In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 99-378V
November 19, 2007
To be Published

JOANNE GRIFFIN,	*	
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Petitioner,	*	
	*	
v.	*	Entitlement; scleroderma after third hepatitis B vaccination
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SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Anne C. Toale, Sarasota, FL, for petitioner.
Catherine E. Reeves, Washington, DC, for respondent.

MILLMAN, Special Master

RULING ON ENTITLEMENT[1]

Petitioner filed a petition on June 14, 1999 under the National Childhood Vaccine Injury Act, 42 U.S.C. §300aa-10 et seq., alleging that hepatitis B vaccine on June 10, 1991, July 23, 1991, and January 23, 1992 caused her an unspecified reaction, subsequently claimed to be

[1] Vaccine Rule 18(b) states that all decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision or designated substantive order is filed, petitioner has 14 days to identify and move to delete such information prior to the document's disclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall delete such material from public access.

diffuse or systemic scleroderma (SSc).[2] These vaccination dates are substantiated in her immunization record at Long Beach Memorial Hospital, where she was a registered nurse. Med. recs. at Ex. 11, pp. 33, 35.

However, her medical records show that she received hepatitis B vaccination on June 10, 1991, July 11, 1991, and November 12, 1991. Med. recs. at Ex. 3, p. 25.

Since the informed consent form and the signature page of the administering nurses reflect the July 23, 1991 and January 23, 1992 dates for the second and third hepatitis B vaccinations, respectively, the undersigned will accept that these were the dates of those vaccinations.

A hearing was held in New York on August 10, 2007. Testifying for petitioner were Maureen Fineman (her sister), Robert Griffin (her brother), petitioner, and Dr. Andrew White. Testifying for respondent was Dr. Carlos Rosé.

Petitioner filed a Post-Hearing brief on October 10, 2007. Respondent filed a Post-Hearing brief on November 8, 2007. Petitioner filed a Post-Hearing Reply Memorandum on November 15, 2007.

FACTS

Petitioner was born on February 25, 1960.

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[2] Systemic scleroderma is "a systemic disorder of the connective tissue characterized by hardening and thickening of the skin, abnormalities of both microvasculature (telangiectasias) and larger vessels (Raynaud's phenomenon), and fibrotic degenerative changes in body organs such as the heart, lungs, kidneys, and gastrointestinal tract. It may be confined to the face and hands for long periods or be progressive, spreading diffusely to become generalized." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1668.

On June 10, 1991, she received her first hepatitis B vaccination. Med. recs. at Ex. 3, p. 25.

On July 23, 1991, she received her second hepatitis B vaccination. Med. recs. at Ex. 11, pp. 33, 35.

On January 2, 1992, petitioner saw Dr. Meryl L. Solomon because she had had 103º fever for two days and had been on Erythromycin (333mg), Robitussin, and Tylenol for five days. Med. recs. at Ex. 8, p. 161. She still had a cough, congestion, and muscle aches. *Id.* Dr. Solomon prescribed Medrol Dosepak, a corticosteroid. Med. recs. at Ex. 13, p. 2.

On January 9, 1992, petitioner telephoned Dr. Solomon because she noticed she had edema. Med. recs. at Ex. 8, p. 159.

On January 23, 1992, petitioner received her third hepatitis B vaccination. Med. recs. at Ex. 11, pp. 33, 35.

On March 11, 1992, petitioner's anti-nuclear antibodies (ANA) were 1:320. Med. recs. at Ex. 3, p. 5.

On March 23, 1992, petitioner saw Dr. Solomon. (This visit is undated but petitioner testified that this was the date.) Petitioner complained of swollen and stiff joints in her hands, knees, and feet bilaterally. Med. recs. at Ex. 8, p. 158. Her ANA was positive at 1:320. *Id.*

On March 24, 1992, petitioner had an x-ray done of her hands. Med. recs. at Ex. 8, p. 134. Dr. Howard J. Gelber diagnosed slight periarticular demineralization. *Id.*

On March 26, 1992, petitioner saw Dr. Sheldon P. Blau, a rheumatologist, having been referred by Dr. Solomon. (The letter is dated April 2, 1992, but petitioner testified that it reflected her visit of March 26, 2002.) Med. recs. at Ex. 8, p. 131. Petitioner had pain and

swelling of her hands and toes for the prior four to six weeks. The illness began with a flu-like syndrome in January and then severe proximal muscle aches and pains in her thighs. The pain was so severe in her thighs that Dr. Solomon gave her a Medrol Dosepak, which resulted in slight improvement. Petitioner had an ANA of 1:320. Dr. Blau thought petitioner's history of sun sensitivity, polyarthritis, and positive ANA meant she had the residua of a viral illness. The second possibility was a connective tissue disease. *Id.*

On June 10, 1992, Dr. Alfred B. Brotman tested a skin specimen from petitioner which he diagnosed as indicative of scleroderma. Med. recs. at Ex. 3, p. 23.

On July 28, 1992, petitioner saw Dr. Harry Spiera. Med. recs. at Ex. 3, p. 1. She had been in good health until Christmastime 1991 when she had a flu-like illness associated with much muscle pain. She was treated with a Medrol Dosepak and felt much better. Shortly afterwards, she developed joint pain and stiffness and the pain worsened. She had blood tests done which revealed an ANA of 1:320. *Id.* She saw Dr. Sheldon Blau, a rheumatologist, and subsequently Dr. Pellman, another rheumatologist, who diagnosed scleroderma as her skin had gotten tight. She denied Raynaud's phenomenon.[3] *Id.* A skin biopsy done on June 10, 1992 was consistent with scleroderma. Her ANA was positive at 1:320 with a speckled pattern. Med. recs. at Ex. 3, p. 3. Her scleroderma seemed to be progressing moderately rapidly. *Id.*

(Dr. Pullman's medical records were unavailable.)

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[3] Raynaud's phenomenon is "intermittent bilateral ischemia of the fingers, toes, and sometimes ears and nose, with severe pallor and often paresthesias and pain, usually brought on by cold or emotional stimuli and relieved by heat; it is usually due to an underlying disease or anatomical abnormality." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1420.

From November 13 to 25, 1992, petitioner was hospitalized at South Nassau Communities Hospital with a discharge diagnosis of:

> malignant hypertension; grand mal seizures; scleroderma, severe and progressive; apneic episodes; metabolic acidosis; right moderate occipital infarct; right small basal ganglia infarct; left small parietal infarct; and acute respiratory distress.

Med. recs. at Ex. 8, p. 119.

On November 18, 1992, petitioner had a renal MRI to examine the health of her kidneys. P. Ex. 7, p. 127. The result was abnormal pertaining to the right kidney which had slightly reduced flow, less function, and was functionally smaller than the left kidney. P. Ex. 7, p. 128.

Other Submitted Material

On March 2, 2007, petitioner filed Ex. 30, "Recruitment of Topoisomerase I (Scl-70) to Nucleoplasmic Proteasomes in Response to Xenobiotics Suggests a Role for Altered Antigen Processing in Scleroderma" by M. Chen, et al., 52 *Arthritis & Rheumatism* 3:877-84 (2005). The authors state:

> Scleroderma, also known as systemic sclerosis (SSc), is a chronic autoimmune disease with clinically heterogeneous systemic manifestations affecting the connective tissue of the skin, the walls of blood vessels, and internal organs such as the lungs, heart, gastrointestinal tract, and kidneys. It is characterized by progressive thickening of the dermis, alteration of the microvasculature, disturbances of the immune system, and massive deposition of collagen and other matrix substances in the connective tissue, leading to a variety of symptoms that can be severely disabling. The prevalence of SSc is reported to be 30-120 per million persons in North America, Australia, and Europe, with new cases reported to be 2-20 per million persons per year.
>
> SSc can be considered a prototype disease for studying the influence of the environment on initiation of autoimmunity, because it is known that exposure to a variety of different environmental substances may lead to the development of disease

> that mimics the clinical and histopathologic features of idiopathic SSc. Moreover, several animal models, such as mice susceptible to xenobiotic-induced[4] autoimmunity and rats treated with mercuric chloride, have been used to investigate SSc. Some reports describe SSc-like diseases induced by chemical compounds.

Id. at 877.

The authors continue:

> [D]rugs such as DNA topo I inhibitors are also reported to induce human SSc.
>
> A unique feature of SSc is the production of autoantibodies against nuclear self proteins. Antinuclear antibodies (ANAs) to DNA topo I, centromeres, fibrillarin, and RNA polymerase I have been identified as disease-specific autoantibodies and diagnostic markers in SSc.... Individual patients with SSc rarely have more than one type of ANA detected in the serum; in other words, there is a restriction of heterogeneity of autoantibody types presented in each patient. Approximately 95% of patients with SSc have an identified ANA specificity, and each may mark a group of patients with distinctive clinical features, disease course, and overall severity. ...However, to date, the molecular mechanisms for such unique autoantibody responses remain unclear. ... Results from other studies and our previous investigations in cell culture and animal models have shown that xenobiotics, such as heavy metals, drugs, and viruses, recruit SSc autoantibodies for antigen processing via proteasomes. Based on these results, we propose the following hypothesis for the generation of systemic autoimmune responses. Xenobiotics alter nuclear structure, inhibit nuclear function, and, in turn, lead to the redistribution of nuclear autoantigens and their recruitment for proteasomal processing. The resulting peptides are subsequently presented on the cell surface to activate specific autoimmune responses.

Id. at 878.

On July 30, 2007, petitioner filed Ex. 53, "Raynaud's Phenomenon and Systemic Sclerosis," Textbook of Rheumatology, 5th ed. (1981) 1134. The authors state:

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[4] Xenobiotic means "a chemical foreign to a given biologic system." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 2069.

> The skin thickening of systemic sclerosis begins on the fingers and hands in nearly all cases.

Id.

On July 30, 2007, petitioner filed Ex. 54, "Classification of Systemic Sclerosis," Rheumatology, 2d ed. (1998) at 3. The authors state:

> Clinical experience suggests that scleroderma often follows a monophasic course with exacerbations being very uncommon. ... Often, the first clinical clue to suggest a diagnosis of scleroderma is skin thickening that usually starts as swelling or "puffy" fingers and hands.

Id.

On September 14, 2007, petitioner filed a translation of a French article she had previously filed as Ex. 36, "Localized Scleroderma After Vaccination Against Hepatitis B" by J.L. Schmutz, et al., 29 *Presse Medicale* 19:1046 (2000). The anecdotal report mentions two cases of recipients of hepatitis B vaccine who developed the limited skin form of scleroderma, the first one month post-vaccination, and the second three months post-vaccination. The authors posit the theory that the vaccination could have caused dysimmune disturbances in predisposed patients. They doubted vaccine causation in the first case but thought it plausible in the second. *Id.*

On March 27, 2007, respondent filed Ex. D, "Association of Microsatellite Markers Near the Fibrillin 1 Gene on Human Chromosome 15q with Scleroderma in a Native American Population" by F.K. Tan, et al., 41 *Arthritis & Rheumatism* 10:1729-37 (1998). The authors state:

> Scleroderma, or systemic sclerosis (SSc), is a multisystem connective tissue disease characterized by cutaneous and visceral fibrosis, Raynaud's phenomenon, and proliferative intimal lesions of the small arteries leading to an obliterative vasculopathy. The

> etiology of SSc is unknown; however, both genetic and environmental factors have been implicated.

Id. at 1729.

TESTIMONY

Maureen Fineman, petitioner's sister, testified first for petitioner. Tr. at 5. She is a registered nurse. Tr. at 7. Prior to 1992, petitioner was very healthy and athletic. Tr. at 8. Ms. Fineman visited petitioner during the Christmas holidays in 1991. *Id.* Petitioner had a cough, congestion, and a high fever, over 101.4.º *Id.* Perhaps her fever was 102.º Tr. at 9. It could have been 103.º *Id.* Ms. Fineman and petitioner talked once a week. Tr. at 12.

Ms. Fineman thought petitioner had returned to normal in January 1992. Tr. at 14. She realized petitioner was having a problem near petitioner's birthday, February 25th. *Id.* Petitioner complained of soreness, muscle pain, and joint pain. *Id.* Ms. Fineman thought it was due to her exercising for a few weeks. Tr. at 15.

Robert Griffin, petitioner's brother, testified next for petitioner. Tr. at 20. He shared a residence with his sister and remembers she had a cold during the Christmas holidays of 1991. Tr. at 21. She was coughing and had a runny nose. Tr. at 21-22.

Petitioner next testified. Tr. at 27. She was physically active prior to Christmas of 1991. Tr. at 28. She had an upper respiratory infection at Christmastime. Tr. at 29. She had a productive cough, chest congestion, muscle aches, fever, a sore throat, and a runny nose. *Id.* The symptoms began December 23, 1991. *Id.* Her temperature rose to 103.º *Id.* She self-treated with Robitussin cough medicine, Tylenol, and Erythromycin. *Id.* Petitioner was a recovery room nurse at the time. Tr. at 30. She worked with Dr. Solomon at the hospital. Tr. at 31. Because

she still had a cough, chest congestion, and some fever, she went to the doctor. Her joints did not ache. Tr. at 32.

Petitioner saw Dr. Solomon on January 2, 1992. Tr. at 33. Dr. Solomon diagnosed petitioner with an upper respiratory infection. *Id.* Dr. Solomon prescribed Medrol Dosepak. *Id.* Petitioner took it from five to seven days and her symptoms disappeared completely. Tr. at 34. She telephoned Dr. Solomon on January 9, 1992 because she had some swelling in her ankles. *Id.* Dr. Solomon returned her call and told her that the ankle swelling was slight fluid retention related to the Medrol Dosepak and, as she tapered off the medication, the swelling would go away. But just to be safe, petitioner should have a complete blood count (CBC) and an SMA8 drawn. Tr. at 35. The results were normal. *Id.* The SMA8 is a metabolic test. Tr. at 36. All petitioner's other symptoms had resolved at that point. *Id.*

Petitioner next saw Dr. Solomon on March 23, 1992. Tr. at 37. Petitioner noticed she was stiff and had some joint pain in her fingers and toes around the beginning of February 1992. *Id.* She had not had joint pain in her fingers and toes before that time. *Id.* She had lab work done on March 11, 1992 because she was concerned that her joint pain and stiffness were due to Lyme's disease. Tr. at 37-38. The Lyme's test came back negative, but an antinuclear antibody (ANA) test came back elevated. Tr. at 38. She had been having symptoms for about a month. *Id.* She remembers telling her family on her birthday February 25th that she had stopped exercising. Tr. at 39. She received hepatitis B vaccine on January 23, 1992. Tr. at 40. She felt well at the time of the vaccination. *Id.*

Petitioner saw Dr. Solomon on March 23rd after she got the lab results. *Id.* Dr. Solomon ordered hand x-rays on that day and wrote "elevated ANA" and complaining of swollen, stiff

joints on hands, knees, feet bilaterally for one month. Tr. at 42. The hand x-rays were done on March 24, 1992. *Id.* The one-month history would mean that onset of her swollen and stiff fingers was February 19, 1992. Tr. at 43. When the undersigned asked petitioner to clarify whether onset was the beginning of February 1992, as she had earlier testified, or February 19, 1992, as she now testified, petitioner said that, at the beginning of February, she felt stiffness which she thought was due to exercise. The joint pain in her fingers and toes did not begin until later in February. Tr. at 44. The early February stiffness was muscles, not joints. *Id.* Her prior stiffness in December 1991 and January 1992 was more of an achiness. *Id.* Petitioner denied telling Dr. Blau on April 2, 1992 that she had pains in her thighs when she saw Dr. Solomon on January 2, 1992. Tr. at 45-46. Petitioner's muscles felt tight in early February 1992. Tr. at 46. But at the end of December 1991 and beginning of January 1992, her muscles felt achy. Tr. at 46-47.

Petitioner had not previously had swollen or stiff joints prior to February 19, 1992. Tr. at 47. On March 23, 1992, Dr. Solomon discussed with petitioner that her hand stiffness might be the beginning of rheumatoid arthritis. *Id.* Her rheumatoid factor test came back negative, but Dr. Solomon said that, sometimes, people do not become rheumatoid positive for a while or even at all. A hand x-ray might show some joint destruction, which would be another indicator of rheumatoid arthritis. Tr. at 47-48. Petitioner has had sun sensitivity her whole life. Tr. at 48-49.

The ankle edema petitioner complained about to Dr. Solomon on January 9, 1992 resolved quickly within three to four days. Tr. at 49. She did not have edema in her hands at that time. *Id.* Petitioner saw Dr. Blau on March 26, 1992. Tr. at 50. Dr. Blau thought she had some type of autoimmune disease, but he could not classify it at the time. He thought she was at too

early a stage. *Id.* At that time, she did not have any skin involvement which would lead to a diagnosis of scleroderma. Tr. at 51. Dr. Blau found petitioner had tenderness of her wrists, fingers, and toes. Tr. at 52.

Petitioner developed skin tightening first in her ankles, hands, and wrists which she first noticed at the end of May on vacation. She thought she had a bad sunburn. Tr. at 53. Petitioner saw Dr. Pellman on June 6, 1992, but we do not have the notes for this visit. Tr. at 54. He said he thought she had scleroderma and asked her how long her hands had been that way. She answered that they had been that way for a week or two. *Id.* She had a skin biopsy done on June 10, 1992 to confirm the diagnosis. Tr. at 55. She saw Dr. Spiera, a top scleroderma expert in the country, on July 28, 1992. *Id.*

Dr. Andrew White, a pediatric rheumatologist, testified next for petitioner. Tr. at 67. He said there are very few disease differences between adult scleroderma and pediatric scleroderma. Tr. at 68. His opinion is that petitioner's illness in December 1991 was likely the flu, characterized by high fever, aches, and pains. Petitioner recovered completely from it. Tr. at 69. Petitioner received hepatitis B vaccine at the end of January 1992 and, weeks later, she had the early symptoms of scleroderma: swelling, puffy, and painful hands and other aches and pains. *Id.*

Dr. White testified that scleroderma has an insidious onset. Tr. at 70. The symptoms usually begin with puffy, red, tender, achy, sore, and then swollen hands. Tr. at 70-71. As the puffiness gets better, the skin on the hands tends to shrink and get tighter. Tr. at 71. Some of the symptoms petitioner had in December 1991 such as aches and feeling bad could be consistent with scleroderma but not the high fever, runny nose, or sore throat. *Id.* Dr. White thought that because she recovered, she did not have the onset of her scleroderma in December or January.

Tr. at 74-75. He thinks the onset of petitioner's scleroderma was mid-February, about four weeks after hepatitis B vaccination. Tr. at 76.

Even though petitioner did not have any symptoms soon after the hepatitis B vaccination, Dr. White was comfortable with his opinion of causation because the immune system takes some time to get revved up. Tr. at 78. Allergic reactions, such as hives and itching, begin right away. But an autoimmune disease reaction takes several weeks. One would check to see if there were an antibody response a month after vaccination. *Id.*

No one really knows the mechanism of scleroderma or any autoimmune disease but medical literature suggests antibodies intended to be developed against the vaccine may be faulty or cause an autoimmune disease like scleroderma, rheumatoid arthritis, or multiple sclerosis. Tr. at 78-79. One of the hallmark signs of scleroderma is scarring of the hands. Tr. at 83. Too much scar tissue in the skin causes tightening and limitation of the joints in the hands. Tr. at 83-84. The immune system initiates a cascade of events that leads to damage and scarring. Tr. at 84. If the body makes an antibody against fibrillin, a piece of connective tissue present in the blood vessels, and attacks it, one would have inflammation, swelling, redness, pain, and warmth, the classic signs of inflammation. When one destroys the fibrillin, the body develops scars. Tr. at 83. The antifibrillin antibody is an example of one of the potential types of autoantibodies that may lead to scleroderma. Tr. at 85. He is not sure which specific antibody is aberrant immunologically in petitioner's case. *Id.*

The development of an autoimmune disease like scleroderma may have an underlying genetic cause. Tr. at 88. The individual may develop the disease spontaneously or after an event such as mycoplasma pneumonii, cytomegalovirus, ingestion of toxic oil, graft versus host

disease, organ transplants, or hepatitis B vaccination. *Id.* Doctors do not generally think that scleroderma is a genetic disease. *Id.* Because he considers scleroderma a reactive disease (unless it occurs spontaneously) and the only environmental challenge here to petitioner was hepatitis B vaccine, Dr. White believes petitioner's scleroderma is a reaction to hepatitis B vaccine. Tr. at 90. If petitioner had not had the vaccination, Dr. White would then believe that the onset of petitioner's scleroderma was spontaneous. Tr. at 90-91.

Molecular mimicry is a reasonable theory for how autoimmune diseases develop. Tr. at 91. There are other potential mechanisms as well because mimicry implies an antibody-mediated phenomenon, and the immune system is more complex than that. *Id.* One could have a cellular component as well where cells attack a specific organ and damage it. Tr. at 91-92.

Scleroderma is a very rare disease. Tr. at 93. Petitioner has diffuse systemic scleroderma or systemic sclerosis. Tr. at 95. In the literature, cytomegalovirus has been thought to be a trigger in scleroderma. *Id.* These were molecular mimicry studies. Tr. at 96. Hepatitis B virus is similar to cytomegalovirus–not the same family, but cousins. *Id.* An antibody can recognize a very small portion of a molecule called an epitope, which is two or three pieces of the molecule. *Id.* Hepatitis B vaccine is made from surface antigen which is a piece of the antigen, probably 500 amino acids long. Tr. at 97. The immune response can take a while to develop, anywhere from a couple of weeks to several weeks. Tr. at 99. It is well known that the onset of scleroderma is difficult to determine because it is vague. *Id.*

Dr. White found petitioner's description of aches in early February hard to sort out when her joint pain onset was not until February 19th or 23rd. Tr. at 100. Petitioner then testified in answer to Dr. White's question that in February, she had muscle discomfort like tightness

someone might have after working out. *Id.* Her muscle aches were in her legs, hands, and feet. Tr. at 101. The muscle aches never went away and got progressively worse, turning into inflammation, then an incredible burning feeling so that she could not sleep at night, and then she also had itching. *Id.* The burning and itching came at the end of May, beginning of June. *Id.*

Dr. White said that scleroderma is a slowly progressive disease. Tr. at 103. Petitioner's hand stiffness in mid-February sounds like scleroderma to him. *Id.* Hepatitis B vaccine delivers hepatitis B surface antigen component. Tr. at 104. Petitioner's immune system mounted an immune response against it by making an antibody against it. *Id.* In autoimmune diseases such as scleroderma, the antibody, while attacking hepatitis B surface antigen, mistakenly attacks part of petitioner's body, either fibrillin or some other component such as topoisomerase, and damages her tissues, blood vessels, the skin of her hands, and her organs, leading to scarring and development of the disease. Tr. at 104-05. He regards the continuation of the disease process as related to continued problems in the immune system. Memory cells remain. Tr. at 106. The immune system perpetuates the disease. Tr. at 107.

Dr. White admitted on cross-examination that it is unusual for someone taking Medrol Dosepaks to develop edema, but it is a recognized complication. Tr. at 108. Edema would probably be more likely in someone taking steroids for a long period of time, but it is possible after five days of taking steroids. *Id.* Scleroderma may occur in someone's ankles. Tr. at 109. Petitioner did later have swollen joints in her feet. Tr. at 109. Scleroderma would not have waxing and waning phases. Once it starts, it is there. Tr. at 110. If petitioner had had any symptoms of scleroderma between January and February, Dr. White would have expected her to return to the doctor. He does not think that December was the beginning of petitioner's

scleroderma. *Id.* Dr. White admitted that none of the medical literature he discussed referenced a homology between hepatitis B surface antigen and human cells. Tr. at 115. Homology would be required for absolute proof of molecular mimicry. *Id.* His theory is based on probability not certainty. Tr. at 120.

Dr. Carlos D. Rosé testified for respondent. Tr. at 122. He is board-certified in pediatric rheumatology and pediatrics. Tr. at 124. He believes that hepatitis B vaccine is irrelevant to petitioner's scleroderma which she may have had before she received her third vaccination in January 1992. Tr. at 126. The discontinuation of petitioner's Medrol could have unmasked an ongoing swelling of the feet or ankles. Tr. at 126-27. Petitioner's infection during Christmas 1991 in which she had a high fever is a much more intense potential trigger of scleroderma than a surface antigen given a month later. Tr. at 127. No one can say exactly when petitioner's scleroderma began. *Id.* He would be suspicious of petitioner's transient swelling of her ankles after she discontinued Medrol. *Id.* Joint pain is an early manifestation of scleroderma as is edema. Tr. at 128.

The nature of scleroderma after onset is progressive and relentless. *Id.* It is a monophasic disease. *Id.* The edema of localized scleroderma improves significantly with corticosteroids. Tr. at 129. The undersigned asked how petitioner could have felt well the rest of January until February if petitioner's scleroderma began in early January, since scleroderma does not wax and wane. Dr. Rosé replied that he questions any history given of events going so many years back. Tr. at 130. The early phase of the disease could last weeks or months and could be waxing and waning as well as steroid-responsive. *Id.* The undersigned reminded Dr. Rosé that petitioner's contemporaneous medical records put onset in either mid-February or early March. Petitioner

did not give a history of feeling bad in January and early February to these medical treaters. *Id.* Dr. Rosé said that some symptoms could be ignored or so mild that petitioner did not pay attention. Tr. at 131. In addition, the Medrol dosepack could have had significant effect on how petitioner felt for the next month. *Id.* Dr. Rosé thought that feet swelling was a very unlikely side effect of Medrol. Tr. at 132. Petitioner's early scleroderma could have been postponed or diminished sufficiently for a few weeks before the scleroderma appeared, but the swelling of the feet was there. *Id.*

Dr. Rosé could not answer how long the ameliorative effect of Medrol would have lasted after petitioner stopped taking it on January 9, 1992. *Id.* He said the ameliorative effect was biologically possible and he had seen it in other patients. Doctors do not prescribe Prednisone in systemic scleroderma and he has no literature upon which to base an answer. *Id.* He agreed with Dr. White that corticosteroids are not prescribed for diffuse systemic scleroderma because after taking them, a patient could have renal failure. Tr. at 132-33. Even when petitioner saw Dr. Blau in March, petitioner had palmar erythema which is a sign of steroid use, causing Dr. Rosé to think petitioner had taken other Medrol. But he realized that she did not take other Medrol and thought the duration of the steroid effect strange. Tr. at 133-34. Palmar erythema is redness of the thumbs. Tr. at 134. Most erythema in the hands of scleroderma patients is in the dorsum (the upper part or back of the hand), not in the palms. *Id.*

The undersigned asked Dr. White if he agreed that petitioner's palmar erythema during her visit to Dr. Blau on March 26, 1992 was due to her steroid use in early January 1992. Tr. at 135. Dr. White responded that he thought palmar erythema three months after steroid use was an unlikely result of that use. *Id.* Dr. Rosé thought his own statement was "a bit of a stretch." Tr.

at 136. He said he was trying to illustrate that steroid sensitivity is valuable and he thought petitioner could have taken Medrol at times between the time she took it in early January 1992 and when she saw Dr. Blau in March 1992. *Id.* He admitted that we do not know that petitioner took more Medrol. *Id.* Respondent's counsel then stated that she had asked petitioner if she had taken more Medrol and she said she had not. *Id.*

Dr. Rosé said that whether molecular mimicry was a reliable scientific explanation for how hepatitis B vaccine could cause scleroderma was a very open question. *Id.* He thinks molecular mimicry may be a viable explanation for many rheumatic diseases. Tr. at 137. But no one has demonstrated cross-reactivity, i.e., mimicry, between hepatitis B surface antigen and the important cells involved in scleroderma because no one has looked at them. *Id.* In scleroderma, endothelial cells die and fibroblasts proliferate. Tr. at 140. Molecular mimicry is alive as a theory for autoimmune diseases. Tr. at 142. But scientists have not unquestionably demonstrated it over 50 years. *Id.* The mimicry is between human tissue and foreign products. Tr. at 144. Homology is not enough. One also has to show cross-reactivity. Tr. at 146-47.

For Dr. Rosé to be convinced that a vaccine can produce a disease, he would like two criteria to be fulfilled: (1) that the wild infection for which someone is vaccinated can clinically present the disease at issue, and (2) that there are some areas of homology between one portion of the antigen at issue and one cell or receptor involved in the disease at issue. Tr. at 148-49. Hepatitis B virus can cause hepatitis, transient reactive arthritis, glomerular nephritis in the kidneys, and cutaneous manifestations, but these have nothing to do with scleroderma. Tr. at 148. Dr. Rosé agreed that diffuse systemic scleroderma is a very rare disease. Tr. at 149-50.

Petitioner's exhibit 48, "Molecular Mimicry and Autoimmunity" by Blank, Barzilai, and Schoenfeld, came up in the discussion. Tr. at 153. Dr. Rosé noted that it was published in 2007 but does not mention molecular mimicry and scleroderma. Tr. at 154. The undersigned asked Dr. White if that omission from the paper on page 3, Table 1, concerned him. *Id.* He said it did not. He said his purpose in providing articles like this was to show that mimicry was still a plausible biologic mechanism for the development of autoimmune disease. The reason that scleroderma is not listed is that there is not a lot of evidence to provide an exact homologous region to prove mimicry. *Id.*

On cross-examination, Dr. Rosé stated that the withdrawal of petitioner's Medrol was the trigger for petitioner's visible edema on January 9th. Tr. at 155-56. Equally possible is that January 9th was the onset of petitioner's scleroderma. *Id.* In the hypothetical petitioner's counsel gave Dr. Rosé, petitioner had onset of ankle edema on January 9th and then a period of wellness until February 23rd, which is 45 days. On February 23rd, petitioner has swollen and stiff joints in her hands and fingers. Petitioner's counsel asked if that scenario was consistent with scleroderma. Tr. at 156-68. Dr. Rosé said that he takes patients' histories with a grain of salt and puts plus or minus four or five days for any piece of information. Tr. at 158. His answer to petitioner's counsel's question was that her scenario was entirely possible because patients' data are not reliable. Tr. at 159. It is very had to pinpoint the onset of scleroderma retrospectively. *Id.* He thinks before the edematous phase in scleroderma, there could be waxing and waning over a short period of time whose length he could not quantify. Tr. at 160. He agreed that systemic scleroderma was a monophasic disease for the most part once someone is in the sclerotic, rather than the edematous, phase. Tr. at 161.

Dr. White agreed that there was an edematous phase and a sclerotic phase in systemic scleroderma. *Id.* He said scleroderma starts with puffiness (edema) usually in the hands which are red. That lasts for weeks to months. It is hard to pin down a specific time. As that gets better, the scarring occurs so the disease enters its sclerotic phase without generally a break between the two phases. It is a relentless, progressive process that goes on for years. *Id.* The edematous phase is usually a single cycle. Tr. at 162. The edema wanes as the disease becomes sclerotic. *Id.* The symptomatology continues in a different form: as one symptom goes away, another takes its place. *Id.* Dr. Rosé agreed totally with Dr. White's testimony about the nature of systemic scleroderma. *Id.*

It did not bother Dr. Rosé that petitioner's edema was in her ankles and not in her hands on January 9th. Tr. at 163. His reason is that, many times, patients do not notice things, particularly when they are sick, and also edema can be present in unexpected locations such as the upper arms and the trunk. (The article to which he referred, P. Ex. 53, p. 4, second paragraph, did not mention ankles as a location.) Tr. at 164, 165. The undersigned asked Dr. Rosé if a patient says that her ankles (but not her hands) bother her because they are swollen was that the same as saying that systemic scleroderma can appear in places other than the hands. Dr. Rosé responded that the patient might not notice the swelling of her hands until she sees a doctor. Tr. at 165-66. He would not rule out onset of systemic scleroderma solely in the feet. Tr. at 167.

Dr. White said that it is possible that systemic scleroderma could start in the ankles but it is more likely to involve the hands and some other parts of the body. Tr. at 169-70. Dr. Rosé admitted that he was speculating when he said that petitioner also had swelling in her hands but she did not realize it when she said she had swelling in her ankles. Tr. at 170. He admitted that

it was hard to know how petitioner could return to her job as a nurse if she could not use her hands. *Id.* He favored the infection petitioner had during Christmas 1991 as the cause of her systemic scleroderma rather than the hepatitis B vaccination. Tr. at 171. Her cough, runny nose, and achiness were not symptoms of scleroderma. Tr. at 172. There is a lot of literature relating infections to scleroderma and no literature relating hepatitis B vaccine to scleroderma. *Id.*

Molecular mimicry is not the only way that an infection can produce a rheumatic disease. Tr. at 173. More and more research is being done on genetic causes of rheumatic diseases. Tr. at 175. We do not know the mechanism of scleroderma. *Id.* An immune response may take a long time–three or four weeks. But we do not know if an immune response is important in scleroderma. It could be a primary proliferative disease of the fibroblast. Tr. at 176. That means the fibroblast continues to proliferate because of a message to duplicate without any inflammation being the primary phenomenon. Perhaps the inflammatory cells are trying to get the fibroblasts out. *Id.* A fibroblast is a cell producing scarring after the edematous phase. *Id.* Scientists are studying mast cells and endothelial cells that line the blood vessels. Tr. at 177. Systemic scleroderma is a vascular disease. *Id.* The blood vessels are distorted in their architecture but not inflamed. *Id.* Mast cells are part of the response of one's immune system to something. Tr. at 180.

There is emerging literature, including a discussion of rheumatoid arthritis, stating that the inflammatory component of the disease is not primary, but the joint cells called synovial cells have tumor-like features. *Id.* What we may be seeing is inflammatory cells attempting to turn down the primary proliferating cells. Tr. at 181. Transforming growth factor is an important

mediator of scleroderma because it can activate fibroblasts into proliferating and releasing collagen. *Id.*

Dr. White commented that mast cells are part of the immune system as sentinels. They live in the skin. Tr. at 183. They have components which enable them to turn on fibroblasts and allow them to proliferate and make too much collagen, which is what is wrong with the hands and organs of someone with scleroderma. *Id.* Blood vessels are involved. People use the term vasculopathy, meaning something pathologically wrong with the blood vessels. *Id.* The endothelial cells are part of the immune system and can release chemicals and components to influence other cells like fibroblasts. Tr. at 184. Transforming growth factor is involved in the growth of blood vessels. Tr. at 185.

Dr. Rosé mentioned earlier in his testimony that if hepatitis B wild virus could cause systemic scleroderma, he would feel more comfortable relating hepatitis B vaccine to systemic slceroderma. The undersigned asked him if the causal relationship of hepatitis B wild virus to polyarteritis nodosa was any help. Tr. at 186. He admitted that hepatitis B wild virus was related to polyarteritis nodosa, which is a vasculitis. Tr. at 187. But since slceroderma is not a vasculitis, it has nothing to do with polyarteritis nodosa. *Id.*

Petitioner's counsel asked Dr. Rosé if his opinion was that petitioner's onset of systemic scleroderma was January 9th. Dr. Rosé said yes. Tr. at 188. In Dr. Blau's examination of petitioner on March 26th, he describes petitioner's hands, fingers, and toes, but says nothing about her ankles. *Id.* When the edema ends, the disease is not waning but manifesting another facet, i.e., the skin involvement. Tr. at 191.

DISCUSSION

To satisfy her burden of proving causation in fact, petitioner must offer by preponderant evidence "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen v. Secretary of HHS, 418 F. 3d 1274, 1278 (Fed. Cir. 2005). In Althen, the Federal Circuit quoted its opinion in Grant v. Secretary of HHS, 956 F.2d 1144, 1148 (Fed. Cir. 1992):

> A persuasive medical theory is demonstrated by "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" the logical sequence being supported by "reputable medical or scientific explanation[,]" *i.e.*, "evidence in the form of scientific studies or expert medical testimony[.]"

In Capizzano v. Secretary of HHS, 440 F.3d 1317, 1325 (Fed. Cir. 2006), the Federal Circuit said "we conclude that requiring either epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect is contrary to what we said in Althen...."

Close calls are to be resolved in favor of petitioners. Capizzano, 1440 F.3d at 1327; Althen, 418 F.3d at 1280. *See generally*, Knudsen v. Secretary of HHS, 35 F.3d 543, 551 (Fed. Cir. 1994).

Without more, "evidence showing an absence of other causes does not meet petitioners' affirmative duty to show actual or legal causation." Grant, 956 F.2d at 1149. Mere temporal association is not sufficient to prove causation in fact. Hasler v. US, 718 F.2d 202, 205 (6th Cir. 1983), cert. denied, 469 U.S. 817 (1984).

Petitioner must show not only that but for the vaccine, she would not have had diffuse scleroderma or systemic sclerosis, but also that the vaccine was a substantial factor in bringing about her diffuse scleroderma or systemic sclerosis. Shyface v. Secretary of HHS, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

In essence, the special master is looking for a medical explanation of a logical sequence of cause and effect (Althen, 418 F.3d at 1278; Grant, 956 F.2d at 1148), and medical probability rather than certainty (Knudsen, 35 F.3d at 548-49). To the undersigned, medical probability means biologic credibility or plausibility rather than exact biologic mechanism. As the Federal Circuit stated in Knudsen:

> Furthermore, to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program. The Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal "compensation program" under which awards are to be "made to vaccine-injured persons quickly, easily, and with certainty and generosity." House Report 99-908, *supra*, at 3, 1986 U.S.C.C.A.N. at 6344.
>
> The Court of Federal Claims is therefore not to be seen as a vehicle for ascertaining precisely how and why DTP and other vaccines sometimes destroy the health and lives of certain children while safely immunizing most others.

35 F.3d at 549.

The Federal Circuit stated in Althen, 418 F.3d at 1280, that "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body."

The Federal Circuit in Capizzano emphasized the special master's considering the opinions of petitioner's four treating doctors. These doctors accepted that hepatitis B vaccine

caused petitioner's rheumatoid arthritis. 440 F.3d at 1326. (Both rheumatoid arthritis and scleroderma are rheumatological diseases.)

As the Federal Circuit stated in Knudsen, 35 F.3d at 548, "Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or medical rules." The undersigned's task is to determine medical probability based on the evidence before the undersigned in this particular case. Althen, 418F.3d at1281 ("judging the merits of individual claims on a case-by-case basis").

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

As for epidemiological support for causation, the Federal Circuit in Knudsen ruled for petitioners even when epidemiological evidence directly opposed causation from a vaccine. In Knudsen, even though epidemiological evidence supported the opposite conclusion, i.e., that viruses were more likely to cause encephalopathy than vaccinations, the Federal Circuit held that that fact alone was not an impediment to recovery of damages. In Knudsen, the Federal Circuit stated:

> The bare statistical fact that there are more reported cases of viral encephalopathies than there are reported cases of DTP encephalopathies is not evidence that in a particular case an encephalopathy following a DTP vaccination was in fact caused by a viral infection present in the child and not caused by the DTP vaccine.

35 F.3d at 550.

There are two issues before the undersigned in the instant action: (1) onset, and (2) causation in fact.

Onset

Petitioner alleges that the onset of her scleroderma was in mid-February 1992, about one month after she received her third hepatitis B vaccination.

Respondent defends that the onset of her scleroderma was on January 9, 1992 when she called Dr. Solomon to complain that she had edema.

The undersigned finds it more likely that the onset of petitioner's scleroderma was in mid-February for three reasons:

(1) the contemporaneous medical records reflect a history that petitioner gave that the onset of her symptoms was in late February or early March;

(2) scleroderma is a monophasic disease and does not wax and wane; if the onset of her scleroderma were January 9th, she should not have been feeling well the rest of the month particularly when she received hepatitis B vaccine on January 23rd and testified she would never have taken the vaccination if she had not felt well; and

(3) the edema about which petitioner complained to Dr. Solomon on January 9th was in her ankles, not in her hands, and the onset of scleroderma is at least in the hands before it moves to other parts of the body.

Confusion arose in this case because scleroderma also causes fatigue and achiness and when petitioner was ill over Christmas 1991, she was fatigued and had muscle aches. But Dr. Rosé's refusal to accept petitioner's testimony at the hearing that the edema was solely in her ankles January 9th because, according to Dr. Rosé, one cannot accept what patients say since they are not accurate, was not helpful to the undersigned. The undersigned found petitioner's

testimony to be helpful and not vague in any way. Petitioner is a nurse and one would expect that she would be familiar with what was occurring to her body and when it occurred.

Moreover, the medical literature filed in evidence confirms Dr. White's testimony that scleroderma almost exclusively begins in the hands. Petitioner was just finishing a round of corticosteroids and swelling or edema as a consequence of steroid usage is not unusual. Thus it makes sense medically that she would experience transient ankle swelling after finishing her course of Medrol Dosepak.

Both doctors agreed that scleroderma is a monophasic disease, that is, it does not wax and wane although Dr. Rosé initially thought that the edematous phase might wax until Dr. White explained that the edematous phase leads into the sclerotic or scarring phase, but there are not two separate phases to the disease.

The undersigned holds that the onset of petitioner's scleroderma was approximately one month after she received her third hepatitis B vaccination.

Causation in Fact

Petitioner's expert Dr. White's theory of causation is that due to a combination of her genetic propensity and the effect of the hepatitis B vaccine on her immune system, petitioner developed an autoimmune reaction to the vaccine that manifested itself in diffuse scleroderma. Certainly, Dr. Rosé agrees, and the medical literature is supportive, that scleroderma is an autoimmune disease.

The undersigned has seen other rheumatologic diseases held to be caused by hepatitis B vaccine. See Cappizzano. The principle underlying that opinion about causation in fact was positive rechallenge.

Diffuse scleroderma involves many organs. The undersigned has held that hepatitis B vaccine caused another petitioner's multiorgan illnesses, which included telangiectasia,[5] which is another vascular phenomenon (scleroderma involves the vasculature). See Dunbar v. Secretary of HHS, No. 98-627V, 2007 WL 2844826, *26 (Fed. Cl. Spec. Mstr. Sept. 14, 2007) (one of petitioner's experts, an immunologist, characterized what happened to petitioner there as an "avalanche of autoantibodies").

Scleroderma is a vasculopathy, but not vasculitis. However, the undersigned has ruled for petitioners in not only Dunbar but also in another case involving vasculitis wherein hepatitis B vaccine exacerbated the symptomatology. The undersigned held that hepatitis B vaccine significantly aggravated petitioner's vasculitis (Wegener's granulomatosis) by causing another vasculitis (polyarteritis nodosa or PAN) in Schrum v. Secretary of HHS, No. 04-210V, 2006 WL 1073012 (Fed. Cl. Spec. Mstr. Mar. 31. 2006). In Schrum, medical literature showed that hepatitis B wild virus can and does cause PAN.

Because petitioner's diffuse scleroderma is still active and involves various organs in her body, the possibility of renal damage is a concern for her and she has had renal MRIs to determine the health of her kidneys. The undersigned has held that hepatitis B vaccine caused a renal illness called focal segmental glomerulosclerosis (FSGS) in a case involving positive rechallenge with a subsequent worsening after MMR vaccine and after an upper respiratory infection. Larive v. Secretary of HHS, No. 99-429V, 2004 WL 1212142 (Fed. Cl. Spec. Mstr. May 12, 2004). In Larive, respondent's expert would have accepted causation if petitioner had

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[5] Telangiectasia is "permanent dilation of preexisting small blood vessels (capillaries, arterioles, venules), creating focal red lesions, usually in the skin or mucous membranes." Dorland's Illustrated Medical Dictionary, 30th ed. (2003) at 1861.

had nephritis instead of nephrosis (just as in this case, Dr. Rosé would have been more inclined to accept causation if petitioner had had vasculitis instead of vasculopathy because hepatitis B wild virus can cause vasculitis). Due to positive rechallenge, the undersigned held for petitioner in Larive.

Scleroderma in petitioner's case also includes a neurological component (she has infarcts in her brain and has had seizures), but not a demyelinating condition. The undersigned has ruled in four cases involving neurological demyelinating diseases in the Omnibus hepatitis B vaccine-demyelinating diseases hearing that hepatitis B vaccine can cause demyelinating diseases such as Guillain-Barré syndrome (GBS), transverse myelitis (TM), chronic inflammatory demyelinating polyneuropathy (CIDP), and multiple sclerosis (MS): Peugh v. Secretary of HHS, No. 99-638V, 2007 WL 1531666 (Fed. Cir. Spec. Mstr. May 8, 2007) (GBS); Stevens v. Secretary of HHS, No.99-594, 2006 WL 659525 (Fed. Cl. Spec. Mstr. Feb. 24, 2006) (TM); Gilbert v. Secretary of HHS, No. 04-455V, 2006 WL 1006612 (Fed. Cl. Spec. Mstr. Mar. 30, 2006) (CIDP); and Werderitsh v. Secretary of HHS, No. 99-310V, 2006 WL 1672884 (Fed. Cl. Spec. Mstr. May 26, 2006) (MS).

In light of all these cases in which hepatitis B vaccine instigated or worsened an autoimmune disease involving various organs, the undersigned holds that it is consistent that hepatitis B vaccine can and did cause diffuse scleroderma or systemic sclerosis occurring one month after hepatitis B vaccination.

The timing here is appropriate for an immune response. Autoimmune reactions take time, in this case one month.

The pathological process described in the medical literature and in Dr. White's testimony is consistent with what happened to petitioner clinically, and shows a logical sequence of cause and effect. Autoimmunity whether operating through molecular mimicry or some other mechanism is a biologically plausible response to an environmental challenge such as vaccination against hepatitis B. The only ingredients missing are pathologic certainty and epidemiologic support, neither of which petitioner legally needs to prove under the Federal Circuit's rulings in Knudsen, Althen, and Cappizanno (petitioner's evidence must be preponderant not certain; petitioner does not have to provide epidemiologic support or objective medical literature confirmation in order to prevail).

Petitioner has shown a logical sequence of cause and effect from the vaccination to the onset of her diffuse scleroderma, a disease in which the body turns against itself because of a combination of genetic proclivity and external immunologic challenge (the vaccination), producing autoantibodies that proceeded to attack her skin and other organs, causing edema, scarring, and multiple organ damage. Petitioner has prevailed in proving causation in fact.

CONCLUSION

Petitioner has prevailed on the issue of entitlement. The undersigned encourages the parties to settle damages in this case. A telephonic status conference shall be set soon to discuss how to proceed with damages.

IT IS SO ORDERED.

November 19, 2007
DATE

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