# In the United States Court of Federal Claims
## OFFICE OF SPECIAL MASTERS

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| HELEN FORREST, | * | |
| | * | No. 14-1046V |
| Petitioner, | * | Special Master Christian J. Moran |
| | * | |
| v. | * | Filed: January 28, 2019 |
| | * | |
| SECRETARY OF HEALTH | * | Entitlement, flu vaccine, |
| AND HUMAN SERVICES, | * | transverse myelitis, timing, |
| | * | shingles, varicella, Shyface, |
| Respondent. | * | concurrent causes |

Curtis R. Webb, Twin Falls, ID, for petitioner;
Colleen C. Hartley, United States Dep't of Justice, Washington, DC, for respondent.

**PUBLISHED DECISION DENYING COMPENSATION**[1]

Ms. Forrest claims that an influenza vaccination, given to her on January 6, 2014, caused her to suffer transverse myelitis. After Ms. Forrest filed her medical records, the undersigned directed that the expert reports could constitute the experts' direct testimony at any hearing. The parties filed a series of reports from Dr. Lawrence Steinman (petitioner's expert) and Dr. Kathleen Collins (respondent's expert).

[1] The E-Government Act, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services), requires that the Court post this decision on its website (https://www.uscfc.uscourts.gov/aggregator/sources/7). This posting will make the decision available to anyone with access to the internet. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

A hearing was started on February 2, 2018, and continued December 6, 2018. The undersigned has considered all the evidence, including the medical records, expert reports, medical articles, and oral testimony.

The undersigned finds that Ms. Forrest has not met her burden of proof. The primary reason is that her transverse myelitis arose too soon after the vaccination for the vaccination to have caused the transverse myelitis. A second reason is that the Secretary has identified an alternative factor, a reactivation of the varicella zoster virus (VZV), that is a much more likely cause of the transverse myelitis than the flu vaccination. Finally, although this reason is less important than the other reasons, the theory Ms. Forrest proposes to explain a causal connection between the flu vaccination and her transverse myelitis, molecular mimicry, is insufficiently developed to be persuasive.

## Facts

Relatively few events in Ms. Forrest's medical record hold significance for determining whether she is entitled to compensation. In her childhood, she suffered a bout of chickenpox. Tr. 49. Chickenpox is caused by a virus known as varicella zoster virus. Exhibit A (Dr. Collins's report) at 4. In adults, reactivation of the varicella zoster virus causes shingles, more formally known as herpes zoster. Id.

Much later in her life, Ms. Forrest became an employee of Walmart and worked there for more than 20 years. Tr. 15, 48. She was basically healthy, having survived breast cancer.

Ms. Forrest presented information about her history of receiving vaccinations. On January 26, 2007, she received a dose of the flu vaccine. Exhibit 62. Based upon information available through FDA lot releases, Dr. Steinman determined that the 2006-07 flu vaccine protected against three strains. Exhibit 63 at 1 (citing exhibit 64). On December 8, 2008, Ms. Forrest received another dose of the flu vaccine. Exhibit 62. Again, Dr. Steinman found that the 2008-09 flu vaccine immunized a person against three strains. Exhibit 63 at 1-2 (citing exhibit 65). These two vaccinations are the foundation for Dr. Steinman's opinion that Ms. Forrest had previously encountered the antigens in the allegedly causal flu vaccine.

The allegedly causal dose of the flu vaccine was given to Ms. Forrest on January 6, 2014. Exhibit 2. The 2013-14 season flu vaccine protected against three strains. Exhibit 63 at 2; exhibit 32 at 6 (FDA lot release).

Late in the evening on January 7, probably around midnight of January 8, 2014, Ms. Forrest felt pain in her left flank as well as weakness and numbness in her left leg. Exhibit 5 at 3. In the morning of January 8, 2014, she went to the hospital, but the hospital discharged her. Exhibit 6 at 14. Although the exact number of hours between the vaccination and onset of neurologic problems is not known for certain, the parties agreed that a reasonable approximation is 36 hours. See exhibit 12 at 1 (Dr. Snyder), exhibit 12 at 9 (Dr. Potter).

Because she did not have motor function in her left leg, Ms. Forrest returned to the hospital. Exhibit 18 at 221. She was admitted to the hospital, where she stayed until discharge on January 15, 2014. Exhibit 18 at 227.

In the emergency room, a doctor recorded that Ms. Forrest had a "macular erythematous rash in the approximate L1-2 distribution. No vesicles." Exhibit 18 at 241. The doctor included "herpes zoster" in his differential diagnosis. Id. A neurologist reported more details about the rash and recommended treatment with acyclovir. Exhibit 18 at 220. Acyclovir is a medication for treating shingles.[2] A doctor requested testing of Ms. Forrest's spinal cord fluid to look for the presence of the varicella virus, but this testing could not be performed due to an insufficient amount of spinal cord fluid. Exhibit 7 at 28.

The possibility that Ms. Forrest suffered shingles complicates her claim that the flu vaccine caused her to suffer transverse myelitis. The Secretary's expert, Dr. Collins, opined that the reactivation of the varicella zoster virus was a potential cause for Ms. Forrest's neurologic problems. Exhibit A at 9, exhibit B at 3. Initially, before Dr. Collins wrote her first report, Dr. Steinman had stated that there was not an alternative cause for Ms. Forrest's transverse myelitis. Exhibit 20 at 28. However, once Dr. Collins identified the varicella zoster virus as a potential cause, Dr. Steinman changed tack. Dr. Steinman then asserted that "[i]f Ms. Forrest suffered VZV reactivation, the combination of the zoster activation and a recall response to the influenza vaccine was a 'perfect storm' for eliciting an autoimmune response to the myelin components resulting in transverse myelitis." Exhibit 63 at 8.

The experts discussed whether Ms. Forrest suffered a reactivation of the varicella zoster virus during their oral testimony. Although Dr. Steinman

[2] Other medications for treating shingles include valacyclovir, which is also known as Valtrex. Exhibit A (Dr. Collins's report) at 2.

expressed some doubt about whether Ms. Forrest actually suffered from shingles during her January 2014 hospitalization, Tr. 83-85, Dr. Steinman ultimately conceded that he believed, on a more-likely-than-not basis, that Ms. Forrest did have a reactivation of the varicella zoster virus. Tr. 142-43. For Dr. Steinman, the critical fact was that the treating doctors had ordered acyclovir to treat the shingles. Id. Thus, a preponderance of evidence supports a finding that Ms. Forrest was suffering a reactivation of the varicella zoster virus when she was also having neurologic problems in January 2014.

In addition to treating Ms. Forrest with acyclovir, her treating doctors attempted to learn more about the potential causes of her neurologic problems. For example, they ordered MRIs for her brain, cervical spine, lumbar spine, and thoracic spine. Exhibit 18 at 470-85. These MRIs did not detect any demyelination. Id. A doctor, who reviewed the results of the MRIs, later stated "[t]here was no spinal cord abnormality." Exhibit 7 at 28.

At discharge, the relevant diagnoses were "left lower extremity weakness" and "suspected transverse myelitis post influenza vaccination." The doctor recorded that Ms. Forrest had responded well to intravenous steroid therapy and was still taking Valtrex. The discharge record also indicates that "the patient did have [a] flu vaccination about one day prior to onset of symptoms." The discharging doctor recommended follow up with a neurologist, continuing medications, and physical therapy. Exhibit 18 at 227-28.

After discharge, Ms. Forrest improved slowly but incompletely. The details of her recovery from transverse myelitis say relatively little about the cause of transverse myelitis.[3] Thus, although the undersigned has reviewed these medical records, they are not set forth in this decision.

One event possibly informing the analysis of causation was in July 2014. Then, Ms. Forrest had a rash on her lower back. Her doctor assessed her as having shingles, and prescribed valacyclovir, which Ms. Forrest had stopped taking. Exhibit 15 at 6.

At hearing, Ms. Forrest recounted that she still has not recovered from transverse myelitis. She uses a cane and a walker to ambulate. She had to stop working at Walmart, a job that she had loved. Tr. 15.

[3] In various records, Ms. Forrest's doctors offered ideas about the possible causes for her neurologic problems. These are discussed in more detail below.

## Standards for Adjudication

Ms. Forrest bears a burden to establish her case on a more-likely-than-not basis. 42 U.S.C. § 300aa-13(a); Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). The elements of an off-Table causation-in-fact case are set out in Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

## Analysis

Ms. Forrest is not entitled to compensation for several overlapping reasons. These include: Ms. Forrest's failure to present a persuasive theory to explain how transverse myelitis can develop within approximately 36 hours (section I), and a failure to establish a logical sequence of cause and effect connecting the flu vaccine to Ms. Forrest's transverse myelitis (section II). In addition, the Secretary has established an alternative cause of Ms. Forrest's transverse myelitis — a reactivation of the varicella zoster virus (section III). Finally, the evidence does not support a finding that the flu vaccine combined with the varicella zoster virus to cause Ms. Forrest's transverse myelitis (section IV).

### I. Theory and Timing

To be entitled to compensation, Ms. Forrest is required to present a theory that explains how the flu vaccination can cause transverse myelitis generally and, for this theory to explain what happened to her, the theory must allow for an onset of neurologic problems within 36 hours. See Langland v. Sec'y of Health & Human Servs., 109 Fed. Cl. 421, 443 (2013) (linking Althen's first prong (theory) to Althen's third prong (timing)). Here, there are gaps and flaws that make crediting Dr. Steinman's opinion not possible.

As a starting step, Dr. Steinman proposes that flu vaccination can cause transverse myelitis via a process known as molecular mimicry. Molecular mimicry is a generally accepted mechanism to explain how some antigens, including those in certain vaccines, cause autoimmune diseases. Exhibit 35;[4] National Vaccine Injury Compensation Program: Revisions to the Vaccine Injury Table, 82 Fed. Reg. 6,294, 6,304 (Jan. 19, 2017) (to be codified at 42 C.F.R. pt. 100) (added Guillain-Barré syndrome as an injury for the influenza vaccine, which was supported by an Institute of Medicine report that acknowledged molecular mimicry

[4] Exhibit 35: Ang et al., Structure of Campylobacter jejuni lipopolysaccharides determines antiganglioside specificity and clinical features of Guillain-Barré and Miller Fisher patients, 70(3) Infect. Immun. 1202 (2002).

as a potential mechanism). Nevertheless, a simple invocation of the term "molecular mimicry" does not carry a petitioner's burden of proof. As explained by the Court of Federal Claims, "Without any empirical evidence that the theory actually applies to the influenza vaccine and [the disease in question], the first prong of Althen would be rendered meaningless." Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 135 (2011), aff'd without opinion, 463 F. App'x 932 (Fed. Cir. 2012).

Then, to explain the 36-hour onset, Dr. Steinman proposes that Ms. Forrest's response to the January 6, 2014 flu vaccination was a recall response. For Dr. Steinman, the January 26, 2007 vaccination and/or the December 3, 2008 vaccination led Ms. Forrest to develop either T cells or antibodies that were then stimulated by the January 6, 2014 flu vaccination. These restimulated portions of Ms. Forrest's adaptive immune system damaged her neurologic system.

A preponderance of evidence does not show that Dr. Steinman has presented a persuasive theory. The deficiencies are discussed below.

Experiments on Molecular Mimicry Generally. Molecular mimicry is a complex process in which several steps must occur for a disease to arise. See exhibit 38[5] (Markovic-Plese) at 38 (stating that the production of auto-antibodies is not enough to produce disease); Tr. 126-27.

To ground his theory of molecular mimicry as a mechanism to link the 2013-14 seasonal flu vaccine and transverse myelitis, Dr. Steinman looked for homology between the portions of the vaccine and components of the nervous system that might be involved in transverse myelitis. See exhibit 20 at 10-24. While Dr. Steinman found some overlap in sequences of amino acids, Dr. Collins and he disputed whether the overlap was sufficient. A close analysis suggests that Dr. Steinman appears to have made errors in proclaiming the degree of similarity that he found (Tr. 94-97), and these errors tend to reduce his credibility on this point.

Regardless, Dr. Steinman, at best, has identified homologies that may or may not be immunologically significant. While Dr. Steinman professes the homologies are meaningful, he has not investigated his hypothesis. Dr. Steinman's opinion in this case contrasts with the work of researchers whose work appears in peer-reviewed journals. After using computers to discover overlaps in amino acid

[5] Exhibit 38: Markovic-Plese et al., High level of cross-reactivity in influenza virus hemagglutinin-specific CD4+ T-cell response: Implications for the initiation of autoimmune response in multiple sclerosis, 169 J. Neuroimmunol. 31 (2005).

sequences, researchers then took a next step. They attempted to determine whether theoretical homology led to actual cross-reactivity. See, e.g., exhibit 46[6] (Birnbaum) (figure 7); Tr. 120 (discussing Birnbaum). This type of experiment would enhance the reliability of an opinion based upon computerized Blast searches because as the Institute of Medicine (IOM) has stated:

> Linear amino acid sequence homology or even similar conformational structure between an exogenous agent and a self-antigen alone are not sufficient to prove that molecular mimicry is the pathogenic mechanism for a disease. Many such homologies exist, and the vast majority of these are not associated with biologically relevant autoimmune phenomena or actual human disease.[7]

This statement from the IOM is consistent with a view that Dr. Steinman expressed in a peer-reviewed article. Exhibit 40.[8] With other researchers, Dr. Steinman wrote that injection with peptides is not sufficient to stimulate disease in healthy animals. The article stated: "A monoclonal antibody (8–18C5) against myelin oligodendrocyte glycoprotein (MOG) induces severe demyelination in mice and rats with mild experimental autoimmune encephalomyelitis (EAE) but does not induce disease in healthy animals because the antibody cannot gain access to the CNS parenchyma." Id. at 211. When asked about this paper, Dr. Steinman stood by his research. Tr. 120. Other experts for petitioners have agreed with the IOM's statement that "similar conformational structure" is not sufficient to establish molecular mimicry as the mechanism for a disease. See Purvis v. Sec'y of Health & Human Servs., No. 14-1025V, 2017 WL 4001683, at *3 (Fed. Cl. Spec. Mstr. Aug. 18, 2017).

Dr. Steinman, Dr. Collins, and the parties promoting their opinions spent a great deal of time discussing whether Dr. Steinman's computer searches yield

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[6] Exhibit 46: Birnbaum et al., Deconstructing the Peptide-MHC Specificity of T Cell Recognition, 157(5) Cell 1073 (2014).

[7] Exhibit 67: Institute of Medicine of the National Academies, Committee to Review Adverse Effects of Vaccines, "Chapter 3: Evaluating Biological Mechanisms of Adverse Events," in Adverse Effects of Vaccines: Evidence and Causality, 57, 70 (Stratton et al., eds., 2012).

[8] Exhibit 40: O'Connor et al., Self-assembling Antigen Tetramers Identify an Autoantibody-associated Form of Acute Demyelinating Encephalomyelitis, 13 Nature Medicine 211 (2007).

results that are consistent with the minimal level of homology that is required for cross-reactivity. Dr. Collins seemed credible in identifying the faults in Dr. Steinman's proposal. However, an exhaustive analysis as to whether Dr. Steinman has, for example, demonstrated a sequence homology for T cells (eight of nine amino acids)[9] is not necessary for this decision. Tr. 96; exhibit 20 at 13-15. For even if Dr. Steinman's identification of computerized homology were accepted entirely, homology is only the first step in the molecular mimicry theory. To explain the etiology of a disease, molecular mimicry also requires that the homology leads to the production of cross-reacting autoantibodies. And even the production of autoantibodies is not sufficient to cause disease because autoantibodies are detected in people who apparently do not suffer from disease. Ms. Forrest has not persuasively grounded the reliability of Dr. Steinman's extended opinion.[10]

Epidemiology. The Secretary introduced epidemiological studies to undermine Ms. Forrest's attempt to establish that the flu vaccine can cause transverse myelitis. See Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief"). Although Althen states that petitioners are not required to present epidemiological studies to prevail, special masters may consider epidemiological studies. Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992); D'Tiole v. Sec'y of Health & Human Servs., 726 F. App'x 809 (Fed. Cir. 2018); Caves, 100 Fed. Cl. at 135.

Here, a strong reason for Dr. Collins's disagreement with Dr. Steinman was the Baxter study. Exhibit D-1.[11] In Baxter, researchers studied a patient-

[9] Dr. Steinman had originally stated the T cell homology as nine of nine amino acids, see exhibit 20 at 13, but Dr. Collins corrected his math. See exhibit A at 7.

[10] The Federal Circuit has indicated that special masters may consider whether an expert's opinion is and has been "testable." Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999). But, the Federal Circuit has also observed that petitioners do not have to prove their cases with scientific certainty. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1380 (Fed. Cir. 2009); Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). The parties have not grappled with this potential tension. See Pet'r's Prehear'g Br. at 12; Resp't's Prehear'g Br. at 30-31. The undersigned is not requiring scientific certainty.

[11] Exhibit D-1: Baxter et al., Acute Demyelinating Events following Vaccines: A Case-Centered Analysis, 63 Clin. Infect. Dis. 1456 (2016).

population who had received 64 million doses of vaccines, including approximately 19 million doses of flu vaccine. The researchers did not detect an increased incidence of transverse myelitis after vaccination. When submitted into evidence in a Vaccine Program case, the Baxter article has served as one reason, although not the primary reason, for not crediting the theory that the hepatitis A and meningococcal vaccines can cause transverse myelitis. Bender v. Sec'y of Health & Human Servs., No. 11-693V, 2017 WL 5381628, at *21 (Fed. Cl. Spec. Mstr. Oct. 6, 2017), mot. for rev. granted, decision vacated, and remanded, 138 Fed. Cl. 197 (2018), decision after remand, 2018 WL 3679637, at *37 (Fed. Cl. Spec. Mstr. July 2, 2018) (special master clarifying that epidemiology was not the primary reason for denying compensation), second mot. for rev. denied and decision sustained, ___ Fed. Cl. ___, 2019 WL 288280 (Jan. 23, 2019).

Other epidemiologic studies carry less weight because the researchers studied a different disease (Guillain-Barré syndrome) and because the population was smaller. Exhibits D-3 (Greene[12]), D-5 (Kwong[13]), and D-7 (Stowe[14]). To the extent that these studies are useful, they too have failed to detect any increased incidence of neurologic disease after flu vaccination.

Evidence regarding the Time for Molecular Mimicry. Even if molecular mimicry could be accepted to explain how the flu vaccine can cause transverse myelitis abstractly, Dr. Steinman faced the additional challenge of demonstrating that molecular mimicry can happen in approximately 36 hours. Here, a preponderance of the evidence shows that molecular mimicry is not likely to happen within 36 hours, even for a recall response. (Whether Ms. Forrest genuinely had a recall response is discussed below).

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[12] Exhibit D-3: Greene et al., Guillain-Barré Syndrome, Influenza Vaccination and Antecedent Respiratory and Gastrointestinal Infections: A Case-Centered Analysis in the Vaccine Safety Datalink, 2009-2011, 8(6) PloS ONE e67185 (2013).

[13] Exhibit D-5: Kwong et al., Risk of Guillain-Barré Syndrome after Seasonal Influenza Vaccination and Influenza Health-Care Encounters: A Self- Controlled Study, 13 Lancet Infect. Dis. 769 (2013).

[14] Exhibit D-7: Stowe et al., Investigation of the Temporal Association of Guillain-Barré Syndrome with Influenza Vaccine and Influenzalike Illness using the United Kingdom General Practice Research Database, 169 Am. J. Epidemiol. 382 (2009).

The term "molecular mimicry" is a shorthand expression for a process that encompasses several steps of the adaptive immune system. Without precisely delineating each of the steps, the IOM has categorized the immune response to contain a "lag phase" and a logarithmic (or "log") phase. Exhibit 67. During the lag phase, the adaptive immune system encounters the antigen, transports the antigen to the regional lymph node, processes the antigen, and initiates the production of antibodies and/or T cells that attack the antigen. During the logarithmic phase, the number of antibodies and/or T cells increase to defeat the antigen. Tr. 265-69 (Dr. Collins's description of the adaptive immune system).

The difference between the lag phase and the log phase is important because several experiments on molecular mimicry start relatively far into the secondary log phase. Tr. 216; see also Tr. 163 (Dr. Steinman's testimony that the Ben-Nun experiment starts with already manufactured T cells). Examples include Ben-Nun (exhibit A-6[15]), Bartholomäus (exhibit 27[16]), and Odoardi (exhibit 28[17]). Even though Dr. Steinman cited the IOM for the basis that the lag phase generally can be as short as one day, exhibit 63 at 6 (citing exhibit 67 at 58), he has not persuasively addressed Dr. Collins's argument that the next step, the log phase, takes a minimum of three days and that actual presentation of symptoms is another step taking additional time. Exhibit B at 2; Tr. 298. When considering the lag and log phase together, Dr. Collins placed the minimum amount of time to develop symptoms following a recall response at six days. Tr. 298.[18]

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[15] Exhibit A-6: Ben-Nun et al., The rapid isolation of clonable antigen specific T lymphocyte lines capable of mediating autoimmune encephalomyelitis, 11(3) Eur. J. Immunol., 195 (1981).

[16] Exhibit 27: Bartholomäus et al., Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions, 462 Nature 94 (2009).

[17] Exhibit 28: Odoardi et al., Blood-borne soluble protein antigen intensifies T cell activation in autoimmune CNS lesions and exacerbates clinical disease, 104 Proc. Nat'l Acad. Sci. 18625 (2007).

[18] To rebut Dr. Collins's proposed timing, Dr. Steinman presented the polio virus as a counter example in his testimony. Dr. Steinman argued that if an immune response derived from the polio vaccine took six days, as proposed by Dr. Collins, then the polio vaccine would be ineffective at preventing polio. Tr. 144-45. In response, Dr. Collins distinguished the body's immune response to the polio virus from the case at hand. Dr. Collins explained that the antibodies created by the polio vaccine persist in the blood for decades and are thereby able to

Dr. Collins's opinion is consistent with other evidence. In animal experiments that support the molecular mimicry theory, the animal did not begin to show clinical symptoms until more than two days passed. Examples include Herges (exhibit 39[19]) (after researchers injected 50 million T cells reactive against myelin, the animal showed signs of neurologic problems six days later), Gautam (exhibit 45 at 770, fig. 3[20]) (incidence of neurologic symptoms did not start until almost day 10) and Ho (exhibit 51[21]) (the change in clinical score starts on day 10).

Collectively, these animal experiments tend to contradict Dr. Steinman's opinion that a recall response can happen as quickly as 36 hours. However, Dr. Steinman has pointed to some evidence supporting his opinion. The two strongest pieces of evidence are Schonberger and Salmon.

Both Schonberger and Salmon are epidemiologic studies examining whether a flu vaccine can cause Guillain-Barré syndrome ("GBS"), a disease only relevant because it is autoimmune and demyelinating. In the course of presenting their data, both Schonberger and Salmon showed that some cases of GBS occurred on either the day of vaccination (day zero) or the day after vaccination (day one). Exhibit 23[22] at 112 (figure 5); exhibit 71[23] at 1464-67. However, how the researchers evaluated the presence of people who had illnesses before receiving the vaccination (and before developing GBS) is not clear. Moreover, the researchers

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respond much faster to the polio virus. Tr. 271-72. Ms. Forrest did not present any rebuttal testimony from Dr. Steinman on this point regarding the polio virus.

[19] Exhibit 39: Herges et al., Protective effect of an elastase inhibitor in a neuromyelitis optica-like disease driven by a peptide of myelin oligodendroglial glycoprotein, 18(4) Mult. Scler. J. 398 (2012).

[20] Exhibit 45: Gautum et al., Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules: Implications in induction of autoimmunity, 91 Proc. Nat'l Acad. Sci. 767 (1994).

[21] Exhibit 51: Ho et al., Identification of Naturally Occurring Fatty Acids of the Myelin Sheath That Resolve Neuroinflammation, 4 (137) Sci. Transl. Med. 137ra73 (2012).

[22] Exhibit 23: Schonberger et al., Guillain Barré Syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977, 100 Am. J. Epidem. 105 (1979).

[23] Exhibit 71: Salmon et al., Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: A meta-analysis, 381 Lancet, 1461 (2013).

did not specifically examine whether the incidence of GBS within two days of vaccination occurred more frequently than expected. Thus, the two events (vaccination and onset of GBS) may be a coincidence. The likelihood that the two events (vaccination and onset of GBS) simply coincided draws some support from the only study in this record that compared the incidence of GBS following flu vaccination within a relatively short amount of time. In Kwong, the researchers found that the relative incidence was 0.95 within one week. Exhibit D-5 at table 2. This finding means that flu vaccine did not affect the incidence of GBS within one week. While one week is not the same as two days, the immune system would be more likely to cause an autoimmune reaction approximately five to seven days after the presentation of the exciting antigen, a time that is in the log phase of the immune response. Thus, Kwong's inclusion of events occurring seven days after vaccination would tend to overstate the relative risk of an adverse event in the first two days. Thus, overall, the epidemiologic evidence concerning an onset within two days is mixed.

The undersigned finds that in determining the amount of time for molecular mimicry to happen, the animal models are more useful than the epidemiologic studies Dr. Steinman cites. The animal experiments show the step-by-step process by which the injection of the antigen can lead to autoimmune disease. For example, in Bartholomäus, researchers grew cells in a petri dish in the lab for months with constant exposure to the relevant antigen. Then, when the researchers injected these specially manufactured T cells into the mice, the T cells still took more than two days to invade the central nervous system. Exhibit 27 at 95; Tr. 299. In short, the level of detail reported from the animal experiments makes them a more reliable source of information about the mechanics of the immune system.

Dr. Collins admitted if a person developed an immune response to a flu antigen contained in one year's flu vaccine, the person could potentially develop a recall response to a subsequent year's flu vaccine. Tr. 303. However, Dr. Collins qualified the possibility of a recall response with the necessity that during the interval between the flu vaccinations a person would need to be exposed to flu antigen so that her immune memory cells remain active and do not transition into a quiescent state. Id. She stated that immune memory cells become quiescent within 7 to 10 days after the pathogen has been destroyed. Tr. 267. After re-encountering an antigen, Dr. Collins testified that quiescent memory cells take three days to increase in number to reach the log phase and then later produce sufficient antibodies to counter the antigen (or, in an autoimmune context, to cause neurological symptoms). Tr. 230-31, 298; see also exhibit A-6 at 196 (where rats were observed for the development of overt paralysis of the hind quarters). Dr.

Collins's opinion is consistent with the Bartholomäus experiment in which researchers kept the immune memory cells in a highly active state to create a faster immune response, but even that response of more than two days is greater than Dr. Steinman's proposed time frame of only 36 hours.[24]

For all these reasons, Ms. Forrest has failed to present a persuasive or reliable theory to explain how the flu vaccine can cause the onset of transverse myelitis within approximately 36 hours. The epidemiologic evidence does not favor a finding of causation. The theoretical (or experimental) basis is confusing and incompletely developed. And, most of all, the timing is wrong.

## II. Logical Sequence of Cause and Effect

Although the finding with regard to timing is a sufficient basis to deny compensation, the evidence regarding Ms. Forrest's case is briefly set forth to demonstrate that the entire record has been reviewed under Althen prong two. For this prong, the Federal Circuit has instructed special masters to consider the statements of treating doctors. Capizzano v. Sec'y of Health & Human Servs., 440

[24] The undersigned's finding that a molecular mimicry reaction, even one predicated on a recall response, probably takes longer than two days is consistent with the undersigned's previous finding that the somewhat shorter time of 24 hours is not sufficient for a molecular mimicry reaction. See Contreras [5] v. Sec'y of Health & Human Servs., No. 05-626V, 2014 WL 8098606, at *37 (Fed. Cl. Spec. Mstr. Oct. 24, 2014) ("Dr. Steinman could present only weak and unpersuasive support for his opinion that all the steps associated with molecular mimicry can happen within one day"). After a motion for review was filed, an opinion determined that this finding was not arbitrary or capricious. Contreras [6] v. Sec'y of Health & Human Servs., 121 Fed. Cl. 230, 247 (2015). While the Federal Circuit vacated the judgment denying compensation, the Federal Circuit did not reach the question of timing. Contreras [7] v. Sec'y of Health & Human Servs., 844 F.3d 1363 (Fed. Cir. 2017).

Contreras [1] also contains an extended discussion of why a comparison to the tuberculin skin test is inapt and why Dr. Steinman's opinion regarding a recall response (referred to as "priming") was not persuasive. Contreras [1] v. Sec'y of Health & Human Servs., No. 05-626V, 2012 WL 1441315, at *18-20 (Fed. Cl. Spec. Mstr. Apr. 5, 2012), motion for review granted, decision vacated and remanded on other grounds, Contreras [2], 107 Fed. Cl. 280, 305-06 n.40 (2012) (accepting the special master's function of "weighing evidence for persuasiveness" in regard to the tuberculin skin test, but ordered re-examination of the importance of this finding), compensation denied on remand, Contreras [3], 2013 WL 6698382, at *48 n.41 (Fed. Cl. Spec. Mstr. Nov. 19, 2013) (special master reaffirmed his finding on the tuberculin skin test), vacated on non-relevant grounds and remanded, Contreras [4], 116 Fed. Cl. 472, 484-85 (2014), compensation denied on remand, Contreras [5], 2014 WL 8098606, at *37 (Fed. Cl. Spec. Mstr. Oct. 24, 2014), motion for review denied, Contreras [6], 121 Fed. Cl. 230, 247 (2015), vacated on other grounds, Contreras [7], 844 F.3d 1363 (Fed. Cir. 2017).

F.3d 1317, 1326 (Fed. Cir. 2006). In addition, there is a question about whether Ms. Forrest experienced a recall response to the 2013-14 flu vaccination.

Treating Doctors

Within the medical records, no treating doctor directly expressed an opinion that the flu vaccine caused Ms. Forrest to suffer transverse myelitis.[25] Some treating doctors noted the temporal sequence in which Ms. Forrest was vaccinated approximately 36 hours before she began to suffer neurologic problems. See, e.g., exhibit 18 at 143 (Dr. Snyder), exhibit 6 at 11 (Dr. Villena referencing a neurology evaluation). However, notations of a sequence of events are distinct from statements of causation. Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1348 (Fed. Cir. 2010). Furthermore, some statements from the treating doctors are couched in terms of "possible," exhibit 6 at 11 (Dr. Villena); "may be," exhibit 18 at 142; and "possibly," exhibit 15 at 6 (Dr. Villena). This language is not an expression of an opinion on a more-likely-than-not basis.

While those statements can be categorized as neutral, other statements from treating doctors point, slightly, away from a finding of causation. Early in Ms. Forrest's hospitalization, a neurologist (Dr. Carrigan) proposed that she was suffering a "viral" transverse myelitis. Exhibit 18 at 221. Months later, on August 28, 2014, Dr. Snyder observed that Ms. Forrest's transverse myelitis "occurred 36 hours after flu vaccination," and then commented: "This is a short time for post vaccinal autoimmune transverse myelitis but temporally hard to dismiss." Exhibit 12 at 1.

Finally, on October 9, 2014, Ms. Forrest saw Dr. Potter, who had learned that Ms. Forrest was pursuing a claim in the Vaccine Program. Other than noting that fact, Dr. Potter did not comment favorably or unfavorably on this claim. Because Ms. Forrest bears the burden of proving her case by presenting some affirmative evidence supporting a finding of causation, Dr. Potter's silence does not help her.

In short, the treating doctor's statements are not persuasive evidence that the flu vaccine caused Ms. Forrest's transverse myelitis.

[25] In her oral testimony, Ms. Forrest stated that one doctor, Dr. Fern, told her that the flu vaccine caused her transverse myelitis. Tr. 45. However, this statement does not appear in any medical record.

Recall response

Neither party disputes the onset of Ms. Forrest's symptoms at approximately 36 hours following vaccination. According to Dr. Steinman's first report, whether the flu vaccination triggered the onset of Ms. Forrest's transverse myelitis within 36 hours depends on "recall response, recall response, recall response." Exhibit 20 at 24. As explained in the Theory and Timing section above, Ms. Forrest has not presented persuasive evidence that a recall response can occur in approximately 36 hours. But, even if she had been persuasive on this theoretical point, she has not demonstrated on a more-likely-than-not basis that her January 2014 vaccination in fact provoked a recall response.

In opining that Ms. Forrest had a recall response, Dr. Steinman assumed that Ms. Forrest "most likely had other exposures to influenza vaccine and probably to natural influenza virus." Id. But, evidence does not validate this assumption. Between the flu vaccination Ms. Forrest received on December 3, 2008, and the flu vaccination on January 6, 2014, the medical records do not support, nor has Ms. Forrest claimed, that she received an interim flu vaccination. Dr. Collins argued that it is unknown whether Ms. Forrest was exposed to the flu antigen again during this interim time. Tr. 304. According to Dr. Collins, to satisfy petitioner's recall response theory, Ms. Forrest's immune memory cells would have to be somewhat active, having had some exposure to flu antigen, for the immune memory cells to have a rapid recall response. Tr. 230-31. Dr. Steinman did not oppose Dr. Collins statement that Ms. Forrest's immune memory cells were quiescent. Tr. 381 ("Dr. Collins may or may not be right about Mrs. Forrest having quiescent cells"). As noted above, since immune memory cells become quiescent 7 to 10 days after the foreign substance, here the flu antigen, is destroyed, Ms. Forrest would have required exposure to the flu virus in a relatively short time frame preceding the January 6, 2014 flu vaccination. Ms. Forrest has not presented sufficient factual evidence to establish on a more-likely-than-not basis that she experienced a recall response.

In sum, the entire record, including statements made by Ms. Forrest's treating doctors, does not support a logical sequence of cause and effect between Ms. Forrest's January 6, 2014 flu vaccination and her subsequent development of transverse myelitis. Thus, Ms. Forrest has not established her vaccine claim on a more-likely-than-not basis for any of the Althen prongs.

## III. Alternative Cause

Because Ms. Forrest has not met her burden under Althen, the Secretary does not bear any burden to establish a factor other than the flu vaccine caused her transverse myelitis. LaLonde v. Sec'y of Health & Human Servs., 746 F.3d 1334 (Fed. Cir. 2014). Nevertheless, because Dr. Collins has put forward the varicella zoster virus as an alternative cause, the undersigned is permitted to consider the evidence regarding the varicella zoster virus. Doe/11 v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1358-59 (Fed. Cir. 2010).

As explained previously, although the evidence that Ms. Forrest suffered a reactivation of the varicella zoster virus is not perfect, a preponderance of the evidence supports a finding that she did have a reactivation in January 2014. Tr. 142-43. This predicate is the basis for analyzing whether the varicella zoster virus caused her transverse myelitis.

Varicella zoster virus can cause transverse myelitis. Dr. Steinman did not dispute that varicella zoster virus can cause transverse myelitis. Tr. 142, 148.

The next question is whether the timing fits. Here, again, the evidence is not perfect. Although at least two doctors noted a rash on Ms. Forrest's back during her hospitalization, see exhibit 18 at 220 and 241, Ms. Forrest did not, in her testimony, recall when the rash began. Tr. 22-23. Thus, the interval between when the varicella zoster virus first reactivated (marked by the beginning of the rash) and when Ms. Forrest had neurologic problems cannot be known with certainty. Nevertheless, the lack of precision in timing is not an obstacle in finding causation when Ms. Forrest was suffering a reactivation of the virus before she started having neurologic problems.[26] See Tarsell v. Sec'y of Health & Human Servs., 133 Fed. Cl. 782, 792 (2017).

The remaining question is whether a logical sequence of cause and effect links the reactivation of the varicella zoster virus in Ms. Forrest caused her transverse myelitis. On this point, the evidence is not particularly strong but preponderates in favor of this. To begin, the treating doctors seemed uncertain as to any cause of the transverse myelitis. As reviewed above, they did not say that the flu vaccine caused the transverse myelitis and they did not say that the varicella zoster virus caused the transverse myelitis. While Dr. Steinman seemed to criticize

[26] In addition, neither Ms. Forrest nor Dr. Steinman has raised any challenge about the appropriateness of the timing between the rash and the neurologic problems.

the treating doctors for not obtaining definitive proof of a reactivation of the varicella zoster virus, he recognized that they prescribed antiviral medication for her. Tr. 391. After she received this medication and steroids in the hospital, she improved. Thus, Dr. Steinman's view that the treaters seemed not to consider the varicella zoster virus as the cause, because they did not do more to treat Ms. Forrest for a varicella zoster virus reactivation, is inaccurate.

While neither the statements nor the actions of the treating doctors persuasively implicate the varicella zoster virus by themselves, the Secretary may rely upon the report of an expert retained for the litigation. See 42 U.S.C. § 300aa-13(a)(1). Here, Dr. Collins has filled this role and presented a persuasive opinion that the varicella zoster virus was a more likely cause of the transverse myelitis. See Tr. 173-81, 316-19.

## IV. Contributing Causes

The final question is whether the flu vaccine combined with the varicella zoster virus to create, in Dr. Steinman's words, "a perfect storm" that led to Ms. Forrest's transverse myelitis. The evidence does not support this conclusion.

Vaccine Program precedent recognizes that a vaccine might join with an ongoing infection to harm a vaccinee significantly. The most prominent example is Shyface. Previously, the undersigned extensively examined Shyface, and concluded that the substantial factor test applies when two forces act in concert. Heinzelman v. Sec'y of Health & Human Servs., No. 07-01V, 2008 WL 5479123, at *2–4 (Fed. Cl. Spec. Mstr. Dec. 11, 2008) (noting that in Shyface, the Federal Circuit stated that the "Restatement recognizes that concurrent forces may bring about a single harm"), mot. for rev. regarding entitlement den'd, 98 Fed. Cl. 808, 812-15 (2011), aff'd on unrelated point of damages, 681 F.3d 1374 (2012).

Here, Dr. Steinman has not presented any evidence that the effects of the flu vaccine acted in concert with varicella zoster virus to cause Ms. Forrest to suffer transverse myelitis. This omission might stem from the fact that Dr. Steinman's first report asserted that the flu vaccine caused the transverse myelitis without mentioning the varicella zoster virus as an alternative or contributing cause. In other words, originally Dr. Steinman saw the flu vaccine as a separate and independent force causing the transverse myelitis. Then, after Dr. Collins identified the varicella zoster virus as an alternative explanation for the cause of Ms. Forrest's transverse myelitis, Dr. Steinman tacked on the idea of a perfect storm. Tr. 155. But, this proposal is clearly an afterthought with Dr. Steinman's

discussion of it consisting of only three sentences. Exhibit 63 at 8. During the hearing, his testimony was similarly cursory. Tr. 79, 156-61.

As Dr. Collins pointed out, the varicella zoster virus can cause transverse myelitis by itself. The flu vaccine is unnecessary. Tr. 204. She stated that she found no reports in the literature of a "perfect storm," and Dr. Steinman testified that he did not look for any literature on this point. Tr. 156, 204. For these reasons, Ms. Forrest's theory that the flu vaccine combined with ongoing varicella zoster virus to produce transverse myelitis is not persuasive.

## Conclusion

Ms. Forrest's transverse myelitis has drastically changed her life and made it more difficult. While Ms. Forrest's situation is sad and warrants sympathy, she has not presented persuasive evidence that the flu vaccine caused her to develop transverse myelitis. Moreover, the Secretary established on a more-likely-than-not basis that that the varicella zoster virus caused Ms. Forrest's transverse myelitis. Thus, Ms. Forrest's petition for compensation is denied.

**IT IS SO ORDERED**.

s/Christian J. Moran
Christian J. Moran
Special Master