In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 99-545V

(E-Filed: October 5, 2009)

BARBARA MURRAY, Petitioner, v. SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, Respondent.	TO PUBLISH Proof of Entitlement to Compensation; Pre-Existing Thyroiditis; Series of Hepatitis B Vaccinations; Developed AZOOR; Later Developed Addison's Disease

Clifford Shoemaker, Vienna, VA, for petitioner.

Glenn MacLeod, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

CAMPBELL-SMITH, Special Master

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless the decisions contain trade secrets or commercial or financial information that is privileged or confidential, or the decisions contain medical or similar information the disclosure of which clearly would constitute an unwarranted invasion of privacy. When a special master files a decision or substantive order with the Clerk of the Court, each party has 14 days within which to identify and move for the redaction of privileged or confidential information before the document's public disclosure. If the special master agrees, upon review of the party's motion, that the identified material falls within the described categories of protected information, the special master shall remove that material from the publicly accessible document.

On July 29, 1999, Barbara Murray (petitioner or Mrs. Murray), filed a petition pursuant to the National Vaccine Injury Compensation Program (Program).[2] 42 U.S.C. §§ 300aa-1 to -34 (2006). Petitioner alleges that she suffered an adverse reaction to the hepatitis B vaccinations[3] administered on August 5, 1992, September 2, 1992, and February 24, 1993. See Petition (Pet.) ¶ 3; Petitioner's Exhibit (P's Ex.) 1 at 1 (Affidavit of Mrs. Murray).

Mrs. Murray relies on a theory of causation in fact. In particular, she asserts that the hepatitis B vaccination series that she received first triggered visual changes that were suggestive of an ocular autoimmune response and then led to her development of Addison's disease. In support of her theory of causation, Mrs. Murray filed: (1) her affidavit; (2) her medical records; (3) the expert opinion of Joseph Bellanti, M.D., an immunologist; (4) supporting medical references; (5) post-hearing briefs; and (6) a letter from her treating vitreoretinal surgeon, Dr. Jeffrey Benner.[4] Respondent challenges Mrs. Murray's theory of causation in the filed expert opinion and hearing testimony of Mitchell Fineman, M.D., a vitreoretinal surgeon, in the provided literature, and in respondent's post-hearing brief.

During a recorded proceeding on February 15, 2008, in Washington, D.C., the undersigned heard the testimony of Mrs. Murray and the parties' respective experts. Based on the developed factual record, the medical literature, and the testimony of the parties' experts and for the reasons set forth in this ruling, the undersigned finds that petitioner has satisfied her burden of proving vaccine causation and is entitled to Program

---

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C.A. § 300aa-10 et seq. (2006) (Vaccine Act or the Act). All citations in this Decision to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

[3] The hepatitis B vaccine is "a noninfectious viral vaccine derived by recombination from hepatitis B surface antigen and cloned in yeast cells; administered intramuscularly for immunization of children and adolescents and of persons at increased risk for infection." Dorland's Illustrated Medical Dictionary 1999 (30th ed. 2003).

[4] A vitreoretinal specialist is an ophthalmologist who concentrates on diseases, often systemic or inflammatory, involving the retina and vitreous (posterior aspect of the eye). See http://www.facs.org/residencysearch/specialties/ophthal.html. An ophthalmologist must complete four years of postgraduate specialty training after the completion of medical school. This postgraduate training requirement includes a three-year residency in eye surgery (ophthalmology) in an approved surgical residency program followed by a one-year internship. Id.

compensation.[5]

I. BACKGROUND

The parties do not agree on several pertinent facts in this case. The parties' disagreement is caused, in part, by certain inconsistencies in petitioner's medical records. A pivotal issue in dispute is when the onset of petitioner's visual symptoms occurred. The parties also dispute the medical significance of petitioner's sore throat and facial rash, other symptoms that were documented to have appeared within the time frame surrounding Mrs. Murray's receipt of her third hepatitis B vaccination. In addition, although the experts do agree that Mrs. Murray now carries a diagnosis of AZOOR (acute zonal occult outer retinopathy) a rare eye disease, they do not agree on whether that eye disease is an autoimmune one. The bases for the expert's offered opinions will be explored in further detail in the discussion section of this ruling.

A recitation of the relevant facts now follows. The uncontested facts in this case are established by the medical records and the testimony of petitioner, Mrs. Murray. For the most part, Mrs. Murray's testimony during the hearing was consistent with her recorded medical history. Mrs. Murray was an earnest and credible witness.

A. The Uncontested Facts

1. Petitioner's relevant pre-vaccination medical history

Mrs. Murray was born on February 12, 1952. Transcript of February 7, 2008 Hearing (Tr.) at 12. She is the mother of two sons and one daughter. Tr. at 11-12. Her pre-vaccination medical history is notable in several respects.

After the birth of Mrs. Murray's second child in 1982,[6] Mrs. Murray was

---

[5] The undersigned is mindful of the delay in the issuance of this decision. The matter became ripe for decision while the undersigned completed her decision in Hazlehurst v. Secretary of Health and Human Services, No. 03-654, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), one of the autism test cases in the Omnibus Autism Proceeding. Upon issuance of the decision on February 12, 2009, the undersigned has turned to pending non-autism matters awaiting decision. The undersigned regrets the delay in the issuance of this decision.

[6] Mrs. Murray is the mother of three children. Her first son was born in 1973, her second son was born in 1982, and her third child, a daughter, was born in 1988. See Tr. 11-12.

diagnosed with hypothyroidism.[7] Tr. at 14. Treated with a synthetic thyroid hormone (known as synthroid) from the time of the discovery of her hypothyroidism, petitioner's condition was well-controlled and she was otherwise healthy prior to her receipt of a third hepatitis B vaccination in 1993. Tr. at 14.

Six years after the diagnosis of her hypothyroidism, Mrs. Murray gave birth to her daughter, her youngest child. See Tr. at 11-12. Her daughter was diagnosed at birth with an eye condition causing blindness.[8] Tr. at 13. Although Mrs. Murray subsequently developed an eye condition, neither of the experts in this case noted any relationship between Mrs. Murray's later developed eye condition and the congenital eye condition of her daughter.

From 1983 to 1993, Mrs. Murray worked as a first assistant nurse for a group of cardiothoracic surgeons. Tr. at 15-16. In connection with this employment, she received a hepatitis B vaccination series.

2. Receipt of the hepatitis B vaccination series and the appearance of various symptoms

On August 5, 1992, Mrs. Murray received her first hepatitis B vaccination. Tr. at 16; see also Petitioner's Exhibit (P's Ex.) 6 at 2. She did not report any problems. Id. On September 2, 1992, she received a second hepatitis B vaccination. Id. Again, she did not report any problems. Id. On February 24, 1993, Mrs. Murray received her third hepatitis B vaccination. Tr. at 17; see also P's Ex. 6 at 2. She testified at hearing that she developed visual problems three days later. Tr. at 17-18. What she noticed first in her right eye was a "dark blob" or a "floater mass."[9] Tr. at 18. She then began experiencing flashes of light, and her vision became cloudy. Tr. at 21-22. She also developed spider web-looking material in her field of vision. Tr. at 22.

On March 10, 1993, two weeks after her third hepatitis B vaccination, Mrs. Murray visited Dr. Benner, a vitreoretinal specialist for evaluation. P's Ex. 7 at 39. In

---

[7] Hypothyroidism is a "deficiency of thyroid activity, characterized by decrease in metabolic rate, fatigue, and lethargy." Dorland's at 900.

[8] The eye condition was identified as pigmented paravenous chorioretinal atrophy. See Tr. at 13.

[9] Floaters are "'spots before the eyes;' deposits in the vitreous of the eye, usually moving about and probably representing fine aggregates of the vitreous protein occurring as benign degenerative change." Dorland's at 711.

the medical records for that visit, she was noted to be a 41-year old woman diagnosed with "PVD [posterior vitreous detachment] yesterday."[10] Id. Also noted in the history section of the records is a complaint from Mrs. Murray of "floaters x 1 month [right] eye[, and] 11 days ago noticed larger web and cloudy v[isual] a[cuity] [left] eye." Id. Another notation made during the office visit indicates that Dr. Benner directed Mrs. Murray to return to him for another examination in two weeks.

Mrs. Murray returned to see Dr. Benner five days later, on March 15, 1993. Again she complained of "floater[s] x 1 month." Id. at 38. Mrs. Murray expressed concern about a "larger floater noticed today. Now nasal and larger (big blob)." Id. Otherwise, her visual acuity was noted to be "stable" Id. Also noted was the appearance one week earlier of an "eczematous facial rash" on Mrs. Murray that had resolved with the use of Decadron, a corticosteroid.[11] Id. Another notation in the record indicated that Mrs. Murray "had [a] protracted 'cold[,]' 1 month pharyngitis." Id.

The following day, on March 16, 1993, Dr. Benner wrote a letter to James Cockey, M.D., Mrs. Murray's internist, to inform him of her ophthalmic condition. Id. at 50. In his letter, Dr. Benner explained that Mrs. Murray had presented with a two week history of having floaters and flashes in her right eye. Id. In Dr. Benner's assessment, Mrs. Murray had "intermediate uveitis." Id. Dr. Benner observed that most cases of intermediate uveitis were idiopathic and probably autoimmune, and he noted that the testing that he had ordered to be performed for other possible infectious agents, such as tuberculosis and syphilis, had been negative. Id. Dr. Benner found it interesting that Mrs.

---

[10] Most of the eye's interior is filled with vitreous, a thick transparent substance composed mainly of water. There are millions of fine fibers intertwined within the vitreous that are attached to the surface of the retina. With the aging process, the vitreous slowly shrinks, and the fine fibers pull on the retinal surface. Occasionally the fibers break, allowing the vitreous to separate and shrink from the retina. This is a vitreous detachment. See http://www.nei.nih.gov/health/vitreous/index.asp. Dr. Fineman noted that Mrs. Murray appears to have had the condition much earlier than usually is seen in patients. Tr. at 176-177 (Dr. Fineman testifying that "posterior vitreous detachment . . .doesn't usually occur in 40-year-old people." Id. For that reason, he speculated that the floaters were the first sign of petitioner's AZOOR. See id.

[11] Decadron "works by decreasing or preventing tissues from responding to inflammation. It also modifies the body's response to certain immune stimulation." Decadron is used to treat "certain conditions associated with decreased adrenal gland function. It is also used to treat severe inflammation due to certain conditions, including severe asthma, severe allergies, rheumatoid arthritis, ulcerative colitis, certain blood disorders, lupus, multiple sclerosis, and certain eye and skin conditions." See http://www.drugs.com/cdi/decadron.html.

Murray had a history of autoimmune thyroiditis and that her eye symptoms had begun two to three days after the third dose of her hepatitis B vaccine. See id. Dr. Benner observed that Mrs. Murray's vision was "still excellent" and that he had decided to withhold treatment of her condition with steroids because he hoped that Mrs. Murray's eye condition would improve spontaneously. Id.

On March 23, 1993, Mrs. Murray visited Dr. Benner for the third time in less than one month. At this visit, her chief complaint was "floater [and] flashes at night." Id. at 38. The notes from this visit reflect that Mrs. Murray's visual acuity was stable. Id. In addition, Mrs. Murray complained of a facial rash that "started up again 2-3 days ago," that appeared to be a recurrence of the earlier facial rash that had resolved after treatment with Decadron. Id. At this visit, Dr. Benner diagnosed Mrs. Murray with "intermediate uveitis." Id. Under the treatment plan section of his notes, Dr. Benner remarked that he would continue to withhold steroids unless Mrs. Murray became unable to function in her job as a surgical nurse or if she began to experience a decrease in her visual acuity. Id. Dr. Benner noted that he was referring Mrs. Murray "to Dr. [Luette] Semmes for [a] derm[atology] consult." Id.

On that same day that Mrs. Murray saw Dr. Benner, Dr. Benner prepared a letter of introduction to Dr. Semmes for Mrs. Murray. See id at 49. Dr. Benner stated that he had been following Mrs. Murray "for intermediate uveitis with vitreous cells in her right eye for the last month." Id. Consistent with the medical history he had described in his earlier letter to Mrs. Murray's internist, Dr. Cockey, Dr. Benner noted in his letter to Dr. Semmes that Mrs. Murray first noticed floaters three days after her last dose of hepatitis B vaccine. See id. Dr. Benner explained that because her vision had "remained normal and the inflammation [was] relatively mild[,] [he] ha[d] withheld steroid treatment." Id. Dr. Benner described Mrs. Murray's first "erythematous[12] facial rash" that resolved with Decadron, and he described the bilateral rash that he observed on her face in the area between the cheek and the ear's opening (the preauricular area). See id. Dr. Benner noted that the lesions were erythematous with maculopapular[13] changes and Mrs. Murray had complained during her office visit "of itching." Id. Dr. Benner asked Dr. Semmes for her thoughts on the etiology of Mrs. Murray's skin lesions and whether she believed

---

[12] Erythematous refers to a "redness due to capillary dilation, usually signaling a pathologic condition (e.g., inflammation, infection)." Stedman's Medical Dictionary 666, 667 (28th ed. 2006).

[13] Maculopapular refers to the circumscribed skin eruption consisting of both macules (flat areas differing perceptibly in color from the surrounding tissue) and papules (solid elevations of up to 1 cm on the skin). See Stedman's 1142, 1143, 1416.

there might be any connection between the skin rash and the uveitis. Id. Dr. Benner recommended that Mrs. Murray return to him in three weeks for her next visit. See id.

Ten days later, on April 1, 1993, three weeks after Mrs. Murray first visited Dr. Benner for floaters in her right eye, Mrs. Murray returned to Dr. Benner with complaints for the first time of a floater in her left eye. Id. at 37. Dr. Benner's notes at this visit referenced the dermatological consult for Mrs. Murray's contact dermatitis and continued to reflect a diagnosis of intermediate uveitis. See id. Dr. Benner recommended that Mrs. Murray return in two weeks.

Two weeks later, on April 14, 1993, Dr. Benner again examined Mrs. Murray. Id. at 37. The medical records from this visit referenced the visit as a follow-up one for a patient with a history of intermediate uveitis. Id. Dr. Benner's notes indicated that his plan was to continue to observe Mrs. Murray's condition and to see her again in four weeks. Id.

When Dr. Benner examined Mrs. Murray again on May 11, 1993, his diagnosis was "resolving uveitis." Id. at 36. His notes show that Mrs. Murray reported that her visual acuity had remained the same since her last visit and that the "flashes of light seem[ed] better." Id.

Two months later, on July 13, 1993, Mrs. Murray returned to see Dr. Benner. Id. at 36. Dr. Benner's notes from this visit reflect that Mrs. Murray's intermediate uveitis was stable, even though she had a slight increase in floaters and her visual acuity had decreased again. Id. Dr. Benner recommended another visit in four months. Id.

3. Petitioner's follow-up eye care and the initiation of treatment for her eye condition

Dr. Benner followed Mrs. Murray for the next two years. See P's Ex. 7 at 30-36. On March 22, 1994, a little more than one year after Mrs. Murray's third hepatitis B vaccination, Dr. Benner treated her with subtenon[14] Decadron injections. Id. at 35.

Dr. Benner examined Mrs. Murray four times over the next nine months to monitor her intermediate uveitis and to follow her progress during her treatment with steroids. At one of the visits, scheduled on October 12, 1994, Dr. Benner treated Mrs. Murray with a

[14] Subtenon is a term used to describe injections through the membrane covering the muscles and nerves at the back of the eyeball. See National Cancer Institute, Dictionary of Cancer Terms, http://www.cancer.gov/templates/db_alpha.aspx?CdrID=350248.

Kenalog injection.[15] Id. at 33. When Dr. Benner saw Mrs. Murray for a follow-up visit nearly two months later, on December 27, 1994, she reported no change in her condition after the Kenalog injection. Id. at 32. During that December 1994 visit, and at Mrs. Murray's next visit to Dr. Benner on February 28, 1995, she complained of an increase in headaches. Id. At the visit in February of 1995, Dr. Benner initiated a circumscribed course of prednisone.[16] The prednisone treatment was not effective, and Dr. Benner discontinued the prednisone treatment two weeks later, on March 10, 1995.

Seven months later, on October 10, 1995, Dr. Benner detected, on examination of Mrs. Murray, optic neuropathy with enlarged blind spots in both eyes. The discovery prompted Dr. Benner to refer Mrs. Murray to Neil Miller, M.D., a neuro-ophthalmologist at the Johns Hopkins Wilmer Eye Institute.

As described in his letter dated October 10, 1995, to Dr. Miller, Dr. Benner's referral was prompted by the finding of "a significant reduction in [Mrs. Murray's] visual field" during a follow-up examination. P's Ex. 2 at 6, P's Ex. 3 at 9. Dr. Benner's reference to a loss in Mrs. Murray's visual field is the first such reference in Mrs. Murray's medical records during the two and one-half years that Dr. Benner had followed her. Dr. Benner explained in the letter to Dr. Miller, that he had been following Mrs. Murray for more than two years for intermediate uveitis in her right eye. Id. Notably, for the period of time between March 1993 and October 1995, Dr. Benner consistently had described Mrs. Murray's eye condition as an intermediate uveitis. P's Ex. 7 at 30-39. During that time, Mrs. Murray's intermediate uveitis worsened on several occasions and was treated with a subtenon's Kenalog injection. See id. Although she initially appeared to respond to the injections, subsequent treatments effected "little change or modification of the number of intravitreous cells in her right eye." Id. Dr. Benner noted that Mrs. Murray first presented in March 1993 with changes in the macular retinal pigment epithelium (RPE) in her one eye, but with normal vision in both eyes. P's Ex. 2 at 6. Dr. Benner further noted that he had performed a standard diagnostic examination for uveitis, and that Mrs. Murray's test results returned normal. Id. Dr. Benner advised that Mrs. Murray also had a dermatology consult to investigate her complaints of a "contact

---

[15] A Kenalog injection is a corticosteroid hormone (glucocorticoid). It works by decreasing the body's immune response to disease and reduces symptoms such as swelling." http://www.webmd.com/drugs/drug-9275-Kenalog+Inj.aspx?drugid=9275&drugname=Kenalog+Inj.

[16] Prednisone is "a synthetic glucocorticoid derived from cortisone, administered orally as an antiinflammatory and immunosuppressant in a wide variety of disorders." Dorland's at 1500.

dermatitis problem." Id.

About one week later, Dr. Miller examined Mrs. Murray and prepared a letter to Dr. Benner. P's Ex. 3 at 4-5. Dr. Miller identified as significant factors in Mrs. Murray's medical history: (1) her hypothyroidism, which had been treated with synthroid since 1982; (2) her seven year-old daughter's diagnosis of the eye condition, "pigmented paravenous chorioretinal atrophy;" and (3) the onset of floaters and flashers in Mrs. Murray's right eye in early March 1993. See id. at 2. Dr. Miller's examination of Mrs. Murray revealed a constricted right visual field nasally with a loss of vision (ring scotoma) and an enlargement of the blind spot in her left eye. P's Ex. 3 at 2-3. Her right pupil was less reactive to light than her left, and an electroretinogram (ERG) showed reduced amplitude and delayed timing of all responses in her right eye but normal responses in the left eye. P's Ex. 3 at 7. The MRI brain scan that Dr. Miller ordered for Mrs. Murray was normal and showed no demyelinating disease. P's Ex. 3 at 7. Dr. Miller identified an as issue in Mrs. Murray's case, "whether she has some type of underlying systemic inflammatory or neurologic autoimmune disorder to explain her progressive visual problem." P's Ex. 3 at 6. Dr. Miller added that "[a]nother issue to be considered," is the question of whether her condition was triggered by the received hepatitis B vaccination. Id. Dr. Miller referred Mrs. Murray to J. P. Dunn, M.D., an ophthalmologist at the Johns Hopkins Wilmer Eye Institute, for an assessment of "whether or not [her eye condition] is an inflammatory process, [or] whether it is somehow related to the disorder in her daughter." P's Ex. 3 at 8-9.

4. The diagnostic impressions of petitioner's eye condition continued to evolve during subsequent consultative examinations

Dr. Dunn evaluated Mrs. Murray on referral nearly three weeks later, on November 22, 1995. It was his impression that she had a "[p]ossible autoimmune retinopathy." P's Ex. 3 at 14. But he noted that "[h]er features [were] very atypical, in that there [was] striking asymmetry on visual field testing, and [the] duration of [her] symptoms ha[d] been two and one-half years." Id. at 14. Based on Mrs. Murray's test results, Dr. Dunn ruled out two eye cancers, namely, carcinoma associated retinopathy (CAR) and melanoma-associated retinopathy (MAR).[17] Id. Dr. Dunn also noted that

[17] Carcinoma associated retinopathy is a "visual paraneoplastic disorder characterized by progressive loss of visual function, clinical signs of retinal degeneration, and reduced electroretinographic response produced by both rod and cone dysfunction." Stedman's Medical Dictionary at 1684 (28th ed. 2006). Melanoma associated retinopathy is observed in a "subset of patients who . . . have metastatic melanoma, [a]nd they . . . develop decreasing vision." Tr. at 159. Dr. Fineman testified that this type of cancer triggers the biological mechanism of

"[d]emyelinating disease appear[ed] unlikely" based on Mrs. Murray's normal MRI brain scan and her normal color vision. Id. Among the other conditions that Dr. Dunn ruled out were: (1) a drug-induced retinopathy based on Mrs. Murray's medical history, the asymmetry in her visual field testing, and the presence of vitreous[18] cells in her right eye; and (2) a factitious disorder.[19] See id. Although Dr. Dunn noted Mrs. Murray's daughter's congenital eye condition, he was not aware of any connection between the daughter's eye disease and the adult onset retinopathy with which Mrs. Murray presented. See P's Ex. 3 at 14. With respect to Dr. Miller's question concerning whether Mrs. Murray's eye condition was an inflammatory disease, Dr. Dunn observed that Mrs. Murray's ocular examination was "very atypical for a vasculitis or other inflammatory disease-associated retinopathy." Id. Nonetheless, because Mrs. Murray did "have some nonspecific joint complaints, and ha[d] a history of a skin rash," Id. Dr. Dunn recommended that Mrs. Murray be evaluated further by a rheumatologist. Id.

On January 24, 1996, Dr. Benner examined Mrs. Murray again. His notes from this visit indicated that Mrs. Murray had progressive retinopathy of "unknown cause ?" a different diagnosis than he had documented previously. His notes also indicated that Mrs. Murray had shown "no improvement on prednisone" but rather was actually "worsening." P's Ex. 7 at 7.

Approximately one month later, on February 16, 1996, Dr. Benner examined Mrs. Murray again. He noted that he had discussed her case with Donald Gass, M.D., a professor of Ophthalmology and Visual Sciences at Vanderbilt Medical Center in Nashville, Tennessee, and the clinician credited with first identifying the eye disorder of AZOOR. Noting that Mrs. Murray had a "progressive retinal degeneration/retinitis of undetermined etiology. . . [but] suspected viral syndrome," id. at 25, Dr. Benner performed a surgical procedure (an anterior chamber paracentesis) involving the drainage

---

"molecular mimicry." Id. He testified that "[t]his is a paraneoplastic syndrome where, for whatever reason, the[] particular tumor ha[s] surface antigens or epitopes that mimic[] the same cells that are in the retina . . . . [W]hen the immune system recognize[s] this as a foreign body – the cancer, specifically – it created antibodies to attack it, which inadvertently attack[] the retina." Id. Dr. Fineman described a third subset of people who don't have cancer or melanoma, who have circulating autoantibodies to the retina. Id. In those individuals, Dr. Fineman explained, we diagnose them with "autoimmune retinopathy" in that "they have circulating antibodies to the retina which damage the photo-receptors, but they don't have cancer." Id.

[18] Vitreous is "glassy; resembling glass." Stedman's at 2139.

[19] A factitious disorder is one that is "[a]rtificial; self-induced; not naturally occurring." Stedman's at 694.

of fluid by needle from Mrs. Murray's eye to permit testing of her eye fluid. Dr. Benner also started Mrs. Murray on a two-week trial of the anti-viral drug Ganciclovir.[20] See id.

Test results were negative for viral agents, including "varicella zoster, CMV, and herpes simplex virus" in Mrs. Murray's eye fluid. P's Ex. 7 at 45. But her cytomegalovirus[21] (CMV) IgG antibody was "markedly positive." See id. Dr. Benner evaluated Mrs. Murray during a subsequent office visit on March 6, 1996. At that time, he noted that Mrs. Murray had experienced "no [decrease] or [increase in her] vision since on Ganviclovir." P's Ex. 7 at 24.

In a return visit to Dr. Benner two weeks later, on March 18, 1996, Mrs. Murray described her vision as "slightly worse." Id. Her CMV IgG and IgM levels remained elevated, suggesting either that she had a new infection or that she had a reactivation of an earlier infection.[22] See id. The office visit notes also indicated that Mrs. Murray had complained that she had a "low grade fever all the time" and that her "joints hurt." Id. As reflected in the treatment plan section of his notes, Dr. Benner planned to discuss with Amy Walsh, M.D., Mrs. Murray's internist at the time, whether Mrs. Murray's treatment with the anti-viral drug should be discontinued. Id.

By letter dated April 1, 1996, Dr. Benner referred Mrs. Murray to Dr. Gass, describing the clinical condition in her right eye as "compatible with AZOOR." P's Ex. 7 at 45. Addressing Mrs. Murray's pertinent medical history, Dr. Benner informed Dr. Gass that petitioner's CMV IgG antibodies were markedly positive. He noted that even

---

[20] As an antiviral drug, Ganciclovir "slows the growth and spread of the cytomegalovirus." See http://www.drugs.com/mtm/ganciclovir-oral-and-injectable.html.

[21] Cytomegalovirus (CMV) is a member of the herpes virus family, which includes the herpes simplex viruses and the viruses that cause chicken pox (varicella-zoster virus) and infectious mononucleosis (Epstein-Barr virus). Between 50% and 80% of adults in the United States are infected with CMV by 40 years of age. Most persons with CMV infection are asymptomatic. See http://www.cdc.gov/cmv/facts.htm.

[22] Two types of CMV antibodies may be found in the blood: IgM and IgG. IgM antibodies are the first to be produced by the body in response to a CMV infection. They are present in most individuals within a week or two after the initial exposure. IgM antibody production rises for a short time period and declines. After several months, the level of CMV IgM antibody usually falls below detectible levels. Additional IgM are produced when latent CMV is reactivated. IgG antibodies are produced by the body several weeks after the initial CMV infection to provide long-term protection. See Lab Tests Online, http://www.labtestsonline.org/understanding/analytes/cmv/test.html.

after she completed antiviral treatment with Ganciclovir, her CMV IgG level remained elevated at greater than 250 AU/ML (less than 15 AU/ML is negative), and that her CMV IgM level was also elevated at 1.33 (measurements greater than 0.6 are considered positive). P's Ex. 7 at 45.

Dr. Gass examined Mrs. Murray two weeks later. Consistent with Dr. Benner's impressions, he also suspected that she had AZOOR. See P's Ex. 4 at 4-5. Dr. Gass recommended that Mrs. Murray discontinue the Ganciclovir based on his diagnostic impression that Mrs. Murray had AZOOR. He explained that, in his experience, no medication has been found "to be of value in the few [AZOOR] patients where we have had the opportunity to place them on treatment during the development of early symptomatology in either the first or the second eye." P's Ex. 4 at 5.

Dr. Gass wrote to Mrs. Murray two weeks later, on May 1, 1996, to inform her that the electroretinogram performed during her visit yielded findings that were "more in keeping with a diagnosis of AZOOR than retinitis pigmentosa." P's Ex. 4 at 7. After the consult with Dr. Gass, Mrs. Murray continued to be followed by Dr. Benner for her eye condition under a diagnosis of AZOOR. P's Ex. 7 at 1-48; P's Ex. 11; P's Ex. 8 at 38, 228.

5. Additional examinations revealed another disease process

Three years later, on October 27, 1999, petitioner saw Jack L. Snitzer, D.O., an endocrinology specialist, on referral from her internist, Dr. Walsh. Dr. Snitzer informed Dr. Walsh by letter that it was his impression that Mrs. Murray was suffering from an adrenal gland insufficiency that was suggestive of Addison's disease. P's Ex. 13 at 4. He tested Mrs. Murray for the presence of antiadrenal antibodies and started her on a course of prednisone. P's Ex. 13 at 4. He noted that Mrs. Murray had reported that "in . . . February of 1993, she received a hepatitis B vaccine[, and a]bout three days later, she had visual problems in the right eye." P's Ex. 13 at 3. Dr. Snitzer wrote:

> I am not certain if this [adrenal insufficiency/Addison's disease] has any thing to do with the hepatitis B vaccine. She has a video on how the hepatitis B vaccine can stimulate the immune systems causing some problems afterward. It certainly may have stimulated her immune systems, in an already predisposed individual, to form antibodies against various things and in this case the adrenal glands. Hopefully, she should start feeling better in the near future.

P's Ex. 13 at 4-5. On November 14, 1999, Dr. Snitzer again wrote to Dr. Walsh confirming his diagnosis of Mrs. Murray's Addison's disease based on her positive test results indicating the presence of antiadrenal antibodies. P's Ex. 13 at 6.

6. The course of petitioner's AZOOR

For a period of time, petitioner's eye condition appeared stable. But in January 2001, she began to notice an increase in the frequency and severity of sparks or flashes (known as photopsias) in her left eye. P's Ex. 7 at 42. At the same time, she developed a "new facial rash that was suspicious for . . . [possible] [l]upus several weeks before her increased photopsias were noted." P's Ex. 7 at 42.

Dr. Benner examined Mrs. Murray on May 8, 2001, and by letter of the same date informed Dr. Gass that he planned to conduct a trial of Famvir for Mrs. Murray "since ma[n]y features of AZOOR point to the possibility of a viral syndrome." Id. (emphasis added). Dr. Benner again examined Mrs. Murray nearly two months later, on June 26, 2001, and noted that her visual field had "improved." Id. at 13. He appeared to question whether the improvement in her visual field was a result of the Famvir trial or was a "random" change related to the natural disease process. See id. at 13.

Notes from a subsequent visit to Dr. Benner three months later, on September 25, 2001, indicate that Mrs. Murray had "finished the course of Famvir," and there had been no change in her eye condition. See P's Ex. 7 at 12. Approximately six months later, on March 18, 2002, Dr. Benner saw Mrs. Murray again. See P's Ex. 7 at 10. By letter of same date to Catherine Smoot-Haselnus, MD, presumably Mrs. Murray's treating ophthamologist, Dr. Benner noted that he was "pleased that [Mrs. Murray's] AZOOR ha[d] stabilized." P's Ex. 7 at 40. He further noted that "her visual field show[ed] improvement a year after being treated with prednisone for reactivation of her AZOOR." Id. His notes reflect that additional efforts had been made to treat petitioner's condition with steroids.

Several years later, in November 2005, Mrs. Murray had pneumonia twice and had several adrenal crises that required various hospitalizations. See P's Ex. 14 at 76. In February 2006, she was hospitalized again with pneumonia.

On further examination of Mrs. Murray in September 2006, Dr. Benner found that her AZOOR was stable and had not progressed. See P's Ex. 7 at 2. His office visit notes reflect that at that time, Mrs. Murray was applying for disability benefits through the Social Security Administration. Id.

B. Contested Facts

1. The Onset of Petitioner's Visual Problems

Petitioner has not been consistent in her recollections of when her vision problems first occurred. In Mrs. Murray's affidavit, filed as Petitioner's Exhibit 1 on September 12, 2006, she stated that "[w]ithin 24 hours after receiving the [third] vaccination [she] started having visual changes including floaters, flashes of light and loss of visual field." P's Ex. 1 at 1; see also P's Ex. 12 at 13 (Roberto Salvatori, M.D., an endocrinologist, noting during his February 2, 2006 exam that patient "experienced dramatic vision loss in her right eye within 24 hours of her third hepatitis B injection."). At hearing in February 2008, however, Mrs. Murray testified that her first symptoms had occurred on Saturday, February 27, 1993, three days following the administration of her third hepatitis B vaccination.[23]

Given the discrepancies in Mrs. Murray's own recollection of events, the undersigned turns to the contemporaneous medical records from her early visits to Dr. Benner for assistance in determining when her eye symptoms first began. Dr. Benner's records from Mrs. Murray's first office visit on March 10, 1993, reflect that she complained of "floaters x 1 month [right] eye[, and] 11 days ago noticed larger web and cloudy v[isual]a[cuity] [left] eye.[24] See P's Ex. 7 at 39. Taken alone, this medical record suggests that Mrs. Murray had been experiencing visual problems for one month and places the onset of her symptoms before the received hepatitis B vaccination on February 24, 1993. The record might also be understood to mean that Mrs. Murray had problems in both of her eyes at the time of her consultation with Dr. Benner.

Mrs. Murray testified at hearing, however, that when she first visited Dr. Benner on March 10 1993, her visual problems were limited to her right eye. Tr. at 26. Mrs.

---

[23] A medical record dated October 27, 1999, also reflects that Mrs. Murray identified the onset of her visual problems "[a]bout three days" following the administration of the third vaccine. P's Ex. 13 at 3.

[24] By Order dated March 7, 2008, the undersigned directed petitioner to obtain from Dr. Benner a translation of the hand-written notes on a medical record filed as page 38 of Petitioner's Exhibit 7. Specifically, the special master asked for Dr. Benner's translation of the phrases "floater x one month" and "had protracted cold for 1 month." Order at 1. Petitioner's counsel filed as Petitioner's Exhibit 27, a letter of clarification from Dr. Benner. See P's Ex. 27. Although the undersigned addresses this filing in the context of other issues, the undersigned finds that there is enough contemporaneous evidence in the medical records to resolve the issue of onset without relying on the later-filed explanation from Dr. Benner.

Murray's testimony at hearing about the unilateral presentation of her symptoms is consistent with and supported by a subsequent and relatively contemporaneous notation in her medical records from a visit to Dr. Benner on April 1, 1993. The notes from that visit reflect that Mrs. Murray had a "h[istory]/o[f] floaters [and] blurry v[isual] a[cuity]" and complained of a mild floater in her left eye that had appeared that day.[25] See P's Ex. 7 at 37 (emphasis added).

In addition to Mrs. Murray's testimony and the medical records of petitioner's first two visits to Dr. Benner, which admittedly are not as clear as might be desired, there is other contemporaneous correspondence from Dr. Benner to Dr. Cockey, petitioner's internist, and to Dr. Semmes, a dermatologist to whom Dr. Benner refers petitioner, in which Dr. Benner describes petitioner's initial symptom presentation as being limited to her right eye. Id. at 49, 50. This correspondence between Dr. Benner and other treating physicians is probative evidence on the onset of Mrs. Murray's symptoms.

By letter dated March 16, 1993, to Dr. Cockey, Mrs. Murray's internist, Dr. Benner reported that Mrs. Murray had presented with a "two week history of having floaters and flashes in her right eye."[26] Id. at 50 (emphasis added). Dr. Benner noted that "[i]t [was] interesting that she ha[d] a history of an autoimmune thyroiditis and that [her] symptoms occurred 2-3 days [earlier] following the third dose of her . . . [h]epatitis B vaccine." Id. (emphasis added). Dr. Benner asked Dr. Cockey for his thoughts regarding the etiology of Mrs. Murray's condition. See id.

By letter dated March 23, 1993, to Dr. Semmes, a dermatologist, Dr. Benner referred Mrs. Murray for an evaluation of her facial rash. See P's Ex. 7 at 49. Dr. Benner wrote "I have been following [Mrs. Murray] for intermediate uveitis with vitreous cells in her right eye for the last month."[27] Id. (emphasis added). As noted in his letter, he found of particular interest Mrs. Murray's report of an onset of floaters in her eye three days after her last dose of hepatitis B vaccine. See id. Dr. Benner asked Dr. Semmes to

---

[25] Although petitioner's "floaters" appear to have become bilateral in less than a month after the third hepatitis B vaccine, Dr. Fineman asserted in his testimony that her visual field loss, which is the hallmark of AZOOR, did not become bilateral until years after the onset of her ocular disease. Tr. at 212.

[26] For Mrs. Murray to have a two-week history when she first presented on March 10, 1993, her symptoms would have appeared on February 24, 1993, the day that she received the vaccination.

[27] Of note, Dr. Benner indicated that he had been treating Mrs. Murray for a month, when in fact, her first visit to him was on March 10, 1993, almost two weeks before.

consider whether there might be a "connection between her skin rash and her uveitis." Id.

Medical records, especially those that are contemporaneous to the medical event in question, warrant consideration as trustworthy evidence because they contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. "With proper treatment hanging in the balance, accuracy has an extra premium." Cucuras v. Sec'y of Health and Human Servs., 993 F.2d 1525, 1528 (Fed. Cir.1993).

The undersigned recognizes that the medical records in this case, particularly those from Mrs. Murray's early visits to Dr. Benner, are not entirely consistent. However, the undersigned is persuaded that Dr. Benner's description of Mrs. Murray's case in the two letters to other physicians for the purpose of obtaining additional clinical evaluations for Mrs. Murray, see P's Ex. 7 at 49, 50, is reliable evidence of what facts Dr. Benner considered to be most relevant for the proper treatment of his patient. Both letters were drafted very close in time to his initial consultations with Mrs. Murray and were written for the purpose of facilitating her treatment. It is the view of the undersigned that Dr. Benner clearly understood what his record notations meant when he reviewed them for the purpose of relating clinical information to the two other health care providers. In the two letters, Dr. Benner communicates that Mrs. Murray's visual problems began two to three days following the administration of the third hepatitis B vaccination, and that her symptoms were limited to her right eye only. See id. Having considered the contemporaneous medical records following Mrs. Murray's vaccination and having examined the record as a whole, the undersigned finds that the evidence supports a finding that Mrs. Murray experienced the onset of her visual symptoms in her right eye on the third day after receiving her third hepatitis B vaccination. Id.

With respect to the other contested facts, specifically, what was the medical significance of petitioner's facial rash and sore throat and whether AZOOR is an autoimmune condition or not, the undersigned necessarily considered the opinions of the parties' experts. Accordingly, these issues are addressed in the discussion section of this ruling examining the views of the experts.

II. DISCUSSION

A. Legal Standards

The Vaccine Injury Table lists certain injuries and conditions that if found to occur within a prescribed time period create a rebuttable presumption of causation between the administered vaccine and the injury or medical condition alleged by a petitioner. 42

U.S.C. § 300aa-14(a). Because neither AZOOR nor Addison's disease is included among the injuries and conditions listed on the Vaccine Injury Table, this is not a Table Injury case, and no presumption of vaccine causation attaches to petitioner's claim. Rather, petitioner must prove causation. See id.

To satisfy the burden of proving causation in an off-Table case, petitioner must show that "the vaccination brought about [the vaccinee's] injury by providing: (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 the vaccination and the injury." Althen v. Sec'y of Health and Human Serve., 418 F.3d 1274, 1278 (Fed. Cir. 2005). Petitioner bears the burden of proving causation by preponderant evidence. See 42 U.S.C. § 300aa-13(a)(1)(A).

Petitioner has an affirmative duty to prove causation. Evidence merely showing "an absence of other causes" is insufficient to establish actual or legal causation of vaccine-related injury. Grant v. Sec'y of Health and Human Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992). While the imposed affirmative duty does not require petitioner to show that the vaccine was solely responsible or even the predominant cause of the injury, the burden rests with petitioner to establish that "the vaccine was not only a but-for cause of the injury, but a substantial factor in bringing about the injury." Shyface v. Sec'y of Health and Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999); see also Pafford v. Sec'y of Health and Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006) (stating that "[u]nder this court's precedent, [petitioner] must prove by preponderant evidence both that her vaccinations were a substantial factor in causing the illness, disability, injury or condition and that the harm would not have occurred in the absence of the vaccination").

Petitioner must support her theory of causation with a "sound and reliable medical or scientific explanation." Knudsen v. Sec'y of Health and Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994). A medical or scientific theory is not valid, however, simply because an expert offers the theory during his or her testimony. The Supreme Court has instructed in Daubert v. Merrell Dow Pharmaceutical, Inc., that the reliability of the offered testimony must be considered. 509 U.S. 579, 592 (1993). The reliability of an expert's theory may be evaluated by considering: (1) whether the theory or technique has been tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error; and (4) whether the theory or technique enjoys general acceptance within the scientific community. Daubert, 509 U.S. at 592-95; see also Kumho Tire Co. v. Carmichael, 526 U.S. 137, 138 (1999) (internal quotation and citation omitted) (noting that the general principles of Daubert apply broadly to "scientific, technical, or other specialized knowledge" and that offered

testimony must have "a reliable basis in the knowledge and experience of [the relevant] discipline"); General Elec. Co. v. Joiner, 522 U.S. 136, 145 (1997) ("Nothing, either in Daubert or the Federal Rules of Evidence[28] requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit [29] of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.")(footnotes added).

Although petitioner must provide a "sound and reliable medical or scientific explanation," see Knudsen, 35 F.3d at 548, petitioner need not provide particular types of evidence (such as medical literature or epidemiologic studies), see Capizzano v. Sec'y of Health and Human Servs., 440 F.3d 1317, 1324 (Fed. Cir. 2006). The Federal Circuit has observed that requiring petitioners to present particular types of evidence would "prevent[] the use of circumstantial evidence envisioned by the preponderance standard and negate[] the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants."[30] Capizzano, 440 F.3d at 1324.

Once petitioner makes the requisite showings, she establishes a prima facie case of vaccine-related causation. See De Bazan v. Sec'y of Health and Human Servs., 539 F.3d 1347, 1352-1353 (Fed. Cir. 2008) (discussing what evidence a special master may consider when deciding whether petitioner has satisfied her threshold burden of proving causation). In the absence of evidence that rebuts petitioner's case, petitioner is entitled to an award of Program compensation. Compare Pafford, 451 F.3d at 1355 with Walther v. Sec'y of Health and Human Servs., 485 F.3d 1146, 1150 (Fed. Cir. 2007) (addressing the issue of which party bears the burden of ruling out potential non-vaccine causes of the alleged injury).

---

[28] Although the Federal Rules of Evidence do not apply in vaccine cases, see Vaccine Rule 8(c), the Federal Circuit has affirmed efforts by special masters to examine the underpinnings of an offered theory of vaccine causation for a "sound and reliable medical or scientific explanation." Knudsen, 35 F.3d at 548; Terran v. Sec'y of Health and Human Servs., 195 F.3d 1302 (Fed. Cir. 1999) (affirming a special master's denial of compensation on the ground that the special master's application of Daubert principles in excluding an expert's causation-in-fact testimony was not improper).

[29] Ipse dixit refers to the Latin phrase "he himself said it." It refers to something asserted but not proved. Black's Law Dictionary 833 (7th Ed. 1999).

[30] Should petitioner elect to provide such evidence, however, the reliability of the offered evidence must be considered. See Knudsen, 35 F.3d at 548 (requiring that petitioner provide a "sound and reliable" medical or scientific explanation).

B. The Parties' Experts' Opinions of Causation

The parties' medical experts offered differing opinions in this case regarding what caused Mrs. Murray to develop AZOOR. Central to their respective opinions is what is known about AZOOR itself, and whether or not it is an immune-mediated syndrome.

1. The qualifications of the parties' experts

In support of her causation claim, Mrs. Murray offered the opinion of Dr. Bellanti, an immunologist. Dr. Bellanti graduated from the University of Buffalo, and then received training in pediatrics at the Children's Hospital in Buffalo. Tr. at 70. After medical school, Dr. Bellanti received post-doctoral training in immunology at the University of Florida, and later at Walter Reed Army Institute of Research in Washington, DC. Id. Currently, Dr. Bellanti is a professor of pediatrics and microbiology-immunology at Georgetown University School of Medicine, and he serves as Director of the International Center for Inter-Disciplinary Studies of Immunology at Georgetown University. Tr. at 71.

To address the opinion offered by Dr. Bellanti, respondent offered the opinion and testimony of Dr. Fineman, a vitreoretinal surgeon. See Tr. at 149. Dr. Fineman obtained his undergraduate degree from Rutgers University and then attended medical school at Emory University School of Medicine. See id. He performed his residency as well as a fellowship in vitreoretinal surgery at Wills Eye Hospital in Philadelphia. Id.

The strength of the qualifications of both experts is undisputed. But, the undersigned notes that the differences in the experts' medical specialties presented certain challenges in evaluating the expert's respective opinions regarding causation.

2. The opinions of the experts

a. Dr. Bellanti

Based on his review of Mrs. Murray's medical records, Dr. Bellanti opined in his report that:

> Mrs. Murray was susceptible to autoimmunity and more likely than not had an autoimmune reaction to her Hepatitis B vaccination. While other factors might have triggered this cascade of events, in this case, the Hepatitis B vaccination did so, accounting for . . . [her] AZOOR. Once a person

> develops problems of chronic autoimmunity, it is not unusual for their course to progress and involve additional body organs. Other factors, like infections, can certainly contribute to that process. According to her ophthalmologists, there was a temporal relationship with the vaccination, and it was deemed the most likely cause of her problems. I agree that but for the vaccination this process would not have begun when it did.

P's Ex. 15 at 13.

In support of his written opinion, Dr. Bellanti referenced three documents.[31] The first is an article (the Jampol article[32]) authored by Lee M. Jampol, M.D.,[33] and Kevin G. Becker, Ph.D.,[34] that explores a hypothesis linking autoimmune and inflammatory diseases. The second is an editorial written by J. Donald Gass, M.D. (the Gass editorial[35]) that critically evaluates the hypothesis set forth in the Jampol article and questions whether AZOOR is an autoimmune disease. The third is an article addressing a similar immune dysregulation hypothesis to the one that Dr. Bellanti has proposed in this case.[36]

The two key elements of Dr. Bellanti's theory are: (1) Mrs. Murray's genetic susceptibility to autoimmune disorders; and (2) the circumstantial evidence that she had an immune-mediated response to her third hepatitis B vaccination that led to the

---

[31] Although Dr. Bellanti referenced these articles, petitioner did not file them in support of Dr. Bellanti's expert opinion. On July 31, 2007, respondent filed a supplemental expert report from Dr. Mitchell Fineman, Respondent's Exhibit C. The Jampol article and Gass editorial were attached as part of this filing.

[32] L. Jampol et al., White Spot Syndromes of the retina: A hypothesis based upon the common genetic hypothesis of autoimmune/inflammatory disease, 135 Am. J. Ophth. 3: 376-379 (2003).

[33] Dr. Jampol is a clinical ophthalmologist. In addition, he is a professor and the chair of the Department of Ophthalmology at Northwestern University in Evanston, Illinois.

[34] Dr. Becker is a staff scientist and heads the Gene Expression and Genomics Unit at the National Institute on Aging at the National Institutes of Health.

[35] J. Gass (Editorial), Are acute zonal occult outer retinopathy and the white spot syndromes (AZOOR complex) specific autoimmune diseases, 135 Am J. Ophth. 3: 380-381 (2003).

[36] A. Vojdani and J. D. Thrasher, Cellular and humoral immune abnormalities in Gulf War veterans. Env. Health Perspectives, 112(8): 840-846 (June 2004).

development of her AZOOR.

I. Mrs. Murray's genetic susceptibility to autoimmune disorders

Dr. Bellanti posited that Mrs. Murray has a particular genetic susceptibility that, in the presence of certain environmental agents, permits her immune system to attack itself and thereby, give rise to autoimmune disorders. He testified that hepatitis B vaccine is an environmental agent that can induce autoimmune disease generally and that it did so in the case of Mrs. Murray causing first an autoimmune attack on her right eye and then a subsequent attack on her adrenal glands. See Tr. at 81, 84.

Dr. Bellanti described Mrs. Murray's genetic susceptibility as a "polyglandular" one that made her vulnerable to the polyglandular disease she now suffers. Tr. at 83. He explained that polyglandular autoimmune disease is an autoimmune disease that affects the endocrine glands, including, among others, the thyroid and the adrenal glands.[37] See Tr. at 81. Because the immune system is driven by antigen and autoimmune responses do not occur spontaneously, Dr. Bellanti asserted that something is needed to either "induce . . . protective immunity or autoimmune disease." See Tr. at 72, 82. He stated that "the interplay of [a] genetic tendency, plus an environmental cause, [is sufficient] to trigger the autoimmune attack." Id. at 72. He opined that Mrs. Murray's eye condition, diagnosed ultimately as AZOOR, resulted from "an immunologically mediated attack . . . on various layers of the eye, that we call the uveal tract and the retina." Tr. at 76. He pointed out that Mrs. Murray later developed Addison's disease, a condition that he described as an autoimmune disease of the adrenal gland. Id.

In Dr. Bellanti's view, Mrs. Murray's immunologic injury of the eye was one of several autoimmune diseases affecting her organs. See Tr. at 76. She developed an autoimmune disease of the thyroid gland following her second pregnancy. Then, after a period of time, she developed an autoimmune disease of her adrenal gland. See id. According to Dr. Bellanti, the development of Mrs. Murray's eye condition was an important component in the development of her polyglandular condition.

ii. Circumstantial evidence that petitioner had an immune-mediated response to her third hepatitis B vaccination that led to the development of her AZOOR

---

[37] The endocrine system is a system of glands and other structures that release hormones into the circulatory system that affect metabolism and other body processes. See Dorland's at 1842.

Dr. Bellanti testified that Mrs. Murray's development of AZOOR was evidence of an immune-mediated response to her third hepatitis B vaccine. Dr. Bellanti testified that "based upon . . . the clinical literature and . . . experimental evidence, I think it's solidly proven that a vaccine such as hepatitis-B can induce autoimmune disease." Tr. at 84. In particular, Dr. Bellanti testified that "the eye is one of the organs that is known to be targeted with an autoimmune attack." Tr. at 83. Dr. Bellanti explained that because Mrs. Murray's immune system was sensitized by her first two hepatitis B vaccines, her third hepatitis B vaccine "amplifie[d] the [immune] response, and caus[ed] the attack" on her eyes. Tr. at 83. In Dr. Bellanti's view, once Mrs. Murray's immune system was stimulated by the hepatitis B vaccines, "not only did the attack occur on [her] eye, but it . . . affect[ed] the thyroid, and subsequently . . . [her] adrenal [glands]." Tr. at 80.

In support of the proposition that hepatitis B can cause an autoimmune response in the eye, petitioner filed several case reports at hearing.[38] The case reports address the development of a variety of ocular symptoms, other than AZOOR, after a received hepatitis B vaccination.[39] See P's Ex. 21-25. In addition, petitioner filed as Exhibit 24 an article reporting on two patients who developed a visual loss identified as "acute posterior multifocal placoid pigment epitheliopathy" (or APMPPE) after a booster administration of recombinant hepatitis B vaccine, at three days, and at two weeks respectively. See P's Ex. 24 at 1. This article is of relevance as circumstantial evidence because APMPPE is one of the inflammatory diseases of the eye briefly referred to in the Jampol article,

---

[38] The case reports that were submitted included: (1) F. Devin et al., Occlusion of central retinal vein after hepatitis B vaccination. Lancet 34: 1626 (June 8, 1996), See P's Ex. 21; (2) A. Brezin et al., Visual loss eosinophilia after recombinant hepatitis B vaccine. Lancet 342: 563-564 (Aug. 28, 1993), See P's Ex. 22; (3) L. Fine et al, Multiple Evanescent White Dot Syndrome Following Hepatitis A Vaccination. Arch. Ophthalmol. 119: 3-4 (Dec. 2001), See P's Ex. 23; (4) A. Brezin et al., Acute Posterior Multifocal Placois Pigment Epitheliopathy After Hepatitis B Vaccine. Arch. Ophthalmol. 113: 1-4 (Mar. 1999), See P's Ex. 24; (5) M. Fried et al., Uveitis after Hepatitis B Vaccination (letter). Lancet 2(8559): 631-632 (Sep. 12, 1987), See P's Ex. 25.

Dr. Fineman criticized case reports as the least desirable form of medical literature. See Tr. at 214. He explained that case reports lend themselves to making assumptions that may not be accurate, and thus are not reliable. He stated that the best data is obtained through "placebo-controlled double-masked studies, where neither the patient nor the treater knows what they're receiving." Tr. at 214. Dr. Fineman did acknowledge, however, that case reports do serve the important purpose of "alert[ing] [clinicians] to something that's not common enough to be in a large trial." Id. at 215. He also observed that case reports may have informative value with respect to rare diseases. Id.

[39] In one of the submitted case reports, the vaccine at issue was hepatitis A.

another article on which Dr. Bellanti relied heavily as support for his opinion. The authors of the article filed as Exhibit 24 suggested that molecular mimicry between a retinal pigment epithelial protein and hepatitis B surface antigen could have played a role in the development of the eye condition. See Tr. at 204.

As support for his opinion that AZOOR is an autoimmune condition, Dr. Bellanti relied heavily on the Jampol article and the Gass editorial. The authors of the Jampol article, Drs. Jampol and Becker, argue in favor of an autoimmune etiology for the eye condition AZOOR. They identify three inflammatory diseases of the eye of unknown etiology, which include multiple evanescent white dot syndrome (MEWDS), multifocal choroiditis with panuveitis (MFC), and AZOOR, and they "present a hypothesis to explain similarities and overlapping cases based upon the common genetic hypothesis of autoimmunity/inflammatory disease." R's Ex. C at 6. The authors suggest that patients with AZOOR share common non-disease-specific genes. It has been shown that these non-specific genetic loci of autoimmune disease tend to cluster at certain places in the genome that already have been identified.

In an editorial in which Dr. Gass, a well-respected physician known for his study of AZOOR, evaluated the Jampol article, he summarized the authors' autoimmune hypothesis as follows:

> (1) each of the AZOOR complex of diseases is a discrete autoimmune clinical disease; (2) the presentation of each disease results from an interplay of genetics, the effects of the immune system pathways, and environmental triggers; (3) all of these patients share relatively common non-disease specific gene clusters at specific genetic loci that predispose the patients to immune dysregulation and autoimmune disease; (4) the interplay between immune dysregulation, specific environmental triggers, and other genes causes development of one or more of the AZOOR complex of diseases; and (5) environmental triggers as well as, in some cases, major histocompatibility antigens explain some of the variability of the clinical course.

R's Ex. C at 10. The hypothesis of the Jampol article–that AZOOR is an autoimmune condition--is supported by Dr. Gass' own reported findings that the disease occurs more predominantly in females and that patients with AZOOR have a greater than normal incidence of developing other autoimmune diseases.[40]

---

[40] Over Dr. Gass' own long-term follow-up of 51 patients with AZOOR, he reported that 14 patients (28 percent) either had or developed one or more autoimmune diseases. See R's Ex.

In addition to his view that AZOOR is an autoimmune condition, Dr. Bellanti also viewed Mrs. Murray's presenting symptoms in her eye, in her throat, and on her face as circumstantial evidence that she had an immune-mediated response to her third hepatitis B vaccine. He pointed to the onset of Mrs. Murray's earliest eye symptoms--specifically, the floaters and inflammation that prompted her visit to Dr. Benner in March of 1993 and that first appeared three days after she received her third hepatitis B vaccination. Tr. at 83. He asserted that the timing of the symptom onset

> fits the . . . immunologic principle of recall. Once you are sensitized with two previous vaccines, the third vaccine initiates what's called the recall, or the anamnestic response . . . [which is the immune system's] ability to remember. And it not only remembers, but it remembers with a vengeance. So the third vaccine stimulates that whole compilation of T-cells that were sensitized prior to that with the first two vaccines, amplifies the response, and caus[es] the attack. And unfortunately, the eye is one of the organs that is known to be targeted with an autoimmune attack.

Id. (emphasis added).

Dr. Bellanti stated that Mrs. Murray's symptoms of a sore throat and a facial rash, that were documented to have appeared about the time that she received her third hepatitis B vaccine provided additional circumstantial evidence that she experienced an immune-mediated reaction to the administered vaccination. Dr. Bellanti speculated that Mrs. Murray's noted sore throat "could very well have been [indicative of] an augmentation or an amplification of the immune system as a result of the hepatitis-B vaccine." Tr. at 80. Dr. Bellanti observed that a sore throat "has been reported in the package insert of the hepatitis-B vaccine" as a symptom that follows hepatitis B vaccination when there is a systemic reaction to the vaccination. Tr. at 81. Dr. Bellanti further observed that the stimulation of Mrs. Murray's immune system by her third hepatitis B shot could have aggravated her ongoing thyroid problem, and caused soreness in her throat. Tr. at 138.

Dr. Bellanti pointed to Mrs. Murray's facial rash as additional evidence of the hyperactivity of her immune system after the administration of the third hepatitis B vaccination. He stated that Mrs. Murray's facial rash "could have been an expression of the ongoing immunologic activation. . . . [I]t would fit as part of an ongoing hypersensitivity or an autoimmune attack." Tr. at 87. According to Dr. Bellanti, the development of Mrs. Murray's sore throat and facial rash near the time that she received the vaccination at issue and developed eye symptoms is suggestive evidence that Mrs.

C at 10; see also R's Ex. D at 8 (noting that of the 14 patients, six had Hashimoto's thyroiditis).

Murray's immune system had been overstimulated.

b. Dr. Fineman's opinion

In response to Dr. Bellanti's expert report, respondent filed an initial expert report and then two supplemental reports, all from Dr. Fineman. See R's Ex. A, C, and E. Dr. Fineman opposed Dr. Bellanti's proposed theory of causation on three grounds: (1) Mrs. Murray's autoimmune conditions were not causally related to her hepatitis B vaccinations; (2) AZOOR is not an autoimmune condition; and (3) the condition of AZOOR is distinguishable from uveitis.

I. Contesting the proposition that Mrs. Murray's hepatitis B vaccination caused her autoimmune conditions

Dr. Fineman opined that Mrs. Murray's AZOOR was not causally associated with her hepatitis B vaccinations. In his initial expert report, he asserted that Mrs. Murray had significant risk factors other than the hepatitis B vaccine for the development of AZOOR. The risk factors to which he pointed included her history of autoimmune disease which continued to develop following the diagnosis of AZOOR, the presence of what might have been a viral prodrome preceding the vaccination of interest here, and Mrs. Murray's age and gender. These identified risk factors are risk factors for the development of autoimmune disease. As Dr. Fineman testified at hearing, he agreed that petitioner was likely to have a genetic predisposition to autoimmune disease, and he does not dispute that petitioner has polyglandular autoimmune disease. Tr. at 175. In his view, however, no external stimulus to Mrs. Murray's immune system was needed--as urged by Dr. Bellanti--because AZOOR can occur in the absence of an identifiable trigger and he believed that "it was going to happen [to her] anyway." Id.

Dr. Fineman also questioned the temporal relationship between petitioner's vaccination and the onset of her injury. He observed that the interval of time between Mrs. Murray's third hepatitis B vaccination and the development of her eye symptoms was longer than the twenty-four hour period of onset reported in the ophthalmic literature.[41] See R's Ex. A at 9.

ii. Challenging the proposition that AZOOR is an autoimmune condition

As set forth in his first supplemental report, Dr. Fineman also challenged Dr.

[41] The referenced ophthalmic literature was in fact a case report that respondent had filed as a supplement to Respondent's Exhibit D (Dr. Fineman's expert report).

Bellanti's hypothesis that AZOOR is an autoimmune condition. In Dr. Fineman's view, several factors militated against such a finding, particularly: (1) the unresponsiveness of the condition to immune suppression treatment; (2) the failure to detect any antibodies to retinal tissue; and (3) the asymmetry of the presenting symptoms in Mrs. Murray's case.

Dr. Fineman explained that autoimmune diseases of the eye ordinarily are responsive to immune suppression drugs, such as prednisone. Tr. at 157. Prednisone is a "broad-based anti-immune system [drug that] suppresses . . . many aspects of [the immune system]. . . . It works in many of the[] [autoimmune] diseases, even if we don't know exactly what part of the immune system we're suppressing." Tr. at 156. In contrast, the eye syndrome AZOOR does not respond to immunosuppressive medications. Tr. at 157-158. And in Mrs. Murray's case, there is some record evidence that her condition actually worsened after an initial prednisone treatment. P's Ex. 7 at 27; Tr. at 157. In Dr. Fineman's view, AZOOR's failure to react to immune suppression treatment "lends a lot of credence to the idea that it may not be an autoimmune disease." Tr. at 158.

Although Dr. Fineman took a hard view of AZOOR's failure to respond to immune suppression medication, Dr. Gass–whom Dr. Fineman regarded as an authority on AZOOR–noted in his follow-up study of AZOOR patients that "[i]nterpretation of treatment results [is] difficult because of the frequency with which AZOOR stabilized within weeks or several months after onset." R's Ex. D at 11. And, Dr. Fineman himself attributed the worsening of Mrs. Murray's symptoms after the administration of prednisone not to the treatment but to "the natural history of the disease process." Tr. at 158.

The second factor that Dr. Fineman believed militated against a finding that AZOOR is an autoimmune condition is the lack of any findings, to date, of antibodies to retinal tissue. The failure to detect retinal tissue autoantibodies in AZOOR patients is distinguishable from what has been found in other known autoimmune-mediated illness of the eye, such as cancer-associated retinopathy ("CAR") and melanoma-associated retinopathy ("MAR"). See Tr. at 158-60. As Dr. Fineman explained, "the fact that [antibodies to retinal tissue] weren't seen here, and have never been seen with AZOOR, again [gives rise to the question] whether . . . [AZOOR] is due . . . [to] an autoimmune disease." Tr. at 160-161 (Dr. Fineman noting there has never been a reported case of an AZOOR disorder that has been accompanied by the documented detection of circulating antibodies to any part of the retina).

The third factor that informed Dr. Fineman's view in this case that AZOOR is not an autoimmune disorder was the asymmetry of Mrs. Murray's presenting eye symptoms. He stated that most autoimmune illnesses of the eye present bilaterally, but Mrs. Murray's

AZOOR "presented unilaterally," with floaters only in one eye. Tr. at 163. Dr. Fineman did not define the time period within which symptoms must present in both eyes to be deemed bilateral, but he observed that a two- or three-year period of time before the other eye becomes affected is too long. Tr. at 164. Here, however, Mrs. Murray's symptoms appeared in her left eye about one month after the same symptoms appeared in her right eye. Without more about what constitutes a bilateral presentation, in particular, whether both the timing of symptom presentation and the type and degree of symptoms presented must be considered, it is difficult to evaluate, as Dr. Fineman has urged, this particular factor in Mrs. Murray's case.

Dr. Fineman also criticized two of the documents that Dr. Bellanti cited as support for his position, namely the Jampol article and the Gass editorial. Dr. Fineman asserted that the Jampol article on which Dr. Bellanti relied merely proposed a hypothesis in the absence of "proven, documented evidence that AZOOR or other types of uveitis are autoimmune diseases." R's Ex. C at 4.

Then, pointing to the Gass editorial on which Dr. Bellanti also relied, Dr. Fineman asserted, that at this time, evidence that the AZOOR complex of disorders is a group of autoimmune diseases is lacking. Dr. Fineman noted that, in the absence of proof that AZOOR is an autoimmune condition, Dr. Gass speculated that AZOOR could be an infectious disease, caused by a yet unidentified infectious agent. Id. Dr. Fineman testified that, although Dr. Gass is now deceased, he is still considered to be the authority on AZOOR. Tr. at 152.

Dr. Fineman described Dr. Bellanti's characterization of AZOOR as an autoimmune disease as an "overstate[ment] [of] the evidence." R's Ex. C at 4. But when asked to address the possibility that AZOOR has an autoimmune mechanism, Dr. Fineman conceded that "the jury is really out." Tr. at 152.

Pointing to the opinions expressed by Dr. Gass in the filed Gass editorial, Dr. Fineman stated:

> Dr. Gass, who is considered the authority on this disease -- [because] he described this disease -- . . . was quite convinced that there were many holes in the autoimmune theory regarding this disease. And based on multiple factors, [Dr. Gass] felt as though it may have been infectious, possibly viral, but certainly did not follow the pattern of classic autoimmune diseases that we see in the eye."

Tr. at 152 (emphasis added). Dr. Gass had "proposed either cytomegalovirus or one of

the herpes viruses" as the causal viral agent. Tr. at 161.

Persuaded that AZOOR is unlikely to be an autoimmune disease, Dr. Fineman addressed the differences between uveitis and AZOOR.

iii. Distinguishing between the conditions of uveitis and AZOOR

Although Mrs. Murray was diagnosed with uveitis when she first presented to Dr. Benner with eye symptoms after the vaccination of interest, her ultimate diagnosis was AZOOR. Important to Dr. Fineman's opinion in this case are the distinctions between uveitis and AZOOR.

Dr. Fineman stated that "intermediate uveitis is a diagnosis of exclusion after other infectious causes" have been excluded. Tr. at 153. When a patient presents with inflammation in the eye, the prescribed clinical evaluation typically includes testing for infectious agents. See id. Dr. Fineman elaborated that, "you check for syphilis, you check for Lyme disease." Id. And then when "everything else turns out negative, then you call [the presentation] intermediate uveitis, because you don't have anything else to call it." Id. What "[y]ou know [is that] you have inflammation that's bilateral, and it's very responsive to steroids. So we know it's the immune system mediating the response, but we're not sure what stimulated it." Tr. at 154.

Intermediate uveitis is an autoimmune condition.[42] Tr. at 152. Dr. Fineman testified that the retinal surgical community has a long history with intermediate uveitis and its treatment. Uveitis is an inflammation of the inside of the eye, specifically in the layer of the eye known as the uvea. Intermediate uveitis refers to inflammation toward the front of the vitreous and peripheral retina of the eye. See emedicine.medscape.com/article/1208794-overview. The condition of intermediate uveitis is recognized as potentially the first expression of an autoimmune disease in a patient. Id.

Dr. Fineman described the differences between uveitis and AZOOR. He stated that uveitis is "usually bilateral at presentation. . . [and is] exquisitely sensitive to steroids, [particularly] to prednisone treatment." Tr. at 153. But, AZOOR "can present in many different ways, [and] . . . is really resistant to any kind of treatment." Tr. at 153. Emphatic that uveitis is "an entirely different disease process [than AZOOR]," Dr. Fineman added that uveitis is characterized by "inflammation. It does not [involve] visual field loss, [as does] AZOOR. Tr. at 188.

[42] The condition is also known as pars planitis.

Acute zonal occult outer retinopathy or AZOOR is "a disease of unknown etiology." Tr. at 186. The name of the disease is the "acronym of the descriptive term that was given to th[e] constellation of symptoms and signs" that appear in that particular spectrum of retinal disorders. Tr. at 186. Dr. Fineman testified that at present, "[t]here is no [known] precipitating factor." Tr. at 186.

C. Evaluating the Presented Evidence

As stated earlier, petitioner must prove causation by showing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing the vaccination was the reason for the injury; and (3) a proximate temporal relationship between the vaccination and the injury. Althen, 418 F.3d at 1278. The undersigned addresses each of the prongs of the Althen standard in turn.

1. Petitioner's Offered Medical Theory

Petitioner must offer a medical theory causally connecting the vaccination and the injury. Althen, 418 F.3d at 1278.

Dr. Bellanti testified that it was his opinion that Mrs. Murray has a genetic propensity to develop autoimmune disease and autoimmune phenomena. He asserted that here, "the hepatitis[]B vaccine was but one of perhaps other triggers that triggered her immediate problem, which was the eye problem. But also most probably the Addison's disease subsequently." Tr. at 76.

Dr. Bellanti explained that a healthy immune system is "a system in balance that is activated not only by the cells, but by the cell products that we call cytokines . . .[which are] communication proteins that communicate between and among cells." Tr. at 74. Dr. Bellanti explained further that "some of these cytokines promote inflammation; others dampen inflammation." Id. The majority of "what we call the adaptive or the specific immune system, are called T- and B-cells." Id. "The T-cells are cells that come from the thymus, under the control of the thymus, and regulate cellular responses. The B-cells are the cells that make antibody, [and it is] these extra-cellular products that can neutralize or combine with antigens." Id. Dr. Bellanti testified that the T-cell system is not a single cell, it is several populations of T-regulatory cells that regulate the functions of the immune system. See id. Dr. Bellanti added that many diseases such as those involving autoimmunity, reflect an imbalance of the T-regulatory cells. See id.

As described by Dr. Bellanti, in the case of autoimmunity, "we want the T-reg[ulatory] cells to be elevated to dampen the immune system," because when there are

too few T-regulatory cells, the inflammatory part of the immune system is exaggerated, which manifests as allergic disease or autoimmune diseases. See id. at 75. In individuals that "suffer from immunologically mediated diseases that we call autoimmunity, the T-reg[ulatory] cells seem to be lower than normal. . . and that's genetically controlled." Id. And that is why these events, fortunately, occur rarely. Id.

Dr. Bellanti testified that in general, hepatitis B, is a very good vaccine, and the vast majority of the population that receives the vaccine has a favorable immune response with no problems at all. Tr. at 84. But, he observed, "there are the outl[i]ers. They [are] either . . . low responders or high responders." Id. And those individuals, like Mrs. Murray, are the individuals that experience adverse effects from administered hepatitis B vaccinations. See id.

Dr. Bellanti opined that Mrs. Murray's thyroiditis–an autoimmune condition involving the thyroid with which Mrs. Murray had been diagnosed and treated successfully prior to her receipt of the hepatitis B vaccination series–was strong evidence that Mrs. Murray "ha[d] a genetic susceptibility to becoming sensitized to something in the external environment, which then trigger[ed] [her] immune system in th[e] autoimmune attack" on her eye. Id. at 82.

Dr. Bellanti distinguished Mrs. Murray's polyglandular autoimmune syndrome from a thyroiditis condition, which many women have as an isolated event. He testified that "it's a different genetic susceptibility that allows other glands to be involved." Tr. at 133. Here, Dr. Bellanti opined that Mrs. Murray's autoimmune disease process was of the variety that is "genetically determined, [and] with the right kind of environmental agent . . . w[ould] go on to other [gland] involvement." Id. He testified that his proposed "immunologic theory would require that there be an environmental stimulus to cause the progression" in the disease process. Tr. at 132.

Dr. Bellanti's hypothesis concerning Mrs. Murray's genetic susceptibility to develop autoimmune disease is consistent with Dr. Gass' observation in his follow-up study of AZOOR patients that the "predilection for AZOOR to affect young and middle-aged women, and its association with one or more autoimmune diseases . . . suggests that AZOOR patients have a predisposition for autoimmune disease."[43] R's Ex. D at 11.

[43] In the Gass article filed as Respondent's Exhibit D, the authors reported on the long-term follow-up of 51 patients with AZOOR. The authors found that 25 of the 51 patients (49 percent) had one or more events within days or weeks prior to the onset of AZOOR. Ten patients (20 percent) had a viral-like illness and seven patients (13 percent) had headaches, two of whom reported migraine headaches. See R"s Ex. D at 7. Fourteen of the 51 patients that Dr. Gass

Dr. Fineman agreed that petitioner was likely to have had a genetic predisposition to autoimmune disease, and he did not dispute that petitioner has polyglandular autoimmune disease. See Tr. at 175. But, in his view, no trigger by an external stimulus was needed because AZOOR can occur in the absence of an identifiable trigger, and Dr. Fineman is of the opinion that AZOOR is not an autoimmune disease. According to Dr. Fineman, Mrs. Murray's eye condition was not an immune-mediated response to the hepatitis B vaccination series she received.

Dr. Fineman did not challenge the plausibility of petitioner's medical theory of causation on immunologic grounds. Rather, respondent sought to call petitioner's medical theory into question by presenting evidence showing how little is known or understood about AZOOR.

Dr. Fineman himself conceded that the disease is "very rare." Tr. at 150. The disease is "probably only about 20 years old," Tr. at 153, and he has only seen five cases. See Tr. at 150. Dr. Fineman noted that the Gass article is the "largest review [article] we have on [AZOOR]" and Dr. Gass scrupulously reported his observations in "a follow-up study of every patient with AZOOR, either examined by him or referred to him as a mail consultation."[44] See Tr. at 153, R's Ex. D at 4. Dr. Fineman added that the prospects for a better understanding of AZOOR appear quite limited because "there aren't enough people [who have the disease]," and thus, "[t]here will never be a large trial of AZOOR, where we randomize half the patients to one treatment versus another." Tr. at 215.

Dr. Fineman explained that, in the absence of more certain information, there are two competing theories about the underlying nature of AZOOR, as illustrated by the opinions expressed in the Jampol article and the Gass editorial that were filed as attachments to Dr. Fineman's supplemental expert report. See Tr. at 189; see also R's Ex. C. One theory is that AZOOR has a viral etiology, and the other is that AZOOR is autoimmune. See Tr. at 189.

Dr. Fineman testified that prior to his death, Dr. Gass "was quite convinced that there were many holes in the autoimmune theory regarding [AZOOR]. And based on multiple factors, felt as though it may have been infectious, possibly viral, but certainly

---

examined with AZOOR had one or more autoimmune diseases. Id. at 8. A review of medical records for sex and age-matched controls revealed that none had a history of autoimmune diseases. See R's Ex. D at 11.

[44] Mrs. Murray was examined by Dr. Gass and is one of the patients included in his review article.

did not follow the pattern of classic autoimmune diseases that we see in the eye." Tr. at 152. Dr. Fineman continued that the prevailing view of AZOOR in the ophthalmology community "is . . . moving away from an autoimmune cause, and moving towards an infectious cause with no known etiology at this time." Tr. at 232.

A critical underpinning for the parties' experts' opinions about causation in this case is the experts' respective views on whether or not AZOOR is an autoimmune condition. The experts agree that the condition is a relatively novel one and is not well understood. Moreover, based on what is known about the condition, the parties' experts agree that if AZOOR is an autoimmune condition, it does not present as a typical autoimmune disease.

Underscoring the division in the ophthalmologic community concerning whether AZOOR is an autoimmune disease or is of viral etiology are the differing views in this case of Dr. Benner, petitioner's treating vitreoretinal specialist, and Dr. Fineman, who is also a vitreoretinal specialist. These specialists presented different opinions regarding whether petitioner's third hepatitis B vaccination triggered an autoimmune response in her eyes. The medical records of Dr. Benner's treatment of petitioner indicate that he perceived Mrs. Murray's eye condition to be an autoimmune one based on her history of autoimmune disease, her presenting eye symptoms, together with her facial rash, and purported cold, and her subsequent development of another autoimmune condition. And at hearing, Dr. Fineman acknowledged that as of the time of the hearing in this case, the autoimmune theory had neither "been proven or disproven. . . . [W]e're nowhere closer to deciding whether [AZOOR is] autoimmune today than we were six years ago, or even 10 years ago." Tr. at 183.

Petitioner's expert presented a theory that petitioner has developed polyglandular autoimmune disease based on her genetic susceptibility to autoimmune disease involving multiple glands that appear to respond adversely to select environmental triggers. Petitioner here had a pre-existing autoimmune condition, specifically thyroiditis before she received the hepatitis B series (which petitioner's expert asserts has been associated with autoimmune conditions in general, and with autoimmune conditions of the eye in particular). After receipt of the third hepatitis B vaccination, Mrs. Murray developed symptoms that initially were suggestive of an autoimmune condition of the eye, and symptoms developed within a time frame appropriate for an anamnestic autoimmune reaction. Not only did petitioner develop a condition of the eye, AZOOR, for which there is supportive evidence for a finding that the condition is an autoimmune condition--although an atypical presentation of an autoimmune condition of the eye--but, she later developed another autoimmune condition of her endocrine glands, specifically, Addison's disease.

In light of the current uncertainty regarding whether AZOOR is an autoimmune-mediated disease, and in the presence of circumstantial evidence that an anamnestic response to petitioner's third hepatitis B vaccination occurred, the undersigned finds petitioner's theory to be a biologically plausible one.

Dr. Fineman's credentials and experience treating AZOOR and known autoimmune conditions of the eye are beyond reproach. However, the factual circumstances of this case, and petitioner's proposed biological mechanism, necessitated an evaluation of broader immunological issues surrounding autoimmunity in multiple glands. In the absence of expert testimony on respondent's behalf, from one who is qualified to address broader issues of immunology, and who could provide an assessment of the soundness of Dr. Bellanti's proposed vaccine causation theory, the undersigned finds that petitioner has satisfied her burden of proof under the first prong of the Althen standard.

Consistent with the requirements of Althen, petitioner has offered a medical explanation that links her received hepatitis B vaccination series to the development of her polyglandular autoimmune disease, a component of which was her AZOOR. See Althen, 418 F.3d at 1278; see also Grant, 956 F.2d at 1148. As presented, the offered explanation is biologically plausible even if not medically certain. See Knudsen, 35 F.3d at 548-49. And because "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 has instructed that consideration may be given to a presented theory that involves a link between a vaccination and a certain injury, premised upon "a sequence hitherto unproven in medicine." Althen, 418 F.3d at 1280. In the circumstances presented here, petitioner has met her burden under the first prong of Althen.

2. The Sequence of Cause and Effect

The Federal Circuit has observed that an offered medical theory is persuasive when accompanied 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[.]'" Althen, 418 F.3d at 1278 (quoting Grant, 956 F.2d at 1148)).

As already addressed in this ruling, central to petitioner's theory of causation are the opinions of Dr. Bellanti, petitioner's expert immunologist, and Dr. Benner,

petitioner's treating vitreoretinal specialist, that the eye condition AZOOR is an autoimmune disorder. In part, it is the atypicality of the disorder's presentation that persuades respondent's expert, Dr. Fineman, that the disorder is likely a viral one.

In this case, Drs. Bellanti, Benner, and Fineman all looked to the research performed by and opinions expressed by Dr. Gass concerning AZOOR patients. Dr. Gass openly questioned whether AZOOR is an autoimmune condition.

Identifying multiple conditions as part of the "AZOOR complex,"[45] R's Ex. C at 10, Dr. Gass suggested that the AZOOR complex of diseases may represent "a group of overlapping clinical syndromes that may be caused by a single or perhaps closely related group of triggering infectious agents,"[46] R's Ex. C at 11. Dr. Gass set forth his own hypothesis that AZOOR is of a viral etiology, positing that viral or other infectious agents enter the receptor cells at the optic nerve head and cause the zones of acute receptor cell loss that are characteristic of the AZOOR complex of disorders. Dr. Gass theorized that an infectious agent--likely to be a virus--could "gain entrance into the receptor cells, spread from cell to cell, and yet cause no dysfunction until its presence [was] recognized by the patient's immune system." R's Ex. C at 11.

Although Dr. Gass found that there was a high prevalence of autoimmune disease in patients with AZOOR, he was not persuaded that the basis for AZOOR was primarily an autoimmune one based on the same factors that were of concern to Dr. Fineman, specifically: (1) the asymmetric nature of the retinal involvement in AZOOR patients; (2) the failure of patients with AZOOR to respond to steroid treatment; and (3) the difficulty in detecting circulating retinal antibodies in patients with AZOOR. See R's Ex. D at 12. Dr. Gass did observe, however, that the immune systems of AZOOR patients could be stimulated by a variety of factors, noting that "fifty percent of patients [he studied] with AZOOR ha[d] the onset of visual loss associated with events that include[d] infectious mononucleosis, herpes simplex dermatitis, herpes zoster dermatitis, other viral-like syndromes, immunization injections, tick bite, migraine headaches, and pregnancy and delivery." R's Ex. C at 11. Although he was not convinced that the autoimmunity theory proposed by Drs. Jampol and Becker was correct, Dr. Gass "look[ed] forward to the results of their genetic investigations of patients with the AZOOR complex and familial

---

[45] The conditions include in particular, MEWDS, MFC, punctate inner choroidopathy (PIC), acute idiopathic blind spot enlargement, acute macular neuroretinopathy, acute annular outer retinopathy, and AZOOR.

[46] In contradistinction to the hypothesis proposed by the Jampol article authors, Dr. Gass did not believe that the AZOOR complex of diseases was a discrete disorder.

autoimmune disease." R's C at 11.

The reluctance of respondent's expert, Dr. Fineman, to give credence to the autoimmune theory proposed by petitioner was informed by Dr. Gass' position and was based his own observation that AZOOR does not adhere to the pattern of classic autoimmune diseases that are seen in the eye. See Tr. at 152.

Petitioner's expert, Dr. Bellanti asserted, however, "there's ample evidence in the literature to suggest that many vaccines, but particular[ly] hepatitis B, ha[ve] a propensity to stimulate an adverse effect in the form of autoimmune disease." Tr. at 82 (emphasis added). He added that the eye can be a target for both an immune-mediated reaction and a viral infection. Acknowledging that testing did reveal a high CMV titer and thus, a viral infection, in Mrs. Murray's case, Dr. Bellanti dismissed that viral agent as an important consideration in petitioner's case because Mrs. Murray's treatment with anti-viral medication did not appear to effect a change in her eye condition. See id.

In support of his theory of an immune-mediated reaction to the administered hepatitis B vaccination, Dr. Bellanti addressed Mrs. Murray's testimony regarding the soreness of her throat after the third vaccination. Dr. Bellanti observed that when an attack is occurring in patients with thyroid disease–by lymphocytes destroying the thyroid–such patients do complain of pain . . . that can be confused with an infectious pharyngitis." Tr. at 80. Dr. Bellanti opined that the pain that Mrs. Murray described in her neck could have been "an augmentation or an amplification of the immune system [response to] . . . the hepatitis B vaccine." Tr. at 80. Dr. Bellanti conceded that he could not say definitively that this was what happened in Mrs. Murray's case but he observed:

> it's a logical sequence and a plausible sequence of events, that would suggest that when her immune system [response] was heightened after the hepatitis-B, not only did the attack occur on the eye, but it was affecting the thyroid, and subsequently, as I've said, the adrenal [gland].

Tr. at 80.

Dr. Fineman disagreed with this aspect of Dr. Bellanti's testimony asserting that even if Mrs. Murray had a cold, he did not believe that it could have acted as the infectious agent that damaged her retina and caused her AZOOR. He stated that the rhinovirus, the most common cause of the cold, "has never even been speculated to infect the retina." Tr. at 180. But, he conceded, that Dr. Gass found that a viral prodrome had preceded the onset of eye symptoms in ten of the fifty-one AZOOR patients he examined. See Tr. at 180; see also R's Ex. D at 7 (noting that ten patients had flu-like symptoms in

the days or weeks prior to the onset of AZOOR).

As additional support for the theory that Mrs. Murray experienced an autoimmune reaction after she received her third hepatitis B vaccination, Dr. Bellanti pointed to Mrs. Murray's recurrent facial rash after the vaccination of interest. Dr. Bellanti stated that in patients that have "an autoimmune disease, [together] with the heightened production of cytokines that are pro-inflammatory, [the appearance of a facial rash] could be an expression of the ongoing immunologic activation . . . . [The development of a rash] would fit as part of an ongoing hypersensitivity or an autoimmune attack." Tr. at 86.

Dr. Bellanti also pointed out that the onset of Mrs. Murray's earliest eye symptoms--specifically, the floaters and inflammation that prompted her visit to Dr. Benner in March of 1993--occurred three days after she received her third hepatitis B vaccination. Tr. at 83. The timing of the onset

> fits the . . . immunologic principle of recall. Once you are sensitized with two previous vaccines, the third vaccine initiates what's called the recall, or the anamnestic response . . . [which is the immune system's] ability to remember. And it not only remembers, but it remembers with a vengeance. So the third vaccine stimulates that whole compilation of T-cells that were sensitized prior to that with the first two vaccines, amplifies the response, and caus[es] the attack. And unfortunately, the eye is one of the organs that is known to be targeted with an autoimmune attack.

Id. (emphasis added).

The opinion offered on petitioner's behalf by Dr. Bellanti also found support in a letter of clarification, requested by the undersigned and addressed to petitioner's counsel, from Dr. Benner, petitioner's treating vitreoretinal specialist. In the letter, which was prepared after the hearing in this case, Dr. Benner expressed the opinion that Mrs. Murray's third hepatitis B vaccine triggered an autoimmune-mediated attack on her eyes. Dr. Benner stated that in his view, the third hepatitis B vaccination most likely caused Ms. Murray's AZOOR. The Federal Circuit has observed that 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.'" Capizzano v. Sec'y of Health and Human Servs, 440 F.3d 1317, 1326 (Fed. Cir. 2006). But such opinions are not necessarily dispositive of the issue of causation. Here, however, the opinion that Dr. Benner expressed in his later-provided letter (filed as P's Ex. 27) is of note because it is highly consistent with the views he first expressed during his treatment of Mrs. Murray shortly after she received the hepatitis B series.

In the letter of clarification, filed as Petitioner's Exhibit 27, Dr. Benner draws attention to the March 16, 1993 letter he wrote to Dr. Cockey, Mrs. Murray's internist, questioning whether there might be a causal association between the appearance of Mrs. Murray's symptoms of what seemed to be an intermediate uveitis and her receipt of the third Recombivax hepatitis B vaccine. See P's Ex. 27 at 4. Offering a later interpretation of his letter to Dr. Cockey, Dr. Benner stated that he had considered the possibility "that an immune-mediated reaction to the hepatitis B vaccine was a likely cause of [petitioner's] ocular problems" and that is why he included it in his "differential diagnosis." Id. Dr. Benner observed that "[a]s things progressed over the years and every other potential cause of her problems had been ruled out, [he] came to conclude that the vaccine [had] triggered an immune[-]mediated attack on her eyes." Id.

Respondent urges the undersigned to afford little weight to Dr. Benner's observations because "although Dr. Benner's records note a temporal relationship between Ms. Murray's symptoms and her third Hep B vaccination, at no time prior to April 21, 2008, did Dr. Benner express the opinion that the Hep B vaccination actually caused Ms. Murray's AZOOR." R's Post-Hearing Brief at 19. Although it is true that Dr. Benner had not stated explicitly in the medical records that Mrs. Murray's AZOOR was causally related to her receipt of the hepatitis B vaccination series, in both letters that he wrote to colleagues in the month following the vaccination of interest, Dr. Benner made clear that he considered the fact that Mrs. Murray received a third dose of the hepatitis B vaccination three days prior to the onset of her intermediate uveitis to have potential clinical relevance. See P's Ex. 7 at 49, 50. Moreover, on February 10, 2006, Dr. Benner noted in Mrs. Murray's medical records that "it [was] likely that all of her conditions, including her loss of sight, are related to the same underlying autoimmune condition." Pet. Ex. 7 at 48 (emphasis added).

Petitioner's expert Dr. Bellanti testified that, in his opinion as a board certified immunologist, the third hepatitis B vaccination Mrs. Murray received on February 24, 1993, more likely than not, caused her vision problems that were later diagnosed as AZOOR. Tr. at 84. Dr. Bellanti noted that he was also of the opinion that a causal link existed between the hepatitis B vaccination Mrs. Murray received on February 24, 1993, and her subsequent development of Addison's disease, and while his opinion about the causality between the vaccine and the Addison's disease was not as strong as the causal link between the vaccine and her development of AZOOR, it still reached the level of more likely than not. Tr. at 84.

It is of interest to the undersigned that the opinion offered by Dr. Bellanti--particularly that Mrs. Murray's AZOOR resulted from an autoimmune-mediated attack on

her eye--was supported as well by the strong belief held by Dr. Benner, a specialist trained to treat autoimmune diseases of the eye and the primary treating physician for Mrs. Murray's AZOOR.

In the view of the undersigned, petitioner's pre-existing autoimmune disease and the presentation of her symptoms following her third hepatitis B vaccination that led to the development of her AZOOR and the subsequent development of her Addison's disease provide circumstantial evidence in this case that Mrs. Murray more likely than not experienced an immune-mediated response to her third hepatitis B vaccination. Careful consideration of the factual circumstances here as well as of the two competing, but yet unproven, medical theories about the etiology of AZOOR, permit a finding that the received hepatitis B vaccination series was causally associated with the development of petitioner's polyglandular autoimmune disease, which included the development of her AZOOR. Because the sequence of cause and effect that petitioner has proposed is logical, petitioner satisfies the second prong of Althen.

3. The Temporal Relationship between the Vaccination and the Injury

Petitioner must show more than a proximate temporal relationship between the vaccination and the injury to satisfy the burden of showing actual causation. Althen, 418 F.3d at 1278; see also Grant v. Secretary of Health and Human Services, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Specifically, petitioner must demonstrate that the first symptoms of Mrs. Murray's AZOOR occurred in a time frame that would be consistent with an immune-mediated disorder caused by the vaccinations at issue.

Dr. Bellanti testified that:

> Ms. Murray . . . had two prior . . . hepatitis B [vaccinations], and she didn't sustain any response or injury following the first two, but . . . after the third one, the timing is right . . . . Three to four days is within the [time] period . . . [for the occurrence of a] booster or recall phenomenon of an immune response following a vaccine, [whe]ther beneficial, or [as] in this case detrimental.

Tr. at 105. Dr. Bellanti further testified that:

> the sequence of events that occurred I think fits immunologic principle[s] very perfectly. . . . [S]he received the third vaccine . . . [a]nd then within three to four days, the symptoms, the floaters, the progression of difficulty with vision,

> the ophthalmologic confirmation looking at the retina that's amply described in the records, progressed. And this [sequence of events] fits [with] the . . . immunologic principle of recall. Once . . . sensitized with two previous vaccines, the third vaccine initiates . . . the recall, or the anamnestic response…the ability to remember. And it not only remembers, but remembers with a vengeance. So the third vaccine stimulates that whole compilation of T-cells that were sensitized prior to that with the first two vaccines, amplifies the response, and caus[es] the attack. And unfortunately, the eye is one of the organs that is known to be targeted with an autoimmune attack.

Tr. at 83.

Dr. Bellanti expanded on his theory that Mrs. Murray's first hepatitis B vaccination sensitized her immune system throughout her body:

> It's in lymph nodes, spleen, and various parts of the body. And those T- and B-lymphocytes are ready to go. They're making presumably protective antibody against the hepatitis viral antigen.
>
> But they're also stimulating that other part of the immune system which is detrimental. May not be to . . the level that can cause overt disease, nor could the second [vaccination]. But the second [vaccination], given I think it was a month later, can now augment those cells.
>
> Comes the third one, then you get the big bang. You get enough replication of sensitized T-lymphocytes and their accompanying cytokines to now cause the target cell injury in the eye. And this is called a recall, or an anamnestic or booster response . . . [T]his is [a] solid immunologic principle.

Tr. at 106.

Respondent argued that Mrs. Murray failed to establish the requisite temporal relationship in this case because "petitioner presented no reliable evidence as to an accepted medical time-frame for AZOOR to develop following vaccination or any other environmental 'trigger.'" R's Post-Hearing Brief at 13. As Dr. Fineman argued in his initial expert report, "[t]he interval of time between the third hepatitis B vaccine injection and the development of [petitioner's] ocular symptoms is . . . longer than other cases reported in the ophthalmic literature." R's Ex. A at 12.

In support of Dr. Fineman's claim about the timing of the onset of petitioner's eye symptoms, respondent filed a case report cited by Dr. Fineman entitled "Multiple Evanescent White Dot Syndrome After Hepatitis B Vaccine," authored by Dr. Eduardo Baglivo.[47] As previously discussed in this ruling, AZOOR is believed to be "pathologically and etiologically related" to other eye syndromes, including MEWDS. See R's Ex. D at 13. In the reported case, the patient developed eye symptoms twenty-four hours after a second intramuscular booster injection of hepatitis B vaccine. See id. at 15-16. It is this case report that informed respondent's position that the time frame between Mrs. Murray's vaccinations and the presentation of her eye symptoms was not appropriate for finding a causal association.

The undersigned does not find respondent's argument to be a persuasive one. Although respondent has challenged petitioner's theory regarding the time period required for the development of AZOOR, respondent did not challenge Dr. Bellanti's testimony regarding the immunologic principle of recall. Nor did respondent challenge Dr. Bellanti's theory that petitioner had an anamnestic response in this case.

Because the undersigned has found that Mrs. Murray's first symptoms of her visual problem, which was characterized initially as intermediate uveitis, occurred on February 27, 1993, three days after petitioner's third hepatitis B vaccination, Mrs. Murray's symptoms fall within an appropriate time period for an "anamnestic" or "booster response" to have occurred, as proffered by Dr. Bellanti.

In the view of the undersigned, petitioner has met her evidentiary burden with respect to the temporal relationship between the third hepatitis B vaccine she received and the onset of symptoms in her eye, one of several of Mrs. Murray's organs that was targeted for an autoimmune-mediated attack. Petitioner has satisfied the third prong of Althen.

II. CONCLUSION

For the foregoing reasons, the undersigned finds that petitioner has established entitlement to Program compensation for her polyglandular autoimmune condition, that specifically includes the development of AZOOR and the later development of Addison's disease. The parties shall contact the undersigned's law clerk, Camille Collett, at (202) 357 - 6361 **on or before October 30, 2009**, to schedule a status conference to address the determination of damages.

---

[47] E. Baglivo et al., Multiple Evanescent White Dot Syndrome After Hepatitis B Vaccine, Am. J. Ophthalmol. 122 (Sep. 1996): 431-432.

IT IS SO ORDERED.

s/Patricia E. Campbell-Smith
Patricia E. Campbell-Smith
Special Master