IN THE UNITED STATES COURT OF FEDERAL CLAIMS
OFFICE OF SPECIAL MASTERS

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ELIZABETH SHAPIRO,	*	No. 99-552V
	*	Special Master Christian J. Moran
Petitioner,	*	
	*	
v.	*	Filed: January 10, 2012
	*	
SECRETARY OF HEALTH	*	Entitlement; hepatitis B
AND HUMAN SERVICES,	*	vaccine; thyroid condition;
	*	autoimmune disease; decision
Respondent.	*	after remand; medically
* *		appropriate interval

Clifford J. Shoemaker, Shoemaker and Associates, Vienna, VA., for petitioner; Lynn E. Ricciardella, United States Dep't of Justice, Washington, D.C., for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Elizabeth Shapiro alleged that a series of hepatitis B vaccinations caused her to develop two conditions, thyroid disease and systemic lupus erythematosus. On April 27, 2011, the undersigned found Ms. Shapiro was not entitled to compensation for either condition. Ms. Shapiro filed a motion for review. The

[1] Because this published decision contains a reasoned explanation for the special master's action in this case, the special master intends to post it on the United States Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002).

All decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When a decision is filed, a party has 14 days to identify and to move to delete such information before the document's disclosure. If the special master, upon review, agrees that the identified material fits within the categories listed above, the special master shall delete such material from public access. 42 U.S.C. § 300aa–12(d)(4); Vaccine Rule 18(b).

Court denied the motion for review with respect to SLE. However, the Court granted the motion for review on the thyroid claim. The Court vacated the April 27, 2011 decision and remanded to consider this claim in light of a different set of facts regarding when Ms. Shapiro's thyroid problem began.

After remand, Ms. Shapiro's claim is again denied, because Ms. Shapiro failed to meet her burden of proof regarding the Althen prongs. In particular, Ms. Shapiro has not established, by a preponderance of the evidence, a reliable medical theory causally connecting the hepatitis B vaccine to a thyroid disorder. Additionally, Ms. Shapiro has not established that the manifestation of her thyroid disorder occurred within a time that medical science would accept as supporting an inference that the hepatitis B vaccine caused her thyroid disorder. Finally, Ms. Shapiro has not presented a logical sequence of cause and effect showing, by a preponderance of the evidence, that the hepatitis B vaccine caused her thyroid disorder. Consequently, the Clerk's Office is instructed to enter judgment in accord with this decision unless another motion for review is filed.

I. Procedural History[2]

Ms. Shapiro filed her case in 1999. It came to a hearing on November 24, 2008, during which Ms. Shapiro's expert, Dr. Shoenfeld, testified. The secretary's expert, Dr. Ward, testified on January 8, 2009. After the hearing, the parties filed additional evidentiary materials, including supplemental reports from Dr. Shoenfeld (exhibit 114) and Dr. Ward (exhibit I). These supplemental reports provided each expert an opportunity to address the points and criticisms of their colleague with an opposing viewpoint. The parties also filed briefs.

On April 27, 2011, the undersigned issued a decision. For the thyroid claim, the undersigned found Dr. Ginsburg's statement that Ms. Shapiro had problems starting in October 1991 persuasive. This finding prevented Ms. Shapiro from establishing that hepatitis B caused the thyroid problem because the thyroid problem existed before Ms. Shapiro was vaccinated.

Ms. Shapiro filed a motion for review, arguing that the undersigned was arbitrary and capricious in finding fact. The Court agreed. The Court vacated the portion of the April 27, 2011 decision that denied compensation for the thyroid

[2] A more detailed recitation of this case's procedural history can be found in the undersigned's April 12, 2011 decision, 2011 WL 1897650, and the Court's October 31, 2011 opinion, 2011 WL 5543699.

condition and remanded for additional adjudication. The Court did not specifically find when Ms. Shapiro's thyroid problem began.

On remand, the parties were offered an opportunity to file additional materials. Both parties declined. In addition, the parties were encouraged to explore resolving the case. However, any efforts were not successful and the parties have requested a decision on the thyroid claim.

With an eye focused on the thyroid claim, the undersigned has again reviewed the record. This assessment shows that the parties developed the SLE claim more extensively than the thyroid claim, possibly because the SLE has affected Ms. Shapiro more significantly. Nonetheless, both parties have had an opportunity to present their cases and the record is adequate for making a decision.

II. Facts

Due to the dispute over when Ms. Shapiro's thyroid problem was manifest, factual findings must be made. The evaluation of the record is guided by the Court's discussion of those materials because the Court's opinion is binding. Hanlon v. Sec'y of Health & Human Servs., 40 Fed. Cl. 625, 630 (1998).

Ms. Shapiro maintains that she was "very healthy" prior to 1992. Tr. 14-15; tr. 133; exhibit 39 ¶ 4. The April 27, 2011 decision did not accept this testimony, and found, instead, that Ms. Shapiro had constipation, gained weight, and experienced prolonged menstrual periods starting in October 1991. Upon review, the Court held that this fact-finding was arbitrary and capricious because it was not based upon an adequate discussion of all materials.

For reasons explained in section IV.B. below, when Ms. Shapiro started having these problems is, ultimately, not material to the outcome of Ms. Shapiro's case. Consequently, the undersigned accepts that Ms. Shapiro did not have any problems associated with hypothyroidism (such as constipation, gaining weight, and prolonged menstrual periods) until after the April 13, 1992 hepatitis B vaccination.[3]

Ms. Shapiro received the first dose of the hepatitis B vaccine on April 13, 1992. Exhibit 39, exhibit 52, exhibit 86. On April 29, 1992, Ms. Shapiro saw her

[3] This conclusion is in accord with the Court's recitation of various medical records created between April 1992 and September 1994. See October 31, 2011 opinion, 2011 WL 5543699, at *1-2 and *9-10.

gynecologist, Dr. Sylvan Frieman. Although Dr. Frieman's records are difficult to read, it appears he recorded that Ms. Shapiro had abdominal bloating and weight gain. Exhibit 110 at 3; see also exhibit 1 at 1 (Dr. Frieman's letter from 2001). Ms. Shapiro testified that she saw Dr. Frieman for irritability, constipation, and a change in menses approximately two weeks after receiving her first hepatitis B vaccination.[4] Exhibit 39 ¶ 6; tr. 23-27.

Ms. Shapiro received the second dose of the hepatitis B vaccine on September 21, 1992. Exhibit 39 ¶ 7, exhibit 52, exhibit 86. Ms. Shapiro describes experiencing a worsening of symptoms, including palpitations, lightheadedness, serious fatigue, and a decreased ability to finish her sentences. Exhibit 39 ¶ 7; tr. 27. Ms. Shapiro's testimony is credited because she saw Dr. Richard Berg for these symptoms on October 19, 1992. Exhibit 51 at 2.

Dr. Berg reported that on October 14, 1992, Ms. Shapiro awakened with an intense headache and neck ache that worsened as the day progressed. She felt lightheaded and sweaty. Her heartbeat was rapid and irregular. Exhibit 51 at 2. Dr. Berg ordered a test of Ms. Shapiro's thyroid. Ms. Shapiro's thyroid stimulating hormone (TSH) was 66.67 micro IU/ML. A finding of 6.12 micro IU/ML or greater is consistent with hypothyroidism.[5] Exhibit 111 at 5. Because her result was more than ten times a normal level, Dr. Berg prescribed Synthroid at 100 micrograms. Exhibit 51 at 2. Synthroid is thyroid replacement therapy. Tr. 289.

About one month later, Ms. Shapiro saw Dr. Berg for a follow up visit. Her palpitations and lightheadedness were gone. Exhibit 51 at 2. Her menstrual period was improved. However, she still had some constipation. For this condition, Dr. Berg recommended more fiber. Id. Ms. Shapiro's thyroid was normal. Exhibit

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[4] Dr. Shoenfeld assumes that Ms. Shapiro experienced both constipation and palpitations after her first vaccination (Tr. 175); however, neither the medical records nor Ms. Shapiro's own testimony supports his assumption regarding palpitations. Ms. Shapiro reported in her affidavit and testified that she experienced palpitations after the second vaccination. Exhibit 39 at ¶ 7; tr. 27; see also exhibit 51 at 2 (Dr. Berg's November 19, 1992 report mentioning palpitations).

[5] Hypothyroidism occurs when there is a "deficiency of thyroid activity." Manifestations of this condition include a decrease in one's basal metabolic rate, fatigue, and lethargy. Dorland's Illustrated Medical Dictionary (32d ed. 2012) at 900.

111 at 16 (laboratory reports from Nov. 19, 1992). She did not return to Dr. Berg for several months.

On February 8, 1993, Ms. Shapiro received the third dose of the hepatitis B vaccine. Exhibit 39 (affidavit) ¶ 8, exhibit 52, exhibit 86. Ms. Shapiro reports that after the vaccination, she had "anorexia" and "severe weight loss." Exhibit 39 ¶ 8; tr. 35-36. However, Dr. Ginsberg's history recounts that Ms. Shapiro had been experiencing a "recurrent *increase* in weight" since about February of this year, which was the time she received her third vaccination. Exhibit 8 at 10. This conflict in the evidence is likely not significant. Ms. Shapiro testified that she had been gaining weight prior to taking the Synthroid medication. Tr. 35. This would support Dr. Ginsberg's assertion. And Ms. Shapiro's recollection of weight loss after the third vaccination is supported in Dr. Joyce Burd's history of the patient in July 1994. Dr. Burd notes that during the time that Ms. Shapiro's Synthroid medication was being adjusted, she lost approximately 23 pounds. Exhibit 6 at 25. Therefore, a preponderance of the evidence supports finding that Ms. Shapiro's weight fluctuated around the time of this third vaccination while her dosage of Synthroid was being adjusted.

Weight gain and weight loss are particularly useful when diagnosing a thyroid condition. Weight loss is indicative of hyperthyroidism, and weight gain suggests hypothyroidism. Dorland's at 889, 900. Ms. Shapiro reported weight gain after receiving her first and second vaccinations. Following this third vaccination, she reported weight loss (Tr. 35-36) and experienced weight fluctuations in response to changes in dosing of her thyroid medication. Tr. 288-89; see also exhibit 51at 3-4.

In March 1993, Ms. Shapiro returned to Dr. Berg with complaints of worsening symptoms, including palpitations, nausea that lasted all day, and abdominal pain. Exhibit 39 ¶ 8; tr. 37-38; exhibit 51 at 3. In response, Dr. Berg adjusted Ms. Shapiro's thyroid medication. Id.; exhibit 39 ¶ 9; see also exhibit 111 at 21 (various thyroid tests were within normal range) at 25 (showing thyroid stimulating hormone was at the low end of the normal range). Dr. Berg also referred Ms. Shapiro to Dr. Frieman. Exhibit 51 at 3.

In April 1993, Ms. Shapiro continued experiencing nausea and discomfort in her abdomen. Dr. Ginsberg could not identify a cause for these problems. Exhibit 8 at 10. A CT scan of her abdomen was normal. Exhibit 112 at 6. An upper endoscopy was performed, resulting in a diagnosis of gastritis, which is inflammation of the stomach. Exhibit 8 at 13-14; Dorland's at 757.

In April, May, June and July 1993, Ms. Shapiro saw Dr. Berg five times.[6] In response to various complaints including joint pain, Dr. Berg adjusted her thyroid medication. Exhibit 51 at 3-4; see also exhibit 109 at 3 (labs from March 30, 1993), exhibit 112 at 21 (labs from May 24, 1993).

Thyroid tests were again normal in July 1993. Exhibit 112 at 56. Based upon these results, Dr. Shoenfeld stated that Ms. Shapiro's "thyroid function was in the appropriate range because her oral thyroid medication was effectively tailored to her needs." Exhibit 114 (Dr. Shoenfeld's supplemental report) at 3.

Due to the medication's apparent control of Ms. Shapiro's thyroid problem in July 1993, the recitation of facts ends here. Most of Ms. Shapiro's subsequent medical history seems primarily related to her SLE, which is outside the scope of this remand. This history was summarized in the April 27, 2011 decision, 2011 WL 1897650, and the Court's October 31, 2011 opinion, 2011 WL 5543699. Consistent with the Court's October 31, 2011 opinion, this decision resolves Ms. Shapiro's claim that the hepatitis B vaccine caused her thyroid disorder.

III. Standards for Adjudication

Petitioners' burden of proof is a preponderance of the evidence. 42 U.S.C. § 300aa–13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958,

[6] Ms. Shapiro reported her symptoms after the vaccinations to the manufacturer of the vaccine and the Vaccine Adverse Event Reporting System (VAERS) in July 1993. She reported weight loss, lightheadedness, palpitations, weight on chest, fatigue, and nausea, among others. Exhibit 27 at 5. Problems such as weight gain and a difficulty finding her words were mentioned in an appendix to her July 1993 VAERS report. Exhibit 118 at 5; see also tr. 369.

961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty). In this regard, "close calls regarding causation are resolved in favor of injured claimants." Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1280 (Fed. Cir. 2005).

The Court's opinion directs the undersigned to consider whether Ms. Shapiro has fulfilled the Althen factors. Opinion, 2011 WL 5543699, at *10. Althen states that the petitioner's

> burden is to show by preponderant evidence that the vaccination brought about [the] 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 vaccination and injury.

Althen, 418 F.3d at 1278. These prongs are evaluated separately below, although the analysis does not follow the same sequence.

IV. Analysis

A. *Althen* Prong One – A Medical Theory Causally Connecting The Vaccination And The Injury

"[A] petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be legally probable, not medically or scientifically certain." Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1346 (Fed. Cir. 2010) (citation and quotation marks omitted). Ms. Shapiro's proof rested upon Dr. Shoenfeld's opinion and his articulation of four different theories. See Pet'r Br., filed April 7, 2010, at 24-26.[7] As noted in the previous adjudications, Dr. Shoenfeld has studied and written about immunology and vaccines extensively. See opinion, 2011 WL 5543699, at *3; decision, 2011 WL 1897650, at *2.

[7] Ms. Shapiro also filed a report from Dr. Bellanti, but did not call him to testify. Dr. Bellanti did not offer the opinion that the hepatitis B vaccination caused her autoimmune thyroid problem. Exhibit 28.

Despite Dr. Shoenfeld's impressive background, his opinion is not credited automatically. As the Court stated in its opinion, "'proof of causation entails more than having a well-qualified expert proclaim that the vaccination caused a disease.'" 2011 WL 5543699, at *12 n.15, quoting Doyle v. Sec'y of Health & Human Servs., 92 Fed. Cl. 1, 8 (2010). The evidence on which the special master bases a decision must be "reliable." Campbell v. Sec'y of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006). Campbell's discussion of reliability foreshadowed the Federal Circuit's discussion of reliability in Moberly. There, the Federal Circuit stated that "Finders of fact are entitled – indeed, expected – to make determinations as to the reliability of the evidence presented to them." 592 F.3d at 1326.

Dr. Shoenfeld's initial report presents four theories: (a) molecular mimicry, (b) bystander activation through an adjuvant, (c) superantigen / interferon alpha, and (d) polyclonal activation. Exhibit 53 at 10-13. This list appears generic, not necessarily tied to the hepatitis B vaccine and autoimmune thyroid disease. In his testimony, Dr. Shoenfeld explained:

> So all these mechanisms are in the air and you have to fit them to each one of the infecting agents, into each one of the vaccines and the ingredients which are around the vaccine, including the adjuvant.
>
> * * *
>
> I give just an example. I just wanted to show the variety of different mechanisms. I also proposed four different mechanisms, and I didn't say which one pertains for hepatitis B or other vaccine, but I just gave a plausible mechanism how it can cause.

Tr. 217-18. In another portion of his testimony, Dr. Shoenfeld commented:

> So there are at least four plausible mechanisms that biologist, autoimmunologists, rheumatologists, whoever deals with autoimmune disease will accept as a plausible mechanism. Not all of them were shown, not for all of them [do] we have evidence, but we have explanation. This is plausible how they can cause the autoimmune disease.

Tr. 195.[8] Each of the four theories is discussed below.

1. Molecular Mimicry

According to Dr. Shoenfeld, the most plausible mechanism for autoimmunity is molecular mimicry. This theory postulates that the molecular structure of the hepatitis B vaccine resembles the molecular structure of thyroid tissue. When the body responds to the vaccine, the body's immune system is misdirected at its own tissue. Tr. 190-91; see also Hennessey v. Sec'y of Health & Human Servs., 91 Fed. Cl. 126, 131 n.10 (2010) (discussing Dr. Shoenfeld's testimony that vaccines can cause type 1 diabetes via molecular mimicry).

Ms. Shapiro has not demonstrated the reliability of molecular mimicry as a basis for how the hepatitis B vaccine can cause an adverse reaction. As Dr. Ward explained, an editorial that Ms. Shapiro submitted and that Dr. Shoenfeld co-authored essentially refutes this theory. Tr. 271-72; tr. 380-81. This article states that the hepatitis B vaccine "genome is known but there is no obvious similarity with human proteins." Exhibit 72 (Carlo Selmi et al., "Vaccines in the 21st century: the genetic response and the innocent bystander," 4 Autoimmunity Reviews 79 (2005)) at 2. In reference to the hypothesis that the hepatitis B vaccine can cause autoimmune disease via molecular mimicry, Dr. Ward stated that this idea is having its "last gasp or dead." Tr. 272.

Neither Dr. Shoenfeld nor Ms. Shapiro had any effective response. In Dr. Shoenfeld's supplemental report in response to Dr. Ward's testimony, Dr. Shoenfeld quotes portions of Dr. Ward's testimony discussing the Selmi editorial. However, Dr. Shoenfeld does not offer any specific explanation of why Dr. Ward's opinion is incorrect. Exhibit 114 at 7. Dr. Shoenfeld merely stated that he expects a similarity between the hepatitis B vaccine and human tissue "will be described eventually." Tr. 190. A prediction about what will be found is not a basis for reliable testimony. Similarly, Ms. Shapiro's reply brief does not address Selmi. See Pet'r Reply at 10-11 (repeating the initial brief's discussion of molecular mimicry).

[8] In these passages and in other places in his testimony Dr. Shoenfeld describes the theories as "plausible." However, "plausibility" does not meet Ms. Shapiro's burden of proof. Moberly, 592 F.3d at 1322.

2. Bystander Activation through Adjuvant

The second theory asserted by Dr. Shoenfeld is based upon adjuvants. Adjuvants "increase the reaction of our body . . . to foreign particles." Tr. 191 (Dr. Shoenfeld); accord tr. 274 (Dr. Ward); Dorland's at 32. The adjuvant in the hepatitis B vaccine is a type or more than one type of aluminum salts, sometimes collectively known as alum. Aluminum salts have been used as adjuvants in many types of vaccines given to humans. Exhibit E, tab 1 (Erik B. Lindblad, "Aluminum compounds for use in vaccines," 82 Immunology and Cell Biology, 497 (2004)); tr. 259, 265, 274-75.

Dr. Shoenfeld expressed his adjuvant theory as a theory that explains how any autoimmune disease can be caused, not specifically an autoimmune thyroid disease. In Dr. Shoenfeld's initial report, he stated that adjuvants have "led to a more severe manifestation expressed as severe [central nervous system] and lung involvement of SLE as well as the multiple autoimmune diseases and manifestations." Exhibit 53 at 9. Likewise, Dr. Shoenfeld's testimony used adjuvants to explain how the hepatitis B vaccine "can induce autoimmunity, including SLE and especially SLE because SLE is a polyclonal disease. Everything is erupting. It's like a volcano." Dr. Shoenfeld's focus on SLE was apparent when he continued: in systemic autoimmune disease, "every system in our body from the brain to the joints, from the blood to the bone marrow, from the lung to the heart are involved in SLE because of this avalanche of all autoimmune reaction." Tr. 192.

While Dr. Shoenfeld discusses the adjuvant mechanism, he did not present any material that demonstrates the reliability of the theory that adjuvants cause autoimmune thyroid disease. See Exhibit 53 at 13. Similarly, Ms. Shapiro's post-hearing brief did not explain why the adjuvant theory is reliable. Pet'r Br. at 25.

Dr. Ward disagreed with the theory that adjuvants cause autoimmune disease. He estimated that the aluminum salts have been given to "many, many billions of individuals," tr. 275, and are safe. Dr. Ward's initial report cited to an article that supported his conclusion: "There is no evidence that aluminum adjuvants themselves should be immunogenic . . . accordingly they are not likely to cause harmful immune complex reactions and observations of contact hypersensitivity reactions are rare. The aluminum adjuvants are not in themselves pyrogenic and there is no evidence of carcinogenicity or teratogenicity attributed to their use." Exhibit E, tab 1 (Lindblad) at 502.

Dr. Ward's opinion that aluminum adjuvants do not cause autoimmune disease is more persuasive than Dr. Shoenfeld's opinion that they do.

3. Interferon Alpha

According to Dr. Shoenfeld, when a cell encounters a virus, the cell produces interferon alpha to prevent the virus from replicating. Tr. 193-94. Dr. Ward agrees with this definition of interferon alpha and emphasizes that interferon alpha is part of the immune system's response to living things that are trying to replicate. Tr. 277-80. The connection between interferon and living things is reflected in a medical dictionary's explanation of interferon: "Production of interferon can be stimulated by viral infection, especially by the presence of double-stranded RNA, by intracellular parasites . . . , by protozoa . . . , by bacteria. . . and bacterial products (endotoxins)." When this dictionary defines interferon alpha, it states that interferon alpha is "the major interferon produced by virus-induced leukocyte cultures." Dorland's at 948.

Dr. Shoenfeld opined that the hepatitis B vaccine can induce the production of interferon alpha, just as a virus induces the creation of interferon alpha. Tr. 194; tr. 218. To assess how Dr. Shoenfeld's opinion measured to the criteria announced in Daubert, see Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999), Dr. Shoenfeld was asked whether anyone has studied hepatitis B vaccine and interferon alpha. Dr. Shoenfeld replied that he was not aware of any studies. Tr. 218-19. The Secretary labels Dr. Shoenfeld's hypothesis as "purely speculative." Resp't Br. at 13.

Dr. Ward disagreed with extending interferon alpha from replicating virus to the hepatitis B vaccine. A primary difference between a virus and the hepatitis B vaccine is that the hepatitis B vaccine contains only a portion of the surface antigen, not the entire virus. Thus, the hepatitis B vaccine does not replicate. Tr. 259; exhibit I (Supp'l Rep't) at 6. For Dr. Ward, the lack of replication distinguishes a virus from the hepatitis B vaccine. Dr. Ward would not expect "a dead antigen, an inactive nonliving antigen, even a viral antigen, to induce the interferons because that's not what they were designed to respond to." Tr. 279. Dr. Ward further supports his opinion by citing three studies in which people who are infected with the hepatitis C virus, a disease that "elicits a strong type-I

interferon response," are safely administered the hepatitis B vaccine. Exhibit I at 9.[9]

Dr. Shoenfeld's reply to Dr. Ward's opinion that the hepatitis B vaccine does not induce the production of interferon alpha was unpersuasive. Dr. Shoenfeld did not cite any scientific studies. Instead, Dr. Shoenfeld discussed France's decision to suspend its hepatitis B vaccination program in 1998 without any discussion of whether this decision was related to autoimmune thyroid disease. Exhibit 114 (Supp'l Rep't) at 8.[10]

Here, Dr. Ward has given a specific reason for questioning the reliability of the theory that the hepatitis B vaccine stimulates the production of interferon alpha. Although Ms. Shapiro and Dr. Shoenfeld were given an opportunity to explain why a non-replicating substance like the hepatitis B vaccine induces the production of interferon alpha, they did not present any persuasive evidence. Thus, Ms. Shapiro has not met her burden of showing that it is more probable than not that the hepatitis B vaccine induces interferon alpha.[11]

4. Polyclonal Activation

The final theory mentioned by Dr. Shoenfeld's is polyclonal activation. Like the bystander activation theory, Dr. Shoenfeld discusses polyclonal activation in relation to SLE, not autoimmune thyroid disease. Tr. 195; see also Pet'r Br. at 27 (stating "With SLE, the [f]ourth mechanism that the Hepatitis B Vaccine can

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[9] Dr. Ward cites exhibit Q (Emmet B. Keeffe, "Hepatitis A and B Superimposed on Chronic Liver Disease: Vaccine-Preventable Diseases," 117 Transactions of the Amer. Clin. & Climatological Ass'n. 227 (2006)), exhibit V (Lawrence Pfeffer et al., "The Induction of Type I Interferon Production in Hepatitis C-Infected Patients," 29(5) J. of Interferon & Cytokine Res. 299 (2009)), and exhibit R (Erik Seth Kramer et al., "Response to Hepatitis A and B Vaccine Alone or in Combination in Patients with Chronic Hepatitis C Virus and Advanced Fibrosis," 54 Dig Dis Sci 2016 (2009)).

[10] One study has questioned whether this decision was beneficial. Exhibit M (F. Denis and D. Levy-Bruhl, "Mass Vaccination Against Hepatitis B: The French Example," 304 Current Topics in Microbiol & Immunol. 115 (2006)).

[11] Furthermore, even if the hepatitis B vaccine were found to lead to the production of interferon alpha, there was no evidence showing how the production of interferon alpha leads to an autoimmune thyroid disease.

cause the Petitioner's injuries is polyclonal activation."). In the context of SLE, Dr. Shoenfeld's testimony was extremely cursory, stating a vaccine "stimulates the immune system and again only in special persons, rare persons who . . . have the genetic background, and then you have the polyclonal activation, and this is the reason why in SLE you have so many autoantibodies." Tr. 195. Dr. Shoenfeld's report on polyclonal activation was similarly short. Exhibit 53 at 11.

Dr. Ward acknowledged that some substances, such as the Epstein-Barr virus and malaria, cause polyclonal activation. However, for the hepatitis B vaccine, Dr. Ward stated that "there's no evidence." Tr. 283-84.

Again, Dr. Shoenfeld did not fill this gap with some basis for finding that the hepatitis B vaccine induces polyclonal activation. In his supplemental report, Dr. Shoenfeld summarizes Dr. Ward's testimony regarding polyclonal activation but Dr. Shoenfeld fails to present any evidence that the hepatitis B vaccine is a polyclonal activator. Exhibit 114 at 9.

5. Summary Regarding *Althen* Prong One

Ms. Shapiro bears the burden of presenting evidence of "a medical theory causally connecting the [hepatitis B] vaccination and the injury." Althen, 418 F.3d at 1278. Ms. Shapiro's evidence must be "reliable." Vaccine Rule 8(b)(1); Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010) (discussing Vaccine Rule 8).

Here, Ms. Shapiro's case falls short of the preponderance of the evidence standard. Ms. Shapiro has presented four theories without any basis for finding the theories happened here. In addition, the countervailing evidence introduced by the Secretary raises considerable doubt about the likelihood of Dr. Shoenfeld's theories. Consequently, the record in this case does not support a finding that the hepatitis B vaccine can cause autoimmune thyroid disease.[12]

[12] The finding that none of the four theories offered by Dr. Shoenfeld are persuasive makes evaluating the epidemiological evidence offered by Dr. Ward unnecessary. It is worth noting, however, that although Dr. Ward cited to various studies measuring the incidence of SLE in the context of vaccinations, none of the articles evaluated autoimmune thyroid disease.

B. *Althen* Prong Three - Timing

Ms. Shapiro also must establish a "showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278. Although the timing prong is listed third in Althen, it is discussed second to facilitate an understanding of the difference between what is known about autoimmune thyroid disorders and what happened to Ms. Shapiro.

Appropriate onset has to be determined in light of how the particular disease begins. There must be "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). When reviewing the case with reference to SLE, the Court stated that the "petitioner was first required to establish the timeframe for which it is medically acceptable to infer causation, that is, the timeframe in which symptoms would be expected to arise if the SLE was caused by the vaccination. Then she was obliged to show that the onset of her SLE occurred during this period." Order, 2011 WL 5543699, at *11. The same approach to deciding prong 3 of Althen will be used here in reference to the thyroid claim.

1. How Autoimmune Thyroid Disease Begins

The etiology of an autoimmune thyroid disease appears to be months or years. Dr. Ward explained that autoimmune thyroid disease progresses slowly:

> More common, however, is that the autoimmune process begins slowly, autoantibodies are produced and there is a trickling damage to the thyroid gland. . . . like repeated pin pricks to the thyroid with the release of a little bit of thyroid hormone, but at no time does the person become acutely ill with evidence of excess thyroid hormone.
>
> And, again, the natural course of this type of thyroid disease, again, it's autoimmune, you get just a slow slippage into the hypothyroid state, which is often very difficult. For those of you who read the Kafka book Metamorphosis where somebody changes from a human being, a bedridden man changes from a human being into a cockroach, but in very, very slow incremental stages so

> that nobody recognizes that he's turned into a cockroach because you just changed so slowly.
>
> That's what happens in hypothyroidism in this latter case. You slowly become different. It happens so slowly that even your friends and relatives don't really notice until symptoms become intolerable.

Tr. 291-92. [13]

An exhibit in this case confirms Dr. Ward's explanation. "Autoimmune thyroiditis generally causes a slow failure of thyroid hormone production, thus symptoms may be insidious, developing over years." Exhibit E, tab E (Bijay Vaidya and Simon H S Pearce, "Management of hypothyroidism in adults," 337 British Medical Journal 284 (2008)).

When the thyroid initially is functioning poorly, the person may not display any symptoms. If there happens to be a laboratory study of the person's thyroid, the results will be out of the normal range. In such a case, the person suffers from "subclinical hypothyroidism." Exhibit 18, tab E (Vaidya and Pearce) at 284. "Subclinical" means "without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests." Dorland's at 1790.

Through Dr. Shoenfeld's supplemental report, Ms. Shapiro had an opportunity to address Dr. Ward's opinion about the onset of autoimmune thyroid disease. However, Dr. Shoenfeld was silent.

2. The Appropriate Temporal Relationship between Vaccination and Onset

As the Court stated, "the 'etiology' of the disorder determines the appropriate temporal relationship." Opinion, 2011 WL 5543699, at *11 (quoting Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 356, 2011 WL

[13] Dr. Ward recognized that a different type of thyroid disorder can have a rapid onset. In this disease, a large quantity of hormones is released very quickly, leading to a hyperthyroid state. Signs and symptoms of hyperthyroidism include neck swelling, discomfort, fevers, palpitations, and weight loss. Ms. Shapiro did not experience these symptoms until her dose of thyroid replacement therapy was increased in March 1993. Exhibit I at 3.

4888776, at *12 (Sept. 29, 2011) (quoting Bazan, 539 F.3d at 1352)). Ms. Shapiro presented relatively little evidence directly relevant to showing the expected medical interval between an administration of the hepatitis B vaccine and the onset of an autoimmune thyroid disorder. See Pet'r Br. at 19 (discussing only when Ms. Shapiro's symptoms began and not the time expected by medical science). Dr. Shoenfeld briefly touched upon this element when he stated that an onset of Ms. Shapiro's autoimmune thyroid disease, which was two to three weeks after the first dose of the hepatitis B vaccine, constituted a "classic" temporal relationship.[14] Tr. 198; accord tr. 206.

Dr. Ward disagreed with the assertion that the hepatitis B vaccine can cause autoimmune thyroid disease in only three weeks. To Dr. Ward, this proposed time course "just makes no sense." Tr. 292. Dr. Ward's supplemental report repeats his opinion regarding timing: "In order for the initial [hepatitis B] vaccination to have been 'causal' in the development of her autoimmune thyroiditis, Ms. Shapiro would have had to develop autoantibodies that destroyed her thyroid in the first two weeks after the 1st dose of [the hepatitis B vaccine]. This is simply not plausible." Exhibit I at 3.

Dr. Shoenfeld recognized that Dr. Ward stated that the proposed timing between the first dose of the hepatitis B vaccination and the onset of symptoms of an autoimmune thyroid disease "makes neither medical nor scientific sense." Exhibit 114 (Supp'l Rep't) at 9, citing tr. 296-97 (Dr. Ward's testimony). Dr. Shoenfeld, however, does not explain why his proposed timing (a two-week interval) makes sense.

Dr. Ward's testimony is persuasive. As discussed above, the medical community understands that autoimmune thyroid disorder develops very slowly. Thus, even if the hepatitis B vaccine could cause an autoimmune thyroid disorder, the expected amount of time would be measured in months or possibly years.

3. Onset of Ms. Shapiro's Autoimmune Thyroid Disease

As discussed in section II above, Ms. Shapiro's testimony that she gained weight, had menstrual irregularities, and had constipation by the end of April 1992 is credited. There appears to be no dispute that these symptoms are manifestations of an autoimmune thyroid disease.

[14] As discussed below, although Dr. Shoenfeld states that Ms. Shapiro's autoimmune thyroid disease began two to three weeks after her hepatitis B vaccination, Dr. Ward disputed this assertion.

Dr. Shoenfeld appears to assume that Ms. Shapiro's constipation by the end of April 1992, marked the beginning of her autoimmune thyroid disease. See Tr. 177-78. However, this analysis does not take into account the medical knowledge that the overt display of autoimmune thyroid disease occurs after months or years.

Dr. Ward considered what is known about the course of autoimmune thyroid disease in opining when Ms. Shapiro disease began. He stated: "Ms. Shapiro developed autoimmune thyroid disease around the time that she received her series of [hepatitis B] vaccines. Although the onset of hypothyroidism cannot be pinned down with certainty in retrospect, it seems very likely that she was becoming hypothyroid long before she received her first dose (possibly as early as October 1991)." Exhibit C at 10-11.

The information available shows that it is likely that Ms. Shapiro's weight gain, menstrual irregularities, and constipation in April 1992 were a consequence of a thyroid disease process that began months or years earlier. Whether Ms. Shapiro also experienced any of these problems in October 1991, is irrelevant. Even if it is assumed that Ms. Shapiro was accurate in stating that she first experienced these symptoms in April 1992, her disease still began before April 1992. [15]

[15] In the sense that Ms. Shapiro started to experience symptoms of her (long-standing but undetected) thyroid disease only after her vaccinations, her case is comparable to another case involving a disease with a subclinical presentation, autoimmune hepatitis. In that case, the undersigned found that the petitioner's autoimmune hepatitis must have begun before the hepatitis B vaccination even though it was discovered after the vaccination. Rotoli v. Sec'y of Health & Human Servs., No. 99-644V, 2008 WL 4483739, at *17-18 (Fed. Cl. Spec. Mstr. Sept. 11, 2008). On review, the Federal Circuit held that this analysis was not arbitrary and capricious. Porter v. Sec'y of Health & Human Servs., __ F. 3d. __, Nos. 2010-5162, 2010-5163, 2011 WL 5840315, at *11 (Fed. Cir. Nov. 22, 2011).

The Court of Federal Claims has used the arbitrary and capricious standard in reviewing other findings that when vaccinated, a petitioner was afflicted with a disease that was not manifest or recognized until after the vaccination. In each case, the Court ruled that the special master's finding was not arbitrary. See W.C. v. Sec'y of Health & Human Servs., 100 Fed. Cl. 440, 452-53 (2011) (multiple sclerosis); Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 725 (Crohn's disease), appeal docketed, No. 2011-5131 (Fed. Cir. Sept. 15, 2011); Hennessey, 91 Fed. Cl. at 140-41 (2010) (type 1 diabetes).

Ultimately, Ms. Shapiro bears the burden of presenting "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." Bazan, 539 F.3d at 1352. The etiology of autoimmune thyroid disease is such that a relatively long interval between vaccination and the onset of symptoms would be expected. However, Ms. Shapiro's manifestation of autoimmune thyroid disease occurred too quickly. Consequently, the evidence does not preponderate in favor of finding that Ms. Shapiro established the third prong of Althen.

C. *Althen* Prong Two – A Logical Sequence Of Cause And Effect Showing That The Vaccination Was The Reason For The Injury

Another element in a petitioner's case is to submit preponderant evidence establishing "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." As a matter of logic, this prong relates to the other prongs. See Capizzano, 440 F.3d 1317, 1327 (Fed. Cir. 2006) ("We see no reason why evidence used to satisfy one of the Althen III prongs cannot overlap to satisfy another prong."). If it is found that the vaccine "did cause" an injury, then the vaccine must be capable of causing the injury. Conversely, if there has not been a showing that the vaccine "can cause" an injury, then the vaccine cannot be said to have caused the injury for a specific petitioner. See Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 145 (2011), appeal docketed, No. 2011-5108 (Fed. Cir. July 13, 2011).

Under this prong, relevant evidence is evidence specific for the petitioner, as opposed to evidence about causation in general. Caves, 100 Fed. Cl. at 144. The types of evidence that may be probative on second prong include the statements of treating doctors and evidence of challenge-rechallenge. Capizzano, 440 F.3d at 1326.

Ms. Shapiro has not identified any treating doctor who stated that the hepatitis B vaccine caused her autoimmune thyroid disorder. See Pet'r Br., at 17-19 (discussion of second Althen prong in the context of thyroid disease).[16] Consequently, Ms. Shapiro is relying upon Dr. Shoenfeld's opinion.

[16] Ms. Shapiro's reply brief states "numerous treating doctors identified the vaccination series as significant." However, Ms. Shapiro identified only one doctor, Dr. Burd, by name. Pet'r Reply at 14. Dr. Burd and Ms. Shapiro co-authored a case report, describing Ms. Shapiro's experience after the hepatitis B

Dr. Shoenfeld opined that the hepatitis B vaccine caused Ms. Shapiro's autoimmune thyroid problem. One reason for Dr. Shoenfeld's opinion is that Ms. Shapiro did not develop her autoimmune thyroid problem when she was exposed to other potential causes, such as pregnancy or infections. Tr. 187. Another reason is that Ms. Shapiro's case is an instance of challenge-rechallenge. Tr. 198-200.

Challenge-rechallenge "occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine." Capizzano, 440 F.3d at 1322. Dr. Ward added that the challenge-rechallenge paradigm can assist in identifying a cause when there is not "any other potential cause." Tr. 295; tr. 369. For example, the challenge-rechallenge method was the basis for concluding that the hepatitis B vaccine can cause alopecia. Tr. 332-35; see also tr. 294-95. Challenge-rechallenge is simpler to analyze when the beginning of the disease is easily recognizable and is more difficult to use when the onset of the disease is hard to detect. Tr. 336. In the proper circumstances, challenge-rechallenge may be compelling evidence that a vaccine caused a particular petitioner's condition. E.g. Hall v. Sec'y of Health & Human Servs., No. 02 -1052, 2007 WL 3120284, at *7 (Fed. Cl. Spec. Mstr. Oct. 4, 2007); see also Porter, 2011 WL 5840315, at *10 (indicating that special master recognized the potential probative value of challenge-rechallenge).

Ms. Shapiro argues that her history demonstrates that her autoimmune thyroid disease worsened with each dose of the hepatitis B vaccine. Pet'r Br. at 17-19. The Secretary contends that Ms. Shapiro's course is typical for autoimmune thyroid disease (or the treatment of autoimmune thyroid disease). The Secretary maintains the hepatitis B vaccinations did not affect Ms. Shapiro's thyroid. Resp't Br. at 19-21.

Whether Ms. Shapiro's course of thyroid disease was an expected and normal course for thyroid disease was answered, to some degree, in the earlier adjudications. As part of evaluating Ms. Shapiro's claim that the hepatitis B vaccine caused her SLE, the undersigned found persuasive Dr. Ward's opinion that "all of Ms. Shapiro's symptoms prior to and immediately following her first and

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vaccine. Dr. Burd and Ms. Shapiro stated that they were reporting "an additional case of possible vaccine-associated SLE." Exhibit 30, tab 2 (Elizabeth Shapiro and Joyce Kopicky Burd, "Comment on the Article 'Can Immunization Precipitate Connective Tissue Disease? Report of 5 Cases of Systemic Lupus Erythematosus and Review of the Literature'" 30(3) Seminars in Arthritis and Rheumatism, 215 (2000)). As a report about SLE, Dr. Burd's article is not helpful in addressing autoimmune thyroid disease.

second doses of the hepatitis B vaccine are compatible with hypothyroidism." Decision, 2011 WL 1897650, at *15. When Ms. Shapiro filed her motion for review, she argued that some of these problems were manifestations of her SLE. However, the Court rejected this argument, stating the finding connecting Ms. Shapiro's health problems to her thyroid disorder was "supported by the record." Order, 2011 WL 5543699, at *12 n.15.

If Ms. Shapiro had met her burden of establishing that it is likely that the hepatitis B vaccine can cause autoimmune thyroid disorder and if she had met her burden of showing that her disease began in the time that medical science would recognize as an appropriate interval from which to infer causation, then Ms. Shapiro's challenge-rechallenge evidence could have been sufficient to establish the second prong of Althen. However, as explained above, these postulates are not present in this case. Ms. Shapiro's evidence does not establish a basis for finding that it is likely that the hepatitis B vaccine can cause autoimmune thyroid disease (section IV.A above). The evidence also supports a conclusion that the April 1992 symptoms of Ms. Shapiro's autoimmune thyroid disease were actually manifestations of a disease process that started much earlier (section IV. B above).

Given these two findings, it cannot be found that Ms. Shapiro has met her burden of providing "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Instead, the evidence supports a finding that the sequence of hepatitis B vaccinations only happened around the same time as (and was coincident to the time when) Ms. Shapiro started to manifest clinical symptoms of her autoimmune thyroid disease. Ms. Shapiro's challenge-rechallenge argument is not a persuasive reason for finding causation in this case because her clinical history is entirely consistent with a course of autoimmune thyroid disease, unaffected by vaccination.

V. Conclusion

The Court's opinion required a re-examination of Ms. Shapiro's claim that the hepatitis B vaccine caused her to develop an autoimmune thyroid disease. This claim has been analyzed through the Althen factors as stated by the Court. This evaluation shows that Ms. Shapiro has failed to meet her burden of proof for any of the three Althen prongs, especially the prongs relating to a medical theory and an appropriate temporal interval.

Consequently, Ms. Shapiro is not entitled to compensation. The Clerk's Office is instructed to enter judgment in accord with this opinion unless a motion

for review is filed and is instructed to provide a courtesy copy of this decision to the presiding judge. See Vaccine Rule 28.1(a).

IT IS SO ORDERED.

S/Christian J. Moran
Christian J. Moran
Special Master