255, 256. The authors state:

> In a **susceptible individual**, an unknown **antigenic trigger** stimulates production of circulating immunoglobulin (NMO-IgG). These antibodies are able to reach their target antigen, aquaporin-4, through a breach in the blood-brain barrier. Binding of the antibody and activation of complement leads to an inflammatory response. The complement fragments and cytokines such as interleukin-17 and interleukin-8, which are known to be elevated in NMO, recruit further inflammatory cells. The disruption of the cellular water transport mechanisms and the intense inflammatory necrosis characteristics of NMO may explain the radiologic and pathologic findings in NMO. [emphasis added.]

Id. at 256.

Tab S attached to Ex. 42 is an article entitled "Antibody to aquaporin-4 in the long-term course of neuromyelitis optica" by S. Jarius, et al., 131 Brain 3072-80 (2008). The target antigen of NMO-IgG is aquaporin-4 (AQP4), which is the most abundant water channel in the central nervous system. Id. at 3072. The authors state "[T]he presence of AQP4ab [antibody] alone may not be sufficient to cause disease; other factors, for instance, disease-specific T cells, raised cytokines, **unspecific stimulation by exogenous triggers** or damage to the blood brain barrier, might be required to initiate or cause tissue damage [emphasis added]." Id. at 3078.

Respondent filed an expert report from Dr. Martin Bielawski as Exhibit A. He states there are only theories and speculation that influenza vaccine can potentially cause NMO. Id. at 8. However, there are several studies showing that influenza vaccine does not cause central nervous system demyelinating disease, especially multiple sclerosis. Id. Dr. Bielawski mentions the Schattner, DeStefano, Patel, Confraveaux, and Kerr studies. Id. He states "it is not possible to distinguish whether a demyelinating event occurring shortly after vaccination is causal or coincidental. This requires careful, well-controlled epidemiologic studies. . . ." Id. at 9. Dr. Bielawski also mentions there are no animal models for NMO. He rejects analogizing NMO to ADEM because they are separate diseases. Id. "Therefore, factors that may trigger ADEM, such as vaccination, should not be assumed to trigger NMO." Id. Dr. Bielawski states the only demonstrable association between petitioner's demyelinating disease and flu vaccine is a temporal one and this does not prove causation. Id. Dr. Bielawski distinguishes the two cases of NMO Wingerchuk reported following swine flu vaccine from the instant action because swine flu vaccine is not seasonal flu vaccine which is the vaccine involved in this case. Id. at 9, 10. In addition, petitioner has relapsing NMO whereas the two patients in Wingerchuk's article had monophasic NMO and, therefore, Wingerchuk's article does not apply to this case. Id. at 10.

Dr. Bielawski states, "Perhaps there are genetic and environmental factors that influence the development and type of NMO, as is likely the case with multiple sclerosis." Id. He concludes that petitioner's NMO has no clear etiology. Id.

Respondent filed Dr. Bielawski's CV as Exhibit B, followed by Exhibits C through H consisting of medical articles.

Respondent's Exhibit D is an analytical review entitled "Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines" by A. Schattner, 23 Vaccine 3876-86 (2005). The author states, "The enigma of autoimmunity and autoimmune diseases appears to be driven by a complex interplay of genetic, hormonal and environmental factors." Id. at 3876. Autoimmune diseases reported after influenza vaccination included meningoencephalitis/encephalitis, optic neuritis, transverse myelitis, Guillain-Barré syndrome (GBS), brachial neuritis, and Bell's palsy. Id. at 3879. The author admits that seasonal flu vaccine can cause GBS amounting to 10.5% of recent GBS cases studied from 1992-1994. Id. He states, "Notably other neurological syndromes involving the CNS may rarely coexist, or occur independently following influenza vaccination." Id. at 3880. The author concludes that the autoimmune reactions identified "are suggestive, though not unequivocal, of autoimmunity; they form a well defined pattern of several types of organ damage consistent with autoimmunity …; they follow the vaccination and occur after a latent period of about 2 weeks …; no alternative explanation can be identified and in some instances a response to immunosuppressive therapy had been noted . . . ." Id. at 3881. He also states, "The effect of re-challenge, the diversity of autoimmune manifestations and an occurrence in identical twins suggest causal relationship in susceptible persons." Id. at 3882. "These characteristics provide supportive evidence for an association between vaccination and at least some of the reported

reactions…." Id. The author notes that studies ruling out an association lacked "the statistical power to rule out an *extremely rare* causal relationship…, as even a few well-documented case reports may suggest [emphasis in original]." Id. He states, "In conclusion, an extensive critical review of the literature reveals that very rare individual patients may develop certain restricted patterns of autoimmune damages following some of the viral vaccines, the most potentially serious being the neurological CNS and PNS reactions." Id. at 3883.

Respondent's Exhibit E is chapter 26 from Iatrogenic Neurology, ed. J. Biller (1998), entitled "Complications of Immunization" by H. Patel and B.P. Garg, 485-500. Referring to influenza vaccination, the authors say that the reported complications are too infrequent to establish a causal relationship except for GBS following swine flu vaccination. Id. at 496.

Respondent's Exhibit F is an article entitled "Vaccinations and the Risk of Relapse in Multiple Sclerosis" by C. Confavreux, et al., 344 NEJM 5:319-26 (2001). The authors found no risk of relapse of MS in MS patients following tetanus, hepatitis B, or influenza vaccination. Id. at 324.

Respondent's Exhibit G is an article entitled ""Immunopathogenesis of Acute Transverse Myelitis" by D.A. Kerr and H. Ayetey, 15 Curr Opin Neurol 339-47 (2002). The authors state it is unclear what are the triggers for acute transverse myelitis (ATM), but the disorder exists on a continuum of neuroinflammatory disorders including Guillain-Barré syndrome (GBS), multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica (NMO). Id. at 339. They write there are many common features in these disorders involving inflammation and neural injury. Id. They state there are a variety of humoral and cellular immune derangements that potentially result in neuronal injury and demyelination. Id.

The authors comment:

> Several reports of ATM following vaccination have recently been published. Indeed, it is widely reported in neurology texts that ATM is a post-vaccination event. One publication reports a case of post 'flu vaccine myelitis in which a 42-year-old man with a history of bilateral optic neuritis developed ATM 2 days after an influenza vaccination. A separate study reported a 36-year-old individual who developed a progressive and ultimately fatal, inflammatory myelopathy/polyradiculopathy 9 days after a booster hepatitis B vaccination. The patient had no fever or systemic illness and did not respond to extensive immunotherapy. Autopsy evaluation of the spinal cord revealed severe axonal loss with mild demyelination and a mononuclear infiltrate, predominantly T lymphocytes in nerve roots and spinal ganglia. The spinal cord had perivascular and parenchymal lymphocytic cell infiltrates in the grey matter, especially the anterior horns. The suggestion from such studies is that a vaccination may induce an autoimmune process resulting in ATM. However, it should be noted that extensive data continue to show overwhelmingly that vaccinations are safe and are not associated with an increased incidence of neurological complications. Therefore, such case reports must be viewed with caution, as it is entirely possible that two events occurred in close proximity by chance alone. [references omitted.]

Id. at 340-41.

The authors list in Figure 1 an "Immediate diagnostic approach to acute myelopathy" including criteria for a history and physical examination:

- Confirm acute myelopathy
- Elicit time c[o]urse and extent of deficits
- Determine signs, symptoms or prior history suggesting infection, systemic inflammatory disease, vascular/ischemia, neoplasia, multiple sclerosis, radiation exposure, neuromyelitis optica, or trauma
- **Determine if recent history of vaccination** or systemic illness [emphasis added.]

Id. at 341.

The authors then discuss the mechanisms by which exposure to an environmental antigen may induce ATM. They discuss molecular mimicry first. Id. at 342. They describe how GBS occurs among those who, due to the host's genetic factors, are susceptible to developing a

humoral response against their own myelin. Id. Transferring this knowledge about how molecular mimicry works in a genetically susceptible host, the authors then discuss this same process in ATM as the development of autoantibodies in response to an antecedent infection. They posit another mechanism by which ATM may occur, which is microbial superantigen-mediated inflammation. Id. They move on to the discussion of humoral derangements in patients with neuromyelitis optica (NMO) and recurrent ATM:

> The development of abnormal antibodies may then potentially activate other components of the immune system or recruit additional cellular elements to the spinal cord. Recent studies have emphasized distinct autoantibodies in patients with NMO and recurrent ATM. The high prevalence of various autoantibodies seen in such patients suggests polyclonal derangement of the immune system.
>
> However, it may not just be autoantibodies, but high levels of even normal circulating antibodies that play a causative role in ATM. A case of ATM was described in a patient with extremely high serum and cerebrospinal fluid (CSF) antibody levels to hepatitis B surface antigen after booster immunization. Such circulating antibodies may form immune complexes that deposit in focal areas of the spinal cord. Such a mechanism has been proposed to describe a patient with recurrent transverse myelitis and high titers of hepatitis B surface antigen. Circulating immune complexes containing hepatitis B surface antigen were detected in the serum and CSF during the acute phase, and the disappearance of these complexes after treatment correlated with functional recovery. [references omitted.]

Id. at 343.

The authors conclude:

> In summary, emerging evidence suggests that a variety of immune stimuli, through such processes as molecular mimicry or superantigen-mediated immune activation, may trigger the immune system to injure the nervous system. The activation of previously quiescent autoreactive T lymphocytes or the generation of humoral derangements may be effector mechanisms in this process.

Id. at 344. Eleven references at the end of the article are to papers discussing demyelinating illnesses after vaccination: reference 20 (flu vaccine and myelopathy); reference 21 (hepatitis B vaccine and inflammatory polyradiculoneuropathy with spinal cord involvement and death); reference 22 (MMR vaccine and GBS); reference 23 (swine flu vaccine and GBS); reference 24 (swine flu vaccine and GBS); reference 25 (hepatitis B vaccine and MS); reference 26 (flu vaccine, hepatitis B vaccine, intercurrent infections, and MS); reference 27 (hepatitis B vaccine and MS); reference 28 (vaccinations and risk of relapse in MS); reference 29 (flu vaccine and MS); and reference 85 (hepatitis B vaccine and acute transverse cervical myelitis). Id. at 345.

Respondent's Exhibit H is a review entitled "Disseminated encephalomyelitis in adults" by V.V. Brinar and C.M. Poser, 110 Clin Neurol Neurosurg 913-18 (2008). The focus of the article is disseminated encephalomyelitis (DEM) which the authors view as a separate disease from neuromyelitis optica (NMO). Both have similarities in that they involve demyelination of the spinal cord and can be monophasic or multiphasic. Id. at 913. The authors discuss four cases of DEM. In the first case, three weeks after receiving hepatitis B vaccine, a woman developed a left hemisensory deficit. Her MRI showed several paraventricular demyelinating changes typical of DEM. Id. at 914. In the second case, two weeks after a respiratory infection, a woman developed vertigo and ataxia. Her MRI showed extensive demyelination involving cortical and subcortical structures. Id. In the third case, a man developed recurring DEM with no obvious cause, but his relapses were triggered by different infections. Id. at 914-15, 917. In the fourth case, a woman developed recurring myelitis and she ultimately died from respiratory failure. Id. at 916.

The authors state that in addition to infections, different types of vaccines, particularly hepatitis B vaccine, may act as triggers of DEM which may explain the etiology of DEM in the

first discussed case. Id. at 917. They state, "Why one person after being challenged with a specific antigen develops DEM, and another person exposed to the same trigger does not develop disease, and yet another develops MS, is probably due to individual genetic susceptibility" [references omitted]. Id. They also state that DEM may be monophasic, recurrent, or multiphasic depending on different immune challenges and the individual's genetic make-up. Id.

Respondent's Exhibit I is an article entitled "Inflammatory/Post-Infectious Encephalomyelitis" by L. Bennetto and N. Scolding, 75 J Neurol Neurosurg Psychiatry (Suppl. 1) i22-28 (2004). The authors discuss forms of post-infectious and inflammatory encephalomyelitis, including acute disseminated encephalomyelitis (ADEM), post-infectious encephalomyelitis, and post-vaccination encephalomyelitis. ADEM includes post-infectious encephalomyelitis and post-vaccination encephalomyelitis. Id. at i22. MMR vaccine is most commonly associated with post-vaccination encephalomyelitis. Id. at i24. In Figure 1, the authors suggest treatment in a flowchart for ADEM. One of their suggestions is to avoid vaccinations for at least six months. Id. at i26. They state that because ADEM has been known to relapse into multiphasic demyelinating encephalomyelitis following routine vaccinations, "it would seem sensible to avoid vaccinations (or other immune stimulation) for at least six months following a diagnosis of ADEM." Id. at i27. They comment that it appears likely that parallel B- and T-cell mediated reactions generate central nervous system inflammatory change in ADEM. Id. They mention that molecular mimicry may be involved in the pathology of ADEM. Id.

TESTIMONY

Dr. J. Griffith Steel testified first for petitioner. Tr. at 4. (Petitioner's counsel called him Dr. John Steel.) He is a board-certified adult neurologist. Tr. at 6, 7. He treats patients with

demyelinating disorders of the peripheral nervous system, such as GBS and CIDP, and the central nervous system, such as MS, ADEM, neuromyelitis optica, optic neuritis, and transverse myelitis. Tr. at 8. Besides treating patients with neurological disorders, Dr. Steel is currently involved in a diabetic peripheral neuropathy clinical trial and about to be involved in a Parkinson's disease clinical trial, both for a large research organization. Tr. at 9. Dr. Steel is immediate past president of his county's medical society, and president elect for the North Carolina Neurological Society. Tr. at 10.

Dr. Steel is petitioner's treating neurologist and has been so since June 26, 2006. Id. When he saw her first, she was septic from decubitus ulcers and he hospitalized her. Id. He took a history from her that she received flu vaccine on December 19, 2005 and, shortly thereafter, experienced pain and paresthesias in her right leg, which progressed over a day or two to both legs, plus difficulty urinating. She became somewhat encephalopathic in that she was confused and had a headache. Tr. at 11. She was hospitalized on January 12, 2006 with weak legs and a sensory level in the thoracic region. Tr. at 12. An MRI of the cervical and thoracic spine showed abnormal swelling and contrast enhancement of a very large segment of her spinal cord. Id. The diagnosis during that hospitalization was transverse myelitis. Id.

When Dr. Steel became petitioner's neurologist in June 2006, after he reviewed her medical records, examined her, and learned she had a prior attack of optic neuritis, he changed her diagnosis from transverse myelitis to neuromyelitis optica. Tr. at 12-13. Neuromyelitis optica is also called Devic's disease. The old term, Devic's syndrome, is still used. Neuromyelitis optica is abbreviated as NMO. Tr. at 13. Devic's syndrome is in the same spectrum of disorders as MS, but is a distinct disorder. Tr. at 22. Dr. Steel testified:

> NMO is classified in standard neurology textbooks as an autoimmune demyelinating disease. That is, if you look in any

> standard neurology textbook. It's grouped together with other demyelinating disease and presumed autoimmune causation…. [I]t has a couple of hallmarks. One is limited spacial distribution in the spinal cord and/or the optic nerves, largely sparing the intervening brain.
> And then it also has a time course that somewhat differentiates it from multiple sclerosis. The time course for the initial attack tends to be very abrupt, relatively sudden with rapid progression, and then there are other differences both clinical and laboratory differences between it and the other demyelinating diseases, but they also share a great deal in common.

Tr. at 13-14.

Dr. Steel defined autoimmunity and the mechanisms through which it occurs:

> Well, all autoimmunity is an attack by the immune system against the body, against the self, and so fundamentally autoimmune disorders are disorders of the immune system failing to recognize itself or distinguish itself from non-self, and there are really two major theories as to what may go wrong with the immune system. One is the – it's called bystander hypothesis[.] [T]he other is the molecular mimicry hypothesis. Molecular mimicry hypothesis, which I believe everyone present knows, is that there is an autoantigen that is closely structurally similar to a true antigen, and the body's immune defense system cannot distinguish between normal and not normal, and so it attacks a normal constituent of the body.
> The bystander hypothesis differs somewhat in that the major theory there is that the immune reaction accidently causes collateral damage to adjacent healthy tissues, somewhat like collateral damage in a military attack, if you will. So you can think of, because I'm a military guy in the past, the collateral damage theory, the bystander hypothesis as collateral damage, and the molecular mimicry hypothesis as friendly fire.

Tr. at 14-15.

Dr. Steel described how flu vaccine can lead to the development of NMO:

> In my opinion, the flu vaccination that Lisa Calise received about three weeks prior to her disease was causally related, and a trigger to what ultimately developed into neuromyelitis optica in Lisa. The flu vaccination, as everyone knows, is virus particles. Virus is really not present but it is ground up, it is inactivated, and the

vaccination consists of basically ground up virus particles, so that the virus actually doesn't even exist. It cannot replicate. However, it can induce an immune response on the part of the body which is, of course, the purpose of all immunization is to vaccinate the patient.

Now, in this particular case, a very rare circumstance but in this particular case what I think happened was the viral particle, and it could be a protein particle, it could have been a fragment of the virus nucleotide, it really doesn't matter, frankly, what part of the virion particle triggered, but most likely some particle became attached to an MHC that's measure history compatibility complex type 1 protein which lines the endothelial cells. All endothelial cells, in fact, all nuclei cells of the entire body have MHC Type 1 protein attached to membranes.

Now, these proteins function similarly to antibodies. Technically they are not antibodies because they don't look like antibodies from a protein structure standpoint, but they function as antibodies because they recognize and capture alien particles in the blood. Now, the MHC Type 1 complex is, among other places … along the endothelial cells, and they are also in the brain, everywhere in the body. Now, if a particle, a virion particle latches onto a MHC Type 1 receptor, and incidently there are about 10,000 of these … proteins per cell, then that would trigger a change in the conformation of the MHC protein, thereby changing its confirmation such that a circulating T-cell, which can be thought of as the cop on the beat, recognizes that as a change, and the cell has changed. The cell surface proteins have changed …[and] they are now glommed onto or they have captured a virion particle. That process elicits an immune response that's primarily CD-8, T-8 cell cytotoxic reaction. That CD-8 cell is going to come in, and there is good evidence for this, that's what happens when MHC Type 1 receptors get activated because they [attr]act cytotoxic T-cells, which are also called CD-8 cells, and a cytotoxic T-cell then destroys the cell. …

Now if that happens, then you have to look at what's beneath the cell. [S]ay it's an endothelial cell in the brain that's been attacked by the T-cell, destroyed[.] [T]hat's what indeed exposes the astrocytic foot process where the aquaporin-4 protein resides. … The target antigen and the major discovery that has led to improved understanding of NMO in the last 10 years has been the discovery of two things: One, the NMO IgG antibody and, two, the target for that antibody, which is a protein called aquaporin, and specifically it's aquaporin-4. There are nine aquaporins. [A]quaporin-4 protein happens to be the protein that lines – the constituent protein of the brain water channels, particularly located in the spinal cord, diencephalon, and the optic nerves.

> … The exposure of the astrocytic foot process by destruction of the overlining protective endothelial cell exposes the aquaporin-4 protein to the blood which then precipitates a classic antibody antigen reaction immune-mediated initially by fixation of complement, and then cellular cytotoxicity … leading to a fairly rapid destruction of what the body views to be a foreign protein. This is a sequestered protein[;] other terms are cryptic antigen. The aquaporin-4 protein would be regarded as a cryptic or hidden antigen, and that elicits an immune response which then destroys the astrocyte, liberating more foreign protein, which then accelerates the antibody antigen reaction and therefore creating a chain reaction.
> [T]he net of all of that is you have a rather explosive immune-mediated response against the cryptic antigen, which is AQP4, led by a newly manufactured protein, which is the … NMO IgG protein, and the net effect is a destructive process that leads to necrosis of multiple cellular elements in the region, and I think this theory accounts for a lot of the biological plausible steps along the way in this immune process….

Tr. at 15-19.

The undersigned asked Dr. Steel what humoral immunity is. He replied:

> Hum[o]ral immunity was the prime point of a couple of article[s] published early on by Lucchinetti and a group of people from the Mayo Clinic, pointing out that, unlike multiple sclerosis, for example, NMO is presumed to be primarily mediated by the hum[o]ral immunity system, and there is certainly very good evidence for that.
> The primary evidence is the existence of the NMO IgG antibody itself, but then Lucchinetti also described, for example in the pathological specimens of spinal cord and optic nerve of some persons who had NMO, the presence of eosinophils, for example, which is evidence for hum[o]ral mediation, and also complement clusters, clusters that complement in the area of destruction. So the theory from the Mayo Clinic was that this is primarily a hum[o]ral mediated process.

Tr. at 19-20.

Continuing in his analysis of the biological mechanism underlying NMO, Dr. Steel said that the general immune response kills everything around it, including the astrocytes. Tr. at 20. This is important because scientists looking at pathological specimens from patients with NMO

made a histopathological microscopic finding of necrosis and cavitation, which means that all the cellular elements, not just the astrocytes but also the neurons, oligodendroglia cells, and supporting cells, were destroyed. Id. Even the vascular endothelium was rendered abnormal. Id. Fibrotic capillaries and arterials are in histopathological specimens in patients with NMO. (The transcript has "thybrotic.") Tr. at 20-21. Dr. Steel described this process as a very nonspecific, broad-based human reaction that basically kills everything and is more like ADEM than MS. Tr. at 21.

In explaining how the NMO IgG antibody forms, Dr. Steel said that something exposes the aquaporin-4 protein to the blood, resulting in a generalized large scale necrotizing inflammatory response. Id. The NMO IgG antibody is manufactured in response to the release of the aquaporin-4 potential from its home. Id. Aquaporin is a transmembrane protein anchored in the astrocytic foot process, i.e., an anchored stationary protein. Tr. at 22. It does not float around. Id. It has to be freed from its anchor in order for the plasma cells, which ultimately form an antibody against it, to ingest the aquaporin. Id. Dr. Steel stated what liberates the aquaporin from its anchor is the T-cell cytotoxic reaction first and then the plasma cells which ingest it and make antibodies to it, which then accelerates the process so that it becomes self-sustaining. Id.

Aquaporin is a protein and a constituent protein of water channels. Tr. at 23. The water channels, surrounded by the aquaporin protein, regulate the influx and efflux of water in and out of brain tissue. Tr. at 22-23. The distribution of aquaporin-4 protein is very asymmetric and is concentrated in the spine and optic nerves as well as the deep center part of the brain, called the diencephalon region, and the ependymal cells lining the ventricles. (The transcript has pendimal

instead of ependymal.) Tr. at 24. The location of aquaporin-4 is the same as the vulnerable regions in neuromyelitis optica. Id.

The current treatment for neuromyelitis optica is designed to reduce the population of B-cells by use of Rituximab or Rituxan, a treatment of choice not based on double-blind placebo trials because the disorder is so rare, one could never find enough patients to conduct such a trial. Tr. at 25. In at least 50 percent of NMO cases, NMO is a relapsing disorder and the key to treatment is to prevent the relapses. Id. Reducing the B-cell population reduces the amount of NMO IgG in the system. Tr. at 27.

T-cells are involved very early in NMO and serve only as the initiating factor. After that, the sustaining factor in NMO and the most likely cause of relapses is primarily humoral immunity, which is a B-cell function. Tr. at 25-26. The aquaporin-4 antigen is a key target of the NMO IgG antibody. The NMO IgG antibody is a pathological antibody and the key agent in the disorder. Tr. at 26. The level of the NMO IgG antibody correlates with the likelihood of having a relapse. Tr. at 28. A rising level of antibodies preceded clinical relapses while treatment aimed at reducing the level of NMO IgG antibodies seemed to prevent relapses. Id.

When the undersigned asked Dr. Steel what role, if any, influenza vaccine plays in the occurrence of neuromyelitis optica, he replied:

> I feel that the influenza vaccine served as a trigger to unmask by binding of the MHC-1 proteins with the virion particles, the vaccination particles, that served to kill the endothelial cells, at least some endothelial cells, thereby exposing the astrocytic foot processes. So the flu vaccine, in my opinion, in Lisa's case in particular, is the prequel or the precedent antecedent event that leads to the exposure of the aquaporin-4 protein which then leads to the production of the antibody, then leads to the explosive and progressive and relapsing nature of this disorder.

Tr. at 29-30.

Dr. Steel testified that it was his understanding that all neuromyelitis optica occurrences happen because of some trigger. Tr. at 31. There is a very high co-morbidity of individuals who have or develop NMO who have preexistent autoimmune diseases. Id. In his opinion, Dr. Steel stated that any immunogenic stress can trigger an autoimmune response. That can include a vaccination, or even stepping on a nail. Tr. at 32. Dr. Steel had a patient when Dr. Steel was a resident who pricked his thumb on a rose thorn which triggered a violent and destructive immune-mediated process against his spinal cord called acute necrotizing myelitis, leaving him a paraplegic. Id. Dr. Steel does not know if anyone can enumerate all the triggers, but there have been causal relationships established between an infection, such as cholera, Epstein-Barr virus, cytomegalovirus, campylobacter jejuni, and tuberculosis, and autoimmune diseases. Tr. at 33.

For example, the axonal variant of Guillain-Barré syndrome has a homology with an intestinal bacterium called campylobacter jejuni. Id. There is a similarity or homology between the structure of the bacterial wall and the coat of the bacterium campylobacter jejuni and peripheral myelin. One of the treatments for the axonal variant of GBS is to treat the stomach with antacid and antibiotics, which improves the odds of the patient getting better. Id.

Dr. Steel agreed that, for reasons that science does not yet understand and which may be genetic, there are certain people who, when exposed to an antigenic challenge from a vaccine, a nail, a rose thorn, a bacterium, or a virus, do not react as the rest of us do, but in a way that destroys their body. Tr. at 34. This opinion is widely supported by many experts. Id. Genetic research on NMO has not advanced as far as it has for multiple sclerosis. In MS, there are individuals from Northern Europe, who have certain HLA alleles linked to MS. NMO, on the other hand, is very common among Asians implying a genetic/racial difference in prevalence in those diseases. Tr. at 34-35.

Dr. Steel's opinion is that if petitioner had not received flu vaccine, she would not have had NMO or at least not at the time she did, based on the flu vaccine being a trigger and petitioner's having no other known trigger. Tr. at 35. The time frame between her flu vaccination and the onset of her NMO is appropriate for a relationship between the two. Id. Petitioner became ill about 20-21 days after receiving the vaccination. Tr. at 36. Dr. Steel stated:

> [I]t takes a little while for the body to gear up and make the protein antibody once vaccinated. If you or I receive a vaccination, it takes our bodies a little while, and there [are] some graphical charts in introductory immunology textbooks that show a rise in the antibody titer over days following a vaccination, typically peaking at between 14 and 21 days after receipt of the vaccination, and there[after] beginning to slowly tail off over a long period of time. So vaccine-related injuries seem to be most likely to occur in the timeframe between 14 and 21 days, plus or minus….

Tr. at 37.

In his expert report, Dr. Steel emphasized certain similarities between NMO and ADEM and this is significant because medical literature has quite frequently associated prior vaccinations with ADEM over the same temporal period. Tr. at 37-38.

In response to respondent's expert Dr. Bielawski's report in which he stated he would not support causation of NMO from flu vaccine because of the absence of epidemiological studies, compared to anecdotal reports, and the absence of animal experiments, Dr. Steel stated that the first is a statistical argument. Tr. at 38. He estimates that the incidence of NMO is about 1/1000 prevalent as MS based on his own experience of having 2,000 new MS patients, but only two NMO cases, over a 30-year career. That makes the incidence of NMO about .008 for 100,000 person-years or .08 per million. Tr. at 39. Retrospective population-based survey studies have a sensitivity of about one per million, i.e., they can detect a signal of about one per million

persons. But the natural incidence of NMO is far below one per million person-years so a survey study will not detect it. It is too rare. Id. As for animal studies, Dr. Steel does not know if there is any animal model for NMO because he has not reviewed all the literature. In the last three years alone, there have been 850 abstracts in the National Library of Medicines Pub. Med. database on neuromyelitis optica. Tr. at 40.

Dr. Steel has advised petitioner not to have future flu vaccinations. Id. He feels that flu vaccine was the key trigger that initiated the immune response that ultimately led to petitioner's NMO. Tr. at 41. Biological plausibility underlies his opinion. Id. First, there is the temporal relationship. Secondly, there is the innate immune system with its MHC Type 1 receptors on the endothelial cells which, when confronted with an antigen, results in the triggering of a cytotoxic CD-8 cell reaction against the endothelial cells. This is a logical and defensible theory of causation in a stepwise fashion, which is how the immune system works. Tr. at 41-42. Dr. Steel considers "trigger" and "cause" to be pretty much the same. Tr. at 42. His opinion is that flu vaccine played a substantial role in causing petitioner's NMO. Tr. at 43. In summary, his opinion is that flu vaccine can cause NMO, that it did cause NMO in petitioner, and that the temporal interval between flu vaccination and onset of NMO was medically appropriate for causation. Tr. at 43-44.

On cross-examination, Dr. Steel was asked about petitioner's bronchitis in November causing her NMO in January. Tr. at 46. Dr. Steel replied that the timing was not reasonable for causation. Id. It would be unlikely that the bronchitis caused petitioner's NMO. Tr. at 47. Petitioner's pre-vaccination immunological status was abnormal in that her ANA was elevated at one to 160. Id. She also had hypothyroidism which can sometimes be autoimmune. Id. Dr. Steel's opinion is that NMO is the result of two hits. Tr. at 55. He stated:

> [T]he two hits are referring to the sequence of immune events leading to NMO. The first event is vaccine-related, in my opinion, and has to do with the uncovering or unmasking of the aquaporin-4 protein, which is a sequestered protein. I think any theory of causation has to account for the unmasking of this sequestered protein …. [T]he first hit is the vaccine-related nonspecific immune response which results in disruption of the blood brain barrier by destruction of the endothelial cell, thereby exposing the aquaporin-4 protein, thereby leading to a complement-mediated second hit which then is the rest of the story.
> THE COURT: So it's not external, the second hit, complement-mediated second hit is internal?
> THE WITNESS: In terms of the body, yes. … It's a hum[o]ral-mediated immune response.

Tr. at 55-56.

When asked if his theory was speculative, Dr. Steel responded that "a theory is an attempt to explain what is heretofore unexplained, so all theories are speculative. We're making educated guesses. We try to stay well grounded in basic science. We try to stay well grounded in what's plausible, what's testable, what's reasonable, and that is what I have tried to say today." Tr. at 57. He continued:

> In this testimony today with the Lisa Calise case I have at no time said speculation. That word is not going to be seen in the transcript, so I do not believe that what I am saying is speculation. I think it is theory. It is testable. It is not off the top of my head. I've put many hours into this case and read extensive literature, and I think that the sequence of events, the sequence of immunological events going on in the body, Lisa's body following her receiving the flu vaccine is entirely plausible. So no, I am not speculating.

Tr. at 59.

Dr. Steel previously testified in another case named Davis[6] which also involved NMO after flu vaccine, and in Davis, he stated that his opinion was speculative. Tr. at 59. Dr. Steel

[6] Davis v. Sec'y of HHS, No. 07-451V, 2010 WL 1444056 (Fed. Cl. Spec. Mstr.), aff'd, 94 Fed. Cl. 53 (2010), appeal docketed, No. 10-5159 (Fed. Cir. Oct. 26, 2010).

explained that in the year between Davis and the instant action, he had continued his studies and matured in his thinking , and he felt that his ability to put together a coherent and reasonable theory had improved. Tr. at 60. He learned two key items. First was that MHC Type 1 receptors are ubiquitous in the body, including the endothelial cells, and they function as antibodies even though technically they are not antibodies. They grab onto foreign antigens. Id. Secondly, he learned that cytotoxic T-cell processes occur very early after the MHC Type 1 proteins latch onto a foreign particle, and those cytotoxic T-cells can and do attack and kill those cells. Tr. at 61. Dr. Steel explained that when he testified in the Davis case, he was not quite knowledgeable about the micropathology going on at the cellular level. Id.

He based his testimony that flu vaccine can breach the blood-brain barrier on an article entitled "Induction of CDA Positive Cytotoxic T-Cells by Immunization that Kills Influenza Virus, and the Effect of Cholera Toxin B Subunit" (which was not submitted into evidence). Id. This article shows that Class 1 MHC combined with cytotoxic T-cells in mice are activated by the influenza vaccine. Tr. at 61-62. He has not found an article specifically describing a breach of the blood-brain barrier. Tr. at 62. Breach of the blood-brain barrier is the second step of the process of an immune response. The first step is the binding of the virus or virion particles, i.e., the influenza vaccine particle, to an MHC Type 1 receptor. Id.

Dr. Steel stated that just about any immunogenic stress can in susceptible individuals trigger and alter an excessive immune response that harms the individual. Tr. at 64-65. Petitioner, being then sworn in, testified that she has been pricking her finger three to four times a day since 1990 because she has diabetes. Tr. at 67. Dr. Steel admitted that theoretically petitioner's pricking her finger could be an immunogenic stress. Tr. at 65. Petitioner was diagnosed with hypothyroidism in May 2000. Tr. at 69. Dr. Steel ruled out petitioner's pricking

her finger as a potential cause of her NMO since she has been pricking her finger for years, but developed NMO once. Tr. at 70. There is no temporal relationship between any particular finger prick and the onset of petitioner's NMO. Id. The logical assumption is that her finger pricking did not cause an immune response. Tr. at 71. When Dr. Steel, as a resident in the 1970s, saw the patient who had pricked his finger on a rose bush and had a spinal cord lesion and acute transverse myelitis, he asked him if he had had any vaccinations, infections, surgical procedures, or fever as part of the standard questioning that a neurology resident does and he replied that he pricked his thumb badly while tending his roses. He showed Dr. Steel his swollen thumb. Id. The treating physicians assumed that the patient had transverse myelitis as a result of an immune reaction initiated by an injury, in that case, the rose bush prick. Id. Petitioner in the instant action then stated that her daily pricking of her fingers for years did not cause them to be inflamed or swollen. Tr. at 72, 73. She rotates the fingers that she pricks so it is not always the same finger. Tr. at 73. Dr. Steel said that the thorn bush is something dirty and his former patient's thumb became secondarily infected when pricked, whereas petitioner in this case uses a sterile device to prick her finger daily. Tr. at 88.

Dr. Steel defined "pathological" as causing harm in describing the aquaporin-4 antibody as pathological in NMO. Tr. at 76. However, one of the articles in the literature filed in this case states that high AQP4AB (aquaporin-4 antibody) levels are not always associated with clinical disease. Id. Dr. Steel agreed there are always exceptions to the rule about the AQP4AB being pathologic. Tr. at 77. As for temporal association, Dr. Steel said that there seems to be a fairly strong correlation between the level of the antibody engendered by the antigen in two to three weeks and the onset of illness. Tr. at 78. He would be less comfortable if petitioner's NMO

began two days after vaccination. Tr. at 79. The level of association falls off at about 30 days. Id.

Dr. Steel explained his theory again. The patient receives the vaccine first. Her body engenders an excessive and abnormal immune response and, in petitioner's case, her body did so by manufacturing antibodies called NMO IgG thatbecame an important component of a more generalized immune response, resulting in necrosis and destruction of a very large portion of her spinal cord. Tr. at 80. Instead of a "two-hit" process, Dr. Steel agreed that it was one hit and a process. Id. He thinks it unlikely that coincidence was involved in this case, perhaps 10 percent likely, because the weight of the evidence is that the vaccine was causal. Tr. at 81. His theory came to him before he heard of the vaccine program. Id. It goes back to his training when taking a history is important and you make a theory and think of potential explanations. The demyelinating diseases as a group are considered to be largely autoimmune in etiology. Tr. at 81-82. When he was standing in petitioner's hospital room after he hospitalized her for decubitus ulcers, wondering what triggered all this, he interviewed her again. Tr. at 82. He interviewed her any number of times and asked if she had had any antecedent illnesses, injuries, surgical procedures, or vaccinations. Id. Petitioner told him she had a flu vaccination. Then things started to fall in place. He was not aware of the vaccination compensation program until sometime thereafter. Id.

When petitioner told Dr. Steel that she had received flu vaccine three weeks before the onset of illness, he came to the conclusion that the virus vaccine was likely causal. Tr. at 84. He knew any theory of causation had to address the issue of how the AQP4 protein became exposed to the blood and engendered antibodies against itself when it is normally sequestered and behind the blood-brain barrier. Id. at 85. Something had to strip away the blood barrier and, after his

subsequent reading and continued thinking, he realized it was due to the CD8 T-lymphocyte attacking the endothelial cell that had become non-self because of the MHC-1 protein grabbing onto a virion particle. Id. The central nervous system with a few exceptions is invested in protective tissue collectively called the blood-brain barrier, including endothelial tight junctions, astrocytic foot processes, and endothelial cells. Tr. at 86. Dr. Steel is not aware of any literature in preparation that describes flu vaccine breaching the blood-barrier and causing NMO. Tr. at 86-87.

On redirect, Dr. Steel stated the AQP4 antibody is pathological, i.e., causes harm. Tr. at 90. When the B-cells that produce the antibody are treated with Rituximab, thus decreasing antibody production, patients have a better outcome. Id.

Dr. Martin Bielawski, a neurologist, testified for respondent. Tr. at 91. He is an associate clinical professor of neurology at Tufts University School of Medicine, and on the medical consulting staff at a number of hospitals. Tr. at 93. About 10 percent of his adult patients have demyelinating disorders, mainly multiple sclerosis. Tr. at 94. Over the last 35 years of practice and training, he has seen three cases that he thought were NMO. Id. This was before the NMO IgG was used to diagnose NMO. All three patients were women aged forty to the fifties. Two of them had a preceding viral infection. One patient had idiopathic NMO or an unknown cause. All died from respiratory complications. Tr. at 94-95. He agrees that petitioner in the instant action has NMO. Tr. at 96. His opinion is that flu vaccine did not cause petitioner's NMO. Tr. at 97. His basis is that there have been no case reports showing that flu virus causes NMO, no laboratory evidence (either animal studies or in vitro) of a mechanism showing that flu virus causes NMO, no epidemiologic evidence that flu virus causes NMO, and

the only relationship petitioner's NMO has to her flu vaccination is temporal, which is not proof of cause. Id.

Dr. Bielawski agreed with some of Dr. Steel's testimony, e.g., several general theories about immunology which are accepted, such as molecular mimicry and bystander activation. Id. As for whether an individual needs a trigger in order to have NMO, Dr. Bielawski responded: "I can't say for sure because I don't think there are enough cases of NMO to know about that…." Tr. at 99. Because the etiology of some cases of NMO is unknown, he would say that we cannot talk about a trigger being necessary if the case is idiopathic. Id. The undersigned asked Dr. Bielawski:

> THE COURT: You mentioned the three cases that you're familiar with on a professional basis, and you said two of the women who had NMO had preceding viral infection, and one you didn't know what the etiology could be.
> In your mind, in your opinion, do you think that the two women who had NMO with preceding viral infection, that the viral infection had a causal relationship or trigger to their NMO?
> THE WITNESS: That was the speculation at the time, and those are certainly some of the questions we would have asked individuals because generally speaking if one is dealing with an autoimmune disease one would like to assess whether the patient was exposed to any sort of mechanism that could trigger an autoimmune phenomenon.
> THE COURT: When you speak of autoimmune disease, does autoimmune disease mean there should be a trigger even if you can't find it?
> THE WITNESS: The assumption is that an autoimmune disease has some sort of instigating event, so yes, there should be some sort of triggering event.

Tr. at 99-100.

Dr. Bielawski said he is not aware of any evidence that flu vaccine breaches the blood-brain barrier. Tr. at 101. Except for Dr. Steel's opinion that flu vaccine breaches the blood-brain barrier, Dr. Bielawski is in agreement with Dr. Steel's general immunologic theory and he

believes "that in general this sort of thing can happen, and I would agree that this cascade of events is a generally acceptable immunologic theory." Tr. at 102. Dr. Bielawski testified that there needs to be a disruption of the blood-brain barrier in order for the immunologic process to lead to NMO. Tr. at 102, 103.

Dr. Bielawski disagreed with Dr. Steel that because ADEM has some overlap with NMO and can be a post-vaccination phenomenon, it is analogous to NMO being a post-vaccination phenomenon. Tr. at 103-04. First, ADEM and NMO are different diseases in that ADEM is considered mainly a T-cell based disorder whereas NMO is primarily a B-cell mediated disorder. Tr. at 104. In ADEM, large demyelinating lesions are seen on brain MRI, but not in NMO. Id. Secondly, ADEM involves the gray and white matter with lymphocytes, macrophages, and demyelination developing in a sleeve-like pattern in areas of hypercellularity, with axons only minimally injured, consistent with a good recovery. Id. NMO pathology includes macrophages and granulocytes with a strong emphasis on eosinophils, and there is significant demyelination and axonal injury, which is why NMO patients have poor recovery. Tr. at 105. According to the Huynh article alluding to a Japanese survey of ADEM cases from 1994 to 2004, the number of cases of ADEM that flu vaccine recipients had was three out of 38 million, which is practically zero. Therefore, Dr. Bielawski does not think NMO is a post-influenza vaccinal sequela. Tr. at 105-06. When asked if Dr. Bielawski thought flu vaccine caused those three cases of ADEM, he said it was just "extremely, extremely rare." Tr. at 106. When asked whether flu vaccine can cause ADEM and is a rare event, Dr. Bielawski said yes. Id.

Dr. Bielawski was not impressed with the Wingerchuk article showing that two persons out of 71 NMO cases at the Mayo Clinic over a 45-year period had received swine flu vaccine because swine flu vaccine is directed against a different type of virus than the seasonal flu

vaccine, and therefore the occurrence of NMO after swine flu vaccination is not relevant to the occurrence of NMO after a seasonal flu vaccination as in this case. Tr. at 108. These two patients had monophasic NMO after swine flu vaccine. Tr. at 111.

Dr. Bielawski commented that if petitioner's diabetes were immune-mediated, some literature, e.g. Wingerchuk, observes that patients with NMO might have a predisposition to NMO because they have concomitant autoimmune diseases. Tr. at 111-12. Wingerchuk discusses antecedent illnesses in the context of a patient having a predisposition to react to an antigenic insult, but there is no lab evidence or any epidemiologic evidence of that. This is an observation like a case report. Tr. at 112.

Dr. Bielawski stated that whether or not the NMO IgG is pathological is still being researched and some authors do not accept that it is because animal models do not exist. Another article notes that there are cases where high NMO antibody levels are not always associated with a clinical relapse. In other words, the presence of the NMO IgG antibody alone may not be sufficient to cause the illness. Tr. at 113. However, Dr. Bielawski allowed that the NMO IgG is certainly involved with NMO pathology. Tr. at 114.

When asked whether or not NMO requires any hit or two hits, Dr. Bielawski replied:

> I believe the autoimmune process would be considered a hit. Now, you know, two hits generally, if you're looking at the literature is discussing two autoimmune events. One is an initial hit, which would be an event that produces an antibody antigen complex, and then the T-cells have a memory of it, and then a second inflammatory, or a second event causes those T-cells and the memory of the antibodies to engender the immune response. That's generally what a two-hit theory is all about.
> But here I would say that it requires a hit, which is an immune process developing and causing the disease.

Tr. at 117.

Dr. Bielawski stated that the NMO IgG antibody is not a requirement for getting NMO. It is often seen with NMO, but it is not a requirement. Tr. at 118. His opinion is that petitioner's NMO had a triggering event, but he just does not know what it was. Id. He thinks that three weeks is satisfactory for an immune process to develop when he was asked about the timing between petitioner's flu vaccination and the onset of her NMO. Tr. at 119. Dr. Bielawski believes that petitioner's NMO is idiopathic. Tr. at 120. He would advise a patient who has NMO to receive flu vaccine. Id.

On cross-examination, Dr. Bielawski admitted that in Kerr's article on the immunopathogenesis of acute transverse myelitis, which is respondent's Exhibit G, in Figure 1 listing questions for a history and physical examination, the last item is "Determine if recent history of vaccination with systemic illness," and that indicates that Dr. Kerr believes that vaccination can trigger transverse myelitis. Tr. at 129. Dr. Bielaski agreed that there are some vaccinations that can trigger transverse myelitis. Tr. at 130. But Dr. Kerr is referring in his article to transverse myelitis in general which many times involves a single spinal cord segment whereas NMO usually involves three or more spinal cord segments. Id.

In describing the overlap between ADEM and NMO, Dr. Bielawski stated that most demyelinating diseases can have monophasic or relapsing courses, and both ADEM and NMO have lesions in the spinal cord. Tr. at 134-35.

DISCUSSION

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. Sec'y

of HHS, 418 F.3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Sec'y 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. Sec'y of HHS, 440 F.3d 1317, 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 . . . ." Such an approach is inconsistent with the use of circumstantial evidence. *Id*.

The Federal Circuit stated in Althen, 418 F.3d at 1280, that "While this case involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, a sequence hitherto unproven in medicine, 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 Althen affirmed the finding of the judge that the special master was in error to dismiss, and holding that petitioner's "TT vaccination caused her central nervous system demyelinating disorder." 418 F.3d at 1282.

Close calls are to be resolved in favor of petitioners. Capizzano, 1440 F.3d at 1327; Althen, 418 F.3d at 1280.

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 need not show that the vaccine was the sole or predominant cause of her injury," just that the vaccine was a substantial factor in causing her injury. De Bazan v. Sec'y of HHS, 539 F.3d, 1347, 1351 (Fed. Cir. 2008).

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 v. Sec'y of HHS, 35 F.3d 543, 548-49 (Fed. Cir. 1994)). To the undersigned, medical probability means biologic credibility rather than specification of an 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 in Capizzano emphasized that the special masters are to evaluate seriously the opinions of the vaccinee's treating doctors since "treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury." 440 F.3d at 1326. See also Andreu v. Sec'y of HHS, 569 F.3d 1367, 1375 (Fed. Cir. 2009).

As the Federal Circuit stated in Knudsen, 35 F.3d 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, 418 F.3d at1281 ("judging the merits of individual claims on a case-by-case basis").

The Federal Circuit in Knudsen, 35 F.3d at 549, also stated: "The special masters are not 'diagnosing' vaccine-related injuries."

As for epidemiological support for causation, the Federal Circuit in Knudsen, 35 F.3d at 551, ruled for petitioners even when epidemiological evidence directly opposed causation from DPT vaccine. The case concerned the cause of a baby's encephalopathy after a vaccination. Respondent provided evidence that more encephalopathies are caused by viruses than by vaccines, convincing the special master to rule against petitioners. Even though epidemiological evidence supported respondent's view that viruses are more likely to cause encephalopathy than vaccines, 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.

The special masters "are entitled–indeed, expected–to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence." Moberly v. Sec'y of HHS, 592 F.3d 1315, 1325 (Fed. Cir. 2010) .

In the instant action, both experts agree on the process involved in neuromyelitis optica. The effect of IgG, an antibody, is to expose aquaporin-4 to the blood stream, where through a

complicated cascade of events, the spinal cord and optic nerves are decimated. NMO is one of a spectrum of demyelinating diseases where an aberrant antibody response to an antigenic trigger turns against the host and wreaks havoc on the host's myelin. Dr. Bielawski agrees that an antigenic trigger (what he called an instigating event) is necessary to prompt an autoimmune disease, although he was reluctant to agree that a viral infection in two of the three NMO patients he saw as a resident was the trigger in those cases, an assumption that his colleagues did entertained. Dr. Bielawski does not agree that flu vaccine in the instant action is an antigenic trigger because there are no epidemiologic articles, animal studies, in vitro experiments, or case reports to support that opinion. This may be a laudatory approach for a medical doctor, but in the legal sphere, the Federal Circuit does not require medical literature, whether epidemiological studies or case reports, animal studies, or in vitro testing, in order for petitioner to prevail. According to the three Althen prongs, what petitioner needs in order to prevail is a medical theory connecting flu vaccine and NMO (the "can it?" question), a logical sequence of cause and effect that flu vaccine caused her NMO (the "did it?" question), and a medically appropriate temporal relationship between vaccination and onset. Knudsen, Althen, Capizzano.

Moreover, petitioner's expert is her treating neurologist who suspected flu vaccine caused her NMO even before she filed her petition. There are also two other treating physicians who thought, when petitioner was diagnosed with transverse myelitis, that the flu vaccine was the antigenic trigger. On January 12, 2006, Dr. Richard E. Bird, a neurologist, wrote, "The only possible antigenic focus would be a flu shot taken 3-4 weeks ago. She has had no insect bites. She has had no other viral illnesses." Ex. 5, p. 17. On June 29, 2006, in his discharge summary at Craven Regional Medical Center, Dr. Wright D. Shields noted that petitioner's neuromyelitis optica was "possibly vaccine related due to temporal association of flu vaccination." Ex. 14, p.

23. Dr. Bird and Dr. Shields, just like Dr. Steel, accepted that an antigenic insult can lead to the formation of autoantibodies that assail the host's myelin, in this case, in her spinal cord and optic nerves, and that antigenic insult includes flu vaccine. The Federal Circuit placed great emphasis on the opinions of treating physicians in Capizzano and Andreu.

From the testimony and the medical articles submitted in this case, the undersigned finds that neither NMO IgG nor AQP4 causes NMO. They are pathological in that they are instrumental in causing demyelination and devastation in the cascade of steps that Dr. Steel described and with which Dr. Bielawski agreed. But the cause is a combination of a genetic susceptibility to developing the disease once the patient is exposed to an antigenic trigger. Something triggers IgG to develop in an individual susceptible to developing NMO. IgG is a biomarker for NMO, enabling neurologists to discern that one of their patients has NMO and not MS. Medical literature that both petitioner and respondent filed posits that a genetic problem is the cause of susceptibility to demyelinating disease, here NMO. But the genetic problem needs an antigenic trigger in order to start the NMO, or any demyelinating disease, process. Once that antigenic trigger starts the cascade, with the IgG antibody attacking various cells that leads to exposure of AQP4 to the blood, resulting in further antibody attacks on the myelin sheath in the spinal cord and the optic nerves, the patient manifests NMO.

Dr. Bielawski conceded that when he was in training and encountered three patients with NMO, two of whom had prior viral infections, the others doctors treating these patients entertained the view that the viral infections triggered the NMO because they were antigenic stimuli. When asked if he considered the viral infection to be the trigger of these two patients' NMO, Dr. Bielawski said that was the thought at the time, although he termed it speculation. When further asked if there had to be a trigger for an autoimmune disease, Dr. Bielawski

responded, "The assumption is that an autoimmune disease has some sort of instigating event, so yes, there should be some sort of triggering event." Tr. at 100.

Dr. Bielawski does not believe that NMO can be lumped together with other demyelinating diseases, such as ADEM. But that is exactly what the medical literature does and Dr. Steel's testimony is consistent with the approach of the medical literature. Both respondent's and petitioner's exhibits discuss NMO in the context of other demyelinating diseases. Demyelinating diseases are autoimmune, triggered by some antigenic insult, resulting in demyelination. Particular to the disease is whether the myelin involved is located in the central nervous system or the peripheral nervous system, whether or not it involves the axons, and whether the individual is likely to recover. But no matter what the particular demyelinating disease is, the depiction of the trigger is the same, e.g., infection (either bacterial or viral), surgery, or vaccination. Dr. Steel mentioned an infection in a prior patient due to a prick from a rose thorn, leading to a badly infected thumb, and this was the antigenic trigger in his case. Respondent's counsel asked Dr. Steel about a prior bronchial infection petitioner had before her onset of NMO to see if that were the trigger of her NMO, but Dr. Steel said the time interval between her bronchial infection and her onset of NMO was too great to be causal. Both parties are well aware that an autoimmune disease such as NMO needs an antigenic trigger.

The literature that the parties submitted discusses numerous types of demyelinating disease within the articles. The Huynh article (tab E of petitioner's exhibit 42) discusses ADEM, stating it is one of several categories of primary inflammatory demyelinating disorders of the CNS (central nervous system) which also include NMO, MS, transverse myelitis, and optic neuritis. Huynh et al. write that influenza vaccine can cause ADEM. They note that "patients who have a certain underlying genetic predisposition may be more prone to developing ADEM

post-vaccination." Tab E, Ex. 42, p. 1317. An antigenic insult, such as a vaccination, triggers the demyelinating disease in someone with a certain underlying genetic predisposition to developing that demyelinating disease. Huynh et al. discuss a case in which a man had optic neuritis occurring three weeks after he received influenza vaccine and ultimately had encephalomyelitis. Huynh et al. conclude that the influenza vaccine caused the patient's optic neuritis and later encephalomyelitis. Tab E, Ex. 42, p. 1322.

The Matiello article (tab K of petitioner's exhibit 42) discusses neuromyelitis optica and states that an antigenic insult triggers production of the circulating immunoglobulin NMO-IgG in a susceptible individual. Tab K, Ex. 42, p. 256.

The Jarius article (tab S of petitioner's exhibit 42) discusses neuromyelitis optica and states that stimulation by exogenous triggers might be required to initiate tissue damage. Tab S, Ex. 42, p. 3078.

The Schattner article (respondent's exhibit D) is an analytical review of autoimmune manifestations after viral vaccines. Schattner states "The enigma of autoimmunity and autoimmune diseases appears to be driven by a complex interplay of genetic, hormonal and environmental factors." Id. at 3876. That means the cause of autoimmune disease depends on genetic susceptibility, hormonal factors, and environmental influence. Antigenic insults are included in environmental influence. The Schattner article discusses one type of antigenic insult, i.e., viral vaccines. Schattner discusses numerous autoimmune diseases reported after influenza vaccination, including meningoencephalitis/encephalitis, optic neuritis, transverse myelitis, Guillain-Barré syndrome (GBS), brachial neuritis, and Bell's palsy. Id. at 3879. Schattner admits that seasonal flu vaccine can cause GBS amounting to 10.5% of recent GBS cases studied from 1992-1994. Id. He states that other neurological syndromes involving the central nervous

system may rarely occur after influenza vaccination. Id. at 3880. He notes that in susceptible individuals, very rare occurrences of central and peripheral nervous system diseases may be due to influenza vaccine. Id. at 3882, 3883.

The Kerr article (respondent's exhibit G) discusses acute transverse myelitis. Kerr et al. state that acute transverse myelitis exists on a continuum of neuroinflammatory disorders including Guillain-Barré syndrome (GBS), multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica (NMO). Id. at 339. They write there are many common features in these disorders involving inflammation and neural injury. Id. They state there are a variety of humoral and cellular immune derangements that potentially result in neuronal injury and demyelination. Id. They discuss the case of a 42-year-old man with a history of bilateral optic neuritis who developed transverse myelitis two days after an influenza vaccination, suggesting that a vaccination may induce an autoimmune process resulting in acute transverse myelitis. Id. at 340-41. They offer a list of questions for the practicing neurologist to ask his or her patient, including whether or not the patient had a preceding vaccination, in evaluating the patient for acute transverse myelitis or a number of other diseases including neuromyelitis optica. Id. at 341. They discuss the process by which acute transverse myelitis occurs, including exposure to an antigenic trigger, followed by molecular mimicry or superantigen-mediated immune activation in a genetically susceptible individual, with a segue into the pathology of GBS following exposure to a bacterium. Id. at 341-43. In their list of references, 11 of those references are to various demyelinating illnesses following vaccination, such as flu vaccine and myelopathy; MMR vaccine and GBS; hepatitis B vaccine and inflammatory polyradiculoneuropathy with spinal cord involvement and death; swine flu vaccine and GBS; hepatitis B vaccine and MS; flu vaccine, hepatitis B vaccine, intercurrent infections,

and MS; vaccinations and risk of relapse in MS; influenza vaccine and MS; and hepatitis B vaccine and acute transverse cervical myelitis.

The Brinar article (respondent's exhibit H) discusses disseminated encephalomyelitis (DEM), which is distinguished from neuromyelitis optica, although there are similarities. Two of the four cases the authors discuss involve a preceding vaccination or infection. The authors state "Why one person after being challenged with a specific antigen develops DEM, and another person exposed to the same trigger does not develop disease, and yet another develops MS, is probably due to individual genetic susceptibility" [references omitted]. Id. at 917.

The Benneto article (respondent's exhibit I) discusses, inter alia, ADEM, including post-vaccination encephalomyelitis. The authors caution that anyone with ADEM should not receive vaccinations for six months. Id. at i27. They comment that it appears likely that parallel B- and T-cell mediated reactions generate central nervous system inflammatory change in ADEM, and mention that molecular mimicry may be involved in the pathology of ADEM. Id.

Respondent's expert Dr. Bielawski admits in his written report that genetic predisposition and environmental factors (i.e., antigenic stimuli) are necessary in order for someone to have NMO: "Perhaps there are genetic and environmental factors that influence the development and type of NMO, as is likely the case with multiple sclerosis." Ex. A, p. 10.

All this case comes down to is whether or not flu vaccine was the antigenic trigger for petitioner's NMO. Weighing the seriousness of Dr. Steel's investigation, which started before petitioner ever filed her petition, the opinions of two other doctors who considered the causal role of petitioner's flu vaccination, against Dr. Bielawski's view that until there are epidemiologic studies, animal models, and in vitro testing to verify that flu vaccine is an antigenic trigger (none of which the Federal Circuit requires petitioners to prove in order to

prevail), the undersigned views petitioner's expert Dr. Steel as more credible. His opinion is consistent with the medical literature that both petitioner and respondent submitted. The undersigned accepts that NMO is an extremely rare occurrence, but that does not mean that it cannot be a vaccine reaction. As the Federal Circuit explained in Knudsen and as Dr. Steel testified, when an illness is extremely rare, scientists and doctors are never going to have enough cases to do an epidemiologic study.

The Vaccine Program was set up for someone like petitioner in this case who has an unfortunate illness that a vaccination triggered. The medical literature is replete with references to genetic susceptibility. It is also not petitioner's burden to prove a specific biological mechanism. Knudsen. All she needs to do to satisfy the first Althen prong is show a plausible medical theory connecting the flu vaccine and NMO. This she has done. In great detail, Dr. Steel enumerated the various steps in what he terms a cascade of events that results in the necrosis and cavitation of petitioner's spinal cord and injury to her optic nerves. As her treating neurologist, Dr. Steel has advised her not to have any future flu vaccinations. Dr. Bielawski agreed with Dr. Steel's description of the cascade of events except for the identity of the antigenic trigger. He thinks it was not flu vaccine, but he does not know what it was. He accepts, however, that autoimmune diseases need an antigenic trigger.

Flu vaccine can be the antigenic trigger for NMO based on the activity of various T- and B-cell effectors, IgG antibody production, breaching of the blood-brain barrier, the unsequestering of aquaporin-4 protein, and subsequent antibody-antigen reactivity, culminating in NMO devastation. This satisfies the first Althen prong.

Flu vaccine in this case was the antigenic trigger for petitioner's NMO based on the lack of any other antigenic trigger and the testimony of Dr. Steel and confirming medical literature

that flu vaccine has been associated with other demyelinating illnesses. This satisfies the second Althen prong.

Petitioner's flu vaccine was administered three weeks before the onset of her NMO. This is appropriate timing in order for the flu vaccine to be the antigenic trigger for petitioner's NMO. Both Dr. Steel and Dr. Bielawski (if he were to accept that flu vaccine could be an antigenic trigger) stated that three weeks is an appropriate temporal relationship for causation. This satisfies the third Althen prong.

The fact that the petitioner in Davis, a case decided in 2010, did not prevail when she alleged that flu vaccine caused her NMO three weeks after vaccination does not affect the undersigned's decision in this case. "Special masters are neither bound by their own decisions nor by cases from the Court of Federal Claims except, of course, in the same case on remand." Hanlon v. Sec'y of HHS, 40 Fed. Cl. 625, 630 (1998).

Petitioner has proven causation in fact.

CONCLUSION

Petitioner has prevailed in this case. The undersigned will schedule a telephonic status conference soon to discuss damages.

IT IS SO ORDERED.

March 14, 2011
DATE

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