In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 09-426V
September 30, 2011
To be Published

DAVID A. BROWN,	*	
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Petitioner,	*	
	*	
v.	*	Encephalitis vs. ADEM; flu vaccine; upper respiratory infection; strokes; two-month onset from vaccination
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SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Lisa A. Roquemore, Irvine, CA, for petitioner.
Lara A. Englund, Katherine C. Esposito, Washington, DC, for respondent.

MILLMAN, Special Master

RULING ON ENTITLEMENT[1]

Petitioner filed a petition on June 29, 2009 under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10 et seq., alleging that flu vaccine which he received on November 6, 2007 caused him acute disseminated encephalomyelitis (ADEM).

A hearing was held on September 1 and 2, and on November 4, 2010. Testifying for petitioner were his wife, mother-in-law, and Dr. Lawrence Steinman. Testifying for respondent were Dr. Thomas Leist and Dr. Raoul Wientzen, Jr.

[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 redact 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 redact such material from public access.

After both parties filed additional material after the hearing, petitioner filed his post-hearing brief on February 10, 2011, respondent filed her post-hearing brief on March 14, 2011, and petitioner filed his reply brief on March 24, 2011.

FACTS

Petitioner was born on April 21, 1971.

On November 6, 2007, he received influenza vaccine. Med. recs. at Ex. 1, p. 125.

On December 3, 2007, at 8:53 a.m., petitioner had his blood tested. His potassium level measured 5.10, which was high (the normal range being between 3.5-5.0 meq/l). Ex. 14, p. 813.

On December 6, 2007, petitioner's youngest child, Raedyn, saw Dr. David D. Lah for a high fever for two days, eye discharge for five days, and a mild cough and cold. P. Ex. 20, p. 10. Dr. Lah diagnosed Raedyn with upper respiratory infection, bilateral otitis media, and acute conjunctivitis. Id. at 11.

On December 13, 2007, all of petitioner's four children saw Dr. Connie Lew Cheng because of viral symptoms. Id. at 1-10. Fourteen-year-old Robert had a cough for one week and congestion for two days. Id. at 1. Ten-year-old Tiffany had congestion for one week, an upper respiratory infection for one week, and bilateral eye irritation for two days. Id. at 3. Three-year-old Cole had a cough for two weeks, congestion for two weeks, bilateral ear pain for one week, and bilateral eye irritation for five days. He had been seen the prior week for bilateral otitis media. Id. at 5. Eighteen-month-old Raedyn had a cough for two weeks, congestion for two weeks, bilateral ear pain for five days, and bilateral eye pain for five days. She had been seen the prior week for bilateral otitis media. Id. at 8.

December 19, 2007 was the last day petitioner worked, according to a Documentation of Medical Impairment (DMI) form dated January 15, 2008. R Ex. J, p. 8. The diagnosis on the form was viral encephalitis. Id.

After his flu vaccination on November 6, 2007, petitioner did not have a doctor examine him until December 31, 2007 when he saw Dr. Kenji Shibata at High Desert Medical Offices, complaining of flu-like symptoms. Petitioner gave a history that he had sinus problems on December 3, 2007 and now had nausea, vomiting due to gastroesophageal reflux disease (GERD), diarrhea (for one day), and headache with head pressure. Petitioner reported headaches, congestion, cough, sputum production, and shortness of breath. On physical examination, petitioner was alert, oriented, not toxic, and not distressed. Dr. Shibata diagnosed petitioner with sinusitis and GERD. Med. recs. at Ex. 1, p. 7. Dr. Shibata prescribed Omeprazole,[2] Amoxicillin,[3] Phenylephrine-Guaifenesin,[4] and Promethazine-Codeine.[5] Id. at 7-8.

On January 7, 2008, petitioner saw Dr. Gary McLarty at the Kaiser Permanente Fontana Medical Center Emergency Services. R Ex. J, p. 57. The chief complaint was decreased mental status that began on January 5, 2008. He had chills and generalized right-sided weakness. He

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[2] Omeprazole is "a proton pump inhibitor used in the treatment of dyspepsia, gastroesophageal reflux disease, and gastric hypersecretory conditions…." Dorland's Illustrated Medical Dictionary, 31st ed. (2007) ("Dorland's") at 1339.

[3] Amoxicillin is "a semisynthetic derivative of ampicillin effective against a broad spectrum of gram-positive and gram-negative bacteria; used especially in the treatment of infections due to susceptible strains of *Haemophilus influenza, Escheria coli, Proteus mirabilis, Neisseria gonorrhoeae,* streptococci (including *Streptococcus faecalis* and *S. pneumoniae*), and nonpenicillinase-producing staphylococci." Dorland's at 66.

[4] Phenylephrine is "a direct-acting sympathomimetic amine that stimulates α-adrenergic receptors and is a powerful vasoconstrictor." Dorland's at 1452. Guaifenesin is "an expectorant believed to act by reducing sputum viscosity…." Id. at 821.

[5] Promethazine is "a phenothiazine derivative having marked antihistaminic activity as well as sedative and antiemetic actions…and as an ingredient in cough and cold preparations…." Dorland's at 1549. Codeine is "a narcotic alkaloid obtained from opium or prepared by methylating morphine." Id. at 386.

did not have a headache, cough, nausea, or vomiting. He had a history of hypertension and hyperlipidemia. His right pupil was round and reactive to light. His left pupil was round and constricted. He was lethargic. He had weakness of his right leg. On a head CT scan, he had lacunar infarct[6] present involving the basal ganglia (one on each side of the thalamus). Id. Dr. McLarty diagnosed petitioner with fever, changed mental status, possible viral meningitis, and possible encephalitis. R Ex. J, p. 58. The head CT scan showed a nine-millimeter hypodense area in the left thalamus representing lacunar infarction whose age was uncertain, as well as a nine-millimeter lacunar infarction in the posterior medial portion of the right thalamus which might distend inferiorly to the anterior aspect of the right mid brain. Differential diagnosis should include infectious/inflammatory disease or neoplasm. Dr. Chih-Cheng Chen also noted moderate right maxillary sinusitis and moderate sinusitis or mucoperiosteal thickening of the left maxillary sinus. R Ex. J, p. 282.

On January 7, 2008, an emergency nursing record at Kaiser Permanente notes as the chief complaint an altered level of consciousness (ALOC) with a history of flu-like symptoms for two weeks. Med. recs. at Ex. 1, p. 123. Petitioner's temperature was 101.1° Fahrenheit. He had slurred speech, and he was weak and sluggish. Id.

Also on January 7, 2008, at 12:34 p.m., at the Kaiser Permanente Fontana Medical Center Emergency Services, petitioner was the historian. Med. recs. at Ex. 1, p. 204. He stated that he

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[6] An infarct is "an area of coagulation necrosis in a tissue due to local ischemia resulting from obstruction of circulation to the area, most commonly by a thrombus or embolus." Dorland's at 948. A lacunar infarct is "a small (less than 1.5 cm) infarct occurring in the basal ganglia, internal capsule, pons, and white matter of the brain, usually in older hypertensive patients and diabetics; depending on their location, lacunes may be asymptomatic or cause significant impairment." Id. A thrombus is "a stationary blood clot along the wall of a blood vessel, frequently causing vascular obstruction." Id. at 1949. An embolus is "a mass, which may be a blood clot or some other material, that is brought by the bloodstream through the vasculature, lodging in a vessel or bifurcation too small to allow it to pass, obstructing the circulation…." Id. at 614.

had decreased mental status starting two days earlier. Id. He also had generalized right-sided weakness and chills, but no headache, cough, nausea, or vomiting. Id. His temperature was 101.6° and he was lethargic. Id.

On admission January 7, 2008 to Kaiser Permanente, petitioner saw Dr. Dennis R. Nagel. Petitioner's wife said petitioner had been sick for a few weeks with low-grade infections and cold-like symptoms with temperatures ranging from 99° to 103° F. On one day, he had a temperature of 104° F. R Ex. J, p. 59. On December 31, 2007, petitioner was started on Amoxicillin with a presumptive diagnosis of sinusitis. He had not improved, but on January 6, 2008, he became ataxic and his speech became slurred. No one else in the house was ill in a similar fashion. His past medical history included chronic headaches and hypertension. Id. He was minimally arousable. However, there was no purposeful movement. A complete blood count showed 300 white blood cells and a lumbar puncture showed elevated protein at 68. Dr. Nagel diagnosed petitioner with probable viral encephalitis. Id. at 60. His left pupil was relatively pinpoint. His right pupil was mid position. CT scan of the brain showed a couple of nine-millimeter lacunar infarcts of the thalamus area, but the radiologist could not say whether these were old or new. Id. and p. 282. Dr. Chih-Cheng Chen interpreted the CT scan of the head and said the differential should include infectious/inflammatory disease or neoplasm. R Ex. J, p. 282.

On January 8, 2008, Dr. Jana Kubrin did an infectious disease consultation. Petitioner was admitted the night before with meningitis and a recent lacunar infarct. R Ex. J, p. 177. Petitioner's wife gave the history that petitioner and his whole family started becoming sick before Christmas, about December 23, 2007. At that time, he had flu-like symptoms including headache, stuffy nose, neck pain, and fevers ranging from low grade to 103°. His four children

had problems with eye and ear infections. Petitioner's wife also had upper respiratory tract infections. Petitioner had some congestion and saw the doctor on December 31, 2007 who diagnosed him with severe sinusitis and prescribed Amoxicillin. Petitioner took this through the prior weekend, but on Sunday, January 6, 2008, he slept the entire day. Id. He had a lot of phlegm. When he woke on Sunday, he had a loss of equilibrium and slurred speech. He refused to go to the hospital until the prior night. A CT scan of his head was done which showed a nine-millimeter lacunar infarct in each thalamus. Spinal fluid analysis showed an elevated white count of 300 white cells with 98% monocytes, protein of 68, and glucose of 54. His serum glucose was 104. Id. He was started on Acyclovir and Ceftriazone the prior evening and was also on Dexamethasone, Fluconazole, and Vancomycin. R Ex. J, p. 178. Petitioner had multiple animal exposures, including cats, dogs, horses, cows, ducks, and chickens, because he lives on a ranch. His mother had cerebrovascular accident and coronary artery disease as well as diabetes. Id. On examination, petitioner's left eye was pinpoint; his right eye was reactive to light. R Ex. J, p. 179. He had some nuchal rigidity and was generally stiff. He moved all extremities.

Dr. Kubrin diagnosed petitioner with meningitis, most likely viral in etiology. However, petitioner could have a partially treated bacterial meningitis. Other possibilities included a fungal meningitis, such as coccidioidomycosis. She discontinued petitioner's Decadron since his cerebrospinal fluid had no organisms in it, and increased his Vancomycin. She added Doxycycline to his medications and ordered a brain MRI. Id.

On January 8, 2008, petitioner had a brain MRI done with and without contrast to evaluate encephalitis. R Ex. J, p. 281. Dr. Susan J. Rice wrote that petitioner had foci of abnormal hyperintense diffusion weighted signal and hyperintense flair/T2 signal in the upper right paracentral mid brain and in the left thalamus. He also had a two-centimeter area of

abnormal hyperintense diffusion weighted signal in the corona radiata adjacent to the posterior body of the left lateral ventricle extending into the left lateral basal region which was only minimally hyperintense on FLAIR and T2. Dr. Rice stated these lesions might be related to encephalitis or acute/subacute infarcts. Id.

On January 9, 2008, Dr. Francisco R. Torres did a neurologic consultation. Petitioner had been battling a viral infection for at least the prior two weeks. He was admitted to the hospital with slurred speech, and decreasing cognition and responsiveness. A spinal tap on admission showed 300 white blood cells and a protein of 68. His white blood cell count on January 9, 2008 was 15,000. R Ex. J, p. 175. A brain MRI showed bilateral upper mid brain lucencies that went into the lower thalamus, more on the left than on the right in the corona radiata. The ischemic findings were inconsistent with vasculitis; therefore, Dr. Torres was considering this an infectious problem. Id. Petitioner appeared to have an encephalitis based on the clinical history and the spinal fluid results. It was most likely viral. He was being treated with Acyclovir, Doxycycline, Vancomycin, and Diflucan. Id. at 176. Dr. Torres did an EEG on January 9, 2008 which was very mildly abnormal. Id. at 268.

On January 15, 2008, a doctor at Kaiser Permanente filled out a form for petitioner entitled Documentation of Medical Impairment stating that the last day he worked was December 19, 2007 due to viral encephalitis. R Ex. J, p. 8.

Also, on January 15, 2008, petitioner had another brain MRI. Med. recs. at Ex. 12, p. 810. Dr. Daksha Tribhuvandas Bhansali wrote that, clinically, petitioner had worsening stroke. Diffusion-weighted images showed moderate localized hyperintensity along the tegmentum of the mid brain. Consistent with clinical signs, there appeared to be progression of these hyperintensities seen on the diffusion-weighted images, now extending into the right thalamus

and the posterior limb of the internal capsule. Still present were hyperintensities along the left lateral basal ganglia, the left corona radiata, the left thalamus, and the posterior limb of the internal capsule. The progressive hyperintensities were now seen in the right thalamus, the right posterior limb of the internal capsule, and the globus pallidus. Previous angiogram showed occlusion of the posterior cerebral artery at the P1-P2 junction. The findings were related to the occlusion of the brainstem perforators arising from the distal basilar artery and the P1 segment of the posterior cerebral artery deep thalamic perforators. Dr. Bhansali's impression was progressive infarct now with extension to the right involving the right thalamus, the posterior limb of the internal capsule, and the globus pallidus. Id.

On January 16, 2008, a neurologist noted in the progress sheet that petitioner was slightly more alert and would be treated as having ADEM. The neurologist discussed the action plans with infectious disease specialists and internal medicine specialists and would give Solu-Medrol[7] 1000 mg per day for five days. Med. recs. at Ex. 1, p. 93.

On January 16, 2008, Dr. Duane A. Collins wrote an interim summary stating that petitioner's principal diagnosis was viral encephalitis. R Ex. J, p. 50. Petitioner had a history of hypertension and had been complaining of headaches and sinus pressure. He went to the outpatient clinics and received treatment for sinusitis. He developed ataxia and was brought to the emergency room where a computerized tomography scan showed two lacunar infarcts in the thalamus, and mastoid sinusitis. A lumbar puncture showed protein of 68 in the cerebrospinal fluid. The picture was consistent with viral encephalitis. Over the next 24 to 48 hours, petitioner became less responsive and more groggy. He developed pupil inequality. Id. None of the

[7] Solu-Medrol is a "trademark for a preparation of methylprednisolone sodium succinate." Dorland's at 1756. Methylprednisolone is a synthetic glucocorticoid used as an anti-inflammatory and immunosuppressant. Id. at 1171.

cultures done was positive. Id. at 51. Petitioner had a low grade temperature. A repeat MRI showed new hyperintensities on the right side of his brain. A chest x-ray showed atelectasis[8] at both bases, and petitioner had very poor breath sounds. Id. The most recent MRI raised the possibility of vasculitis involving the deep perforating arteries in the mid brain. Dr. Kubrin, an infectious disease specialist, ordered a cerebral angiogram to evaluate this. If the study suggested vasculitis, petitioner might need a vascular biopsy to confirm the diagnosis before treating petitioner with a long course of steroids. In the meantime, Dr. Torres, petitioner's neurologist, started petitioner on 1000 mg of Solu-Medrol. Med. recs. at Ex. 1, p. 122.

On January 18, 2008, a cerebral carotid bilateral angiography was performed to evaluate petitioner for vasculitis. R Ex. J, p. 279. The results were two small focal areas of ectasia[9] from branches of the left middle cerebral artery in the parietal region which could be secondary to vasculitis. There was no other evidence of vasculitis. R Ex. J, p. 280.

On January 22, 2008, Dr. Yelena Y. Sergeyeva, an internist, wrote a progress note stating petitioner had meningoencephalitis. The doctor had written cerebral vasculitis with a question mark and then crossed it out. Med. recs. at Ex. 1, p. 35.

On January 23, 2008, a test for E. chaffeensis[10] IgM showed 1:80 which was noted as high, although the comment was "Equivocal." Med. recs. at Ex. 1, p. 371.

On January 25, 2008, Dr. Sergeyeva wrote an interim summary stating the principal diagnosis was disseminated meningoencephalitis with multiple cerebrovascular accidents. There

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[8] Atelectasis is "incomplete expansion of a lung, or a portion of a lung." Dorland's at 173.

[9] Ectasia is "dilatation, expansion, or distention." Dorland's at 597.

[10] E. chaffeensis or Ehrlichia chaffeensis is a species "that causes human monocyte ehrlichiosis." Dorland's at 603. Ehrlichiosis is "a type of tick-borne fever caused by infection with bacteria of the genus *Ehrlichia*." Id. at 604.

was suspicion of vasculitis after an angiogram was done, but the doctors discussed this with a neurologist and it did not seem that petitioner had vasculitis. R Ex. J, p. 48.

On January 30, 2008, Dr. Bertrand H. Vipond wrote an interim summary stating the principal diagnosis was meningeal encephalitis due either to an undetected organism vs. acute disseminating encephalomeningitis vs. multiple strokes due to vasculitis. R Ex. J, p. 46. Petitioner was stuporous, and had myoclonic jerks mainly in the lower extremities and occasionally his left arm. There was no movement in his right arm. Id. Neurology had a conference that day which Dr. Torres presented to his colleagues who felt petitioner should have at least three more days of plasmapheresis. Id.

Also on January 30, 2008, Dr. Sohail Saeed did a hematologic consultation because the neurology services requested plasmapheresis[11] for petitioner since he had acute disseminated meningoencephalitis with multiple cerebellar accidents. R Ex. J, p. 174.

On February 1, 2008, a neurologist noted in the progress sheet that petitioner's case was presented in a neurological conference. The diagnosis of choice was ADEM. The treatment was plasmapheresis for four days followed by a physical therapy evaluation. Petitioner was to discontinue steroids which he was currently tapering. On examination, petitioner had right hemiplegia and right third nerve palsy. Med. recs. at Ex. 1, p. 55.

On February 1, 2008, petitioner received plasmapheresis. He was sedated on morphine. He could track with his left eye and follow simple commands with his right eye. Petitioner was diagnosed with ADEM likely secondary to a recent upper respiratory infection, and with meningoencephalitis. Med. recs. at Ex. 1, p. 56.

[11] Plasmapheresis is "the removal of plasma from withdrawn blood, with retransfusion of the formed elements into the donor." Dorland's at 1477.

On February 4, 2008, Dr. Michael Adair wrote an interim summary, stating that petitioner had altered mental status which was most likely secondary to acute disseminated encephalomeningitis (ADEM) vs. meningeal encephalitis due to another undetected organism. R Ex. J, p. 44. He also had right upper extremity deep vein thrombosis associated with peripherally-inserted central catheter line which had then been removed. Id. He was on Doxycycline intravenously for a mildly positive test for Ehrlichia. Id. Regarding acute disseminated encephalomeningitis, he was on steroids, IVIG, and plasmapheresis for four days. Id.

On February 5, 2008, petitioner had a brain MRI which showed infarct of the right thalamus, right posterior limb of the internal capsule, and right basal ganglion. He had infarct over the left posterior periventricular corona radiata region. Med. recs. at Ex. 1, p. 126.

On February 6, 2008, Dr. Douglas K. Mack did a rehabilitation consultation for petitioner due to nontraumatic brain injury with altered mental status secondary to acute disseminated encephalomeningitis vs. meningeal encephalitis due to undetected organism. R Ex. J, p. 172. Petitioner was post-antibiotics and plasmapheresis treatment. R Ex. J, p. 173. Also on February 6, 2008, petitioner was started on anticoagulation. Med. recs. at Ex. 1, p. 66.

On February 7, 2008, petitioner had a second test for E. chaffeensis IgM which showed 1:40 which was again above normal, but the comment was again "Equivocal." Med. recs. at Ex. 1, p. 150. Also on February 7, 2008, petitioner was diagnosed with meningoencephalitis likely secondary to vasculitis. Med. recs. at Ex. 1, p. 66.

On February 13, 2008, Dr. James Phuong Dinh wrote an interim summary. Petitioner's principal diagnosis was acute disseminated encephalomeningitis. He had borderline-positive Ehrlichia, right upper extremity cephalic venous thrombosis, probably heparin-induced

thrombocytopenia, hypertension, and malnutrition. R Ex. J, p. 41. Petitioner was treated with intravenous antibiotics for possible meningitis/encephalitis, but all studies were unremarkable. Id. at 42. Because petitioner was negative for infection except for the mildly positive Ehrlichia, he was taken off all antibiotics. Id. Because, at the end, it was felt that petitioner had acute disseminated encephalomeningitis, he was treated with steroids, IVIG, and subsequently plasmapheresis. Id.

On February 14, 2008, Dr. Tran, the internist, states in a progress note that petitioner had acute disseminated encephalitis with deep vein thrombosis of the right upper extremity. Med. recs. at Ex. 1, p. 31. Petitioner's anticoagulant level was being monitored. Dr. Tran stated the occlusion of petitioner's cerebral artery with infarct was stable. He questioned whether this was old or new. Petitioner also had deep vein thrombosis of the basilic and cephalic veins of his upper extremity. Id.

On February 15, 2008, petitioner was transferred to Reche Canyon, a skilled nursing facility. R Ex. J, p. 40. Dr. Tran at Fontana Medical Center wrote the transfer summary. Petitioner's diagnosis was acute disseminated encephalomeningitis. He had an additional diagnosis of borderline positive Ehrlichia, and probable heparin-induced thrombocytopenia. He became ill around New Year's Day with an upper respiratory infection and sinus, and became confused. The only abnormal test was the one for Ehrlichia. Med. recs. at Ex. 1, p. 3. On that same date, Dr. Tran filled out a physician discharge order record, diagnosing petitioner principally with encephalitis and vasculitis. An additional diagnosis was reactive vasculitis. R Ex. J, p. 36. Petitioner had brain MRIs done on January 8, 10, 11, and 17, 2008 which showed a progressive infarct of the right thalamus, globus pallides, and post infectious changes. Id.

In another transfer summary that Dr. Tran wrote on February 15, 2008, Dr. Tran states, "In the end, with all the workup, it was found that the patient probably had acute disseminated encephalomeningitis," and developed a right upper extremity thrombosis, the right basilica cephalic upper extremity veins. R Ex. J, p. 39.

On February 24, 2008, Dr. Michael Joseph Adair wrote a "To Whom It May Concern" letter, stating he treated petitioner in conjunction with the neurologist Dr. Torres and several others during his prior hospitalization. Med. recs. at Ex. 12, p. 812. Petitioner was diagnosed with acute disseminated encephalomyelitis (ADEM). Onset of the disorder is sudden. Id. Symptoms may include monoparesis (paralysis of a single limb) or hemiplegia (paralysis on one side of the body). Id. (The date of the letter, February 24, 2008, is 16 months before petitioner filed his petition on June 29, 2009.)

On March 28, 2008, the California Encephalitis Project issued a report called Encephalitis Test Report Form for petitioner. R Ex. J, p. 24. Onset was listed as December 23, 2007. Petitioner's antibody-EIA test of his blood serum was collected on January 17, 2008 when petitioner was in his acute phase and on February 6, 2008 when he was in his convalescent phase. It did not detect antibodies to West Nile Virus, parvovirus B19, rickettsia, typhus, Rocky Mountain spotted fever, Ehrlichia chaffeensis, A. phagocytophilia, or Q fever. The antibody-EIZ test of petitioner's blood did detect that petitioner had a past infection with EBV (Epstein-Barr virus). Id. The test also showed infection or immunization at an undetermined time for mycoplasma pneumoniae, influenza A and B, and adenovirus. PCR (polymerase chain reaction) performed on cerebrospinal fluid (CSF) collected on January 10, 2008 was negative for herpes simplex virus 1 and 2, varicella zoster virus, and human herpesvirus 6. It was questionable for enterovirus. Id. A nasopharyngeal sample from petitioner's throat taken January 10, 2008 was

negative for influenza A and B, adenovirus, human metapneumovirus, respiratory syncytial virus, enterovirus, and mycoplasma. Id.

On April 8, 2008, petitioner saw Dr. Torres, his neurologist, for 30 minutes. Half the time was spent counseling, coordinating care, and discussing acute disseminated encephalomyelitis post flu vaccination vs. flu episode. Med. recs. at Ex. 1, p. 2.

Other Submitted Material

Petitioner filed his declaration in support of his petition on June 29, 2009 with his petition. He states that he received influenza vaccine on November 6, 2007 and, sometime in the same month, started having cramping in his feet, and later his thighs, with calf pain. Decl., p. 2, ¶ 4. Around December 3, 2007, he had severe headache, nausea, vomiting, and fever, as well as back spasms, jaw pain, leg cramps, and photophobia. By December 12, 2007, he had mid to upper back spasms. On December 30, 2007, the cramping had moved to his neck and jaw. Id.

Filed with petitioner's expert Dr. Steinman's report are a number of articles, including one entitled "Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein" by K.C. O'Connor, et al., www.naturemedicine.com/naturemedicine doi:10.1038/nm1488 (2007). P Ex. 2, pp. 62-68. The authors state that animal models of central nervous system (CNS) demyelinating diseases recognize epitopes on the surface of myelin or myelin-producing oligodendrocytes. Id. at 62. Myelin oligodendrocyte glycoprotein (MOG), although a minor component of myelin, is located on the outer surface of the myelin structure and, thus, is accessible to antibodies. Id. Certain individuals with ADEM had MOG autoantibodies. This was evidence of antibody-associated autoimmunity. Id. at 66. The response of some ADEM patients to plasmapheresis or IVIG suggests that pathogenic autoantibodies may play an important role in their ADEM. Id. at 67.

Another article petitioner filed with Exhibit 2 is entitled "Guillain-Barré Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-77" by L.B. Schonberger, et al., 110 Amer J Epidemiology 2:105-23 (1979). P Ex. 2, p. 112. The authors studied the incidence of GBS following swine flu vaccination and calculated there was an increased incidence over baseline GBS lasting nine or 10 weeks. Id. at 119.

The next article petitioner filed with Exhibit 2 is entitled "An Epidemiological and Clinical Evaluation of Guillain-Barré Syndrome Reported in Association with the Administration of Swine Influenza Vaccines" by A. Langmuir, et al., 119 Amer J Epidemiology 6:841-79 (1984). P Ex. 2, p. 131. The authors reassessed the Schonberger data from the epidemiological article published in 1979 and concluded that the increased incidence of GBS among swine flu vaccinees over baseline GBS lasted eight weeks. Id. at 156.

Filed with Dr. Steinman's Supplemental Expert Report are three articles (P Ex. 6), two of which are relevant to the issues herein. The first article is "Original Communication. Acute disseminated encephalomyelitis in adults: a reappraisal of clinical, CSF, EEG, and MRI findings" by P. Höllinger, et al., 249 J Neurol 320-29 (2002). P Ex. 6, p. 7. The authors analyzed 10 cases of adults who had ADEM in whom preceding infections were generally viral. Most of the infectious diseases lasted days, but, in one patient, the infection lasted for almost two months. Id. at 8. Brain MRI was normal in five of the patients. Id. at 10. The authors discuss four of the 10 cases in detail. Case 3 concerns a 39-year-old woman who had flu-like symptoms for almost two months until she developed laryngitis, fever, and exanthema in the face. Id. at 12. She was treated with Acyclovir, plasma exchange, intravenous immunoglobulin (IVIG), and oral prednisone. Id. at 13. The authors state, "The corner-stones of ADEM, which have been described variably, are clinical: acute onset, monophasic and often self-limited course, symptoms

and signs of disseminated diffuse or multifocal CNS [central nervous system] involvement, a preceding infection (mostly viral of respiratory or gastrointestinal tract) or vaccination." Id. The authors state that ADEM usually occurs in younger patients and that when adults get ADEM, they tend to have less aggressive inflammation with headache, fever, meningismus, optic neuritis, and impaired consciousness being rarer. Id. at 14. Adults with ADEM, however, have a more prolonged recovery and persistent residual sequelae than younger people with ADEM. Id. In the 10 patients the authors studied, severity of ADEM did not correlate with the extent of brain MRI abnormalities, and five of the 10 patients they studied had normal brain MRIs. Id. Because "MRI as a structural imaging method does not necessarily allow for a conclusive assessment of brain function," the authors believe "that MRI should not be relied upon when defining a diagnosis of ADEM." Id. The CSF (cerebrospinal fluid) of 5 of the 10 patients the authors studied was normal. The authors state, "Assessment of CSF is important to diagnose an infectious disease." Id. But they note that normal CSF findings do not exclude an inflammatory or antibody-mediated CNS infection. Id. In none of the authors' 10 patients was a diagnosis of a specific microbe causing the ADEM established. Id. at 14-15. The authors found EEG to be of greatest help in proving encephalopathy and the best correlate to the clinical course. Id. at 15.

The second attachment to Ex. 6 is a case report entitled "Case Records of the Massachusetts General Hospital. Weekly Clinicopathological Exercises. Case 37-1995," ed. R.E. Scully, et al., 333 NEJM 22:1485-93 (1995). P Ex. 6, p. 17. The case concerned a six-year-old boy who was admitted to the hospital in early August because of rash, meningismus, and diplegia. Id. He had been well until three days earlier when he became fatigued and chilled while swimming. He had spent a week in a camp in Maryland with horses in the vicinity. The next day, he was nauseated and vomiting and had large evanescent erythematous patches on his

face, arms, and legs, followed by pains to his neck and shoulder, and tingling of the legs. The next morning, he could not walk because of weakness. Id. He had elevated white cell count and protein in his CSF. Id. at 18. On his second day in the hospital, ultrasound showed that the child's heart was compromised with tachycardia. His right pupil was 8 mm and unreactive to light and the corneal reflex was absent. Id. The left pupil was 3 mm and briskly reactive to light and the corneal reflex was intact. Id. at 19. On his fourth day in the hospital, the child died. Id. at 19. The doctors discussing the case considered him to have either acute hemorrhagic leukoencephalitis, disseminated encephalomyelitis triggered by a primary enteroviral infection, or acute viral encephalomyelitis and myocarditis. Id. at 21, 22. On pathology, the immediate cause of death was a large right cerebral infract, with massive swelling of the hemisphere and compression of the mid brain. There was no evidence of encephalitis in the cerebral hemispheres. Id. at 22. Demyelination was throughout the respiratory and cardiac control centers in the brain as well as in the spinal cord. Id. The diagnosis was acute disseminated encephalomyelitis. Id. Based on the autopsy, the anatomical diagnoses were acute disseminated encephalomyelitis (postviral encephalomyelitis) and recent cerebral infarct. Id. at 24.

Petitioner filed a series of documents as Exhibit 8. The first document is an information page on acute disseminated encephalomyelitis from the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health. P Ex. 8, p. 1. Synonyms for acute disseminated encephalomyelitis are postinfectious encephalomyelitis and immune-mediated encephalomyelitis. Id. The definition of acute disseminated encephalomyelitis (ADEM) is

> a brief but intense attack of inflammation in the brain and spinal cord that damages myelin—the protective covering of nerve fibers. It often follows viral infection, or less often, vaccination for measles, mumps, or rubella. The symptoms of ADEM come on

> quickly, beginning with encephalitis-like symptoms such as fever, fatigue, headache, nausea, and vomiting, and in severe cases, seizures and coma. It may also damage white matter (brain tissue that takes its name from the white color of myelin), leading to neurological symptoms such as visual loss (due to inflammation of the optic nerve) in one or both eyes, weakness even to the point of paralysis, and difficulty coordinating voluntary muscle movements (such as those used in walking).

Id.

The NINDS states that ADEM usually has symptoms of encephalitis (such as fever or coma) and symptoms of myelin damage (visual loss, paralysis). Id. Treatment for ADEM is directed at suppressing brain inflammation using anti-inflammatory drugs such as intravenous corticosteroids, e.g., methylprednisolone. If corticosteroids do not work, treatment turns to plasmapheresis or intravenous immunoglobulin (IVIG). Id.

Next in petitioner's Exhibit 8 is chapter 35 from Brain's Diseases of the Nervous System, 11th ed., (ed.) M. Donaghy (no date of publication given), entitled "Complications of systemic infections and immunizations" by M. Anderson. P Ex. 8, pp. 4-19. The author describes vaccine-associated encephalopathies. Id. at 17. Encephalopathies can follow from acute infections, mainly viral, and are termed post-infectious encephalomyelitis. Id. Identical manifestations were found following immunizations that are termed post-vaccinial or post-immunization encephalomyelitis. Id. The pathological substrate common to all is acute disseminated encephalomyelitis (ADEM). Id. Vaccinations associated with encephalopathy and ADEM are measles, rabies, diphtheria/tetanus toxoid, pertussis, and influenza. Id. Vaccine-associated encephalopathy resulting in ADEM is felt to be a T-cell mediated autoimmune response against myelin basic protein. Id. Why some people get vaccine-associated encephalopathy while most people do not may stem from genetic control of the immune response. Id. Pathologically, the brain experiences acute swelling and venous engorgement of

white matter with perivascular edema and mononuclear cell infiltration. Id. Days, or more usually, within two or three weeks after vaccination, an encephalitic illness ensues, characterized by headache, fever, confusion, obtundation, epileptic seizures, sometimes focal neurological signs, hemiparesis, hemisensory disturbance, movement disorder, ataxia, optic neuritis, and progression to coma. Id. White matter lesions are often widespread and multiple. Id.

Next in petitioner's Exhibit 8 is a case report entitled "Acute Disseminated Encephalomyelitis Associated with Influenza Vaccination" by J.H. Cheong, et al., 35 J Korean Neurosurg Soc 223-25 (2004). P Ex. 8, p. 20. A 14-year-old girl presented at the hospital with dysarthria and right hemiparesis that had developed over two days. Two weeks before admission, she received influenza vaccine, followed by mild fever with a sore throat. The first sign of her neurological illness was difficulty in raising her right upper limb followed by numbness in the same limb. Within 48 hours, numbness spread to the right lower extremity. Id. All her laboratory tests were normal. CT scans of her brain revealed multiple subcortical white matter lesions. Id. The authors of the case report considered that the girl's ADEM was due to her upper respiratory infection and/or vaccination. Id. at 22. They advise that if multifocal neurological deficits follow influenza vaccine, ADEM may develop. Id.

Next in petitioner's Exhibit 8 is an article entitled "Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children" by R.C. Dale, et al., 123 Brain 2407-22 (2000). P Ex. 8, p. 23. The authors studied 48 children with disseminated inflammatory central nervous system (CNS) disease: 28 with ADEM, seven with MDEM (multiphasic disseminated encephalomyelitis), and 13 with MS (multiple sclerosis). Id. at 26. Seventy-four percent (26 patients) of the ADEM/MDEM patients had a preceding illness in the month before presentation. The mean latency between pre-

demyelinating illness and onset of neurological signs was 13 days (range 2-31 days). Id. The preceding illnesses were described as upper respiratory infection (nine patients), influenza (three patients), tonsillitis (four patients), lower respiratory tract infection (three patients), vaccination (two patients), gastroenteritis (two patients), varicella (one patient), and fever of unknown origin (two patients). Id. at 26-27. Ten children had serological evidence of specific triggers: streptococcus (three patients), mycoplasma (one patient), influenza B (one patient), enterovirus (one patient), Epstein-Barr virus (one patient), varicella (one patient), mumps rubella vaccination (one patient), and BCG vaccination (one patient). Id. at 27.

Of 33 patients who were tested, 64 percent had elevation of the white cell count in the blood. Id. All MRI brain scans of the ADEM/MDEM children showed disseminated CNS lesions. Id. at 30. In the ADEM group, the lesions were primarily in the white matter. Id. Sixty-six percent of the children with ADEM/MDEM "were initially treated for infective meningoencephalitis with antibiotics and antivirals until the correct neuroallergic diagnosis of ADEM had been established." Id. at 32. Once the ADEM diagnosis was made, immunomodulatory treatments were considered. Id. The majority of ADEM patients have a preceding infection in the upper respiratory tract although the actual organism is not serologically identified. Id. at 34. Only two children in this study had vaccine-associated ADEM. Vaccines have previously been reported to precipitate ADEM: flu vaccine, rabies vaccine, Japanese B encephalitis vaccine, and smallpox vaccine. "The majority of these vaccines are dead or inactivated, supporting the theory that ADEM is a neuroallergic phenomenon." Id. The latency period between antigenic triggering and neurological signs was about two weeks. Id.

Although infective agents are closely implicated in the pathogenesis of ADEM, microorganisms have not been isolated within the CNS or the cerebrospinal fluid unlike infective encephalitis. Id. The authors state the process is unclear whereby pre-demyelinating triggers precipitate ADEM, although they found the molecular mimicry hypothesis attractive. Id. Some children presented with a fulminant encephalopathic illness so quickly after the precipitating trigger that clinical evidence of the trigger infection was still present, whereas some patients presented more indolently with a change in behavior, loss of developmental skills, headache, and chronic fatigue. Id. In ADEM patients, brain MRIs show lesions mostly in the subcortical white matter with relative sparing of the periventricular white matter. Id. at 35. Some of the MRI lesions may represent edema. Grey matter cortical lesions may be the only imaging finding in ADEM. Id. Most ADEM patients had disseminated lesions throughout their CNS, but three children with ADEM had only one demyelinating lesion at presentation. Id. Single demyelinating lesions have also been found in adults with ADEM who were biopsied because of the fear that they had a solid tumor. Id. at 36. In discussing their conclusions, the authors state, "It would seem prudent to avoid stimulating the immune system (such as by vaccination) in the aftermath of ADEM for at least 6 months." Id.

Next in petitioner's Exhibit 8 is an article entitled "Acute Disseminated Encephalomyelitis in Childhood: Epidemiologic, Clinical and Laboratory Features" by J.A.D. Leake, et al., 23 Pediatr Infect Dis J 8:756-64 (2004). P Ex. 8, p. 39. The authors state that "microbiologic and serologic testing often fails to reveal evidence of a recent or ongoing infection" associated with ADEM onset. Id. at 40. "Additionally, ADEM has been observed after vaccination with animal brain-derived rabies vaccines and, rarely, after administration of

other vaccines [referring to Japanese encephalitis vaccine, hepatitis A vaccine, hepatitis B vaccine, and tetanus vaccine]." Id. The authors state:

> The lack of evidence for ongoing infection or vaccination in most cases and the usual time lapse of a few weeks between infectious symptoms or signs and ADEM onset have promoted the view that ADEM is a postinfectious immune disease. Molecular mimicry, e.g., similarities between viral epitopes and host myelin antigens such as myelin basic protein, myelin oligodendrocyte glucoprotein and proteolipid protein, has been proposed as an explanation for autoreactive immune responses to CNS white matter after an infectious trigger.

Id.

In the authors' study group of 42 patients with ADEM, two had received recent immunizations: one had varicella and measles-mumps-rubella vaccinations 21 days prior to onset, and one had pneumococcal conjugate vaccine three days prior to onset. Id. at 41. Nearly one-third of the patients in the study reported ill contacts, usually siblings, during the month before onset of ADEM. Id. Eight patients had a history of wild-type varicella infection, but none within the preceding two months. Id. All but three (93%) of the patients had one or more of the following symptoms or signs of infection within the preceding 21 days: fever, cough, rhinorrhea, vomiting, or diarrhea. Id. at 42. Two-thirds (67%) of the patients reported fever, but only one-fourth (24%) were febrile during hospitalization. Nearly one-half (45%) of all patients had upper respiratory symptoms (rhinorrhea, cough or both) usually within about seven days previously, and more than one-half had vomiting, usually within three days of admission. Id. Culture or serology suggested a possible antecedent or coincident infection in only eight of 42 patients. Id. All 42 patients had cranial and/or spinal MRIs showing demyelination, which was a requirement for inclusion in the study. Id. at 43, 45.

The authors state that the principal reason "for using corticosteroids and IVIG to accelerate convalescence in ADEM has been down-regulation of CNS immune activation, e.g., autoreactive T or B cells." Id. at 45. Another therapy besides corticosteroids and IVIG used to improve demyelinating diseases such as ADEM is plasmapheresis. Id. Based on animal studies, the authors suggest that the context in which antigens are presented to the host's immune system is important for determining tolerance or autoimmunity. Id.

The next document in petitioner's Exhibit 8 is an excerpt from a textbook entitled Child Neurology, 7th ed., (ed.) J.H. Menkes, et al. (no date of publication given), pp. 578-82, whose title is "Acute Disseminated Encephalomyelitis." P Ex. 8, p. 49. The unidentified authors define ADEM as "an immune-mediated inflammatory disorder of the CNS, which is commonly preceded by an infection and predominantly affects the white matter of the brain and spinal cord…." Id. at 49. The use of MRI scans has facilitated a more accurate identification of ADEM which was otherwise frequently diagnosed as acute nonspecific meningoencephalitis. Id. "ADEM can occur at any age, but it is much more frequent in children probably because of a higher exposure to infections and immunizations." Id. The presentation of ADEM may be acute or subacute. Id. ADEM over the years has received different names, e.g., postinfectious or postvaccinial encephalomyelitis, acute demyelinating encephalomyelitis. Id. at 49-50. The pathogenesis of ADEM is thought due to disseminated multifocal inflammation and patchy demyelination associated with autoimmune CNS mechanisms. Id. at 50. "Attempts to recover viruses or to demonstrate the presence of viral particles or antigens in the lesions have been unsuccessful. The absence of the typical pathologic findings seen in viral infections indicates that a direct viral invasion of the CNS is not the cause of the disease." Id. On the other hand, the presence of a "'silent' (clinically asymptomatic) interval between an antecedent of infection or

immunization and the beginning of the encephalopathy…supports an autoimmune mechanism…." Id. The authors continue: "Genetic susceptibility explains why encephalomyelitic complications develop only in a small percentage of patients who have infections or receive immunizations." Id.

The brain of someone with ADEM may frequently have frank vasculitis with associated vasogenic edema, which causes variable degrees of brain and spinal cord swelling. Id. Significantly, the inflammatory process involves both white and gray matter, although more prominently the former. Id. The neurological signs and symptoms begin three days to four weeks after a precipitating event, which three-quarters of patients have identified. Id. "Immunizations linked to the development of ADEM are those against measles, mumps, rubella, diphtheria-pertussis-tetanus (DPT), varicella, mumps parotitis, rubeola, influenza, Japanese encephalitis type B, and poliomyelitis…." Id. at 51. The only pathologically proven causal association was with the old antirabies vaccine which is no longer used. Id. The patient at first may complain of nonspecific symptoms, e.g., headache, low-grade fever, myalgia, and malaise. Then, a rapid onset of overt neurologic symptoms follows including acute encephalopathy, hemiparesis or quadriparesis, ataxia, sleepiness, stupor, or coma. Other symptoms and signs include cranial nerve involvement, meningismus, convulsions, migraine, myelopathy, optic neuritis, aphasia, involuntary movements, and paresthesias. Id. Diagnosis of ADEM is based on MRI evidence of multifocal white matter demyelination in someone with an acute onset of neurologic dysfunction after a latent period preceded by a systemic infection, usually viral, or an immunization. Id. The authors state that the differential diagnosis of ADEM is broad. Id. at 53. If someone has an acute change in mental status, motor focal findings, fever, and partial seizures,

the doctor must rule out acute viral meningoencephalitis, and prescribe antiviral treatment until MRI and virologic studies confirm or rule out viral infection. Id.

The use of high doses of corticosteroids during the acute phase of ADEM is the specific treatment directed against the inflammatory immune process. Id. Use of methylprednisolone is particularly indicated when an ADEM patient has severe impairment of consciousness or optic nerve involvement. Id. Use of IVIG has been satisfactorily used in severe cases that were unresponsive to corticosteroids. Id. Plasmapheresis is also a good option for ADEM patients who have the fulminant form of ADEM without improvement on steroids and IVIG. Id.

The next filing in petitioner's Exhibit 8 are two case reports entitled "Neurologic Complications Associated with Influenza Vaccination: Two Adult Cases" by N. Nakamura, et al., 42 Internal Med 2:191-94 (2003). P Ex. 8, p. 54. The authors state that GBS and ADEM are major neurologic complications after infection or vaccination due to a T-cell-mediated immune reaction to myelin components or oligodendrocytes. Id. They discuss two cases of reactions to influenza vaccine. The first case concerns a 62-year-old man who received flu vaccine and five days later had a generalized convulsion. He was ultimately diagnosed with ADEM after MRI. Id. The second case concerns a 70-year-old man who received flu vaccine and seven days later had backache followed by dysuria and paraplegia. Id. at 54-55. Brain MRI showed only lacunar infarction. Id. at 55. He did have a lesion in the C6-T3 vertebral level of his spinal cord. Id. at 56.

The next document in petitioner's Exhibit 8 is an editorial discussing the Nakamura article just discussed above. The editorial is entitled "The Influenza Vaccination and Neurological Complications" by H. Shoji and M. Kaji, 42 Internal Med 2:139 (2003). P Ex. 8, p. 70. The authors state that with the progress of MRI and other tools, they expect diagnoses of

ADEM or myelitis to increase. They recommend continued vaccination against flu because flu deaths outnumber flu vaccine adverse reactions. Id.

The last document filed in petitioner's Exhibit 8 is an excerpt from Adverse Events Associated with Childhood Vaccines. Evidence bearing on Causality, (eds.) K.R. Stratton, et al., Institute of Medicine (1994), pp. 34-36, 83-84, and 89. P Ex. 8, p. 71. The authors state that ADEM can follow inactivated antiviral vaccination. Id. at 72. ADEM occurs from five days to six weeks following an inciting event. Id. at 75. The authors state "it is biologically plausible that injection of an inactivated virus, bacterium, or live attenuated virus might induce an autoimmune response in the susceptible host, either by deregulation of the immune response, by nonspecific activation of T cells directed against myelin proteins, or by autoimmunity triggered by sequence similarities to host proteins such as those of myelin. The latter mechanism might evoke a response to self-antigen (molecular mimicry) [citation omitted]." Id. at 76.

The next article in petitioner's Exhibit 8 is entitled "Immune Mediated Central Nervous System Disorders in Childhood Viral Infections" by L. Reik, 2 Seminars in Neur 2:106-14 (1982). P Ex. 8, p. 58. In Table 1, the author lists reported precipitants of ADEM. Included among them are "Immunizations and vaccinations," two of which are "Influenza A & B." Id. The incidence of ADEM after vaccination varies widely from country to country and even year to year within the same country. Id. at 58-59. Symptoms usually begin four to 21 days after the inciting event. Id. at 59. Neurologic symptoms can be abrupt or gradual, starting with disturbed behavior, irritability, and restlessness followed by delirium and a slow lapse into stupor or coma. Id. Among the common signs is hemiplegia. Id. Grave sequelae are more common in those with coma, convulsions, and hemiplegia. Id. The author notes lesions in blood vessels before demyelination. Id. at 60. This includes invasion of vessel walls by inflammatory cells,

perivascular edema, and hemorrhage. Id. ADEM is generally believed to be autoallergic. "Identical illness occurs after immunization with killed vaccines, as an adverse reaction to drugs and after serum injection, and begins following a clear latent period during which sensitivity could develop." Id. The character of the host, not the nature or severity of the preceding illness, determines the development of ADEM. Id. Immune complex vasculopathy may be involved in the pathogenesis of ADEM. Id. at 60-61. Small vessel injury can result in perivascular demyelination. Id. at 61. Vascular changes precede mononuclear cell infiltration and demyelination in ADEM. Id.

The next document in petitioner's Exhibit 8 is a case report entitled "Acute Disseminated Encephalomyelitis After Influenza Vaccination" by H. Saito, et al., 37 Arch Neur 564-66 (1980). P Ex. 8, p. 67. Four days after he received influenza vaccine, a 12-year-old boy had ADEM. He had paralysis of the right side of his face and right arm. The left arm was normal. He was completely paralyzed below the T-4 level of his spinal cord. Id. He had transient loss with papilledema. Id. at 68. This was replaced by gradual restitution and optic atrophy. The authors state that the boy's visual symptoms suggest the main pathologic process was demyelination. Id. at 69. They state: "Neurological complications following influenza vaccination are uncommon, but there are several reports covering various clinical syndromes: encephalopathy, meningoencephalitis, Guillain-Barré syndrome, polyneuropathy, peripheral neuritis, and various combinations of these [citations omitted]." Id. The boy described in the case report was not allergic to eggs and had not reacted adversely to six prior influenza vaccinations in his past. Similar cases are recorded in the medical literature. Id.

Filed with petitioner's expert Dr. Steinman's Third Supplemental Expert Report is petitioner's Exhibit 13, including a letter in a section called "Scientific Correspondence" entitled

"An unusual complication of ADEM" by B. Perunovic, et al., 27 Neuropath & Applied Neurobiol 139-41 (2001). Ex. 13, p. 7. The authors describe an unusual complication of ADEM in a patient in whom inflammation and edema in the posterior fossa led to infarction of the brain stem. Id. A 59-year-old woman came to a hospital with rapid onset of fever, occipital headache, and vomiting. Two months previously, she had pleuritic chest pain, a non-productive cough, night sweats, and weight loss, for which she received oxytetracycline with resolution of her symptoms. Id. On hospital admission, she was feverish, drowsy, and dysarthric, and had mild left-sided weakness. No infection or systemic autoimmune disease was discovered as the cause. She died seven weeks after admission. On autopsy, she had lesions in her brain. Those in the cerebral white matter and peduncles were perivenous foci of demyelination. The pontine cavity had histological features of a maturing infarct. She did not have cardiovascular disease. The authors stated the infarction occurred during the acute phase of the demyelinating disease. "We suggest that the infarction probably resulted from vascular compression as a result of severe swelling of the brainstem, as demonstrated radiologically." Id.

Filed as petitioner's Exhibit 19 are supplemental medical articles including an article entitled "Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): Case definitions and guidelines for collection, analysis, and presentation of immunization safety data" by J.J. Sejvar, et al., 25 Vaccine 5771-92 (2007). P Ex. 19, p. 7. The authors from the United States, Holland, Jordan, Switzerland, and Finland, called the Brighton Collaboration Encephalomyelitis/ADEM Working Group, developed case definitions and guidelines for encephalitis, myelitis, and ADEM. Id. The authors state, "Various immunizations have been temporally associated with subsequent ADEM, including Japanese encephalitis, yellow fever, measles, influenza, smallpox, anthrax, and others [citations omitted]." Id. at 8. The only

epidemiologically proven connection is to the old rabies vaccine derived from sheep/mouse brains. Id.

In creating criteria for ADEM diagnosis, the authors created levels 1, 2, and 3 of certainty, with the lowest level of certainty being level 3. Id. at 8, 11, 12. Level 1 of diagnostic certainty for ADEM requires either demonstration of diffuse or multifocal areas of demyelination by histopathology or one or more of the following central nervous system focal or multifocal findings: (1) encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change greater than 24 hours); (2) focal cortical signs (including aphasia and cortical blindness); (3) cranial nerve abnormality or abnormalities; (4) visual field defect or defects; (5) presence of primitive reflexes (e.g., Babinski's sign); (6) either diffuse or focal motor weakness; (7) sensory abnormalities; (8) altered deep tendon reflexes; or (9) cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus. With either histopathological demonstration of diffuse or multifocal areas of demyelination or one or more of the above focal or multifocal findings, the patient should also have MRI findings displaying diffuse or multifocal white matter lesions and a monophasic pattern to his or her illness. Id. at 12, 14.

Level 2 of diagnostic certainty of ADEM omits histopathological demonstration of diffuse or multifocal areas of demyelination, but includes the other factors listed to satisfy level 1 except for proof of a monophasic pattern due to insufficient follow up time. Id. at 15. Level 3 of diagnostic certainty of ADEM is the same as level 2 except there is no MRI information sufficient to distinguish between acute encephalitis and ADEM. Id. In formulating data to evaluate whether an encephalitis/ADEM is an adverse reaction to vaccination, a study participant should classify the nature of the onset of the encephalopathy, i.e., whether it is acute (evolving

over minutes to hours or hours to days) or subacute (evolving over hours to days or days to weeks). Id. at 16.

TESTIMONY

Kim Brown, petitioner's wife, testified first for petitioner. Tr. at 12. Petitioner received flu vaccine on November 6, 2007, and started complaining within a few days about cramping in his feet. Tr. at 22, 23. He thought his shoes were not fitting him correctly and bought a new pair of tennis shoes and two new pairs of work boots because his feet hurt, but they did not help his cramping. Tr. at 23. When petitioner's legs started cramping, petitioner and his wife thought he might have a low potassium level and obtained potassium pills. Id. Petitioner's potassium level was tested at Dr. Ballat's office on December 3rd as part of routine testing for petitioner's blood pressure and cholesterol, and the result was high. The office wanted to know why. Tr. at 25. The office told petitioner to stop taking potassium pills because the level was too high. Id. In December, petitioner got worse, having headaches, nausea, and fever. Tr. at 26. His temperature ranged from 100 to 102 decrees. Tr. at 27. He described his headaches as explosive. Id. This was unlike any of his sinus headaches. Id.

The cramping stated going to his shoulder, neck, and jaw regions by the end of December. Tr. at 30. Starting in mid-December 2007, petitioner slept more. Tr. at 31, 32. On January 5, 2008, he went to bed and slept all day on January 6, 2008. Tr. at 32. After mid-December 2007, Mrs. Brown testified that petitioner did not do much of anything except sleeping 12 hours a day and watching television another four or five hours while wrapped in a blanket. Tr. at 33.

When petitioner consented on December 31, 2007 to go to a doctor, Mrs. Brown told him to ask for a spinal tap. Tr. at 35. When petitioner returned from the examination, he said the

doctor asked him to touch his chest with his chin and, when he did so, told him he did not have meningitis and laughed at him. Tr. at 36. The doctor prescribed some antibiotics and heartburn pills. Tr. at 37. The antibiotics did not help and petitioner got worse. Tr. at 39.

Mrs. Brown testified that no one else in her family got sick in December 2007 or January 2008. Tr. at 40. On January 7, 2008, petitioner was staggering and his speech was slurred. Tr. at 42. His fever was almost 102 degrees. Id. At the emergency room, the doctors thought petitioner had meningitis or encephalitis. Tr. at 47.

Mrs. Brown spoke to petitioner's neurologist Dr. Torres in mid-January and he said he thought petitioner had acute disseminated encephalomyelitis. Tr. at 48. Dr. Torres got the entire neurology and neurosurgery departments together for a big meeting to discuss petitioner and everyone agreed that petitioner should receive steroids, IVIG, and plasmapheresis. Tr. at 48, 49. Dr. Cooper, an infectious disease specialist, thought petitioner might have a vascular problem but Dr. Torres said the test result did not show anything. Tr. at 49. The entire right side of petitioner's body was paralyzed. Tr. at 52.

Mrs. Brown said that Kaiser does paperless work and the doctors are supposed to push buttons, but there was no button for acute disseminated encephalomyelitis so doctors would push the button for acute disseminated encephalomeningitis. Tr. at 53, 54. Dr. Adair wrote a letter dated February 24, 2008 explaining that petitioner actually had myelitis, not meningitis, when he was transferred to Reche Canyon. Tr. at 54.

Mrs. Brown testified that the equivocal Ehrlichia test was probably the result of contamination, according to Dr. Kubrin, the infectious disease specialist. Tr. at 58. After a second sample was sent to the California Encephalitis Institute, the test results came back negative. Id. Mrs. Brown testified that petitioner was able to participate in Christmas activities

with the children in 2007. Tr. at 73. Petitioner was an independent contractor and between Christmas and New Year's, the contractor took a break and the job was supposed to start again the first week of January. Tr. at 75, 76.

Mrs. Brown testified that she told personnel in the emergency room that petitioner had cramping in November and December 2007. Tr. at 86.

The conference Dr. Torres had with other neurologists occurred in late January 2008. Tr. at 92. There were from 15 to 20 people at the meeting. Tr. at 93. Dr. Adair wrote a letter to Reche Canyon stating that petitioner's diagnosis was ADEM in order to clarify what petitioner had for the purpose of rehabilitation. Tr. at 94.

Barbara Harrison, petitioner's mother-in-law, testified next for petitioner. Tr. at 102. Between November and December 2007, petitioner told her that he was not feeling well and having extreme headaches and body pain. Tr. at 105.

Dr. Lawrence Steinman, a neurologist, testified next for petitioner. Tr. at 117. He is a professor of neurology at Stanford and heads the Immunology Department there. Tr. at 118. His main interest is demyelinating disease and he spends a lot of time thinking about acute demyelinating disease, working on both the human and animal sides. The animal version of ADEM is called EAE for experimental autoimmune encephalomyelitis. Id. He has seen, diagnosed, done research on, and published on ADEM. Tr. at 121. He sees a child in the hospital once a week with a differential diagnosis involving meningitis, meningoencephalitis, and acute disseminated encephalomyelitis. Tr. at 122. He uses those terms interchangeably in the clinic. Id. There are often cells in the spinal fluid as part of the manifestation of the disease, representing meningeal inflammation. Id. The cells tell the doctors that there is inflammation at least in the lining of the brain. Tr. at 123. Eighty percent of his research is with people, and 20

percent is with mice. He spends 60 percent of his time on research. Tr. at 124. In his research, he has found cross reactivity between influenza vaccine and myelin basic protein. Tr. at 126.

Dr. Steinman said one could see infarctions with ADEM. Tr. at 127. There is a very close connection between the coagulation cascade and inflammation. Id. In his clinical experience, he has seen ADEM following influenza vaccination 50 times. Tr. at 129.

In 2009, Dr. Steinman was elected to the Institute of Medicine of the National Academy of Sciences. Tr. at 131. He is involved in vaccine programs. Tr. at 132. It is a lifetime appointment. Tr. at 133. Twenty-six percent of his time is devoted to seeing patients. Tr. at 135. His main focus is multiple sclerosis. Tr. at 134. There are differences and similarities between MS and ADEM. Tr. at 137. One does not see stroke, coma, changes in level of consciousness, or seizures in MS, but one can see them in ADEM. Id. There is no single test for ADEM, but there is a definition from the National Institute of Neurologic Disease and Stroke (NINDS), which is petitioner's exhibit 8. Tr. at 138. The NINDS definition of ADEM is encephalitis-like symptoms such as fever, fatigue, headache, nausea, vomiting, and, in severe cases, seizure and coma, which come on quickly. ADEM may damage white matter leading to neurologic symptoms such as visual loss in one or both eyes, weakness to the point of paralysis, and difficulty in coordinating voluntary muscle movements. Tr. at 139. Dr. Steinman agrees with the NINDS definition of ADEM. Id.

Dr. Steinman's opinion is that petitioner's flu vaccination in early November 2007 led to the development of ADEM. Tr. at 140. He stated that encephalomyelitis is a main component of ADEM. Moreover, "acute" means it has not been going on for years. Dr. Steinman said ADEM "comes up with an acute velocity." Id. He also stated that ADEM "can come on over weeks and even a couple of months." Tr. at 141.

Dr. Steinman testified that someone does not need muscle cramps to have a diagnosis of ADEM. Id. Petitioner was not himself after the flu vaccination. He was a stalwart type who normally did not complain, but his wife and mother-in-law stated that he complained about cramps, fatigue, and not being himself. Tr. at 141-42. "But through early December he doesn't have manifestations that could be exclusively called encephalomyelitis." Tr. at 142.

In December, Dr. Steinman stated, petitioner had headaches attributed to sinusitis. Tr. at 143. Dr. Steinman said petitioner's headaches could be attributed to sinusitis, muscle contraction, meningitis, depression, or migraines. Id. Petitioner was a smoker, with a cough and probable chronic lung disease and lung inflammation from smoking one cigarette an hour. Tr. at 144. He had excessive triglycerides and was taking Lopid which has anti-inflammatory effects and may have allowed ADEM to smolder in petitioner. Tr. at 144.

Petitioner saw Dr. Shibata at the end of December and, one week or so later, he became quite sick. The spinal tap showed he has brain inflammation. He went into a coma and had seizures. Imaging showed he had not only brain inflammation, but also associated stroke. Tr. at 145. Although petitioner had one borderline positive test for Ehrlichia, his treating neurologist Dr. Torres diagnosed petitioner with acute disseminating encephalomyelitis, a diagnosis with which Dr. Steinman is in 100 percent agreement. Id. Dr. Steinman spoke to Dr. Torres, who stressed that ADEM was his diagnosis. Id.

Dr. Steinman said that both a vaccination and an infection can cause ADEM. Dr. Steinman thinks flu vaccine, not an infection, was the cause of petitioner's ADEM. Tr. at 146. Dr. Steinman said he does not know at what point petitioner had a clear acute infection instead of his chronic lung disease from smoking. Id. Dr. Steinman admitted that petitioner finally got a fever, but he thought petitioner probably was susceptible to getting upper respiratory infections

because of his chronic pulmonary disease. Id. There may have been an infection, but Dr. Steinman said he did not know what kind of infection, i.e., what organism caused it. Id. However, he does know that petitioner had influenza vaccine and, after he received it, he really felt unwell. Id. Dr. Steinman testified that there is a 60 percent chance that petitioner's ADEM was caused by the influenza vaccine, and a 40 percent chance that it was caused by some other infection, but his problem is he does not know what infection it was. Tr. at 146-47. He might drop the percentages to 65/35 because the infection was not "definitively cultured" and therefore could have been bacterial or viral which "makes it complicated for me." Tr. at 147. Dr. Steinman testified that petitioner probably always had an infection in his lungs because he smoked more than a cigarette every waking hour. Id.

The undersigned asked if it were not true that petitioner had diarrhea in early December. Id. Dr. Steinman agreed, but said that could have been some gastroenteritis. Id. Dr. Steinman testified that there are certain bacteria associated with demyelinating disease, such as campylobacter associated with Guillain-Barré syndrome. Tr. at 148. He also said that certain viruses are associated with encephalitis, such as herpes type 1 and herpes encephalitis. Id.

Dr. Steinman said that it is absolutely reasonable that the influenza vaccine plus the infection led to petitioner's ADEM. Id. The reason is that influenza vaccine can cause ADEM and "infection," whether bacterial or viral. Tr. at 148-49. The first hit is the influenza vaccination. Then an infection occurs a few weeks later and the vaccine and infection are a "double whammy." But without the influenza vaccine, the single whammy would not have led to petitioner's ADEM. Tr. at 149. Dr. Steinman said he was not that concerned with whether petitioner truly had an infection and, if he did, whether it was viral or bacterial, because he has made the determination that the flu vaccine is responsible. Id. He thinks that anyone who

receives flu vaccine and develops ADEM from one to 10 weeks later has ADEM due to the vaccine. Id.

Summing up, Dr. Steinman explained his opinion as follows: his first opinion is that he does not need to consider an infection as the cause of petitioner's ADEM--petitioner's vaccination alone is sufficient to cause his ADEM; his second opinion is, if respondent defends on the basis that petitioner's infection was the cause of his ADEM, that he believes the vaccine was a substantial factor in causing his ADEM. Tr. at 152. He believes that the onset of petitioner's ADEM was before his December infectious process. Id.

The radiological reports about petitioner, according to respondent's expert Dr. Leist, do not show demyelinating disease. Id. Dr. Steinman disagreed. The reports show abnormalities in the white matter. There was a big abnormality of MRI signal in the corona radiata, which is a big white matter tract of the brain. Id. Dr. Steinman said one does not always need white matter damage to diagnose ADEM, but there is white matter damage here. Id. White matter damage equates to demyelination. Id. An inflammatory attack on white matter leads to demyelination. Tr. at 154. The cells that infiltrate white matter include macrophages ("big eaters") which, under the microscope, are full of the fat from a myelin sheath. Id. During the acute phase of petitioner's encephalomyelitis, there was great damage ("a big hit") to his white matter. Id.

Petitioner had diplopia (crossed eyes) with dizziness. Petitioner probably had some inflammation going on in the part of his brain called the brainstem, which controls eye movements. This was a manifestation of his ADEM. Tr. at 156. By mid-January 2008, Dr. Torres had decided petitioner had ADEM. Tr. at 159. Flu vaccine can cause either encephalomyelitis or encephalomeningitis. Id. Dr. Steinman uses those terms interchangeably. Tr. at 160.

The Saito article supports the concept that demyelination can be shown by optical issues. Id. Petitioner's radiologic reports and optic issues satisfy Dr. Steinman that petitioner had demyelination. Tr. at 161. Infarction can occur with ADEM and the article filed concerning infarction as an unusual complication of ADEM is in support of that point. Id. Petitioner's spinal fluid count of 300 white blood cells can indicate either infection or autoimmune process. Tr. at 162. What would distinguish them is if an organism had been cultured. Id. Dr. Steinman feels very comfortable with this 300 white blood cell count because it showed inflammation in the brain that was so intense that it was in the spinal fluid. Id. Absent inflammation, one would not see any white blood cells in the spinal fluid. Tr. at 161.

Dr. Steinman accepts a causal interval of a week or two up to 10 weeks. Tr. at 163. He bases that on the swine influenza vaccination epidemiologic study of Schonberger and the fine tuning of the same data by Langmuir. Tr. at 163-64. If GBS occurred within eight weeks of vaccination, there was a strong statistical argument that the two were related. Tr. at 164. GBS is a cousin of ADEM. Id. In petitioner's case, the disease smoldered from November to January. Tr. at 165. Not only was the Lopid petitioner was taking known to cause delayed inflammation in animals who were being researched, but also, as an adult, petitioner would be more likely than a child to have a polyphasic process, referring to the Dale article contrasting explosively acute onset of ADEM and MS in children with smoldering ADEM/MS in adults. Tr. at 166.

Dr. Steinman does not consider petitioner's course to be chronic, perhaps smoldering, but maybe not. It was certainly explosive when it fully erupted, but petitioner's cramping, lethargy, photophobia, and headaches had been going on for weeks. Id. Petitioner's inability to use the right side of his body could have come from inflammation in the tracts of the left side of his brain such as the corona radiata. Tr. at 167.

With reference to the Reik article, Dr. Steinman noted that ADEM's course is monophasic and the clinical features are the same regardless of the cause of the ADEM. Tr. at 168. Symptoms usually begin from four to 21 days after the inciting event, and include fever, headache, neck stiffness, anorexia, and vomiting, with neurological symptoms following. Tr. at 168-69. The neurologic symptoms can be abrupt with convulsions and coma or more gradual with irritability and restlessness, followed by delirium and a slow lapse into stupor or coma. Tr. at 169. Dr. Steinman said "one could argue that the slow lapse into stupor or coma was preceded by weeks of sitting around in a darkened room and … wanting to just go to sleep and keep all the shades shut. That would be very consistent with an encephalopathic encephalitic process." Id.

Dr. Steinman's explanation for how influenza vaccine can cause ADEM is molecular mimicry which has been proven in animals exposed to certain viruses. Tr. at 170-71. Dr. Steinman has done experiments looking at sequences in influenza A and B and the virus used in making the vaccine after it has been killed. The influenza vaccine shares similarities with myelin proteins. Tr. at 171. If for genetic and other reasons, someone recognizes his own myelin in recognizing the influenza vaccine immunologically, that can lead to ADEM. Tr. at 171-72. Influenza shares homology with myelin basic protein. Once someone breaks tolerance to myelin basic protein, this leads to an immune response against myelin oligodendroglial protein or MOG. Tr. at 173-74. Breaking tolerance means the body makes an antibody as an immunoglobulin response against the myelin sheath. Tr. at 174. One could do this with animals and cause EAE, the animal equivalent of ADEM. Id. It is well-recognized in texts used in medical schools that influenza vaccine is associated with ADEM. Tr. at 178. The Cheong article submitted into evidence reports a girl who had influenza vaccine followed by mild fever with sore throat who developed ADEM that the authors attributed to the flu vaccination. Tr. at 179. The time interval

between vaccination and ADEM with which Dr. Steinman is comfortable is one week to 10 weeks. Tr. at 181. That is based on the Schonberger epidemiologic study arising from swine influenza vaccine and GBS, whereas Langmuir would put it at six to eight weeks, although Dr. Steinman is also comfortable with Langmuir. Tr. at 182. Besides, Dr. Steinman thinks petitioner was having serious neurologic problems within a few weeks of his flu vaccination. Id. The cramping could be a symptom. Tr. at 185. What Dr. Steinman emphasized however was petitioner's photophobia as well as lethargy, sleepiness, and headaches as indications of an encephalopathic process. Tr. at 185-86. These symptoms occurred in mid-December 2007 at the time of the national rodeo on television. Tr. at 186. He said that that onset is easily within an acceptable time frame for causation from the vaccination. Id.

Dr. Steinman disagreed with respondent's expert Dr. Leist's written opinion that, more likely than not, an upper respiratory infection caused petitioner's ADEM based on the Institute of Medicine's 2003 report that it could neither confirm nor deny that influenza vaccine caused demyelinating neurologic disorders. Tr. at 187-88. Petitioner had one borderline reading of an Ehrlichia infection, but one would need more than one titer to make a diagnosis of Ehrlichia-caused encephalitis. Tr. at 191. There was no good evidence that petitioner had sinusitis in early December 2007. Tr. at 193.

On cross-examination, Dr. Steinman admitted that infarctions with ADEM do not happen in the majority of cases. Tr. at 194. An infarct is the same as a stroke. Tr. at 196. Inflammation triggers abnormalities in coagulation that could lead to either hemorrhagic or nonhemorrhagic stroke. Tr. at 198. Perivascular cuffs packed with inflammatory cells are around the veins in ADEM. Id. Petitioner's treating doctors had no trouble seeing those infarctions and still diagnosing petitioner with ADEM and not stroke. Tr. at 199. The breach of petitioner's blood-

brain barrier caused the encephalomyelitis. Tr. at 199-200. If someone has a chronic inflammatory condition, vascular abnormalities are a component. Tr. at 201.

In explaining the neurological basis of petitioner's muscle cramps in November 2007, Dr. Steinman said they could result from a problem in the muscle or the peripheral or central nervous system. Tr. at 203-04. They could be an early manifestation of inflammation or spasms. Cramps are a very nonspecific symptom. Tr. at 204. But Dr. Steinman did not focus on the cramps. He thinks petitioner's lethargy, photophobia, and headache were much more important than the cramps which could just be muscle cramps. Id. As a neurologist, he finds it hard to associate cramps with ADEM. Tr. at 205. Petitioner had a serious encephalopathic process going on in early to mid-December. Id. The cramps could have been one of the first manifestations, but he ordinarily does not think about cramps and encephalomyelitis himself. Id.

When the national rodeo was on television, petitioner was profoundly encephalopathic and wanted to sleep. Id. Mrs. Brown returned to testify that she did not state he specifically had back cramping at that point and wanted her to rub his back, although he was not watching television either. Tr. at 207. As for petitioner's continuing to work when he had symptoms of encephalomyelitis, Dr. Steinman did not think that was inconsistent. Tr. at 212.

Dr. Steinman thinks there was a smoldering period of disease and then an acute process. Tr. at 213. He thinks the vaccination caused it and the infection could also be causative. Tr. at 213-14. Dr. Steinman does not know what infection petitioner had in December 2007. Tr. at 217. If there were no vaccination, but there was an infection, he would probably diagnose someone with ADEM as having a postinfectious basis. Tr. at 222. He would say an appropriate onset interval between ADEM and an infection would be one to 10 weeks, the same interval as

with a preceding vaccination. Id. He bases that statement on Schonberger's article and, if going to just eight weeks, Langmuir's article. Tr. at 224. Those articles apply to GBS. Id.

Dr. Steinman believes that petitioner's symptoms of lethargy, photophobia, headache, and wanting to sleep all the time were smoldering symptoms. Tr. at 227. Dr. Steinman spoke to Dr. Torres, petitioner's neurologist, and Dr. Torres said that petitioner had ADEM. Dr. Torres did not believe Ehrlichia caused petitioner's ADEM because there was only one borderline lab value. Tr. at 228. This conversation occurred a couple of weeks before the hearing. Tr. at 229.

Based on the medical records of petitioner's visit to Dr. Shibata on December 31, 2007 alone, Dr. Steinman said petitioner was not encephalopathic, but he has doubts about the quality of the records. Tr. at 267. But when he looks at the subsequent emergency room and admission records of January 7, 2008, these recount encephalopathic symptoms ongoing for weeks. Tr. at 271. Dr. Steinman said that, if petitioner had not received the flu vaccine, he would not have had ADEM. Tr. at 277.

Dr. Thomas P. Leist, a neurologist, testified next for respondent. Tr. at 293. He is the director of the Multiple Sclerosis Center at Thomas Jefferson University, and division chief of clinical immunology at the hospital. He is board-certified in adult neurology. Tr. at 294. He has had fellowships in neurovirology and neuroimmunology. Id. He is an attending physician in outpatient and inpatient services with 27 residents. Id. He has seen a total of 20 ADEM cases. Tr. at 295. He has seen eight cases with acute hemorrhagic encephalitis. Tr. at 295-96. Dr. Leist was admitted as an expert in neuroimmunology. Tr. at 296. Dr. Leist's opinion is that flu vaccine had no influence on petitioner's condition. Id.

When petitioner was admitted to the hospital on January 7, 2008, he had progressing lethargy and right-sided weakness. Tr. at 297-98. Petitioner had a brain MRI on January 8,

2008, showing a lesion in the left corona radiata (the transcript has this as "chromoraida"). Tr. at 298. Petitioner worked almost up to Christmas 2007 as a construction contractor. Id. Petitioner's right-sided weakness was not present at that time. Tr. at 300. Diffusion brightness or diffusion hyperintensity can be seen in acute strokes and sometimes in larger demyelinating lesions, but if the latter, usually accompanied by gadolinium enhancement. Tr. at 302. Petitioner's brain MRI of January 8, 2008 showed diffusion bright lesions without gadolinium enhancement. This means petitioner had a hyper acute or acute injury. Id. Stroke should be at the highest level of the differential diagnosis. Tr. at 302-03. If this were a demyelinating lesion, then once diffusion brightness is established, one would expect that this bright lesion would also be gadolinium-enhancing. Tr. at 303. If it were a demyelinating lesion, one would expect because of the invasion of the brain tissue by lymphocytes, macrophages, and the whole group of inflammatory cells that the lesion would have a mass effect which would show edema, but the first brain MRI does not show this. Id.

Testimony from Mrs. Brown and her mother shows that petitioner was ambulatory through December, attending family functions, and working as a construction contractor through most of December. Petitioner presented at the emergency room on January 7, 2008 with a cataclysmic event which Dr. Leist feels was a stroke based on the brain MRI. Id. Because of petitioner's experience of repetitive colds in December 2007, Dr. Leist stated that an infectious encephalitis associated with vasculitis is a very reasonable explanation for the occurrence of the cataclysmic event on or about January 7, 2008. Tr. at 304. Petitioner did not have a significant process occurring at the beginning of January. Id.

Dr. Leist discussed the importance of having a diagnosis in order to receive care and support services even if a patient's condition does not satisfy all the criteria to make that

diagnosis. Tr. at 305. On February 15, 2008, Dr. Tran recorded that petitioner probably had an acute disseminated encephalomyelitis. Tr. at 306. Petitioner had finished his course of steroids and intravenous immunoglobulin, and would subsequently receive plasmapheresis. Dr. Leist stated that this did not mean petitioner had an unequivocal case of ADEM. It was a diagnosis reached by decision after the doctors reviewed his case. Id. At first, he was diagnosed with viral encephalitis. Later on, his subsequent diagnosis was agreed upon through consensus. Dr. Leist regarded the diagnosis of ADEM as "convenient." Id. But the abnormalities on petitioner's brain MRI were consistent with multifocal vascular events, i.e., strokes. Id.

Upon the undersigned's questioning of Dr. Steinman at this point, Dr. Steinman said he agreed that one could see diffusion bright in a brain MRI and this type of abnormality in vasculitis, but vasculitis is very much a part of ADEM. Tr. at 307-08. He does not agree with Dr. Leist that the lesion seen in the corona radiata was definitive evidence of a stroke. It is definitive evidence of inflammation in the white matter. Tr. at 308. Dr. Steinman said that the brain MRI of January 8, 2008 could certainly indicate subacute or acute onset. "Subacute" could be going on for days or weeks. Id.

Dr. Leist said that "subacute" means days to perhaps a week or so. Tr. at 309. A stroke does not develop over a long period of time although a vasculitis can build over a period of time. Petitioner may have developed areas of infarcts over the 24 hours when he was in bed and lethargic. Id. The majority of the infarcts on the brain MRI of January 8, 2008 were diffusion bright and there was no rim edge enhancement. Id. On older strokes, one sees edge enhancement. Older strokes are not completely gadolinium-enhanced. Tr. at 310. There was no edema effect. If Dr. Steinman's depiction of the events were correct, Dr. Leist would expect to see lesions of different ages and he would see at least some of the lesions with inflammation or

vast physiogenic edema around the lesions because there was so much inflammation there. Id. The January 8, 2008 shows lesions that had started and the majority were diffusion bright which means recent. Id.

Because petitioner's lesions were not gadolinium-enhancing, the blood-brain barrier breakdown was minimal. Tr. at 311. Dr. Leist stated this speaks against these lesions being inflammatory. The lesions were diffusion bright, indicating recent occurrence, and were multiple, indicating petitioner had encephalitis, not demyelination. Tr. at 312-13. Encephalitis can be caused by a variety of viruses, including those causing upper respiratory tract and gastrointestinal infections. Tr. at 313.

Dr. Leist's opinion is that the neurologic symptoms petitioner had on January 7, 2008 were not present during his December 31, 2007 visit to Dr. Shibata. Tr. at 321. The infection that may have incited petitioner's illness occurred in December 2007. Id.

Patients with ADEM often can point to an antecedent infection. Tr. at 322. Dr. Leist testified that it is not settled whether what petitioner had on January 7, 2008 was ADEM or strokes secondary to vasculitis. Id. However, he opined that, more than likely, petitioner's brain MRI of January 8, 2008 does not represent ADEM. Tr. at 322-23.

Dr Leist testified that petitioner's upper respiratory tract infection at the beginning of December 2007 or the process that involved diarrhea at the end of December 2007 can be the infectious process that led to petitioner's encephalitis and vasculitis manifested in early January 2008. Tr. at 327. If it were the upper respiratory tract infection at the beginning of December 2007 that caused the strokes in early January 2008, Dr. Leist envisioned the inciting agent colonizing the brain, causing an increased stickiness of the blood vessel walls that ultimately led to the strokes. Tr. at 328. This process could possibly take up to a month. Id. There is no

evidence that a flu vaccine, which is not a live-virus vaccine, can cause vasculitis or encephalitis and inflammation of the brain. Tr. at 329. The fact that petitioner's deficits are enduring makes it more likely that he had a stroke rather than a demyelinating disease. Tr. at 332.

As for petitioner's having Ehrlichia, Dr. Leist stated petitioner had two laboratory tests for Ehrlichia, the first yielding a titer of 1:80 IgM value, and the second yielding a titer of 1:40 IgM value. Tr. at 333. Petitioner was twice positive for Ehrlichia and one has to take this seriously since antibiotics can treat Ehrlichia. Id. When one has a critically ill patient, one does not know exactly what is going on and one of the approaches for care is to address all potential issues. Tr. at 334. When petitioner was hospitalized, he was put on Acyclovir in case he had herpes encephalitis, but the PCR test was negative. However waiting for the results of the test would prove ruinous if he had not been put on Acyclovir as soon as possible. Id. Petitioner also had a conceivable Ehrlichia infection and his treaters put him on antibiotics to cover that possibility. Id.

Initially, when petitioner was hospitalized, he was treated as having encephalitis. When he was diagnosed with ADEM, he was put on steroids. Then he was treated with IVIG and subsequently plasma exchange. Tr. at 335. The intent was to reduce petitioner's inflammation. Id. The undersigned asked Dr. Leist if petitioner had had a stroke, why he was not treated with TPA. Tr. at 336. Dr. Leist responded that petitioner did not have a vascular occlusion. His stroke was not because of a single lesion. He had multiple infarcts. By the time his imaging study was done, he also had hyperintensities. Moreover, onset was unclear and "his presentation with changes in mental status is not characteristic for a focal stroke." Id. In order for petitioner to have mental status changes with a stroke, he would have had to have had a middle cerebral block occlusion. Tr. at 337. Without that type of occlusion, the patient with a small stroke

remains alert. Id. Dr. Leist said he stood his ground that the MRI on January 8, 2008 showed lesions that favored a vascular, rather than an inflammatory demyelinating, etiology. Id. That is where he and Dr. Steinman differ. If it had been an inflammatory process, then the presence of diffusion brightness in a demyelinating lesion would also be associated with gadolinium enhancement in that lesion, which was not there. Id. Moreover, if there were so many inflammatory cells, edema would be present in that particular tissue bed, which was not described. Tr. at 337-38.

Dr. Leist's opinion is that petitioner had encephalitis causing vasculitis. Tr. at 341. Ehrlichiosis is possible, but not probable. Id. A notation for February 1, 2008 diagnoses petitioner with ADEM likely secondary to a recent upper respiratory infection. Tr. at 342. A neurological note of the same date says petitioner's case was presented in a neurological conference and ADEM was the diagnosis of choice. Treatment was for petitioner to have plasmapheresis four times a day. Tr. at 343. Dr. Leist stated that a "diagnosis of choice" is the same as a working diagnosis. Id. To Dr. Leist, this is not the same as a statement that petitioner had ADEM ("It is not saying this is ADEM …."). Id. Dr. Leist stated a very reasonable argument can be made that petitioner did not have ADEM, and actually had viral encephalitis with associated strokes which caused his enduring disability. Tr. at 343-34. He said no evidence links a killed virus vaccine, such as flu vaccine, with this condition 60 days after vaccination, and the much more likely cause is the intervening infection or infections. Tr. at 344.

Dr. Leist stated that, considering the incubation period, Dr. Steinman's opinion that the flu vaccine caused the illness even if it were ADEM does not make sense. Tr. at 345. Dr. Leist believes the infection of either December 3, 2007 or December 30, 2007 was the proximate cause. Id. Flu vaccine did not cause either of those infections. Id. It is not logical that a killed

vaccine that does not result in acute manifestations would be the agent of a vasculitis or an encephalitis. Tr. at 349. The lesions in petitioner's initial brain MRI were diffusion bright, meaning they were contemporaneous or nearly contemporaneous, without edge enhancement. Tr. at 349-50. If petitioner had had subacute strokes, there would have been edge enhancements. Tr. at 350. These areas of signal abnormality caused neurologic dysfunction. On December 31, 2007, they were not there. Id. Symptoms of dysfunction were occurring on or about January 7, 2008. Id. The MRI does not show lesions of different ages. Id.

Dr. Leist did not find Dr. Steinman's theory of synergy between the flu vaccination and the infection to be logical because it was a relatively long time for the vaccine to linger and affect an infection occurring December 3, 2007. Tr. at 351. The immune effect of the vaccine would persist, but the protein component of the vaccine more likely than not would have been significantly eliminated. Id. On page 129 of the 2003 IOM Report, the IOM discusses bystander activation. Tr. at 354-55. In order for a flu vaccine to cause neuronal injury, the vaccine would have to act as an adjuvant or contain myelin to act as a neuro-antigen. Tr. at 355. Dr. Leist stated it was unlikely that petitioner suffered a neuronal injury when he received flu vaccine because there were no direct complications in the minutes or hours afterward. Id. The IOM considers the evidence linking flu vaccine to demyelinating diseases to be weak. Tr. at 358.

Dr. Leist believes that the infection or infections petitioner had were the proximate event or events to his having his condition in January 2008. Tr. at 363-64. Infection resulting in encephalitis occurs within days or weeks. ADEM can occur relatively shortly after a viral infection. He would say that somewhere in the two- to four-week range is the maximum effect of a pathogen and the resulting injury. Tr. at 364. He does not think the flu vaccine, which is a killed-virus vaccine, was the cause because it does not persist in the body like a live attenuated

virus vaccine which replicates the virus throughout the body. Tr. at 365. Dr. Leist said that ADEM involves changes in the blood vessels but does not involve vasculitis as the predominant feature. Tr. at 369. In ADEM, the cells that come out of the blood vessels are all inflammatory cells. Tr. at 370.

He thinks it remarkable that Dr. Steinman saw 50 cases of ADEM caused by flu vaccine. Tr. at 347. Dr. Leist is not a member of the Institute of Medicine. Tr. at 348. He does not have the very intense research background that Dr. Steinman has. Id. Dr. Steinman has not only been recognized by the IOM but also by the Multiple Sclerosis Society. Id.

(Because of the lack of time, respondent's next expert Dr. Wientzen began his direct testimony on September 2, 2010 directly after Dr. Leist testified on direct examination. Cross-examination for both doctors was delayed until trial resumed on November 4, 2010. To facilitate ease of understanding the testimony, however, the undersigned includes Dr. Leist's cross-examination here in the decision as if it occurred immediately after his direct testimony.)

In the last 10 years, Dr. Leist has seen 30 to 35 patients with ADEM. Tr. at 500. Among that group, there had been patients who had received flu vaccine within 90 days of onset of ADEM. Id. This group of patients also had upper respiratory infection, pneumonia, or significant gastrointestinal infections much closer to the onset of ADEM. Id. Thus, he did not attribute the ADEM to the flu vaccine but to the temporally closer infection. Tr. at 500-01. In ADEM, clinical symptoms can occur before the brain MRI shows lesions. Tr. at 501. He thinks that about three cases of the 30 to 35 cases of ADEM that he has seen had antecedent vaccinations within 90 days of vaccination. Tr. at 504. In all three cases, there was an intervening event between vaccination and onset of ADEM. Tr. at 504-05.

Dr. Leist stated that he accepts that potentially a vaccine could cause a demyelinating injury. Tr. at 508. Returning to his opinion in the instant action, however, Dr. Leist said that petitioner did not have ADEM. He believes petitioner had viral encephalitis, which caused vasculitis, i.e., inflammation within the blood vessels, leading to strokes. Tr. at 516. Petitioner's lumbar puncture early in his hospitalization showed an elevated white count of 300 white cells with 98 monocytes, indicating an inflammatory process consistent with an infection in the brain. Tr. at 542. Dr. Leist believes that petitioner had encephalitis which caused underlying changes in his blood vessels and tissue, leading to acute strokes. Tr. at 542-43. Before the strokes, petitioner was moving. After the strokes, he became lethargic. Tr. at 543. Dr. Leist pinpoints the onset of the strokes as between January 5 and 7, 2008. Id. He assumes the cataclysmic event was closer to January 7th. Id.

The elevation of petitioner's cerebrospinal fluid protein at 68 is consistent with an inflammatory or destructive process in which plain tissue was destroyed. Tr. at 543-44. Destruction of brain or spinal cord tissue is consistent with encephalitis. Tr. at 544. Dr. Leist stated that the presence of 98 percent monocytes in the cerebrospinal fluid is significant because it indicates that petitioner probably had a bacterial infection. Id. But then he seemed to change his mind about petitioner having a bacterial infection because he stated that very early bacterial infections can present with a monocytic preponderance, but normally this monocyte percentage is congruent with a viral encephalitic process. Id. Dr. Leist also thought it less likely that petitioner had a bacterial infection because his cerebrospinal fluid glucose was 54, which is normal. If he had had a bacterial brain infection, that glucose level would have been lower. Id.

Dr. Leist testified that the initial MRIs did not show a lot of edema around the lesions, i.e., not a lot of swelling. Id. The inflammation along the blood vessel walls makes the blood

vessel walls much thicker. There can be local embolic events that are essentially an occlusion of the blood vessels, which is what a stroke is. Tr. at 545. The stroke causes a lack of blood supply to a certain area of the brain. Id. The vasculitis causes the strokes. Tr. at 547. Petitioner was not eligible for TPA, which is administered to occluded vessels, because the underlying event was probably not thromboembolic. Tr. at 546. Moreover, the age of the stroke could not be established, and administration of TPA is administered only within the first three hours of a stroke. Tr. at 545-56. Early in petitioner's treatment, the doctors diagnosed him with encephalitis, not a thromboembolic event. Tr. at 546. It is not unusual for someone with encephalitis to develop strokes as a consequence. Id. One would not give TPA to an encephalitis patient. Tr. at 547.

Dr. Leist distinguished between encephalitis and ADEM. Tr. at 550. Encephalitis has an underlying pathogen, i.e., a virus, directly inciting the inflammation within the brain. Id. The inflammation is a focal response to the areas in which the pathogen replicates. Id. Because of this response to the virus, an inflammatory cascade arises, leading to up-regulation of adhesion molecules. Id. This increases the stickiness of the blood vessels, which shows up on imaging studies as vasculitis as the blood vessels start to constrict. Tr. at 550-51. That is when the risk of stroke occurs. Tr. at 551. This is what Dr. Leist thinks happened to petitioner. Id.

ADEM is an inflammatory process in which cells start demyelinating the wrapping of the nerve cells in the brain containing myelin. Id. There is no actual pathogen there. That is the first fundamental difference between encephalitis and ADEM for Dr. Leist. Id. The second fundamental difference is that an ADEM lesion on imaging shows edema because there is a lot of swelling in that area. Tr. at 551-52. This can lead to an opening of the blood vessel wall because of cytokines and the inflammatory milieu, which will be seen as gadolinium

enhancement. Tr. at 552. In petitioner's brain MRIs during his acute stage, gadolinium enhancement was not seen, which speaks against this massive accumulation of local cells that cause demyelination. Id. Generally, ADEM is not associated with stroke. Id.

When Dr. Leist uses the term "lesion," he means an abnormal area of tissue in the brain. Tr. at 555. In ADEM, the inflammatory response takes away the myelin sheath and may also injure nerve cells. Tr. at 556. In stroke, the blood cannot get to a particular area either because the inflamed blood vessels react and constrict or because of a clot. Id. To Dr. Leist, petitioner had a stroke from the encephalitis because the encephalitis induced constriction of the blood vessels. Tr. at 557. In petitioner's case, the doctors did not identify the pathogen, which is not unusual. Tr. at 559. Viral pathogens are normally identified early in the infectious process, but they were looked for later in the process. Tr. at 560. To Dr. Leist, petitioner's history of a cold makes encephalitis from a virus a higher likelihood than encephalitis from ehrlichia chaffeensis. Tr. at 561, 563.

Because petitioner worked until December 19th and participated in additional activities of daily living during that period of time, there was no significant neurological injury present as of that date. Tr. at 563-64. The significant neurological issue arose cataclysmically around the time period January 5th through 7th. Tr. at 564.

Dr. Leist said he would question a diagnosis of ADEM in an adult if the brain MRI was negative for demyelination. Tr. at 566. It is possible, however, for later MRIs to show lesions. Id. The process may be so fulminant that there had not yet been time on an early MRI for it to establish itself, but the overall inflammation had already led to the patient's dysfunction. Tr. at 567. Petitioner's MRI did not show significant brain swelling. Tr. at 568. Encephalitis will lead to constriction in the blood vessels. Tr. at 571. This occurs through spasms. Tr. at 572. Dr.

Leist understands Dr. Steinman's opinion to be there was so much inflammation in the brain that there was pressure against the blood vessels from outside the vessels so that those areas collapsed. Id. In order to have that much inflammation in the brain, there would have to be edema in the brain. Id. But petitioner's lesions did not have significant swelling around them. Tr. at 573. If those lesions had been that swollen, there would have been gadolinium enhancement associated with them. Id.

Dr. Leist said that ADEM is an acute new lesion, with gadolinium going out of the blood vessels and blood-brain barrier breakdown. But petitioner's lesions did not enhance and did not have significant edema around them. The lesions were bright on diffusion rated images, but without gadolinium enhancement, and no significant swelling. Id.

Dr. Leist testified that just because petitioner's treating neurologist Dr. Torres wrote "will be treated as ADEM" does not mean it was ADEM. Tr. at 575. In order for petitioner to have access to IVIG after other treatments failed, the doctor needed to shift or broaden his diagnosis. Id. IVIG is not an indicated use for viral encephalitis. Id. That the medical records stated ADEM is the diagnosis of choice does not state it is the diagnosis. Id. The infectious diseases doctors kept the diagnosis of viral encephalitis. Id.

The neurological conference dated February1, 2008 to discuss petitioner's case occurred when petitioner had not improved. Tr. at 576-77. "And so, at that juncture, in order to make accessible additional treatments, one has to say well, what if this is ADEM, then we will do IVIG. Okay, let's do IVIG." Tr. at 577. The steroids had not helped and the doctors switched to plasma exchange. Id. Petitioner had right hemiplegia, but his left side did not have full movement either. Tr. at 578.

On January 25, 2008, the doctors noted that it did not look like petitioner had vasculitis at that time. Tr. at 579. This does not rule out that he had vasculitis earlier in the disease. Id. On February 15, 2008, Dr. Tran, in the discharge summary, writes encephalitis plus vasculitis, or reactive vasculitis. Tr. at 582. Because petitioner did not respond to earlier treatments, the diagnosis of choice was ADEM so that he could receive other treatment, i.e., plasmapheresis. Tr. at 583. Petitioner got steroids and antivirals. Tr. at 584. In the majority of ADEM cases, patients will show some improvement and spontaneous remyelination occurs. Id. But once someone has a stroke, the patient does not recover. Therefore, with an encephalitis leading to stroke, the patient does not recover. Tr. at 585. There is no treatment for a completed stroke other than physical therapy. Tr. at 587-88. Petitioner did not recover because the strokes caused permanent injury. Tr. at 607-08.

Petitioner had strokes in a small-vessel distribution because he had an encephalitis that caused vasculitis. Tr. at 597. An angiogram showed some caliper change in some of the smaller blood vessels. Tr. at 598. A valid alternative diagnosis to encephalitis is Ehrlichia. Tr. at 602. But it is only possible. Id. Petitioner's four brain MRIs in January 2008 did not show any midline shift. Tr. at 608. This means there was no structural shifting of the brain due to edema because, on the first brain MRI, there was no significant edema. Tr. at 609.

Respondent's next expert, Dr. Raoul. L. Wientzen, Jr., a pediatric infectious disease specialist, testified. Tr. at 400-01. He retired from clinical practice in July 2009 and devotes his time to an international children's health foundation. Tr. at 401. He has seen a significant number of ADEM cases, most of them post-chickenpox before varicella vaccine became available. Tr. at 401-02. In total, he has probably seen 70 cases of ADEM. Tr. at 402. He is no

longer board-certified because he has stopped clinical practice. Id. ADEM is more commonly seen in children than in adults. Tr. at 405.

Dr. Wientzen's opinion is that there is no relationship whatsoever between the flu vaccination petitioner received on November 6, 2007 and the course of events manifest at the time of his hospitalization in January 2008. Tr. at 407. He is a big proponent of the molecular mimicry theory and thinks molecular mimicry is the basis of the many ADEM cases he has seen as a clinician. Tr. at 407-08. He absolutely subscribes to the theory. Tr. at 408. He does not think the theory applies to the instant action. Id. Dr. Wientzen believes the infectious process that occurred in December 2007 is the cause of petitioner's problems in January 2008. Id.

Dr. Wientzen believes that petitioner had viral encephalitis. Tr. at 409. His basis is that there was a clear cut preceding viral illness on or around December 31, 2007. Id. There is a reasonable interval of about seven to nine days, maybe even as long as several weeks, and then the onset of the syndrome manifesting as confusion, lethargy, and focal neurologic signs, with evidence on MRI of multiple infarcts. Tr. at 409-10. He relates the multiple infarcts to viral encephalitis. Tr. at 410. It is possible that the December 3, 2007 illness was viral with bacterial sinusitis and was still lingering during the December 31, 2007 office visit. He does not know. Id. It appears that there were two distinct and separate illnesses, December 3rd and 31st. Id. He does not link the earlier December infectious process with the later December infectious process. Tr. at 412.

Dr. Wientzen thinks that Ehrlichia is an unanswered question as to whether petitioner's illness was in fact ehrlichiosis. Tr. at 412-13. He thinks viral encephalitis is 60 percent likely and Ehrlichia is 40 percent likely the cause of the infectious encephalitis petitioner had, based on statistics and a few other epidemiologic features of the case. Tr. at 413.

When petitioner saw Dr. Shibata on December 31, 2007, he did not have any encephalopathy because Dr. Shibata noted that petitioner was oriented, not toxic, and not distressed. Tr. at 420. Petitioner was alert as well. Tr. at 421. This was a very good office evaluation and would have taken longer than five minutes. Tr. at 421-22. It probably would have taken 10 to 15 minutes. Tr. at 422. He did not have viral encephalitis at that time. Tr. at 424.

Dr. Wientzen stated that anyone, such as petitioner, who is a smoker and a borderline diabetic, and who has high triglycerides and hypertension, is at increased risk for stroke. Tr. at 425. Dr. Wientzen stated that he would never consider the 5.1 level of petitioner's potassium on December 3, 2007 to be indicative of elevated potassium. Id. He recognizes that Kaiser had an upper limit of 5.0 in its range of normalcy. But petitioner's level was a trivial elevation. Tr. at 425-26. Dr. Wientzen said that photosensitivity is a nonspecific manifestation of many things. Tr. at 427. As for cramping, he has never seen a patient who defines the onset of a central nervous system disease with muscle cramping. Tr. at 427. He does not believe muscle cramping has ever been described in the medical literature as a sign of a central nervous system inflammatory process. Id. He does not recognize muscle cramping as a neurologic sign or symptom. Id.

Dr. Wientzen said that 70 percent of people with encephalitis who are cultured for the virus causing it have no etiology forthcoming. Tr. at 430. This has always been the stumbling block for an etiologic diagnosis of encephalitis. Id. Dr. Wientzen commented on the "kitchen sink" approach for treating petitioner because he was a very sick man and the doctors could not wait to have the result of a positive culture before starting a cycle of care. Tr. at 431. Acyclovir works only for herpes encephalitis but not for any other viral encephalitis. Tr. at 432. The

doctors also treated petitioner for bacterial meningitis. They prescribed Doxycycline in case petitioner had microplasma or Ehrlichia and other pathogens. Tr. at 432. Only nine days into petitioner's treatment, January 16, 2008, did the doctors think to treat him as if he had ADEM. Id. That is when the doctors started petitioner on methylprednisolone. Id. This is a steroid. Tr. at 433. The doctors had done everything they could to treat bacterial causes and petitioner was not getting better. They decided, then, to treat him for non-bacterial causes, one of which is vasculitis, and another is ADEM. Steroids are therapeutic for vasculitis and sometimes help ADEM. Then they proceeded to the next line of therapy, plasmapheresis. Id. All of their actions were very appropriate. Id.

Dr. Wientzen commented that petitioner's spinal fluid protein on January 7, 2008, the beginning of his hospitalization, was 68. Tr. at 444. This level is above the upper normal level of 40 milligrams percent, but it is only mildly elevated. Tr. at 445. This is the kind of spinal fluid elevation that one would see in someone with an ongoing acute process that has developed over a day or two, potentially even three days or so, but has not been ongoing for weeks or months. The level of spinal fluid protein that one would expect to see in someone who has been affected with an ongoing persistent inflammatory process of the central nervous system for weeks or months would be in the many hundreds. Id. For example, in patients with subacute meningitis, meningoencephalitis, and fungal infections of the central nervous system, their spinal fluid protein counts commonly are in the many hundreds. Tr. at 445-46.

Dr. Wientzen stated that a spinal fluid protein count of 68 is very compatible with ADEM caused by petitioner's prior viral infection on December 31, 2007. Tr. at 446. He does not believe petitioner had ADEM. That protein count, however, is not compatible with someone

who has had raging headaches because of ongoing central nervous system inflammation dating back to mid-November 2007. This is not possible. Id.

Dr. Wientzen said that petitioner's 300 white blood cell count was a "pristine perfect number" for someone with viral encephalitis and a fine number for anyone with ADEM. Tr. at 447. It is compatible with acute ADEM, although that is redundant because ADEM is acute. He does not accept a two-month history of ADEM with a protein of 68 and white blood cells of 300. Id. This was not a two-month longstanding central nervous system smoldering process based on the brain scans, lab tests, spinal fluid tests, and contemporaneous medical histories. Tr. at 448.

Dr. Wientzen stated he had never seen a patient with ADEM and infarcts. Id. He has seen patients with viral encephalitis and infarcts. Tr. at 449. Although he does not think that petitioner had ADEM, if the undersigned ruled he did, then Dr. Wientzen is convinced that its only cause was the viral illness petitioner had at the end of December 2007. Tr. at 455. The time interval between the flu vaccination on November 6, 2007 and the onset of neurological symptoms on January 5 or 6, 2008 is too far for the vaccine to hold any weight in his consideration of the case, particularly since there were two intervening processes, one on December 3, 2007 and the other roughly December 31, 2007, with a potential third process, Ehrlichia, that are reasonable causes of petitioner's illness. Id. If the cause were petitioner's sinusitis December 3, 2007, that would put the interval until ADEM at one month, which is a window that Dr. Wientzen would consider, but that is as far as he would take the interval. Tr. at 456. However, if petitioner had viral encephalitis, the December 3, 2007 sinusitis would be too far removed in time to be causative. Tr. at 457. Only if petitioner had Epstein-Barr virus or cytomegalovirus, both well known to cause chronic infection, would he consider a month's interval to be appropriate for causality. Id.

Dr. Wientzen testified that if the December 31, 2007 illness were the cause, a one-week interval between infectious illness and neurological onset was very acceptable for both ADEM and viral encephalitis. Tr. at 459. The triage nurse's notes in the emergency room on January 7, 2008 reflect a two-week history of illness which is also fine causally for both encephalitis and ADEM. Id. The incubation period for Ehrlichia is one to two weeks from the time of the tick bite and then a prodromal illness resembling flu. Photophobia is a very common manifestation of Ehrlichia, together with headache and vomiting. Id. Petitioner could have had ehrlichiosis on December 31, 2007 and then gone on to develop encephalitis five or six days later. Tr. at 460.

Dr. Wientzen does not believe it is biologically plausible for influenza vaccine to cause ADEM. Tr. at 469. He also does not see a logical sequence of cause and effect here because the medical record is silent about any neurologic syndrome developing in petitioner over the many weeks following flu vaccination. Id. Petitioner had four opportunities to give a history of symptomatology over two months, but failed to do that: (1) the visit to Dr. Shibata on December 31, 2007; (2) the visit to the emergency room on January 7, 2008 when petitioner and his wife gave a history to the ER triage nurse; (3) the visit to the ER doctor who took a history from petitioner; and (4) the visit with the admitting doctor later the same day who took a history from petitioner's wife. Tr. at 470. There was no mention of severe headaches, muscle cramping, or profound lethargy. Id. Lastly, Dr. Wientzen does not believe that the time frame between vaccination and onset of disorder is compatible with causation. Id. Dr. Wientzen testified that the synergy between vaccination and infectious illness about which Dr. Steinman testified and that forms the basis of part of Dr. Steinman's testimony does not exist. Tr. at 470-71.

Dr. Wientzen believes that vaccines can occasionally cause neurologic problems. Tr. at 614. He described peripheral neurologic disorders as a consequence of influenza vaccine as a

proven entity. Tr. at 615. He thinks there is insufficient evidence to affirm or deny that influenza vaccine causes central nervous system disorders. Id. It potentially could happen very rarely. Id. When he had a patient with a central nervous system disorder before him, Dr. Wientzen always asked if the patient had received any vaccinations, as well as been exposed to drugs, medicines, insect bites, tick exposures, animal exposures, and venom. Tr. at 617. These are routine questions. Id. Dr. Wientzen believes that petitioner had infectious encephalitis that caused infectious vasculitis causing his lacuna infarcts. Tr. at 619. "Lacuna" means small as in an amount of brain tissue supplied by a small branching artery in the brain which dies because of lack of blood profusion. Id.

Dr. Wientzen has seen a significant number of children and adolescents like petitioner who develop viral encephalitides of various kinds, manifested by a significant measure of inflammation of the blood vessels in their brain and who develop strokes during the course of their recovery. Tr. at 619-20. This is not a rare development with any central nervous system infection. Tr. at 620. About five percent of all children who have bacterial meningitis develop strokes because of inflamed blood vessels. Id. From the bacterial infection, the blood vessels develop a clot inside them because inflamed blood vessels tend to clot. The children develop a stroke, but they do not have cardiovascular disease. They are young children. Id. There are also vasospasms which cause the strokes. Id.

Dr. Wientzen has never before seen the expression "diagnosis of choice" in 35 years of reading medical records. Tr. at 621. This is a way for the doctors to say they do not really know what the diagnosis is. Id. Diagnosing petitioner with ADEM after his diagnoses of encephalitis and bacterial infection opened new therapy for him. Tr. at 621-22. This was the right procedure to take but it does not mean petitioner had ADEM. Tr. at 622. But none of the ADEM therapies,

i.e., IVIG, steroids, and plasmapheresis, benefited petitioner. Id. He thinks the failure of these therapies is another piece of evidence against the diagnosis of ADEM. Id. The doctors did not even reach the diagnosis of ADEM until January 16, 2008, nine days after admission, signifying that everyone thought this was encephalitis, either viral or Ehrlichia, or they would have started steroids on the second or third day when the bacterial cultures and the herpes PCR were negative. Tr. at 623-24.

Dr. Wientzen distinguished between ADEM and encephalitis by stating that encephalitis is infectious inflammatory, involving a precipitating agent in the blood vessels of the brain and potentially in the brain tissue that will elicit a continuing inflammatory response in place. On the other hand, ADEM is a peripheral immune reaction actually affecting the brain as a bystander. If one suppresses that peripheral immune reaction, one could potentially spare the brain some injury. Tr. at 624.

When asked if petitioner actually just had a smoker's cough when he saw Dr. Shibata on December 31, 2007, Dr. Wientzen said he had upper respiratory congestion, headache, vomiting, and diarrhea, all indicative of a viral process. Tr. at 626-27. Moreover, when petitioner's wife gave a history on January 8th or 9th to the infectious disease doctor, she said that the whole family had become sick right around Christmas, around December 23, 2007. This corroborates that the onset of petitioner's stuffy nose occurred in the context of the family's having a respiratory process and it was a new symptom. Tr. at 627.

Dr. Wientzen said there are similarities between viral encephalitis and ADEM in that their initial presentations can look the same, i.e., fever, headache, changes in the level of consciousness, seizures, and coma. Tr. at 628. The closer the neurological presentation is to the preceding illness, the more likely it is part of that illness and not an immune reaction consequent

to that illness. Tr. at 629. The 12 days between December 23, 2007 and the onset of the neurological disorder was about 12 days, which is good timing for either ADEM or viral encephalitis or Ehrlichia encephalitis if there were Ehrlichia. Id. On MRI, if someone did not have white matter disease at the beginning but just infarcts, it would be extraordinarily unlikely to be a case of ADEM. Id. Absent marked increased intracranial pressure and cerebral edema, one does not find infarcts in patients with ADEM. Tr. at 630. With a 300 white blood cell count, Dr. Wientzen would lean toward an infectious cause rather than ADEM, but it is okay for both. Id. Dr. Wientzen would doubt very seriously that someone had ADEM if the MRI did not show demyelination. Tr. at 631. Heavy smoking would not cause a pervasive immune disorder, but would cause local dysimmunity. Tr. at 635.

Dr. Wientzen defined "acute" in terms of an ADEM presentation as going from the onset of symptoms to reasonably full manifestations of neurologic involvement in a very short period of time, i.e., several days. Tr. at 645. He has never seen an adult with a longer smoldering presentation of ADEM. Id.

Dr. Wientzen thinks that the notes reflecting petitioner's visit to the infectious disease specialist at the hospital in January 2008 are significant because they resonate with Dr. Shibata's notes during petitioner's visit on December 31, 2007, wherein petitioner gave a history of flu-like symptoms starting with sinusitis on December 3, 2007 and, then, with the word "now" meaning something recent, he had new-onset headache, nausea, vomiting, and diarrhea. Tr. at 650. Dr. Shibata's notes reflect a December 23, 2007 timeframe for these new symptoms of headache and stuffy nose. Tr. at 651. Petitioner did not have constant headaches which predated December 23, 2007. Id. The infectious disease specialist at the hospital, Dr. Kubrin, wrote her impression of petitioner, which was that he had meningitis, most likely viral in etiology. Id.

Petitioner's brain MRI showed a nine-millimeter lacuna infarct in each thalamus. Together with Dr. Kubrin's physical examination of petitioner, history from petitioner, and cerebrospinal fluid results of a protein of 68 and white blood cell count of 300, Dr. Kubrin felt that petitioner was suffering from an infection in his central nervous system. Tr. at 651-52.

Dr. Wientzen believes that this particular viral process caused an inflammatory reaction in petitioner's arteries in his brain. Tr. at 652. The inflammatory process caused his strokes, which to some great degree caused his disability. Id. Dr. Wientzen agrees with Dr. Leist that the infectious disease occurring toward the end of December 2007 caused petitioner's viral encephalitis, which led to vasculitis, which led to strokes. Tr. at 652-53. Dr. Wientzen's understanding is that on or about December 23, 2007, petitioner acquired or had acquired a respiratory viral process that was going through his family, including his four children and his wife, and over the course of the next day, this viral agent gained access to his central nervous system and set up another site of infection in his brain. This elicited an inflammatory response and damaged his brain. Tr. at 653. The 12 days between December 23, 2007 and January 5, 2008 would be appropriate if the ultimate diagnosis was ADEM, encephalitis, or Ehrlichia. Tr. at 653-54.

Petitioner's wife resumed the stand and testified that during the January 31, 2008 conference concerning petitioner's condition, which she attended, present with Dr. Torres were neurologists and neurosurgeons, primarily. Tr. at 655. Dr. Torres put up petitioner's brain MRIs and asked the other neurologists and the neurosurgeons what they thought, i.e., stroke versus ADEM. They all came to the conclusion that it was not stroke. It was ADEM. Tr. at 655-56. Petitioner has not recovered but he has improved. Tr. at 656. When she brought him to the hospital on January 7, 2008, by January 10th, he was in a coma. The doctors started him on high-

dose steroids when they started treating him for ADEM. They also gave him IVIG and plasmapheresis. Id. He went from being in a coma to being barely arousable with painful stimulus to being able to follow commands. Id. He got back movement on his left side during that time period and he was able to become conscious. Tr. at 656-57.

Dr. Steinman testified on rebuttal. Tr. at 659. He stated he did not want to speculate on what the intentions were of the treating physicians. "If Dr. Torres, with whom I spoke and whose notes I read, said it was ADEM and discussed it at a conference, then I think ADEM is a reasonable diagnosis." Tr. at 666. Dr. Steinman described the physical process of what occurred in petitioner's brain. Tr. at 668. If one looked under a microscope at viral encephalitis or ADEM, what one would see is lymphocytes streaming out of the blood vessels, largely out of venules rather than arteries. In viral encephalitis, they stream out to get to the virus and attack it. In ADEM, the lymphocytes stream out because they think they saw a virus or may once have seen a virus, but when they enter the brain, they attack it instead. Id. Increased inflammatory molecules cause the infarcts. Dr. Leist mentioned cytokines, and they induce adhesion molecules to activate platelets and other portions of the coagulation cascade, causing strokes. Id.

Dr. Steinman found very interesting that strokes were on both sides of petitioner's brain. Tr. at 669. These were small infarctions associated with brain inflammation which could have been due to viral encephalitis or ADEM or both. Id. Dr. Steinman feels it was ADEM because his clinical picture is consistent with ADEM, the doctors could not find a virus, and the treating doctors, especially the treating neurologist, thought it was ADEM. Tr. at 669-70. Petitioner had high titers to influenza A, measured on the California Encephalitis Project results. Dr. Steinman does not know if this is from his 2007 flu vaccination, a prior flu vaccination, or exposure to influenza A. Tr. at 671-72. These antibodies were higher than any other antibodies he had to

anything else and they buttress a molecular mimicry theory for ADEM because they show immunity detectable to influenza. Tr. at 672. Dr. Steinman thinks the onset of petitioner's ADEM was further back than December 23, 2007 because petitioner's wife testified about his having photophobia and headaches earlier than that. Tr. at 678-79. He disagrees that a vaccine must be live-virus in order to cause an ADEM reaction. Tr. at 679. An immune cell and an antibody do not see the whole virus at once, but a very small component of it. There is nothing live about the virus when the immune system is interacting with it on a molecular level. Id. It kills the underlying cell with which the virus is associated. Tr. at 679-80. It does not go out and target the virus, which is the job for T-cells. Tr. at 680. A component of a killed virus can just as easily provoke this response as one from a live virus. Id.

It bothers Dr. Steinman a little that there was no edema seen on petitioner's brain scans, but that is seen only 50 percent of the time. Tr. at 681-82. Demyelination was not there either. Tr. at 682. The corona radiata, which is a big white-matter band, was abnormal, probably suggesting inflammation occurring there. Id. The stroke involving the corona radiata had radiologic abnormalities. A lacuna infarct in the thalamus suggests abnormalities in the white matter. One would not call these abnormalities demyelinating, but they may have been. Id.

Dr. Steinman agreed with Dr. Leist that there was no treatment for petitioner's stroke. Tr. at 683. Petitioner had a meningeal component to his illness because he had so many cells in his cerebrospinal fluid (300 white blood cells and 68 protein). Tr. at 685. This indicates a robust inflammatory response. Id. Meningitis is not unusual for ADEM. Tr. at 686. One does not need the persistence of killed-virus influenza vaccine to trigger a genuinely strong immune response that will neutralize the virus from which the vaccine was made. Tr. at 691-92. The basis for saying that a person vaccinated against influenza may get ADEM is that there are

structures in flu vaccine that are shared with portions of the brain. Tr. at 698. The virus petitioner experienced December 23, 2007 could have synergized with whatever had been occurring since the flu vaccine to cause his injury. Tr. at 602. His explanation for this synergy, presuming adenovirus in December, was:

> The hypothetical adenovirus infection revved up his immune system to make gamma interferon, tumor necrosis factor, interleukin 17, and the immune response that had been smoldering along against the influenza was further activated by TNF activating his B-cells and gamma interferon activating the T-cells and caused that influenza response to get up to the next gear and cause ADEM through molecular mimicry.
> So a completely coherent, plausible argument based on things that can happen. Did it? We don't know because we don't know what virus it was in December.

Tr. at 703-04. What he was describing was a subclinical process that ultimately culminated in ADEM. Tr. at 704. After the flu vaccination, things were under control enough so that petitioner could get to work, but when the family and he got sick, it pushed him over the edge. Tr. at 705. Dr. Steinman stated that synergy did occur in this case. Tr. at 714. Meningitis and encephalitis can occur with ADEM. Tr. at 715-16. There is a huge amount of overlap between ADEM and meningoencephalitis. Tr. at 716. Within a few weeks of vaccination, there is the highest risk of illness, and the further out one goes, the risk declines of an adverse reaction. Tr. at 721.

DISCUSSION

To satisfy his 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:

> 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 the holding that petitioner's tetanus toxoid "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).

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) .

According to the three Althen prongs, what petitioner needs in order to prevail is a medical theory connecting flu vaccine and ADEM (the "can it?" question), a logical sequence of

cause and effect that flu vaccine caused his ADEM (the "did it?" question), and a medically appropriate temporal relationship between vaccination and onset. Knudsen, Althen, Capizzano.

Encephalitis vs. ADEM

In order to determine whether petitioner has made a prima facie case of causation in fact, the first issue is whether or not he had encephalitis or ADEM before doing an Althen three-prong analysis. Lombardi v. Sec'y of HHS, ___ F.3d ___, 2011 WL 3890521, at *8 (Fed. Cir. 2011) (the question of causation depends on which injury the petitioner had: transverse myelitis vs. chronic fatigue syndrome vs. systemic lupus erythematosus); Broekelschen v. Sec'y of HHS, 618 F.3d 1339, 1346 (Fed. Cir. 2010 (identifying the injury is a prerequisite to the analysis: transverse myelitis vs. anterior spinal artery syndrome). Petitioner in the instant action does not allege that influenza vaccine caused encephalitis.

When petitioner went to the emergency room on January 7, 2008, he was in a dire condition. Upon admittance to the hospital, he continued to worsen. The doctors appropriately treated him with an antiviral Acyclovir in case he had herpes encephalitis, and Doxycycline, an antibiotic, in case he had Ehrlichia because of a borderline positive test result. There was no time to wait for confirming positive test results. When petitioner continued to worsen, slipping into a coma, and testing proved negative for viral infection and subsequently negative for bacterial infection, the doctors switched their diagnosis to ADEM and administered steroids, the first level of treatment for ADEM. Petitioner's dire state continued. The doctors then administered intravenous immunologlobulin, the second level of treatment for ADEM. Petitioner's dire state continued. The doctors lastly administered plasmapheresis, the third level of treatment for ADEM. The fact that petitioner did not improve, although he did regain movement on his left side, is not evidence that the diagnosis of ADEM was wrong. As Dr. Leist,

respondent's neurologist stated, petitioner had completed strokes. The damage was done and only physical therapy might alleviate petitioner's symptoms.

Dr. Leist emphasized the medical record notation that ADEM was the diagnosis of choice as if none of petitioner's treating physicians, including his neurologist, Dr. Torres, thought he had ADEM. Dr. Wientzen, respondent's infectious disease expert, stated that the treatment for ADEM did not work, implying that petitioner therefore did not have ADEM because he received treatment for the wrong disease. But this is contrary to Dr. Leist's other testimony that petitioner's continuing damage is due to his completed strokes. Petitioner's expert neurologist Dr. Steinman agreed that the strokes are responsible for petitioner's continuing damage.

Another reason Dr. Leist thought petitioner did not have ADEM but had encephalitis was that MRI imaging of petitioner's brain did not show demyelinating lesions of petitioner's white matter. But Dr. Steinman testified that, in 50 percent of ADEM cases, there is no MRI detection of white-matter demyelination. The Höllinger article (P Ex. 6, p. 7) supports that position. In 50 percent of the ADEM patients that Höllinger discusses, the MRI scans did not show white-matter demyelination.

Moreover, the Brighton Collaboration Encephalomyelitis/ADEM Working Group composed of doctors from the United States, Holland, Jordan, Switzerland, and Finland, created case definitions and guidelines for doctors to use in order to diagnose ADEM vs. encephalitis and myelitis (P Ex. 19). The authors created three levels of diagnostic certainty, with Level 1 being the highest level of certainty. Petitioner's signs and symptoms satisfy level 3 of the Brighton group's case definitions and guidelines for diagnosing ADEM because they involve at least one of the following central nervous system focal or multifocal findings: (1) encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change

greater than 24 hours); (2) focal cortical signs (including aphasia and cortical blindness); (3) cranial nerve abnormality or abnormalities; (4) visual field defect or defects; (5) presence of primitive reflexes (e.g., Babinski's sign); (6) either diffuse or focal motor weakness; (7) sensory abnormalities; (8) altered deep tendon reflexes; or (9) cerebellar dysfunction, including ataxia, dysmetria, and cerebellar nystagmus. P Ex. 19, pp. 12, 14, 15. Level 3 does not require MRI findings displaying diffuse or multifocal white matter lesions in order to diagnose ADEM.

Dr. Leist also objected to the diagnosis of ADEM because petitioner had strokes due to brain inflammation which he attributed to encephalitis, and patients with ADEM rarely have strokes. Dr. Steinman admitted that the appearance of strokes in an ADEM patient is rare, but it still occurs. Petitioner filed, in a collection of articles in Ex. 8, two case reports by Nakamura involving reactions to influenza vaccine. The second case concerned a man who received flu vaccine and seven days later had backache followed by dysuria and paraplegia. Brain MRI showed only lacunar infarction (stroke), and he had a lesion in the C6-T3 vertebral level of his spinal cord. Petitioner also filed as Ex. 13 the Perunovic article discussing ADEM resulting in infarction in the brain. The ADEM was preceded two months earlier by an upper respiratory infection. Perunovic and his co-authors stated, "We suggest that the infarction probably resulted from vascular compression as a result of severe swelling of the brainstem, as demonstrated radiologically." P Ex. 13, p. 7. Both articles support Dr. Steinman's testimony that, although rare, ADEM can cause infarction in the brain.

The final support for petitioner's allegation that he had ADEM is the diagnosis of his treating physician Dr. Torres and other treating physicians, such as Dr. Adair. Dr. Steinman spoke with Dr. Torres recently and he has not wavered from his diagnosis. The Federal Circuit

has emphasized in Capizzano and Andreu the importance of considering the diagnoses of treating physicians.

The undersigned holds that petitioner had ADEM, that the treating physicians, including Dr. Torres, were faced with a cataclysmic situation when petitioner was admitted to the hospital, and made the appropriate medical decisions to treat him as if he had viral encephalitis, bacterial infection, and ADEM. Dr. Steinman and Dr. Wientzen testified that the physicians absolutely did the right thing in administering Acyclovir and then Doxycycline to petitioner until testing showed he had neither a viral nor a bacterial problem. The neurologists and neurosurgeons held a conference to arrive at a diagnosis of choice not so they could justify to insurance companies administering plasmapheresis, but because this was a difficult case. But two weeks before that conference, on January 16, 2008, Dr. Torres had already diagnosed petitioner with ADEM and administered steroids, followed by the use of IVIG. The undersigned accepts Dr. Torres's diagnosis and finds Dr. Steinman's testimony more persuasive on this issue than that of respondent's experts.

Althen Prong One

The first prong of Althen is can influenza vaccine cause ADEM. Petitioner's expert Dr. Steinman stated that molecular mimicry explains how the vaccinee's immune system mistakes a portion of the flu vaccine to form antigen to its own brain tissue, resulting in ADEM. Both of respondent's experts Dr. Leist and Dr. Wientzen state that killed-virus vaccines, such as influenza vaccine, do not cause ADEM, although Dr. Wientzen is supportive of molecular mimicry in other autoimmune disease situations.

The experts discussed the Schonberger and Langmuir epidemiological articles in the context of the appropriate time interval between vaccination and onset of ADEM, but

Schonberger and Langmuir wrote these articles in another context as well—that of a killed-virus vaccine causing demyelination. The disease at issue was Guillain-Barré syndrome, a peripheral demyelinating disease, not ADEM, which is a central demyelinating disease. But the same set of facts applies here—that of a killed-virus vaccine causing demyelination. The Schonberger study arose from the passive reporting system VAERS set up during the swine flu vaccination program in 1976. When the Secretary of the Department of Health, Education, and Welfare (the predecessor of respondent herein) saw that there were greater numbers of GBS among swine flu vaccinees than among non-vaccinees, he halted the vaccination program. P Ex. 2, pp. 112-13. The litigation that arose from complaints of vaccine reaction resulted in the federal government making a policy decision to accept liability if a vaccinee had GBS within an appropriate time period after vaccination. Unthank v. US, 732 F.2d 1517, 1520 (10th Cir. 1984). Schonberger went out to 10 weeks in his study as indicative of a causal association. Langmuir saw that the data Schonberger used included children, cleaned up the data, and went out to eight weeks. P Ex. 2, pp. 135, 148. The bell curve Langmuir produced for causal association of GBS among swine flu vaccinees was highest at two to three weeks, but extended above baseline GBS cases until eight weeks. P Ex. 2, p. 156.

Besides the Schonberger and Langmuir epidemiologic studies showing causation from a killed-virus influenza vaccine of a demyelinating disease, medical literature that petitioner filed also supports the concept that killed-virus influenza vaccine can cause ADEM. In petitioner's collection of articles filed as Ex. 8, Brain's Diseases of the Nervous System has a chapter describing ADEM after influenza vaccine. Also in P Ex. 8 is an article describing a Korean girl who had ADEM two weeks after influenza vaccine and an upper respiratory infection. The Dale article, which is also in P Ex. 8, states that flu vaccine may cause ADEM, calling it a

neuroallergic phenomenon. The Menkes article in P Ex. 8 describes ADEM after flu vaccine. The Reik article in P Ex. 8 also describes ADEM after flu vaccine. The Saito article in P Ex. 8 describes ADEM after flu vaccine. The last document in P Ex. 8 is an excerpt from the Institute of Medicine's Adverse Events Associated with Childhood Vaccines. Evidence bearing on Causality, in which the authors state that ADEM can follow inactivated antiviral vaccination, finding it "biologically plausible that injection of an inactivated virus …might induce an autoimmune response in the susceptible host … by autoimmunity triggered by sequence similarities to host proteins such as those of myelin. The latter mechanism might evoke a response to self-antigen (molecularly mimicry)." P Ex. 8, p. 76. The Brighton Collaboration Encephalomyelitis/ADEM Working Group, comprised of doctors from five countries, states that various immunizations, including influenza, have been associated with ADEM. P Ex. 19, p. 8.

The undersigned holds that influenza vaccine can cause ADEM based on the testimony of Dr. Steinman, and the various articles, case reports, and epidemiologic studies in the medical literature.

Althen Prong Three

Because the two-month interval between petitioner's influenza vaccination and the onset of his ADEM has played an important part in this case, the undersigned discusses the third prong of Althen (appropriate temporal interval for causation) before discussing the second prong of Althen (did flu vaccine cause ADEM in this case).

Part of respondent's experts' difficulty with accepting causation in this case is the two-month interval between vaccination and onset of ADEM. The other part of respondent's experts' difficulty with accepting causation is the presence of at least one and perhaps two infectious

disease episodes in December 2007 which occurred closer in time to the onset of petitioner's ADEM in early January 2008.

As for the two-month interval, as discussed supra in the context of Althen prong one, both the Schonberger and Langmuir epidemiologic studies on swine influenza vaccine showed an increased incidence of GBS out to at least eight weeks, which is two months.

Respondent in four of the undersigned's cases involving delayed onset of demyelinating disease following receipt of hepatitis B vaccine, which is not a live-virus vaccine, but a recombinant vaccine made from hepatitis B surface antigen, has stated at a certain point in the litigation that she would no longer defend the case and asked for a ruling on the record. The undersigned ruled on the record in favor of petitioners in those cases: (1) Pecorella v. Sec'y of HHS, No. 04-1781V, 2008 WL 4447607 (Fed. Cl. Spec. Mstr. Sept. 17, 2008) (hepatitis B vaccine followed two months later by transverse myelitis); (2) Lilley v. Sec'y of HHS, No. 09-31V, 2009 WL 3320518 (Fed. Cl. Spec. Mstr. Sept. 28, 2009) (hepatitis B vaccine followed six weeks later by transverse myelitis); (3) Jane Doe/29 v. Sec'y of HHS, No. [redacted], 2009 WL 180078 (Fed. Cl. Spec. Mstr. Jan. 21, 2009) (hepatitis B vaccine followed two months later by Devic's disease, a variant of multiple sclerosis); and (4) John Doe/64 v. Sec'y of HHS, No. [redacted], 2010 WL 1783539 (Fed. Cl. Spec. Mstr. Apr. 28, 2010) (hepatitis B vaccine followed two months later by multiple sclerosis).

Subsequently, when the undersigned has had cases involving hepatitis B vaccine followed two months later by a demyelinating illness, the undersigned has held that that length of time was an appropriate interval denoting causation: Hawkins v. Sec'y of HHS, No. 99-450V, 2009 WL 711931 (Fed. Cl. Spec. Mstr. Feb. 27, 2009) (hepatitis B followed two months later by ADEM; upper respiratory infection occurred just before ADEM clinical signs); Fisher v. Sec'y

of HHS, No. 99-432V, 2009 WL 2365459 (Fed. Cl. Spec. Mstr. July 13, 2009) (hepatitis B vaccine followed two months later by optic neuritis).

The undersigned accepts that two months between vaccination and demyelinating injury is the outermost time period that is appropriate for a causal relationship based on the Schonberger and Langmuir epidemiologic articles, and the decisions supra involving hepatitis B vaccine and demyelinating diseases.

Althen Prong Two

Respondent's experts testified that if the undersigned held that petitioner did have ADEM, their opinion was that petitioner's upper respiratory infection beginning December 23, 2007 when his entire family was ill and possibly including December 3, 2007 when he had sinusitis are more likely the cause of his ADEM than the influenza vaccination he received in early November 2007. Dr. Steinman, petitioner's expert, testified that there was synergy from the flu vaccination and the upper respiratory infection or infections so that both or all three caused petitioner's ADEM. The closest analogue to this case is the Hawkins decision, supra, in which petitioner had hepatitis B vaccination followed almost two months later by an upper respiratory infection and then closely thereafter by ADEM. Hawkins was an easier case than the instant action because brain MRI showed she had demyelinated lesions in her brain which predated the upper respiratory infection according to her neurologic expert. However, the thesis of both cases is the same. The influenza vaccine began the autoimmune process that the later upper respiratory infection exacerbated.

The undersigned has ruled in numerous other cases that infectious disease processes and vaccinations together caused illness: Herkert v. Sec'y of HHS, No. 97-518V, 2000 WL 141263 (Fed. Cl. Spec. Mstr. Jan. 19, 2000) (cytomegalovirus and DTaP followed by transverse

myelitis); Nash v. Sec'y of HHS, No. 00-149V, 2002 WL 1906501 (Fed. Cl. Spec. Mstr. June 27, 2002) (pneumococcus and DPT followed by pneumococcal meningitis); Camerlin v. Sec'y of HHS, No. 99-615V, 2003 WL 22853070 (Fed. Cl. Spec. Mstr. Oct. 29, 2003) (otitis media and HiB vaccine followed by transverse myelitis or ADEM); Pearson v. Sec'y of HHS, No. 03-275V, 2008 WL 5093378 (Fed. Cl. Spec. Mstr. Nov. 6, 2008) (upper respiratory infection and hepatitis B vaccine followed by transverse myelitis); and Mouille v. Sec'y of HHS, No. 05-1204V, 2009 WL 44566207 (Fed. Cl. Spec. Mstr. Nov. 17, 2009) (upper respiratory infection and influenza vaccine followed by encephalitis). The reasoning of all these decisions followed the Federal Circuit decision in Shyface v. Sec'y of HHS, 165 F.3d 1344 (Fed. Cir. 1999) (DPT and E. coli infection followed by high fever and death). These decisions involved simultaneous infections and vaccinations, in which petitioners proved that the vaccines were substantial factors in causing the illness and/or death.

In the instant action, as in Hawkins, the infectious process was not simultaneous to the vaccination, but followed it, in Hawkins by nearly two months, and in the instant action by one month and three weeks (unless the early December sinusitis is viewed as a viral/bacterial infection, in which case the infection occurred one month after vaccination). The principle is the same: when the vaccination affects adversely the immune system of the recipient, any contemporaneous or subsequent infection also affects the same immune system to the recipient's detriment. Dr. Steinman called it a double whammy, and later in his testimony, synergy. The process is molecular mimicry. The disease involves demyelination.

Demyelinating diseases are autoimmune, triggered by some antigenic insult. In the instant action, the antigenic insult began with the influenza vaccination, which medical literature has associated with ADEM and which epidemiologic studies based on the swine influenza

vaccine say can lead to a greater incidence of demyelinating disease among vaccinees than among non-vaccinees up to eight weeks after vaccination. The addition of petitioner's one or two infectious episodes one month or more after vaccination added a greater imposition upon petitioner's immune system, resulting in ADEM.

Petitioner has satisfied the three prongs of Althen and 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.

September 30, 2011
DATE

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